# Tenofovir disoproxil fumarate

**Brand Name: Viread**
**Drug Class: Nucleoside Reverse Transcriptase Inhibitors**

## Drug Description

Tenofovir is an acyclic nucleotide analogue of deoxyadenosine 5'-monophosphate. Tenofovir disoproxil fumarate (tenofovir DF) is the water-soluble diester prodrug of the active ingredient tenofovir. Specifically, tenofovir DF is a fumaric acid salt of a bis-isopropxycarbonyloxymethyl ester derivative of tenofovir. [1]

## HIV/AIDS-Related Uses

Tenofovir DF was approved by the FDA on October 26, 2001.[2] Tenofovir DF is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.[3] Tenofovir DF has also been studied for the treatment of lamivudine-resistant hepatitis B virus (HBV) infection in patients who are coinfected with HIV and HBV.[4] A current clinical trial is testing tenofovir DF's efficacy on improving dyslipidemia in treatment-experienced HIV infected adults.[5] Tenofovir as an antimicrobial vaginal gel is also being investigated for use by women to prevent the sexual transmission of HIV.[6]

## Non-HIV/AIDS-Related Uses

Tenofovir DF demonstrates anti-HBV activity in vitro.[7] On August 11, 2008, the FDA approved tenofovir DF for the treatment of HBV in adults.[8]

The efficacy of tenofovir DF in the treatment of HBV has been compared with adefovir dipivoxil in clinical trials. Patients treated with tenofovir DF showed a strong and early suppression of HBV DNA within a few weeks whether they were coinfected with HIV or were without comorbidity. In contrast, patients treated with adefovir dipivoxil showed considerable individual variations in HBV DNA decline. These data suggest tenofovir DF may become an effective alternative for the treatment of patients with lamivudine-resistant HBV infection.[9]

In addition, tenofovir DF has been evaluated in clinical trials in patients coinfected with HBV and HIV.[10]

## Pharmacology

Tenofovir DF is the orally bioavailable form of tenofovir and requires metabolism to the active metabolite. Tenofovir DF is absorbed and then metabolized by diester hydrolysis to tenofovir, which is then metabolized by phosphorylation to the pharmacologically-active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits reverse transcriptase by competing with the natural substrate, deoxyadenosine 5'-triphosphate. Tenofovir diphosphate is incorporated into HIV viral DNA, causing DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases alpha, beta, and gamma and of mitochondrial DNA polymerase.[11]

Oral bioavailability of tenofovir DF in fasted patients is approximately 25%. Administration of tenofovir DF with a high fat meal increases the oral bioavailability, with an increase in tenofovir area under the plasma concentration-time curve (AUC) of approximately 40% and an increase in maximum plasma concentration (Cmax) of approximately 14%. Food delays the time to tenofovir Cmax by approximately 1 hour. Following oral administration of a single 300-mg dose of tenofovir DF to HIV infected patients in the fasted state, Cmax is achieved in approximately 1 hour. Cmax and AUC values are approximately 296 ng/ml and 2,287 ng(h)/ml, respectively. The pharmacokinetics of tenofovir are dose proportional over a wide dose range and are not affected by repeat dosing.[12] Following IV administration of tenofovir in doses of 1 mg/kg and 3 mg/kg, the volume of distribution at steady-state is approximately 1.3 l/kg and 1.2 l/kg, respectively.[13]

Tenofovir DF is in FDA Pregnancy Category B. No adequate and well-controlled studies have been conducted in pregnant women. Reproduction studies have been performed in laboratory animals at doses up to 19 times the human dose and revealed no evidence of impaired fertility or harm to the fetus. To monitor fetal outcomes of pregnant women exposed to tenofovir DF and other antiretrovirals, an Antiretroviral Pregnancy Registry has been established. Health care providers are encouraged to register patients online at http://www.APRegistry.com or by calling

## Pharmacology (cont.)

1-800-258-4263. It is not known whether tenofovir is excreted in human milk; however, tenofovir has been found in the milk of laboratory animals.(4)

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 of 0.01 to 25 mcg/ml.[14] In vitro studies indicate that neither tenofovir DF nor tenofovir are substrates of cytochrome P450 (CYP450) enzymes. Following IV administration of tenofovir, approximately 70% to 80% of the dose is recovered in the urine as unchanged drug within 72 hours of dosing. After multiple oral doses of tenofovir DF under fed conditions, approximately 32% of the administered dose is recovered in urine over 24 hours. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.[15]

Tenofovir is principally eliminated by the kidneys by a combination of glomerular filtration and active tubular secretion.[16] Dosing adjustment is recommended in all patients with CrCl less than 50 ml/min. Dosage adjustments for renal impairment are available in the prescribing information. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single dose of tenofovir DF, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose. Tenofovir is not metabolized by liver enzymes; consequently, the impact of liver impairment should be limited. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment following a single 300-mg single dose of tenofovir DF. The manufacturer states that no change in tenofovir dosing is required in patients with hepatic impairment.[17]

The virologic response to tenofovir DF therapy has been evaluated in treatment-experienced patients participating in clinical trials. In these studies, 94% of the participants had baseline HIV isolates expressing at least one nucleoside reverse transcriptase inhibitor (NRTI) mutation. These included resistance mutations associated with zidovudine (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), lamivudine/abacavir (M184V), and others. Varying degrees of cross resistance of tenofovir DF to pre-existing zidovudine-associated mutations were observed and appeared to depend on the number of specific mutations.[18] HIV-1 isolated from 20 patients whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase mutations that included either the M41L or L210W mutation showed a 3.1-fold decrease in the susceptibility to tenofovir. Also, multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir. The K65R mutation selected by tenofovir is also selected in some HIV-1 infected individuals treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross resistance among these drugs may occur in patients whose virus harbors the K65R mutation.[19]

Virologic response to tenofovir DF was not reduced in patients with HIV that expressed the lamivudine/abacavir-associated M184V mutation. Cross resistance between tenofovir DF and HIV PIs is unlikely because of the different enzyme targets involved.[20]

## Adverse Events/Toxicity

The most common adverse effects associated with tenofovir DF include asthenia, diarrhea, nausea, and vomiting. Less common side effects of tenofovir DF include hepatotoxicity, including lactic acidosis; abdominal pain; anorexia; and flatulence. Some side effects of tenofovir DF occurring with undetermined incidence include allergic reaction, dyspnea, Fanconi's syndrome, hypophosphatemia, pancreatitis, proximal tubulopathy, renal failure or insufficiency, and acute tubular necrosis.[21] Higher tenofovir concentrations could potentiate tenofovir DF-associated adverse events, including renal disorders.[22]

Fatal lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues alone or in combination with

## Adverse Events/Toxicity (cont.)

other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside analogue exposure may be risk factors. However, cases have been reported in patients with no known risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease. Treatment with tenofovir DF should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.[23]

Redistribution/accumulation of body fat, including central obesity and dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events is unknown. Bone toxicities were seen in laboratory animals receiving tenofovir or tenofovir DF at exposures greater than or equal to sixfold those seen in humans. The mechanisms underlying bone toxicity are unknown. In a 48-week study in HIV infected patients, decreases from baseline in bone mineral density were seen at the lumbar spine and hip. In addition, there were significant increases in levels of serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide. It is not known if long-term administration of tenofovir DF (greater than 1 year) will cause bone abnormalities.[24]

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tenofovir DF. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (e.g., Mycobacterium avium infection, cytomegalovirus, Pneumocystis pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.[25]

## Drug and Food Interactions

Tenofovir DF may be taken with or without food.[26]

When administered with tenofovir DF, the Cmax and AUC of buffered and enteric-coated didanosine increased significantly; the mechanism of this interaction is unknown. Increases in didanosine concentrations of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy. Coadministration of tenofovir DF and didanosine should be undertaken with caution, and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.[27]

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir or lopinavir/ritonavir and tenofovir DF should be monitored for tenofovir-associated adverse events. Tenofovir DF should be discontinued in patients who develop tenofovir-associated adverse events.[28] Tenofovir DF decreases the AUC and the minimum plasma concentration (Cmin) of atazanavir. When coadministered with tenofovir DF, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg; atazanavir should not be coadministered with tenofovir DF unless given with ritonavir.[29]

When tenofovir DF 300 mg once daily was coadministered with indinavir 800 mg three times daily for 7 days, an increase in tenofovir Cmax and a decrease in indinavir Cmax was observed.[30] Concurrent administration of tenofovir DF and lamivudine resulted in an average 24% decrease in the Cmax of lamivudine.[31]

When tenofovir DF is taken concurrently with saquinavir/ritonavir, an increase in these three drugs' Cmin has been observed.[32] Increases in Cmax and AUC of saquinavir/ritonavir have also been noted. However, these increases are not expected to be clinically relevant, so no dose adjustments for any of the drugs have been recommended by the manufacturer.[33]

Coadministration with other drugs that are eliminated by active tubular secretion, such as adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir, may

## Drug and Food Interactions (cont.)

increase serum concentrations of either tenofovir or the coadministered drug due to competition for this elimination pathway.[34]

Tenofovir did not inhibit drug metabolism mediated by the human CYP450 isoforms CYP3A4, CYP2D6, CYP2C9, and CYP2E1 in vitro. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on these results and the known elimination pathway of tenofovir, the potential for CYP450-mediated interaction with other drug products is low.[35]

Based on data from an open-label randomized study and retrospective database analyses, clinicians are advised to use caution when administering tenofovir DF, enteric-coated didanosine, and either efavirenz or nevirapine in the treatment of treatment-naive HIV infected patients with high baseline viral loads.[36]

## Contraindications

Tenofovir DF is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.[37]

Tenofovir DF is not indicated for the treatment of chronic HBV infection, and the safety and efficacy of tenofovir DF have not been established in patients coinfected with HBV and HIV. Severe acute exacerbations of HBV have been reported in patients who are coinfected with HBV and HIV and have discontinued tenofovir DF. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue tenofovir DF and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.[38]

## Clinical Trials

For information on clinical trials that involve Tenofovir disoproxil fumarate, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Tenofovir disoproxil fumarate AND HIV Infections.

## Dosing Information

Mode of Delivery: Oral.[39]

Dosage Form: Tablets containing tenofovir DF 300 mg, which is equivalent to tenofovir disoproxil 245 mg.[40]

The recommended dosage of tenofovir is 300 mg once daily. The dosing interval of tenofovir should be adjusted in patients with baseline creatinine clearance (CrCl) less than 50 ml/min. Dosing interval recommendations are as follows: CrCl 30 to 49 ml/min, 300 mg every 48 hours; CrCl 10 to 29 ml/min, 300 mg twice weekly; and hemodialysis patients, 300 mg every 7 days.[41]

Storage: Store tablets at a controlled room temperature, 25 C (77 F); excursions are permitted between 15 C and 30 C (59 F to 86 F).[42]

## Chemistry

CAS Name: Bis(hydroxymethyl) [[(R)-2(6-Amino-9H-purin-9-yl)-1-methylethoxy] methyl]phosphonate,bis(isopropyl carbonate) (ester), fumarate (1:1).[43]

CAS Number: 202138-50-9[44]

Molecular formula: C19-H30-N5-O10-P.C4-H4-O4[45]

C43.47%, H5.39%, N11.02%, O35.25%, P4.87%[46]

Molecular weight: 635.52[47]

Physical Description: White to off-white crystalline powder.[48]

Solubility: 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.[49]

## Other Names

GS-4331-05[50]

PMPA Prodrug[51]

# Tenofovir disoproxil fumarate

## Other Names (cont.)

Tenofovir DF[52]

TDF[53]

## Further Reading


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## Manufacturer Information

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## For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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