

Product Monograph

PrViread[®]

(Tenofovir Disoproxil Fumarate Tablets)

300 mg

Antiretroviral Agent

Gilead Sciences, Inc.
Foster City, CA 94404
USA

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Gilead Sciences Canada, Inc.
Mississauga, ON
L5N 2W3

www.gilead.com

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TABLE OF CONTENTS

TITLE PAGE	1
PART I. HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS	5
ADVERSE REACTIONS	10
DRUG INTERACTIONS	22
DOSAGE AND ADMINISTRATION	27
OVERDOSAGE	28
ACTION AND CLINICAL PHARMACOLOGY	29
STORAGE AND STABILITY	32
SPECIAL HANDLING INSTRUCTIONS	32
DOSAGE FORMS, COMPOSITION AND PACKAGING	33
PART II. SCIENTIFIC INFORMATION	34
CLINICAL TRIALS	34
DETAILED PHARMACOLOGY - VIROLOGY (MICROBIOLOGY)	48
PHARMACEUTICAL INFORMATION	50
TOXICOLOGY	50
REFERENCES	53
PART III. CONSUMER INFORMATION	55

PrViread[®]
(Tenofovir Disoproxil Fumarate Tablets)

PART I. HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 300 mg	lactose monohydrate, pregelatinized starch (gluten free).

For a complete listing, see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

HIV-1 Infection

VIREAD[®] (tenofovir disoproxil fumarate) is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 12 years of age and older.

Chronic Hepatitis B

VIREAD is indicated for the treatment of chronic hepatitis B infection in patients 18 years of age and older.

This indication is based on:

- The results from two phase 3 trials in nucleoside naïve (n = 375) and nucleoside-experienced (n = 51) adult patients with HBeAg negative (presumed pre-core mutant) and HBeAg positive chronic hepatitis B virus infection with compensated liver function and evidence of active viral replication. The primary end point in both studies was a composite endpoint which included virological and histological markers.
- The results from a small (N=45 patients treated with VIREAD) phase 2 trial in nucleoside naïve and nucleoside experienced adult patients with HBeAg negative and HBeAg positive chronic hepatitis B infection with primarily Child-Pugh-Turcotte Class A or B decompensated liver disease. Hepatobiliary and renal parameters should be closely monitored in this patient population. The number of patients with Child-Pugh-Turcotte Class C at baseline was too small (N=6) to reach conclusions regarding safety and efficacy. Patients with a history of solid organ or bone marrow transplant and patients with a diagnosis of proximal tubulopathy were not studied and therefore the safety and efficacy of VIREAD in this population have not been demonstrated.

Geriatrics (> 65 years of age)

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

Pediatrics (12 to < 18 years of age)

The safety and efficacy of VIREAD in adolescent patients aged 12 to <18 years is supported by data from one randomized study in which VIREAD was administered to HIV-1 infected treatment experienced subjects. In this study, the pharmacokinetic profile of VIREAD was similar to that found to be safe and effective in adult populations.

Safety and effectiveness in pediatric patients less than 12 years of age have not been established.

CONTRAINDICATIONS

VIREAD (tenofovir disoproxil fumarate) is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

VIREAD should not be used in combination with the fixed-dose combination products TRUVADA[®], ATRIPLA[®], or COMPLERA[™] since it is a component of these products.

VIREAD should not be administered in combination with HEPSERA[®] (adefovir dipivoxil).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Lactic Acidosis and Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, alone or in combination with other antiretrovirals (**see WARNINGS AND PRECAUTIONS**).

- **Post-Treatment Exacerbation of Hepatitis**

Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted (**see WARNINGS AND PRECAUTIONS**).

- **Nephrotoxicity**

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of VIREAD during clinical practice (**see WARNINGS AND PRECAUTIONS**).

General

For the effect of co-administered drugs, see DRUG INTERACTIONS section.

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. 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.

Bone Effects

In HIV-infected patients treated with VIREAD in Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both VIREAD and stavudine treatment arms of the study and significantly greater decreases were seen in the lumbar spine measurement in the Viread group relative to the stavudine group. Clinically relevant fractures were reported in both treatment groups. Increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) were observed, suggesting increased bone turnover. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range (**see ADVERSE REACTIONS, Study 903**). In a clinical study of HIV-1 infected adolescent subjects (Study 321), bone effects were similar to adult subjects. Under normal circumstances, BMD increases rapidly

in adolescents. In this study, the mean rate of bone gain was less in the VIREAD-treated group compared to the placebo group. Six VIREAD treated adolescents and one placebo treated adolescent had significant (>4%) lumbar spine BMD loss in 48 weeks. Among 28 subjects receiving 96 weeks of VIREAD, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in VIREAD-treated adolescents increased bone turnover, consistent with the effects observed in adults. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy and infrequently contributing to fractures) have been reported in association with the use of VIREAD (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**).

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Tenofovir DF did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumors, considered likely related to high local concentrations in the gastrointestinal tract at the high dose of 600 mg/kg/day. The mechanism of tumor formation in mice and potential relevance for humans are uncertain.

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 at doses up to 2000 mg/kg when administered orally to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered at 600 mg/kg/day to male rats for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats. A dose of 600 mg/kg/day is equivalent to 19 times the human dose based on body surface area comparisons.

Endocrine and Metabolism

Fat Redistribution

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

Hepatic/Biliary/Pancreatic

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, including tenofovir disoproxil fumarate, alone or in combination with other antiretrovirals in the treatment of HIV infection. A majority of these cases have been reported in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering nucleoside analogs to any patient, and particularly to those 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 levels).

Pancreatitis

Pancreatitis has occurred during therapy with combination regimens that included VIREAD. Caution should be used when administering nucleoside analogues (including VIREAD) to patients with a history of pancreatitis or risk factors for the development of pancreatitis. Therapy should be suspended in patients with suspected pancreatitis.

Hepatic Impairment

Tenofovir and tenofovir disoproxil are not metabolized by liver enzymes. Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed. Therefore, no dose adjustment is required in patients with hepatic impairment. The safety and efficacy of tenofovir DF has not been established or specifically studied in patients with underlying liver disorders. Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products

Exacerbation of Hepatitis After Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

Immune

Immune Reconstitution Syndrome

During the initial phase of treatment, HIV-infected patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB), which may necessitate further evaluation and treatment.

Angioedema

Cases of angioedema have been reported in patients taking tenofovir DF (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**).

Renal

Nephrotoxicity

Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of VIREAD in clinical practice (see **ADVERSE REACTIONS, Post Market Adverse Reactions and DRUG INTERACTIONS**). 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.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA.

Particular caution should be exercised when administering VIREAD to patients with known risk factors for renal disease and a history of renal dysfunction; however, cases of renal failure have also been reported in patients with no known risk factors. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent.

Dosing interval adjustment is required in all patients with creatinine clearance <50 mL/min (see **DOSAGE and ADMINISTRATION**). 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. The potential benefit of VIREAD therapy should be assessed against the potential risk for renal toxicity.

Special Populations

Patients with HIV and Hepatitis B Virus Coinfection

Due to the risk of development of HIV resistance, VIREAD should only be used in HIV and HBV coinfecting patients as part of an appropriate antiretroviral combination therapy.

HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD.

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. 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. Reduced pup body weights, survival, and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons). Because animal reproduction studies are not always predictive of human response, tenofovir disoproxil fumarate should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus.

Antiretroviral Pregnancy Registry

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

Nursing Women

It is currently recommended that HIV and HBV infected women should not breast-feed to avoid postnatal transmission of HIV-1 and HBV. Studies in rats and rhesus monkeys have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Mothers should be instructed not to breast-feed if they are receiving VIREAD.

Pediatrics

The safety and efficacy of VIREAD in HIV adolescent patients aged 12 to <18 years is supported by data from one randomized study in which VIREAD was administered to HIV-1 infected treatment experienced subjects. In this study, the pharmacokinetic profile of VIREAD was similar to that found to be safe and effective in adult populations.

Safety and effectiveness in patients less than 12 years of age have not been established.

Geriatric

Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than 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 Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

HIV-1 Infection

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 1-3 clinical trials and expanded access studies. A total of 1,544 patients have received VIREAD 300 mg once daily in Phase 1-3 clinical trials; over 11,000 patients have received VIREAD in expanded access studies.

Treatment-Experienced Adult Patients

Study 907 - 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 1.

Table 1. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in $\geq 3\%$ in Any Treatment Group in Study 907 (0–48 weeks)

	VIREAD (N = 368) (Week 0–24)	Placebo (N = 182) (Week 0–24)	VIREAD (N = 368) (Week 0–48)	Placebo Crossover to VIREAD (N = 170) (Week 24–48)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal pain	4%	3%	7%	6%
Back pain	3%	3%	4%	2%
Chest pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
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 2.

Table 2. Grade 3/4 Laboratory Abnormalities Reported in \geq 1% of VIREAD-Treated Patients in Study 907 (0–48 weeks)

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

Treatment-Naïve Adult Patients

Study 903 - 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 stavudine (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 3).

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

Table 3. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥ 5% in Any Treatment Group in Study 903 (0–144 Weeks)

	VIREAD + 3TC + EFV N = 299	d4T + 3TC + EFV N = 301
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Back pain	9%	8%
Fever	8%	7%
Abdominal pain	7%	12%
Asthenia	6%	7%
Digestive System		
Diarrhea	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 stavudine group (14%) compared with VIREAD (3%), 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 4.

Table 4. Grade 3/4 Laboratory Abnormalities Reported in $\geq 1\%$ of VIREAD-Treated Patients in Study 903 (0–144 Weeks)

	VIREAD + 3TC + EFV N = 299	d4T + 3TC + EFV N = 301
Any \geq Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (> 240 mg/dL)	19%	40%
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%
Hematuria (> 100 RBC/HPF)	7%	7%
Neutrophil (< 750 /mm ³)	3%	1%
Fasting Triglyceride (> 750 mg/dL)	1%	9%

In Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients in the VIREAD group compared with patients in the stavudine group (see Table 5). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated patients vs. 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the VIREAD group and 6 patients in the stavudine group. In addition, there were significant increases in 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 and 1,25 Vitamin D 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. The effects of VIREAD-

associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Table 5. Changes in Bone Mineral Density Study 903

	Mean Percent Change (\pm SD) to Week 144 in BMD	
	VIREAD + 3TC+ EFV	d4T + 3TC +EFV
Lumbar Spine	-2.2% \pm 3.9	-1.0% \pm 4.6
Hip	-2.8% \pm 3.5	-2.4% \pm 4.5

Study 934 - Treatment Emergent Adverse Events: Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either VIREAD + EMTRIVA (emtricitabine) 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 other studies in treatment experienced or treatment-naïve patients (Table 6).

Table 6. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in \geq 3% in Any Treatment Group in Study 934 (0–48 weeks)

	VIREAD+FTC+ EFV N = 257	AZT/3TC+EFV N = 254
Blood and Lymphatic System Disorders		
Anemia	< 1%	5%
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Patients who received treatment up to 144 weeks in Study 934 reported adverse events similar in nature and severity to those reported in the first 48 weeks.

Through 48 weeks, 7 patients in the EMTRIVA + VIREAD group and 5 patients in the lamivudine/zidovudine group experienced a new CDC Class C event (10 and 6 patients, respectively, through 144 weeks). Renal safety assessed by laboratory abnormalities was similar in the two groups and no patient discontinued study drug due to renal events. At Week 48 and 144, total limb fat (as measured by dual-energy x-ray absorptiometry) was

significantly less in a subgroup of patients in the lamivudine/zidovudine group compared to the tenofovir/emtricitabine subgroup (see Table 7).

Table 7. Study 934: Total Limb Fat at Week 48 and 144 (Dual-Energy X-Ray Absorptiometry)

	VIREAD + FTC + EFV	AZI/3TC +EFV
Week 48¹	N = 51	N = 49
Total Limb Fat (kg) (Mean ± S.D.)	8.9 ± 5.4	6.9 ± 3.9
Week 144²	N = 145	N = 124
Total Limb Fat (kg) (Mean ± S.D.)	9.2 ± 5.4	6.5 ± 4.3

1 P = 0.03 for the comparison between arms

2 P < 0.001 for the comparison between arms

Laboratory Abnormalities: Laboratory Abnormalities observed in this study were generally consistent with those seen in other studies (Table 8).

Table 8. Grade 3/4 Laboratory Abnormalities Reported in \geq 1% in Any Treatment Group in Study 934 (0–48 weeks)

	EMTRIVA+VIREAD+EFV N = 257	AZT/3TC+EFV N = 254
Any \geq Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (> 240 mg/dL)	15%	17%
Creatine Kinase (M: > 990 U/L) (F: > 845 U/L)	7%	6%
Serum Amylase (> 175U/L)	7%	3%
Alkaline Phosphatase (> 550 U/L)	1%	0%
AST (M: > 180 U/L) (F: > 170 U/L)	3%	2%
ALT (M: > 215 U/L) (F: > 170 U/L)	2%	2%
Hemoglobin (< 8.0 mg/dL)	0%	3%
Hyperglycemia (> 250 mg/dl)	1%	1%
Hematuria (> 75 RBC/HPF)	2%	2%
Neutrophil (> 750/mm ³)	3%	4%
Fasting Triglycerides (> 750mg/dL)	4%	2%

Laboratory abnormalities in patients who received treatment up to 144 weeks in Study 934 were consistent with those observed in the first 48 weeks of treatment.

Adolescent Patients with HIV-1 Infection

Assessment of adverse reactions is based on one randomized study (Study 321) in 87 HIV-1 infected adolescent patients (12 to <18 years of age) who received treatment with VIREAD (N=45) or placebo (N=42) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in adolescent patients who received treatment with VIREAD were consistent with those observed in clinical studies in adults.

Chronic Hepatitis B

Adult Patients

Patients with chronic hepatitis B and compensated liver function received double-blind treatment with VIREAD (n = 426) or HEPSERA (n = 215) for 48 weeks in studies 0102 (HBeAg-) and 0103 (HBeAg+).

The most common adverse events in tenofovir DF treated patients (incidence $\geq 5\%$) identified during the 48-week double blind period of these studies, at any severity and regardless of causality are presented in Table 9.

Table 9. Treatment-Emergent Adverse Events^a ($\geq 5\%$ in tenofovir DF-treated patients) in Pooled Studies GS-US-174-0102 and GS-US-174-0103 (0-48 weeks)

	VIREAD (N = 426)	HEPSERA (N = 215)
Body as a Whole		
Abdominal Pain Upper	7%	5%
Back Pain	7%	5%
Gastrointestinal Disorders		
Nausea	9%	3%
Diarrhea	7%	5%
General Disorders		
Fatigue	9%	7%
Infections and Infestations		
Nasopharyngitis	10%	11%
Nervous System Disorders		
Headache	13%	14%
Dizziness	6%	3%

a regardless of causality and severity

The adverse reactions observed with continued treatment for 192 weeks in Studies 0102 and 0103 were consistent with the safety profile of VIREAD.

Adverse events observed in a double-blind, randomized, controlled study (Study 0106) in which 105 patients previously treated with HEPSERA were treated with tenofovir DF for 48 weeks were similar in nature to those observed in Studies 0102 and 0103. No new adverse events causally associated with tenofovir DF were identified from a double-blind active controlled study (Study 0108) in which patients with decompensated liver disease received treatment containing tenofovir DF (N=90) for up to 48 weeks. This study

was not large enough to detect rare or unexpected adverse events in this patient population. In this study, 7 of 90 patients (8%) receiving a tenofovir DF-containing regimen, including 4 of 45 patients (9%) receiving VIREAD, experienced a confirmed increase in serum creatinine of ≥ 0.5 mg/dL or confirmed decrease in serum phosphorus of <2 mg/dL through Week 48. (see **CLINICAL TRIALS for additional safety information regarding VIREAD**).

Laboratory Abnormalities: In Studies 0102 and 0103, the most frequently occurring Grade 3 or 4 laboratory abnormality during the 48-week double-blind period in the VIREAD treatment group was ALT increased. All patients with treatment-emergent Grade 3 or 4 ALT increases had elevated ALT at baseline. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 10.

Table 10. Grade 3/4 Laboratory Abnormalities Reported in $\geq 1\%$ in Any Treatment Group in Pooled Studies GS-US-174-0102 and GS-US-174-0103 (0–48 weeks)

	VIREAD N = 426	HEPSERA N = 215
Any \geq Grade 3 Laboratory Abnormality	19%	13%
ALT (> 5.00 x ULN)	10%	6%
AST (> 5.00 x ULN)	4%	4%
Serum Amylase (> 2.0 x ULN)	4%	1%
Urine Glucose ($\geq 3+$)	3%	1%
Creatine Kinase (≥ 10.0 x ULN)	2%	3%
Hyperglycemia (> 250 mg/dl)	1%	2%

Grade 3/4 laboratory abnormalities were similar in nature and frequency in patients continuing treatment for up to 192 weeks in these studies. Overall, the following grade 3–4 laboratory abnormalities were reported in $\geq 1\%$ of subjects during open-label VIREAD treatment (Weeks 48-192 of Studies 0102 and 0103): serum amylase (2%), creatine kinase (2%), serum lipase (1%), prothrombin time (4%), ALT (3%), AST (3%) and urine glucose (4%).

Post Market Adverse Drug Reactions: The following adverse reactions have been identified during post-approval use of VIREAD. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with VIREAD.

<i>Immune system disorders:</i>	Allergic reaction (including angioedema)
<i>Metabolism and nutrition disorders:</i>	Lactic acidosis, hypokalemia, hypophosphatemia
<i>Respiratory, thoracic and mediastinal disorders:</i>	Dyspnea
<i>Gastrointestinal disorders:</i>	Pancreatitis, increased amylase, abdominal pain
<i>Blood and lymphatic system:</i>	Thrombocytopenia
<i>Hepatobiliary disorders:</i>	Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, GGT)
<i>Skin and Subcutaneous Tissue Disorders:</i>	Rash
<i>Musculoskeletal and Connective Tissue Disorders:</i>	Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy
<i>Renal and urinary disorders:</i>	Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria
<i>General disorders and Administration Site Conditions</i>	Asthenia

The following adverse reactions, listed under the body system headings above, sometimes appeared to be concurrent with proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalemia, muscular weakness, myopathy, hypophosphatemia.

There have been three post marketing reports of acute renal failure in patients on concomitant NSAIDS therapy where a relationship to VIREAD could not be excluded. These events mostly occurred in medically complex patients, where underlying disease processes confound interpretation.

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 **WARNINGS and PRECAUTIONS**).

In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see **WARNINGS AND PRECAUTIONS, Exacerbations of Hepatitis after Discontinuation of Treatment**).

DRUG INTERACTIONS

Serious Drug Interactions

- **Atazanavir and lopinavir/ritonavir increase tenofovir disoproxil fumarate concentrations which may lead to tenofovir-associated adverse events (see WARNINGS and PRECAUTIONS)**
- **Tenofovir disoproxil fumarate decreases atazanavir concentrations – administer atazanavir with ritonavir (see below)**
- **Tenofovir disoproxil fumarate increases didanosine (ddI) concentrations – the dose of ddI may be reduced but use with caution and monitor for ddI-related adverse events and clinical response (see below)**

Drug-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 coadministered drug, due to competition for this elimination pathway. Some examples include, but are not limited to, didanosine, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

VIREAD should not be administered in combination with HEPSERA (adefovir dipivoxil).

VIREAD has been evaluated in healthy volunteers in combination with abacavir, atazanavir, didanosine, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir and tacrolimus (see **below**). No clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and abacavir, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir and tacrolimus. Tables 11 and 12 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir on the pharmacokinetics of coadministered drug.

Didanosine

Pharmacokinetic studies have shown that coadministration of didanosine and tenofovir DF results in 40–60% increase in C_{max} and AUC of didanosine (see Table 13). The mechanism of

this interaction is unknown. **Increases in didanosine concentrations of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis, and neuropathy.** In addition, suppression of CD4 counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily.

A reduced dose of Videx EC[®] (ddI-EC) is recommended when coadministered with VIREAD. When coadministered with VIREAD, the Videx EC[®] Product Monograph recommends a reduced dose of 250 mg ddI-EC for HIV-infected adults with body weight ≥ 60 kg and creatinine clearance ≥ 60 mL/min. For adult patients with body weight < 60 kg, and creatinine clearance ≥ 60 mL/min, the recommended dose of ddI-EC is 200 mg. Data are not available to recommend a dose adjustment for patients with creatinine clearance < 60 mL/min or for the buffered tablet formulation of didanosine (Videx[®]).

Caution should be used when coadministering reduced-dose didanosine, tenofovir, and an NNRTI in treatment-naïve patients with high viral loads at baseline since such use has been associated with reports of a high rate of virologic failure and emergence of resistance at an early stage. All patients receiving tenofovir disoproxil fumarate and didanosine concomitantly should be closely monitored for didanosine-related adverse events and clinical response.

Atazanavir and Lopinavir/Ritonavir

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations (see Table 11). The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving atazanavir, lopinavir/ritonavir and tenofovir disoproxil fumarate should be monitored for tenofovir-associated adverse events.

Tenofovir decreases atazanavir concentrations (see Table 12). Although safety and efficacy data are limited, it is recommended that atazanavir, without ritonavir, should not be coadministered with tenofovir disoproxil fumarate. The recommended regimen is atazanavir 300 mg given with ritonavir 100 mg when used in combination with tenofovir disoproxil fumarate 300 mg (all as a single daily dose with food).

Table 11. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir¹ in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters ² (90% CI)		
			C _{max}	AUC	C _{min}
Abacavir	300 once	8	↔	↔	NC
Atazanavir sulfate ³	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	↔	↔	↔
Didanosine (buffered) ⁴	250 or 400 once daily × 7 days	14	↔	↔	↔
Efavirenz	600 once daily × 14 days	29	↔	↔	↔
Emtricitabine	200 once daily × 7 days	17	↔	↔	↔
Entecavir	1 mg once daily × 10 days	28	↔	↔	↔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↔	↔	↔
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1250 twice daily × 14 days	29	↔	↔	↔
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	35	↔	↔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔

1. Patients received VIREAD 300 mg once daily.
2. Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
3. REYATAZ[®] Prescribing Information (Bristol-Myers Squibb)
4. Includes 4 subjects weighing < 60 kg receiving ddl 250 mg.

Table 12. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of VIREAD

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

1. Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable

2. REYATAZ[®] Prescribing Information (Bristol-Myers Squibb).
3. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
4. R-(active), S-and total methadone exposures were equivalent when dosed alone or with VIREAD
5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
6. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with VIREAD.
7. Increase in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

Table 13. 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 × 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 ddl 250 mg.

Drug-Food Interactions

Interactions of VIREAD with food have not been established (see **ACTIONS AND CLINICAL PHARMACOLOGY, Effect of Food on Absorption**).

Drug-Herb Interactions

Interactions of VIREAD with herbs have not been established.

Drug-Laboratory Interactions

Interactions of VIREAD with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Adults

For the treatment of HIV or chronic hepatitis B: The dose of VIREAD (tenofovir disoproxil fumarate) is 300 mg once daily taken orally without regard to food.

In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. VIREAD may be discontinued if there is HBsAg loss or HBsAg seroconversion.

Adolescent Patients with HIV-1 Infection (12 Years of Age and Over)

Body weight ≥ 35 kg (≥ 77 lb): Take one 300 mg VIREAD tablet once daily 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 **ACTIONS AND CLINICAL PHARMACOLOGY, Renal Insufficiency**). Therefore, the dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance < 50 mL/min using the recommendations in Table 14. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in moderate to severe renal impairment, therefore, clinical response to treatment and renal function should be closely monitored in these patients. Routine monitoring of creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment (creatinine clearance 50-80 mL/min). (see **WARNINGS and PRECAUTIONS**).

Table 14. Dosage Adjustment for Patients with Altered Creatinine Clearance

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

1. Calculated using ideal (lean) body weight.
2. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

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

No data are available to make dose recommendations in adolescent patients with renal impairment.

Missed Dose

If a patient misses a dose at the regularly scheduled time, but then remembers it that same day, the patient should take the missed dose immediately. The next dose should be taken at the regularly scheduled time the following day. The patient should not take two doses of VIREAD at once to make up for missing a dose.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.
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Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In Study 901 tenofovir disoproxil fumarate 600 mg 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. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug.

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.

ACTION AND CLINICAL PHARMACOLOGY

VIREAD (tenofovir disoproxil fumarate) is an acyclic nucleotide diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis (by non-specific esterases in blood and tissues) for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV reverse transcriptase and HBV polymerase 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 .

VIREAD is a water soluble diester prodrug of the active ingredient tenofovir. Following oral administration of a single dose of VIREAD 300 mg to HIV-infected patients in the fasted state, maximum serum concentrations (C_{max}) of tenofovir are achieved in 1.0 ± 0.4 hours. The oral bioavailability of tenofovir from VIREAD in fasted patients is approximately 25%. Administration of VIREAD following a high-fat meal increases the oral bioavailability, with an increase in tenofovir AUC_{∞} of approximately 40% and an increase in C_{max} of approximately 14% (see **DOSAGE AND ADMINISTRATION**).

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

Pharmacodynamics

Activity in HIV-1

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} 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, stavudine, zalcitabine, and zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and 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 0.5–2.2 μ M).

The antiviral effects of tenofovir disoproxil fumarate monotherapy in reducing HIV-1 viral load and the relationship with dose were assessed in clinical phase 1 studies in treatment-naive and treatment-experienced HIV-infected patients. Doses of tenofovir disoproxil fumarate ranging from 75 mg to 600 mg once daily resulted in statistically significant decreases in plasma HIV-1 RNA levels compared with placebo. In a mixed population of treatment-naive and treatment-experienced patients who received 28 days of repeat daily dosing with tenofovir disoproxil fumarate 300 mg QD (Study GS-97-901) the median decrease in plasma \log_{10} HIV-1 RNA level was 1.22 \log_{10} copies/mL.

Activity in HBV

The in vitro antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC₅₀ values for tenofovir were in the range of 0.14 to 1.5 µM, with CC₅₀ (50% cytotoxicity concentration) values > 100 µM. Tenofovir diphosphate inhibits recombinant HBV polymerase with a K_i (inhibition constant) of 0.18 µM. In in vitro drug combination studies of tenofovir with nucleoside anti-HBV reverse transcriptase inhibitors lamivudine, telbivudine, and entecavir, additive anti-HBV activity was observed. Additive to slightly synergistic effects were observed with the combination of tenofovir and emtricitabine.

Pharmacokinetics

Pharmacokinetics of intravenous tenofovir were evaluated in Study GS-96-701 (N = 16). Following intravenous administration of tenofovir 1.0 and 3.0 mg/kg, pharmacokinetics were dose-proportional with the exception of the estimated terminal half-life (5.3 and 7.8 hours, respectively). The pharmacokinetics of tenofovir were not affected by repeated dosing in the 1.0 mg/kg/day group, with the exception of half-life (5.3 on Day 1 vs. 7.7 on Day 14) and volume of distribution (763 vs. 1320 mL/kg). At the 3.0 mg/kg/day, there was an approximate 27% decrease in serum clearance of tenofovir following 7 days of once daily administration; renal clearance and estimated terminal half-life were also significantly different.

The pharmacokinetics of tenofovir following administration of tenofovir disoproxil fumarate were evaluated in the fasted state in Study GS-97-901 (HIV-infected patients) and Study GS-00-914 (healthy volunteers). The pharmacokinetics in HIV-infected patients and healthy volunteers were similar. The estimated terminal half-life in HIV-infected patients measured over 24 hours was ~12–13 hr. The terminal elimination half-life in healthy subjects assessed over 48 hours was ~17 hours. There were no significant differences in the dose-normalized steady-state pharmacokinetics of tenofovir over the dose range of 75 to 600 mg. Tenofovir exposure following 8 and 28 days was slightly higher than those observed following the first dose.

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-infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hours. C_{max} and AUC values are 296 ± 90 ng/mL and 2287 ± 685 ng•hr/mL, respectively.

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 0.01–25 µg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism

In vitro studies 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. After multiple oral doses of VIREAD 300 mg once daily (under fed conditions), $32 \pm 10\%$ of the administered dose is recovered in urine over 24 hours.

Excretion

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.

Effects of Food on Oral Absorption

Administration of VIREAD following a high-fat meal (~700 to 1000 kcal containing 40–50% 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%. 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•hr/mL following multiple doses of VIREAD 300 mg once daily in the fed state, when meal content was not controlled.

Special Populations and Conditions

Pediatric Patients

Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected adolescent patients (12 to <18 years). All pediatric patients were receiving VIREAD with a ritonavir-boosted protease inhibitor. Mean (\pm SD) C_{max} and AUC_{tau} are 0.38 ± 0.13 μ g/mL and 3.39 ± 1.22 μ g•hr/mL, respectively. Tenofovir exposure achieved in adolescent patients receiving oral daily doses of VIREAD 300 mg was similar to exposures achieved in adults receiving once-daily doses of VIREAD 300 mg.

Geriatrics

Pharmacokinetic studies have not been performed in the elderly.

Race

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

Gender

Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect.

Hepatic Insufficiency

The pharmacokinetics of tenofovir following a 300 mg single dose of VIREAD have been studied in 8 non-HIV, non-HBV infected subjects with moderate hepatic impairment and 8 non-HIV infected subjects with severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in VIREAD dosing is required in patients with hepatic impairment.

Renal Insufficiency

The pharmacokinetics of tenofovir are altered in subjects with renal impairment (see **WARNINGS, Nephrotoxicity**). In non-HIV, non-HBV infected subjects with creatinine clearance < 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} , and $AUC_{0-\infty}$ of tenofovir were increased (Table 15). 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 15. Pharmacokinetic Parameters (Mean \pm SD) of Tenofovir* in Patients with varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	> 80 (N = 3)	50–80 (N = 10)	30–49 (N = 8)	12–29 (N = 11)
C_{max} (ng/mL)	335.5 \pm 31.8	330.4 \pm 61.0	372.1 \pm 156.1	601.6 \pm 185.3
AUC_{∞} (ng•hr/mL)	2184.5 \pm 257.4	3063.8 \pm 927.0	6008.5 \pm 2504.7	15984.7 \pm 7223.0
CL/F (mL/min)	1043.7 \pm 115.4	807.7 \pm 279.2	444.4 \pm 209.8	177.0 \pm 97.1
CL _{renal} (mL/min)	243.5 \pm 33.3	168.6 \pm 27.5	100.6 \pm 27.5	43.0 \pm 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.

STORAGE AND STABILITY

Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F).

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VIREAD is available as tablets. 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 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. 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. Available in bottles containing 30 tablets with a desiccant (silica gel canister or sachet) and closed with child-resistant closure.

PART II. SCIENTIFIC INFORMATION

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.

CLINICAL TRIALS

Clinical Efficacy in Patients with HIV

Study Demographics and Trial Design

Treatment-Experienced Adult Patients

Study 907 - VIREAD + Standard Background Therapy (SBT) Compared to Placebo + SBT: Study 907 was a 24-week, double-blind placebo-controlled 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/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.

Table 16. Study 907: VIREAD + Standard Background Therapy (SBD) Compared to Placebo + SBD

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subject (N = 550)	Mean Age	Gender
GS-99-907	Randomized (2:1), Double-Blind, Placebo-Controlled	<p>Arm 1: tenofovir DF 300 mg QD oral</p> <p>Arm 2: placebo QD</p> <p>Added to stable background regimen for 24 weeks followed by open label tenofovir for all patients for an additional 24 weeks.</p>	<p>Patients on stable antiretroviral therapy with early virologic failure.</p> <p>(N = 550)</p>	<p>42 years</p> <p>(22–70)</p>	<p>Male: 85%</p> <p>Female: 15%</p>

Treatment-Naïve Adult Patients

Study 903 - VIREAD + Lamivudine + Efavirenz Compared to Stavudine + Lamivudine + Efavirenz: Data through 144 weeks are reported for Study 903, a double-blind, active-controlled 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 18–64), 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.

Table 17. Study 903: VIREAD + Lamivudine + Efavirenz Compared with Stavudine + Lamivudine + Efavirenz

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N = 600)	Mean Age (Range)	Gender
GS-99-903	Randomized (1:1), double-blind, active-controlled, equivalence study. Arm 1: tenofovir DF + lamivudine + efavirenz Arm 2: stavudine + lamivudine + efavirenz	Arm 1: tenofovir DF 300 mg tablets QD, stavudine placebo capsules BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD Arm 2: tenofovir DF placebo tablets QD, stavudine ¹ capsules 40/30 mg BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD All for oral (PO) administration for 144 weeks double-blind phase followed by 192-week open-label phase. (Nevirapine 200 mg BID could replace efavirenz in the event of efavirenz-associated central nervous system toxicity or rash.)	Treatment-naïve (HIV-1 RNA > 5,000 copies/mL) (N = 600)	36 years (18–64)	Male: 74% Female: 26%

1. Stavudine/placebo capsules 20/15 mg BID as need for dose reduction.

Study 934 - VIREAD + Emtricitabine+ Efavirenz Compared with Lamivudine/Zidovudine + Efavirenz: Data through 144 weeks are reported for Study 934, a randomized, open-label, active controlled multicenter study comparing VIREAD (300 mg QD) + emtricitabine (200 mg QD) administered in combination with efavirenz (600 mg QD) versus lamivudine 150 mg/ zidovudine 300 mg bid administered in combination with efavirenz (600 mg QD) in 511 antiretroviral-naïve patients. From weeks 96 to 144 of the

study, patients randomized to VIREAD + emtricitabine received TRUVADA with efavirenz in place of emtricitabine + VIREAD. Patients had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4 cell count was 245 cells/mm³ (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL (range 3.56–6.54). Patients were stratified by baseline CD4 count (< or ≥ 200 cells/mm³); 41% had CD4 cell counts < 200 cells/mm³ and 51% of patients had baseline viral loads > 100,000 copies/mL

Table 18. Study 934: EMTRIVA+ VIREAD + Efavirenz Compared with Lamivudine/Zidovudine +Efavirenz

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N = 511)	Mean Age	Gender
GS-01-934	Randomized, open-label, parallel, multicenter, active controlled Arm 1: emtricitabine+ tenofovir DF+ efavirenz Arm 2: lamivudine/ zidovudine + efavirenz	Arm 1 ¹ : Efavirenz 600 mg once daily for oral administration, emtricitabine 200 mg once and tenofovir DF 300 mg once daily Arm 2: Efavirenz 600 mg once daily for oral administration and Combivir (lamivudine/ zidovudine 150/300 mg twice daily). 144 weeks	Antiretroviral naive patients (HIV-1 RNA > 10,000 copies/mL) (N = 511)	Mean 38 years Range 18–80	Male: 86% Female:14%

1. From weeks 96 to 144 of the study, patients received TRUVADA with efavirenz in place of emtricitabine + VIREAD

Study Results

Study 907 - VIREAD + Standard Background Therapy (SBT) Compared to Placebo + SBT: Changes from baseline in log₁₀ copies/mL plasma HIV-1 RNA levels through Week 48 are presented in Table 19.

Table 19. Mean Change from Baseline in Plasma HIV-1 RNA (log₁₀ copies/mL): Study 907 (48 weeks)

Study Week	HIV-1 RNA log ₁₀ copies/mL	
	VIREAD (N = 368)	Placebo (N = 182)
Week 12	-0.65 (n = 354)	-0.08 (n = 175)
Week 24	-0.59 (n = 346)	-0.01 (n = 172)
	VIREAD (N = 368)	Placebo Crossover to VIREAD ¹ (N = 170)
Week 32	-0.55 (n = 346)	-0.61 (n = 167)
Week 40	-0.49 (n = 336)	-0.61 (n = 162)
Week 48	-0.53 (n = 327)	-0.64 (n = 160)

1 For Placebo Crossover to VIREAD, baseline HIV-1 RNA was reset at Week 24

The percent of patients with HIV-1 RNA < 400 copies/mL and outcomes of patients through 48 weeks are summarized in Table 20.

Table 20. 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 (22% and 1%, respectively). Mean change in absolute CD4 counts by Week 24 was +12 cells/mm³ for the VIREAD group and -5 cells/mm³ for the placebo group. Mean change in absolute CD4 counts by Week 48 was +4 cells/mm³ for the VIREAD group.

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

Study 903 - VIREAD + Lamivudine + Efavirenz Compared to Stavudine + Lamivudine + Efavirenz: Treatment outcomes through 144 weeks are presented in Table 21.

Table 21. Outcomes of Randomized Treatment (Study 903)

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

1. Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 144.

2. Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 144.

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 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (\leq or $>$ 100,000 copies/mL) and CD4 cell count ($<$ or \geq 200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of patients in the VIREAD and stavudine 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 stavudine arm.

Through 144 weeks, twelve patients in the VIREAD group and nine patients in the stavudine group experienced a new CDC Class C event.

The proportion of patients who achieved and maintained confirmed HIV RNA < 400 using intent-to-treat analysis at Weeks 24, 48, 96 and 144 in Study 903 are presented in Table 22.

Table 22. Virologic Response Through Week 144, Study 903*†

Study Week	Proportion of Patients with HIV-1 RNA < 400 copies/mL (%)	
	VIREAD + 3TC + EFV (N = 299)	Stavudine + 3TC + EFV (N = 301)
Week 24	86	86
Week 48	79	82
Week 96	74	70
Week 144	68	62

* 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

Study 934 - VIREAD + Emtricitabine + Efavirenz Compared with Lamivudine/Zidovudine + Efavirenz: Treatment outcomes through 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 23.

Table 23. Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

Outcome	At Week 48		At Week 144	
	VIREAD + FTC + EFV (N = 244)	3TC/AZT + EFV (N = 243)	VIREAD + FTC + EFV (N = 227)	3TC/AZT + EFV (N = 229)
Responder ²	84%	73%	71%	58%
Virologic failure ³	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death	< 1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons ⁴	10%	14%	20%	22%

1. Patients who were responders at Week 48 or Week 96 but did not consent to continue study after Week 48 or Week 96 were excluded from analysis.
2. Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.
3. Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.
4. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

In this study, VIREAD + emtricitabine in combination with efavirenz showed statistically significant superiority over lamivudine/zidovudine in combination with efavirenz in achieving and maintaining HIV-1 RNA < 400 copies/mL through 48 weeks and 144 weeks (Table 23). The difference in the percentages of responders, stratified by baseline CD4 cell count (< or \geq 200 cells/mm³), between the VIREAD + emtricitabine group and the lamivudine/zidovudine group was 11.4%, and the 95% CI was 4.3% to 18.6% (p = 0.002) at Week 48 and was 13% at Week 144, 95% CI = 4% to 22% (p = 0.004). Through 48 weeks of therapy, 80% and 70% of patients in the VIREAD + emtricitabine and the lamivudine/zidovudine arms, respectively, achieved and maintained HIV-1 RNA < 50 copies/mL (64% and 56%, respectively, through Week 144). The difference in the percentages of responders, stratified by baseline CD4 cell count (< or \geq 200 cells/mm³), between the VIREAD + emtricitabine group and the lamivudine/zidovudine group was 9.1%, and the 95% CI was 1.6% to 16.6% (p = 0.021) at Week 48 and was 8% at Week 144, 95% CI = -1% to 17% (p = 0.082). The mean increase from baseline in CD4 cell count was 190 cells/mm³ for the VIREAD + emtricitabine + efavirenz arm, and 158 cells/mm³ for the lamivudine/zidovudine + efavirenz arm (p = 0.002) at Week 48 (312 and 271 cells/mm³, respectively, at Week 144, p = 0.089). Through 48 weeks, 7 patients in the VIREAD + emtricitabine group and 5 patients in the lamivudine/zidovudine group experienced a new CDC Class C event (10 and 6 patients, respectively, through 144 weeks).

The difference in the proportion of patients who achieved and maintained HIV-1 RNA < 400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open label study.

Adolescent Patients

In Study 321, 87 treatment-experienced patients 12 to <18 years of age were treated with VIREAD (N = 45) or placebo (N = 42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm³ and the mean baseline plasma HIV-1 RNA was 4.6 log₁₀ copies/mL. The median time-weighted average changes from baseline in plasma HIV-1 RNA at Weeks 24 (DAVG₂₄) and 48 (DAVG₄₈) were -1.58 and -1.42 log₁₀ copies/mL for the VIREAD group compared to -1.55 and -1.35 log₁₀ copies/mL for the placebo group, at Weeks 24 and 48, respectively. The lack of difference in virological response between the two groups was primarily attributable to greater activity of the OBR in the placebo group compared to the VIREAD group.

Genotypic Analyses of VIREAD in Patients with Previous Antiretroviral Therapy (Studies 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 protease inhibitor or non-nucleotide reverse

transcriptase inhibitor use. Virologic responses for patients in the genotype sub-study were similar to the overall results in Studies 902 and 907.

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

Reduced responses to VIREAD were observed in patients with pre-existing zidovudine-associated mutations and appeared to depend on the number of specific 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.

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 $-0.84 \log_{10}$ 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 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-1 protease inhibitors is unlikely because of the different enzyme targets involved.

In treatment-experienced patients, 14/304 (4.6%, studies 902 and 907) isolates from patients failing VIREAD at 96 weeks showed > 1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Phenotypic Analyses of VIREAD in Patients with Previous Antiretroviral Therapy (Studies 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 24 summarizes the HIV-1 RNA response by baseline VIREAD susceptibility.

Table 24. 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 (DAVG₂₄) in log₁₀ copies/mL.

Genotypic Analyses of VIREAD in Antiretroviral-Naïve Patients

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 (Study 903). The K65R mutation occurred in 8 patients on the VIREAD arm and in 2 patients on the stavudine 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.

In Study 934 (VIREAD + emtricitabine + efavirenz compared with lamivudine/zidovudine + efavirenz), resistance analysis was performed on HIV isolates from all patients with > 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed. Resistance to efavirenz occurred in 13/19 (68%) analyzed patients in the VIREAD + emtricitabine group and in 21/29 (72%) analyzed patients in the lamivudine/zidovudine group. The M184V mutation, associated with resistance to emtricitabine and lamivudine, was observed in 2/19(11%) analyzed patients in the VIREAD + emtricitabine group and in 10/29 (34%) analyzed patients in the lamivudine/zidovudine group.

In treatment-naïve patients treated with VIREAD + emtricitabine + efavirenz, none of the HIV isolates from 19 patients analyzed for resistance showed reduced susceptibility to tenofovir or the presence of the K65R mutation.

In Study 321 (adolescent patients 12 - <18 years) (see **CLINICAL TRIALS**), HIV-1 isolates from 43 patients who had plasma HIV-1 RNA ≥ 400 copies/mL were evaluated for tenofovir resistance-associated substitutions. One patient developed the K65R substitution by Week 48.

Clinical Efficacy in Patient with HBV

Study Demographics and Trial Design

HBeAg-Negative Chronic Hepatitis B: Study 0102 was a Phase 3, randomized, double-blind, active-controlled study of VIREAD 300 mg compared to HEPSERA 10 mg in 375 HBeAg- (anti-HBe+) patients, the majority of whom were nucleoside-naïve. The mean age of patients was 44 years, 77% were male, 25% were Asian, 65% were Caucasian, 17% had previously received alpha-interferon therapy and 18% were nucleoside-experienced (16% had prior lamivudine experience). At baseline, patients had a mean Knodell necroinflammatory score of 7.8; mean plasma HBV DNA was 6.9 log₁₀ copies/mL; and mean serum ALT was 140 U/L.

HBeAg-Positive Chronic Hepatitis B: Study 0103 was a Phase 3, randomized, double-blind, active-controlled study of VIREAD 300 mg compared to HEPSERA 10 mg in 266 (HBeAg+) nucleoside-naïve patients. The mean age of patients was 34 years, 69% were male, 36% were Asian, 52% were Caucasian, and 16% had previously received alpha-interferon therapy. At baseline, patients had a mean Knodell necroinflammatory score of 8.4; mean plasma HBV DNA was 8.7 log₁₀ copies /mL; and mean serum ALT was 147 U/L.

The primary data analysis was conducted after all patients reached 48 weeks of treatment.

Table 25. Studies 0102 and 0103: VIREAD Compared to HEPSERA

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subject	Mean Age	Gender
GS-US-174-0102	Randomized (2:1), Double-Blind, Parallel group	<p>Arm 1: tenofovir DF 300 mg QD oral</p> <p>Arm 2: adefovir dipivoxil 10 mg QD oral</p> <p>Double blind phase up to Week 48</p> <p>After double-blind phase, eligible patients were allowed to rollover to open-label tenofovir DF up to Week 384 (8 years)</p>	<p>N = 250</p> <p>N = 125</p> <p>HBeAg-; nucleoside-naïve and nucleoside-experienced; HBV DNA > 10⁵ copies/mL</p>	<p>44</p> <p>(18–69)</p>	<p>Male: 77%</p> <p>Female: 23%</p>

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subject	Mean Age	Gender
GS-US-174-0103	Randomized (2:1), Double-Blind, Parallel group	<p>Arm 1: tenofovir DF 300 mg QD oral</p> <p>Arm 2: adefovir dipivoxil 10 mg QD oral</p> <p>Double blind phase up to Week 48</p> <p>After double-blind phase, eligible patients were allowed to rollover to open-label tenofovir DF up to Week 384 (8 years)</p>	<p>N = 176</p> <p>N = 90</p> <p>HBeAg+; nucleoside-naïve HBV DNA > 10⁶ copies/mL</p>	<p>34 (18–64)</p>	<p>Male: 69% Female:31%</p>

Study Results

Experience in Patients with Compensated Liver Disease at 48 weeks: In HBeAg- and HBeAg + patients VIREAD was shown to be statistically superior with respect to the primary efficacy endpoint (complete response to treatment). VIREAD was associated with significantly greater proportions of patients with HBV DNA < 400 copies/mL when compared to HEPSERA as shown in Table 26.

In study 0103, a significantly greater proportion of patients in the VIREAD group had normalized ALT and achieved HBsAg loss, when compared to HEPSERA.

Table 26. Histological, Virological, Biochemical and Serological Response at Week 48 (Studies 0102 and 0103)

	0102 (HBcAg-)		0103 (HBcAg+)	
	VIREAD (n = 250)	HEPSERA (n = 125)	VIREAD (n = 176)	HEPSERA (n = 90)
Complete Response (%) ^a	71*	49	67*	12
Histology				
Histological Response (%) ^b	72	69	74	68
HBV DNA (%)				
< 400 copies/mL (< 69 IU/mL)	93*	63	76*	13
ALT(%)	76	77	68**	54
Normalized ALT ^c				
Serology (%)				
HBcAg Loss/ Seroconversion	NA	NA	22/21	18/18
HBsAg Loss/ Seroconversion	0/0	0/0	3**/1	0/0

*p value vs adefovir dipivoxil < 0.001, **p value vs adefovir dipivoxil < 0.05, ^a Complete response defined as HBV DNA levels < 400 copies/ml and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis, ^b Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis, ^c The population used for analysis of ALT normalization included only patients with ALT above ULN at baseline.

VIREAD was associated with significantly greater proportions of patients with undetectable HBV DNA (< 169 copies/mL [< 29 IU/mL]; the limit of quantification of the Roche Cobas Taqman HBV assay), when compared to HEPSERA (study 0102; 91%, 56%, $p < 0.001$ and study 0103; 69%, 9%, $p < 0.001$), respectively.

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

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

In Study ACTG 5127, a randomized, 48 week double-blind, controlled trial of VIREAD 300 mg in patients co-infected with HIV-1 and chronic hepatitis B with prior lamivudine experience (90% of patients were lamivudine resistant), the mean serum HBV DNA level at baseline in patients randomized to the VIREAD arm was 9.45 log₁₀ copies/mL (n = 27). Treatment with VIREAD was associated with a mean change in serum HBV DNA from baseline, in the patients for whom there was 48 week data, of -5.74 log₁₀ copies/mL (n = 18). In addition, 61% of patients had normal ALT at Week 48.

Experience in Patients with Persistent Viral Replication at 48 weeks: Study 0106 was a double-blind, randomized study in which 53 nucleoside-experienced patients with persistent viral replication after receiving 24-96 weeks of treatment with HEPSERA were randomized to VIREAD monotherapy. Of these, 81% had HBV DNA < 400 copies/mL, 75% had undetectable DNA (< 169 copies/mL [< 29 IU/mL]) and 41% had ALT normalization at Week 48.

Experience in Patients with Decompensated Liver Disease at 48 weeks: Study 0108 is a randomized, double-blind, active controlled study evaluating the safety and efficacy of VIREAD (N = 45) in patients with decompensated liver disease. Patients had a mean Child-Pugh-Turcotte (CPT) score of 7, mean HBV DNA of 5.8 log₁₀ copies/mL and mean serum ALT of 61 U/L at baseline. Forty-two percent (19/45) of patients had at least 6 months of prior lamivudine experience and 9 of 45 patients (20%) had lamivudine and/or adefovir resistance substitutions at baseline.

The coprimary safety endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine ≥ 0.5 mg/dL or confirmed decrease in serum phosphorus of < 2 mg/dL.

In the VIREAD treatment arm, 3 of 45 patients (7%) discontinued treatment due to an adverse event; 4 of 45 patients (9%) experienced a confirmed increase in serum creatinine of ≥ 0.5 mg/dL or confirmed decrease in serum phosphorus of < 2 mg/dL through Week 48. HBV DNA < 400 copies/mL and normal ALT were observed in 31 of 44 patients (70%) and 25 of 44 patients (57%), respectively. The mean change from baseline in CPT score was -1; the mean absolute CPT score was 6 at Week 48.

Experience Beyond 48 weeks: In Studies 0102 and 0103 patients who completed 48 weeks of double-blind treatment with either VIREAD or HEPSERA rolled over with no interruption in treatment to open-label VIREAD. In Study 0102, 90% and 88% of patients who were randomized to VIREAD and HEPSERA, respectively, completed 96 weeks of treatment and in Study 0103, 82% and 92% of patients who were randomized to VIREAD and HEPSERA, respectively, completed 96 weeks of treatment. In Studies 0102 and 0103, 84% and 74% of the randomized and treated patients continued treatment through Week 192, respectively. At both Week 96 and Week 192, viral suppression, biochemical and serological responses were in general maintained with continued VIREAD treatment. In patients rolling over from HEPSERA to VIREAD at Week 48, HBV DNA rapidly declined in HEPSERA non-responders (HBV DNA ≥ 400 copies/ml at Week 48) and was maintained below 400 copies/ml in HEPSERA responders (HBV DNA < 400 copies/ml at Week 48) (see Table 27).

Table 27. Virological, Biochemical and Serological Response at Week 96 and Week 192 (Studies 0102 and 0103)

Outcomes ^a	0102 (HBeAg-)				0103 (HBeAg+)			
	VIREAD ^f (N = 250)		HEPSERA Rollover to VIREAD ^f (N = 125)		VIREAD ^f (N = 176)		HEPSERA Rollover to VIREAD ^f (N = 90)	
	96 weeks ^b	192 weeks ^d	96 weeks ^c	192 weeks ^c	96 weeks ^b	192 weeks ^d	96 weeks ^c	192 weeks ^e
HBV DNA < 400 copies/mL [< 69 IU/mL]	91%	85%	89%	87%	78%	74%	78%	84%
Week 48 HEPSERA Responder ^e	-	-	100%	100%	-	-	100%	100%
Week 48 HEPSERA non-responder ^h	-	-	100%	100%	-	-	82%	98%
HBV DNA < 169 copies/mL [< 29 IU/mL]	90%	84%	89%	87%	74%	73%	76%	81%
ALT Normalized ALT ⁱ	72%	68%	68%	77%	65%	60%	74%	69%
Serology HBeAg Loss/ Seroconversion	NA	NA	NA	NA	26%/ 23%	34%/ 25%	26%/ 22%	37%/ 30%
HBsAg Loss/ Seroconversion	0/0	0/0	0/0	0/0	5%/ 4%	11%/ 8% ^j	6%/ 5%	8%/ 7% ^j

- a Based on Long-Term Evaluation algorithm (LTE-ITT Analysis) - patients who discontinued the study at any time prior to Week 192 due to a protocol defined endpoint, as well as those completing Week 192, are included in the denominator.
- b 48 weeks double-blind VIREAD followed by up to 48 weeks open-label VIREAD.
- c 48 weeks double-blind HEPSERA followed by up to 48 weeks open-label VIREAD.
- d 48 weeks double-blind VIREAD followed by up to 144 weeks open-label VIREAD.
- e 48 weeks double-blind HEPSERA followed by up to 144 weeks open-label VIREAD.
- f At the discretion of the clinician, patients with HBV DNA \geq 400 copies/mL at Week 72 or later could receive intensification therapy with open label tenofovir DF + 200 mg emtricitabine (administered as fixed dose combination TRUVADA).
- g Patients treated with HEPSERA for 48 weeks whose HBV DNA < 400 copies/mL based on observed (missing = excluded) data (Study 0102, n = 76; Study 0103, n = 12)
- h Patients treated with HEPSERA for 48 weeks whose HBV DNA \geq 400 copies/mL based on observed (missing = excluded) data (Study 0102, n = 33; Study 0103, n = 67)
- i The population used for analysis of ALT normalization included only patients with ALT above ULN at baseline.
- j Cumulative percentages based upon a Kaplan Meier analysis (KM-ITT)
- NA = Not Applicable.

Genotypic Analyses of VIREAD in Patients with HBV (Studies 0102, 0103, 0106 and 0108)

In Studies 0102 and 0103, four hundred and twenty-six HBeAg negative (n = 250) and HBeAg positive patients (n = 176) were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations were performed on all patients with HBV DNA > 400 copies/mL at week 48 (n = 39), week 96 (n = 24), week 144 (n = 6) and week 192 (n = 5). Among the genotypic changes observed, no amino acid substitutions associated with resistance to VIREAD were detected.

In Study 0106, 53 patients (including 15 patients with adefovir or lamivudine resistance substitutions at baseline) received VIREAD for 48 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 15/17 patients with HBV DNA > 400 copies/mL at Week 48. No amino acid substitutions associated with resistance to VIREAD were identified in these isolates.

In Study 0108, 45 patients (including 9 patients with lamivudine and/or adefovir resistance substitutions at baseline) received VIREAD for up to 48 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/mL. No amino acid substitutions associated with resistance to VIREAD were identified in these isolates.

DETAILED PHARMACOLOGY - VIROLOGY (MICROBIOLOGY)

Activity in HIV-1

Tenofovir diphosphate inhibits the activity of HIV 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 .

Anti-HIV Activity In Vitro

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

In Vitro Resistance

HIV 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.

In Vitro Cross-Resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The in vitro activity of tenofovir against HIV-1 strains with zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) was evaluated. Zidovudine-associated mutations may also confer reductions in susceptibility to other nucleoside reverse transcriptase inhibitors (NRTIs) and these mutations have been reported to emerge during combination therapy with stavudine and didanosine. In 20 samples that had multiple zidovudine-associated mutations (mean 3.3), a mean 3.1-fold increase of the IC₅₀ of tenofovir was observed (range 0.8–8.4). Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir. Tenofovir showed slightly increased activity against HIV-1 expressing the M184V resistance mutation.

Activity in HBV

Anti-Hepatitis B Virus Activity In Vitro

The in vitro antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC₅₀ values for tenofovir were in the range of 0.14 to 1.5 µM, with CC₅₀ (50% cytotoxicity concentration) values > 100 µM. Tenofovir diphosphate inhibits recombinant HBV polymerase with a Ki (inhibition constant) of 0.18 µM. In in vitro drug combination studies of tenofovir with nucleoside anti-HBV reverse transcriptase inhibitors lamivudine, telbivudine, and entecavir, additive anti-HBV activity was observed. Additive to slightly synergistic effects were observed with the combination of tenofovir and emtricitabine.

In Vitro Cross-Resistance

Cross-resistance has been observed among HBV reverse transcriptase inhibitors.

In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V mutations associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7 to 3.4-fold that of wild type virus.

HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6 to 6.9-fold that of wild type virus.

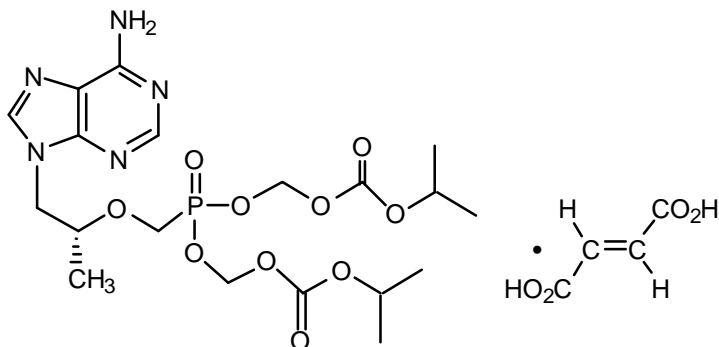
HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9 to 10-fold that of wild type virus.

Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC₅₀ values 1.5-fold that of wild type virus.

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	tenofovir disoproxil fumarate (USAN)
Chemical Name:	9-[(R)-2-[[bis[[isopropoxycarbonyloxy]methoxy]phosphinyl]-methoxy]propyl]adenine fumarate (1:1)
Empirical Formula:	C₁₉H₃₀N₅O₁₀P • C₄H₄O₄
Molecular Weight:	635.52
Structural Formula:	



TOXICOLOGY

The nonclinical safety profile of tenofovir disoproxil fumarate has been studied in mice, rats, guinea pigs, rabbits, dogs, and monkeys. In all species, tenofovir disoproxil fumarate was hydrolyzed to tenofovir following absorption. Tenofovir was cleared exclusively by renal elimination, without further metabolic changes, by a combination of glomerular filtration and tubular secretion.

Single Dose Toxicity

Following single doses, the no-effect-level (NOEL) in rats was 1500 mg/kg. Following single doses in dogs (270 mg/kg), mild renal tubular karyomegaly and/or basophilia were the only effects observed. Single oral doses of tenofovir disoproxil fumarate had no adverse effects on the central nervous system (male rats, 50 or 500 mg/kg) or on cardiovascular and respiratory function (conscious male dogs, 30 mg/kg). An assessment of effects on renal function demonstrated increased urinary electrolyte excretion and urine volume in rats administered tenofovir disoproxil fumarate 500 mg/kg; no effect was observed at 50 mg/kg. When rats were administered tenofovir disoproxil fumarate (0, 50, or 500 mg/kg) to evaluate effects on the gastrointestinal transit of a charcoal meal, there was reduced gastric emptying at 500 mg/kg/day, but no effect at 50 mg/kg/day.

Subacute and Chronic Toxicity

The target organs of toxicity identified in the preclinical program were the gastrointestinal tract, renal tubular epithelium, and bone.

Gastrointestinal Tract

Gastrointestinal (GI) toxicity, observed primarily in rats, was dose related, reversible, and characterized by inflammation of the stomach and intestines, epithelial cytomegaly in the duodenum and jejunum, and villous atrophy of the ileum in rodents.

Kidney

Renal tubular epithelial karyomegaly, a morphologic change without pathologic consequence, was the most sensitive histological indicator of an effect on the kidney and was observed in rats, dogs, and monkeys. In dogs, the species most sensitive to effects on the kidney, additional microscopic alterations reported following chronic administration of tenofovir disoproxil fumarate (≥ 10 mg/kg/day for 42 weeks) included individual cell necrosis, tubular dilatation, degeneration/regeneration, pigment accumulation, and interstitial nephritis. Associated biochemical changes in dogs administered tenofovir disoproxil fumarate 30 mg/kg/day were a slight elevation in serum creatinine, glucosuria, proteinuria, and increased urine volume. The incidence and severity of nephrotoxicity was dose related.

Bone

Chronic administration of high doses of tenofovir or tenofovir disoproxil fumarate in laboratory animals resulted in bone alterations. Minimal decreases in bone mineral density and content were observed in rats and dogs following oral administration of tenofovir DF at the doses of 300 and 30 mg/kg/day, respectively (6 and 10 \times human exposure, respectively). In juvenile monkeys pathologic osteomalacia and hypophosphatemia was observed following subcutaneous administration of tenofovir at the dose of 30 mg/kg/day (25 \times human exposure). Monkeys treated chronically with tenofovir 10 mg/kg/day, sc, (AUC = 4 \times humans), had no clinical or radiographic evidence of bone toxicity.

Bone changes in rats and dogs did not appear to consistently reverse during the recovery period; osteomalacia in juvenile monkeys was reversible.

Studies designed to evaluate the mechanism underlying effects on bone suggest that tenofovir may not have direct toxicity to bone. The mechanism is as yet unclear, however data suggest bone effects may be secondary to negative phosphate balance resulting from tenofovir-related reductions in intestinal phosphate absorption and/or renal reabsorption of phosphate.

Mutagenicity

Tenofovir disoproxil fumarate was equivocal in the in vitro bacterial mutation (Ames) assay (Salmonella-Escherichia coli/ Mammalian-Microsome Reverse Mutation Assay) but positive in the in vitro mouse lymphoma assay (L5178Y TK +/- Forward Mutation Assay), with and without metabolic activation. Tenofovir disoproxil fumarate was negative in the in vivo mouse micronucleus assay at plasma exposure levels of more than 10 \times the human exposure.

Reproductive Toxicity

Reproductive toxicity was evaluated in rats and rabbits. Tenofovir disoproxil fumarate had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day. Tenofovir disoproxil fumarate had no adverse effects on embryo-fetal development in rats at doses 450 mg/kg/day and in rabbits at doses up to 300 mg/kg/day. In a study of effects on peri- and postnatal development in rats, effects considered due to maternal toxicity (450–600 mg/kg/day) were reduced survival and a slight delay in sexual maturation in the F1 generation. There were no adverse effects on growth, development, behavior, or reproductive parameters at non-maternally toxic doses (150 mg/kg/day).

Carcinogenicity

Long-term oral carcinogenicity studies were conducted in mice and rats receiving tenofovir disoproxil fumarate. In the mouse study, (60/sex/group), one male and two female mice in the 600 mg/kg/day group (15 times the human systemic exposure at the recommended human dose of 300 mg/day) had duodenal tumors. The mechanism underlying this effect is uncertain but may relate to high local drug concentrations in the gastrointestinal tract. No treatment-related tumors were seen in mice in the 100 or 300 mg/kg/day groups. In the rat study (60/sex/group) at doses of 30, 100 and 300 mg/kg/day (approximately 5 times human exposure), no treatment-related increase in tumor incidence was observed.

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PART III. CONSUMER INFORMATION

PrViread® (Tenofovir Disoproxil Fumarate Tablets)

This leaflet is Part III of a three-part “Product Monograph” published when VIREAD was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VIREAD. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- VIREAD is a type of medicine called a nucleotide analog reverse transcriptase inhibitor (NRTI).
- Use in the Treatment of HIV-Infection:

VIREAD is a treatment for Human Immunodeficiency Virus (HIV) infection in adults and adolescents age 12 years and older and weighing at least 35 kg (77 lb). VIREAD is always used in combination with other anti-HIV medicines to treat people with HIV infection.

HIV infection destroys CD4 (T) cells, which are important to the immune system. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

- Use in the Treatment of Chronic Hepatitis B:
VIREAD is also used to treat chronic hepatitis B (an infection with hepatic B virus [HBV]) in adults age 18 years and older.
- If you have both HIV and HBV infection and are taking VIREAD, your doctor should be prescribing VIREAD in combination with other anti-HIV medicines (**See: Proper Use of This Medication**).

What it does:

Treatment of HIV infection:

- In patients with HIV infection, VIREAD helps to block HIV reverse transcriptase (enzyme) that is needed for HIV to multiply. VIREAD lowers the amount of HIV in the blood (called viral load).
- VIREAD does not cure HIV infection or AIDS. The long-term effects of VIREAD are not known at this time. People taking VIREAD may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak.

Treatment of Chronic Hepatitis B:

- In patients with HBV infection, VIREAD works by interfering with the normal working of enzymes (HBV DNA polymerase) that are essential for the HBV virus to reproduce

itself. VIREAD may help lower the amount of hepatitis B virus in your body by lowering the ability of the virus to multiply and infect new liver cells.

- We do not know how long VIREAD may help your hepatitis. Sometimes viruses change in your body and medicines no longer work. This is called drug resistance.

VIREAD does not reduce the risk of passing HIV or HBV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

When it should not be used:

- Do not take VIREAD if you are allergic to VIREAD or any of its ingredients (**See: What the important nonmedicinal ingredients are**).
- Do not take VIREAD if you are already taking TRUVADA®, ATRIPLA®, or COMPLERA™ because VIREAD is one of the active ingredients in these products.
- Do not take VIREAD if you have not already discontinued treatment with HEPSERA®.

What the medicinal ingredient is:

Tenofovir disoproxil fumarate

What the important nonmedicinal ingredients are:

Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

What dosage forms it comes in:

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.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The most serious possible side effect is harm to the kidneys, including damage to kidney cells, kidney tissue inflammation and kidney failure. Your doctor may monitor your kidney function before beginning and while receiving VIREAD. Some patients treated with tenofovir disoproxil fumarate (a component of VIREAD) have had kidney problems. Your doctor may need to perform additional blood tests if you have had kidney problems in the past or need to take another drug that can cause kidney problems.
- **If you have Hepatitis B Virus infection or if you have HIV and HBV infection together, “flare-ups” of Hepatitis B Virus infection**, in which the disease suddenly returns in a worse way than before, can occur if you stop taking VIREAD. Do not stop taking VIREAD without your doctor’s advice. If you stop taking VIREAD, tell your doctor immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking VIREAD, your doctor will still need to check your health and take blood tests to check your liver

for several months.

- The class of medicines to which VIREAD belong (NRTIs) can cause a condition called lactic acidosis (build up of acid in the blood). The symptoms that may be signs of lactic acidosis include: feeling very weak, tired or uncomfortable, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, suddenly developing a slow or irregular heart beat. This rare but serious side effect has occasionally been fatal.
- Severe liver problems can happen in people who take Viread or similar medicines. You may develop an enlarged liver (hepatomegaly) or a fatty liver (steatosis). Non-specific symptoms such as yellowing of the skin and eyes, nausea, vomiting, and stomach pain might indicate the development of liver problems.

Lactic acidosis or severe liver problems occur more often in women, particularly if they are very overweight. You should consult your doctor immediately if such symptoms occur while you are receiving VIREAD. If you notice these symptoms, stop taking VIREAD and consult a doctor immediately.

- Tenofovir disoproxil fumarate caused harm to the bones of animals. Tenofovir disoproxil fumarate reduced bone density in humans. If you notice bone pain, suffer a bone fracture, or other bone problem, consult your doctor. If you have bone problems, you may wish to discuss calcium and/or vitamin D supplements with your doctors.
- Changes in body fat have been seen in some patients taking antiretroviral therapy for the treatment of HIV infection. These changes may include increased amounts of fat in the upper back and neck (“buffalo hump”), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.

If you have advanced HIV infection (AIDS) and have an infection, you may develop symptoms of infection and inflammation or worsening of the symptoms of an existing infection once treatment with Viread is started. These symptoms may indicate that your body’s improved immune system is fighting infection. If you notice signs of inflammation or infection, tell your doctor at once.

BEFORE you use VIREAD talk to your doctor or pharmacist if:

- **You are pregnant, planning to become pregnant or breast-feeding:** Pregnant or breast-feeding mothers should not take VIREAD unless specifically directed by the doctor. It is recommended that HIV- or HBV-infected women do not breast feed their infants under any circumstances in order to avoid transmission of the virus. It is therefore recommended that mothers do not breast feed their babies while receiving treatment with VIREAD.
- **You have other medical conditions:** Let your doctor know if you have other medical conditions, especially hepatitis (inflammation of the liver), pancreatitis (inflammation of the pancreas), bone and kidney problems.

- **You have HIV Infection.**
- **You are taking other medicines:** Some medicines can interact when taken together, including prescription and non-prescription medicines and dietary supplements.

INTERACTIONS WITH THIS MEDICATION

Drugs that contain didanosine (Videx[®], Videx EC[®]). Tenofovir disoproxil fumarate (VIREAD) may increase the amount of VIDEX in your blood. **You may need to be followed more carefully if you are taking VIREAD and Videx together.** Also, the dose of didanosine may need to be reduced.

Reyataz[®] (atazanavir sulfate) or Kaletra[®] (lopinavir/ritonavir). These medicines may increase the amount of tenofovir DF (VIREAD) in your blood, which could result in more side effects. You may need to be followed more carefully if you are taking VIREAD and Reyataz or Kaletra together. VIREAD may decrease the amount of Reyataz in your blood. If you are taking VIREAD and Reyataz together, you should also be taking Norvir (ritonavir).

PROPER USE OF THIS MEDICATION

Stay under a doctor’s care when taking VIREAD. Do not change your treatment or stop treatment without first talking with your doctor.

Carefully follow the directions and dosing schedule prescribed by your doctor.

When your VIREAD supply starts to run low, see your doctor or pharmacist for a refill. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to VIREAD and become harder to treat.

If you are taking VIREAD to treat your HIV or if you have HIV and HBV coinfection and are taking VIREAD, always take VIREAD in combination with other anti-HIV medicines. VIREAD and other products like VIREAD may be less likely to work in the future if you are not taking VIREAD with other anti-HIV medicines because you may develop resistance to those medicines.

If you have HBV only (without HIV), VIREAD can be prescribed as a single drug treatment for HBV.

Talk to your doctor about taking an HIV test before you start treatment with VIREAD for chronic hepatitis B.

Only take medicine that has been prescribed specifically for you. Do not give VIREAD to others or take medicine prescribed for someone else.

Usual Adult Dose:

- The usual dose of VIREAD is one 300 mg tablet orally (by mouth) once a day.
- VIREAD may be taken with or without a meal.

Usual Adolescent (12 Years of Age and older) Dose for HIV Infection:

- Body weight ≥ 35 kg (≥ 77 lb): Take one 300 mg VIREAD tablet once daily orally.
- VIREAD may be taken with or without a meal.

Overdosage:

In case of drug overdose, contact your healthcare practitioner (e.g. doctor), hospital emergency department or regional poison care centre, even if there are no symptoms.

Missed Dose:

- If you miss a dose of VIREAD, take it as soon as possible and then take your next scheduled dose at its regular time.
- Do not double the next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of VIREAD are:

- Diarrhea
- Nausea
- Vomiting
- Dizziness

Other side effects include:

- Flatulence (intestinal gas)
- Allergic reaction, including angioedema (swelling of the blood vessels), with symptoms such as skin rash, redness, swelling of the hands, legs, feet, face, lips, tongue or throat with difficulty in breathing
- Stomach pain
- Weakness
- Inflammation of the pancreas
- Shortness of breath
- Headache
- Rash

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptoms/Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Effect: Kidney problems Symptoms <ul style="list-style-type: none"> • Increased or decreased urination as well as increased thirst • Swelling of legs and feet • Feeling listless and tired 		✓ ✓ ✓	
Rare	Effect: Lactic acidosis Symptoms <ul style="list-style-type: none"> • Feeling very weak or tired • Unusual muscle pain • Stomach pain with nausea and vomiting • Feeling cold especially in arms and legs • Feeling dizzy or lightheaded • Fast or irregular heartbeat 		✓ ✓ ✓ ✓ ✓ ✓	
Very Rare	Effect: Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver) Symptoms <ul style="list-style-type: none"> • Jaundice (skin or the white part of eyes turn yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain 		✓ ✓ ✓ ✓ ✓	
Very Rare	Effect: Flare-ups of hepatitis B virus infection following drug discontinuation Symptoms <ul style="list-style-type: none"> • Jaundice (skin or the white part of eyes turn yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain 		✓ ✓ ✓ ✓ ✓	

Lactic acidosis is a medical emergency and must be treated in the hospital. You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleoside analog medicines, like VIREAD, for a long time.

Muscle pain, muscle weakness, bone pain and softening of the bone (infrequently contributing to fractures) have also been reported.

This is not a complete list of side effects. For any unexpected effects while taking VIREAD, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep VIREAD and all other medications out of reach of children.
- VIREAD should be stored at 15–30°C. It should remain stable until the expiration date printed on the label.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health care professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

www.gilead.ca

or by contacting the sponsor, Gilead Sciences, Inc., at:

1-866-207-4267

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Gilead Sciences, Inc.

Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.

Mississauga, ON
L5N 2W3

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