

## Selected Properties of Tenofovir

<b>Other names</b>	<p><b>Viread®:</b> tenofovir disoproxil fumarate; TDF</p> <p>Combination formulations:  <b>Truvada®:</b> tenofovir + emtricitabine  <b>Atripla®:</b> efavirenz/emtricitabine/tenofovir (approved in US July 2006)</p>
<b>Manufacturer</b>	Gilead Sciences, Inc.
<b>Pharmacology/Mechanism of Action</b>	<p><u>Nucleotide</u> analogue. Tenofovir disoproxil fumarate is the water soluble diester prodrug of tenofovir. It requires diester hydrolysis for conversion to tenofovir. Subsequent phosphorylation by cellular enzymes forms tenofovir diphosphate (active form). The diphosphate form inhibits HIV reverse transcriptase via competition with the natural substrate deoxyadenosine 5'-triphosphate and once incorporated into DNA, by DNA chain termination.</p>
<b>Activity</b>	<p>IC<sub>50</sub> = 0.04 – 8.5 µM (in vitro)</p> <p>Active vs HBV</p>
<b>Resistance - genotypic</b>	<p>Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations):</p> <ul style="list-style-type: none"> <li>• K65R</li> <li>• <i>Presence of ≥3 TAMS inclusive of either M41L or L210W leads to reduced response: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E</i></li> <li>• <i>Slightly increased treatment responses observed if M184V present</i></li> <li>• <i>69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.</i></li> </ul>
<b>Resistance - phenotypic</b>	<p>Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (<a href="http://hivdb.stanford.edu/">http://hivdb.stanford.edu/</a>):</p> <p>K65R: 1.9-fold ↑ (intermediate resistance)  M184V + TAMS: ↓ susceptibility to tenofovir  69 Insertion complex: 20-fold ↑ (high resistance)</p>
<b>Cross-Resistance</b>	Pretreatment with didanosine, zalcitabine, or abacavir may select for K65R mutation.
<b>Oral Bioavailability</b>	25% (fasting); 39% (high-fat meal)
<b>Effect of Food</b>	Increase absorption from 25% to 39%. Take with food if possible, however may also be taken on an empty stomach.

<b>Protein Binding</b>	0.7% (human plasma); 7.2% (serum proteins)
<b>Vd</b>	1.3 ± 0.6 L/kg
<b>Tmax</b>	1.0 ± 0.4 hours (food delays Tmax by 1 hour)
<b>Serum T<sub>1/2</sub></b>	17 hours
<b>Intracellular T<sub>1/2</sub></b>	> 60 hours
<b>Drug Concentrations</b>	At 300 mg QD with food at steady state, Cmax 326 ± 119 ng/mL, AUC 3324 ± 1370 ng.h/mL
<b>CSF (% of serum)</b>	Not available.
<b>Metabolism</b>	Not a substrate of CYP450 enzymes.
<b>Excretion</b>	32% ± 10% unchanged in the urine; undergoes glomerular filtration and active tubular secretion
<b>Dosing – Adult</b>	300 mg po once daily Truvada® (1 tablet once daily = tenofovir 300 mg + emtricitabine 200 mg once daily)
<b>Dosing – Pediatric</b>	Neonatal/Infant: unknown Pediatric: Phase I studies underway Study Gilead 926: 175 mg/m <sup>2</sup> /dose PO ONCE daily* Study Gilead 927: Given PO ONCE daily* 10 - < 20 kg: 75 mg 20 - < 35 kg: 150 mg 35 - < 50 kg: 225 mg >50 kg: 300 mg (*Gilead 2003).
<b>Special instructions for pediatric patients</b>	Tablets may be split or chewed (bitter taste). May dissolve tablets in water, grape juice, or grapefruit juice. Once dissolved, take immediately.
<b>Adjust in Liver Dysfunction</b>	Tenofovir pharmacokinetics were similar in subjects with moderate or severe hepatic impairment relative to healthy controls and consistent with historical data in HIV+ patients [Kearney et al. 2004]. No dosage adjustment is required.

<p><b>Adjust in Renal Failure/ Dialysis</b></p> <p><sup>a</sup> CrCl (mL/min) for men: <math>\frac{(140 - \text{age}) (\text{wt}) \times 60}{(\text{Scr}) (50)}</math></p> <p>*CrCl (mL/min) for women: as above multiplied by 0.85</p>	<p>Reduce dose based on CrCl<sup>a</sup>:</p> <p>≥ 50mL/min: 300 mg q 24 h 30-49 mL/min: 300 mg q 48 h 10-29 mL/min: 2 times weekly</p> <p>End-stage renal disease or hemodialysis: 300 mg q 7 days, post-dialysis (assuming 3 x 4 hour sessions weekly); 10% removed in 4-hour hemodialysis session</p>
<p><b>Toxicity</b></p>	<p>Nausea, diarrhea, vomiting, flatulence, asthenia, headache</p> <p><b>Lactic acidosis</b>, mitochondrial toxicity is seen with the use of nucleoside analogs. Potential thought to be lower with tenofovir vs. ddI, d4T, ddC, AZT. Fatal lactic acidosis has been reported with tenofovir + didanosine. [Rivas P 2003, Murphy 2003, Guo Y 2004]</p> <p><b>Pancreatitis</b> reported when used with full dose of didanosine. Dosage reduction of didanosine is recommended with combination (i.e. ddI EC 250 mg po once daily). Caution is still warranted even with dosage reduction. [Kirian, 2004]</p> <p><b>Nephrotoxicity:</b> onset: weeks to months after therapy. Proximal tubulopathy leading to Fanconi syndrome (increased serum creatinine/blood urea, hypophosphoremia, hypouricemia, hypokalemia, non-anion gap metabolic acidosis, glucosuria, proteinuria, uricosuria, phosphaturia, and/or calcuria). [Gaspar G 2004, Rollet F 2003, Karras 2003] Nephrogenic diabetes insipidus, acute tubular necrosis, [Lee JC 2003] nephrolithiasis, hydronephrosis. [Cicconi P 2004] Use of didanosine and lopinaivr/ritonavir may further increase risk.</p> <p><b>Bone toxicity:</b> osteomalacia and reduced bone density seen in animals at high doses</p> <p>Severe acute exacerbations of <b>HBV</b> have been reported in patients who have discontinued tenofovir. Monitor hepatic function closely for several months upon discontinuation.</p>

<b>Pregnancy &amp; Lactation</b>	<p>Pregnancy risk category B. Phase I study in late pregnancy in progress. Due to lack of data and concern about fetal bone effects, avoid use in pregnancy.</p> <p>Secreted into the breast milk of lactating rats.</p>
<b>Drug Interactions</b>	<p>Interactions observed with didanosine, atazanavir, lopinavir/r. Potential for interaction with other renally eliminated drugs. Should not be combined with certain antiretrovirals as first-line therapy in subjects with high viral load and low CD4 count. See separate Drug Interaction chart for more details.</p>
<b>Baseline Assessment</b>	<p>CBC/diff, electrolytes, serum creatinine, blood urea, anion gap, serum bicarbonate, LFTs, serum phosphate, uric acid, urinalysis</p>
<b>Routine Labs</b>	<p>CBC/diff, electrolytes, serum creatinine, blood urea, anion gap, serum bicarbonate, LFTs, serum phosphate, uric acid, urinalysis (glucosuria, proteinuria, uricosuria, phosphaturia, and/or calcuria ) q 3 months</p> <p>Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death.</p> <p><b>D/C drug:</b> Sx of lactic acidosis, serum lactate &gt; 5 mmol/L, amylase &gt;200 (asymptomatic), pancreatitis, LFTs &gt;5xULN, serum creatinine &gt;175 mmol/L or grade 3 clinical or laboratory events (e.g., serum potassium &lt; 2.5 mmol/L, serum phosphorus &lt; 0.48 mmol/L)</p>
<b>Dosage Forms</b>	<p>Viread® (tenofovir) 300 mg (light blue, almond-shaped); DIN 02247128</p> <p><b>Combination formulations:</b></p> <ul style="list-style-type: none"> <li>• Truvada®: 1 tablet= tenofovir 300 mg + emtricitabine 200 mg, DIN 02274906</li> <li>• Atripla®: efavirenz 600 mg/emtricitabine 200 mg/tenofovir 300 mg tablet (approved in US July 2006)</li> </ul>
<b>Storage</b>	<p>Store tablets at room temperature.</p>

## References:

Academic Copyright. M. Foisy, Pharm.D., Edmonton, AB and A. Tseng, Pharm.D. Toronto, Ontario. Pediatric dosing & administration information prepared by Natalie Dayneka, Pharm.D., Children's Hospital of Eastern Ontario, Ottawa. Please note: This chart summarizes selected properties based on current available data. Please consult a health professional whenever beginning, stopping or modifying drug therapy. July 2006. Page 4 of 5

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