

# Tenofovir disoproxil fumarate



**Brand Name: Viread**

## 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. [1]

## HIV/AIDS-Related Uses

Tenofovir DF was approved by the FDA on October 29, 2001.[2] Tenofovir DF is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.[3] Tenofovir DF is also being studied for the treatment of lamivudine-resistant hepatitis B virus (HBV) in patients who are coinfecting with HIV and HBV.[4]

## Non-HIV/AIDS-Related Uses

Tenofovir DF demonstrated anti-HBV activity in vitro.[5] Tenofovir DF is being evaluated in clinical trials in patients coinfecting with HBV and HIV.[6]

## 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 mitochondrial DNA polymerase.

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 (C<sub>max</sub>) of approximately

14%. Food delays the time to tenofovir C<sub>max</sub> by approximately 1 hour. Following oral administration of a single 300 mg dose of tenofovir DF to HIV infected patients in the fasted state, C<sub>max</sub> is achieved in approximately 1.0 hour. C<sub>max</sub> and AUC values are approximately 296 ng/ml and approximately 2,287 ng h/ml, respectively. The pharmacokinetics of tenofovir are dose proportional over a wide dose range and are not affected by repeated dosing.

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. Following intravenous administration of tenofovir in doses of 1.0 mg/kg and 3.0 mg/kg, the volume of distribution at steady-state is 1.3 +/- 0.6 l/kg and 1.2 +/- 0.4 l/kg.

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 14 and 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. Healthcare providers are encouraged to register patients by calling 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.

In vitro studies indicate that neither tenofovir disoproxil fumarate nor tenofovir are substrates of 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.

Tenofovir is principally eliminated by the kidney.

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## Pharmacology (cont.)

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Dosing adjustment is recommended in all patients with creatinine clearance less than 50 ml/min. Dosage adjustments for renal impairment are available in the prescribing information. However, no safety data are available in patients with renal dysfunction who received tenofovir using these guidelines.[7]

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 300 mg single dose of tenofovir. The manufacturer states that no change in tenofovir dosing is required in patients with hepatic impairment.[8]

Genotyping of HIV isolates from study patients treated with tenofovir DF showed that 3% (7 of 237) developed the K65R mutation, a mutation selected by other nucleoside reverse transcriptase inhibitors (NRTIs). Among patients treated with tenofovir DF whose HIV developed NRTI-associated mutations, there was continued HIV RNA suppression through 24 weeks. Phenotypic analyses of HIV isolates after 24 or 48 weeks of tenofovir DF therapy showed no significant changes in tenofovir DF susceptibility unless the K65R mutation had developed.

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 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. 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. Patients treated with tenofovir DF whose HIV expressed three or more zidovudine-associated mutations that included either the M41L or L210W reverse transcriptase mutation showed reduced responses to tenofovir DF 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 tenofovir DF therapy.

Virologic response to tenofovir DF 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 tenofovir DF showed a 0.84 log<sub>10</sub> copies/ml decrease in HIV RNA relative to placebo. In the presence of zidovudine-associated mutations, the M184V mutation did not affect responses to tenofovir DF treatment.

Patients with HIV mutations at K65R or L74V without zidovudine-associated mutations appeared to have reduced virologic responses to tenofovir DF.

The presence of at least one HIV protease inhibitor or nonnucleoside reverse transcriptase inhibitor mutation at baseline did not appear to affect the virologic response to tenofovir DF. Cross-resistance between tenofovir DF and HIV protease inhibitors is unlikely because of the different enzyme targets involved.[9]

## Adverse Events/Toxicity

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Adverse events reported in patients receiving tenofovir DF included abdominal pain, anorexia, asthenia, diarrhea, dizziness, dyspnea, flatulence, headache, hypophosphatemia, lactic acidosis, nausea, pancreatitis, renal impairment, rash, and vomiting.[10]

Higher tenofovir concentrations could potentiate tenofovir DF-associated adverse events, including renal disorders.[11] Renal impairment, which may include hypophosphatemia, has been reported with the use of tenofovir DF. Renal impairment characterized by increased creatinine, renal insufficiency, kidney failure, and Fanconi syndrome has been observed. The majority of these cases occurred in patients with underlying systemic or renal disease or in patients taking nephrotoxic agents; however, some occurred in patients without identified risk factors.[12]

Fatal lactic acidosis and severe hepatomegaly with

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## Adverse Events/Toxicity (cont.)

steatosis have been reported with the use of nucleoside analogues alone or in combination with 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.[13]

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.[14]

Bone toxicities were seen in laboratory animals receiving tenofovir or tenofovir DF at exposures between 6- and 12-fold those seen in humans. The mechanism(s) underlying bone toxicity is unknown. In a 48 week study in 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.[15]

## Drug and Food Interactions

Tenofovir DF may be taken with or without food.

When administered with tenofovir DF, the C<sub>max</sub> and AUC of didanosine, administered as either the buffered or enteric-coated formulations, 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.[16]

In a study of healthy volunteers, coadministration of tenofovir DF (300 mg once daily) with lopinavir/ritonavir (400/100 mg twice daily) for 14 days resulted in increases in tenofovir pharmacokinetic parameters (C<sub>max</sub>, AUC, and C<sub>min</sub>). Decreases in C<sub>max</sub> and AUC for both lopinavir and ritonavir were observed.[17]

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and 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.[18]

Tenofovir DF decreases the AUC and C<sub>min</sub> of atazanavir. When coadministered with tenofovir DF, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg; Atazanavir should not be coadministered with tenofovir DF unless given with ritonavir.[19]

When tenofovir DF (300 mg once daily) was coadministered with indinavir (800 mg three times daily for 7 days), an increase in tenofovir C<sub>max</sub> and a decrease in indinavir C<sub>max</sub> was observed.[20]

Concurrent administration of tenofovir DF and lamivudine resulted in an average 24% decrease in the C<sub>max</sub> of lamivudine.[21]

Tenofovir is primarily excreted by the kidneys through a combination of glomerular filtration and active renal tubular secretion. Coadministration with other drugs that are eliminated by active tubular secretion, such as cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir, may increase serum concentrations of either tenofovir or the coadministered drug due to competition for this elimination pathway.[22]

Tenofovir did not inhibit drug metabolism mediated by the human CYP450 isoforms CYP3A4,

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## Drug and Food Interactions (cont.)

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.[23]

Based on data from an open-label randomized study and retrospective database analyses, clinicians are advised to use caution when administering tenofovir disoproxil fumarate, enteric-coated didanosine, and either efavirenz or nevirapine in the treatment of treatment naive HIV infected patients with high baseline viral loads.[24]

## Contraindications

Tenofovir DF is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.[25]

Tenofovir DF is not indicated for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of tenofovir DF have not been established in patients coinfecting with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting 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 coinfecting with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.[26]

## 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.[27]

Dosage Form: Tablets containing 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil.

The recommended dose of tenofovir is 300 mg once daily. The dosing interval of tenofovir should be adjusted in patients with baseline creatinine clearance less than 50 ml/min. The dosing interval recommendations are: creatinine clearance 30 to 49 ml/min, 300 mg every 48 hours; creatinine clearance 10 to 29 ml/min, 300 mg twice weekly; and hemodialysis patients, 300 mg every 7 days.[28]

Storage: Store at controlled room temperature, 25 C (77 F); excursions permitted to 15 C to 30 C (59 F to 86 F).[29]

## Chemistry

CAS Name: Bis(hydroxymethyl) [[[R]-2(6-Amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonate,bis(isopropyl carbonate) (ester), fumarate (1:1).[30]

CAS Number: 202138-50-9[31]

Molecular formula:  
C19-H30-N5-O10-P.C4-H4-O4[32]

C43.47%, H5.39%, N11.02%, O35.25%, P4.87%[33]

Molecular weight: 635.52[34]

Physical Description: Tenofovir DF is a white to off-white crystalline powder.[35]

Solubility: Tenofovir DF has 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.[36]

## Other Names

GS-4331-05[37]

PMPA Prodrug[38]

Tenofovir DF[39]

TDF[40]

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## **Other Names (cont.)**

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9-[(R)-2-[[bis[[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate(1:1)[41]

## **Further Reading**

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## **Manufacturer Information**

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Tenofovir disoproxil fumarate  
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Foster City, CA 94404  
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## **Viread**

Gilead Sciences Inc  
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## **For More Information**

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

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