Selected Properties of Tenofovir

Other names	**Viread®:** tenofovir disoproxil fumarate; TDF Combination formulations: **Truvada®:** emtricitabine/tenofovir **Atripla®:** efavirenz/emtricitabine/tenofovir **Complera®:** rilpivirine/emtricitabine/tenofovir **Stribild®:** elvitegravir/cobicistat/emtricitabine/tenofovir
Manufacturer	Gilead Sciences, Inc.
Pharmacology/Mechanism of Action	Nucleotide 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.
Activity	IC_{50} = 0.04 – 8.5 uM (in vitro) Active vs HBV
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • K65R • *Presence of ≥3 TAMS inclusive of either M41L or L210W leads to reduced response: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E* • *Slightly increased treatment responses observed if M184V present* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K65R: 1.9-fold ↑ (intermediate resistance) M184V + TAMS: ↓ susceptibility to tenofovir 69 Insertion complex: 20-fold ↑ (high resistance)
Cross-Resistance	Pretreatment with didanosine, zalcitabine, or abacavir may select for K65R mutation.
Oral Bioavailability	25% (fasting); 39% (high-fat meal) The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]
Effect of Food	Increase absorption from 25% to 39%. Take with food if possible, however may also be taken on an empty stomach.
Protein Binding	0.7% (human plasma); 7.2% (serum proteins)

Vd	1.3 ± 0.6 L/kg
Tmax	1.0 ± 0.4 hours (food delays Tmax by 1 hour)
Serum T ½	17 hours
Intracellular T½	> 60 hours
Drug Concentrations	At 300 mg QD with food at steady state, Cmax 326 ± 119 ng/mL, AUC 3324 ± 1370 ng.h/mL In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 4 oz. applesauce) in healthy adult volunteers, the mean C_{max} of tenofovir was 26% lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was similar between the oral powder and tablet formulations. Similarly, comparable tenofovir exposures were observed between oral powder and the tablet formulations under fed (light meal and high-fat meal).[Custodio et al. 2014 IWCPHT] In HIV-infected adolescent patients (12 to <18 years old) taking tenofovir 300 mg QD, steady-state tenofovir PK were similar to exposures achieved in adults: mean (± SD) Cmax and AUCtau were 0.38 ± 0.13 mg/mL and 3.39 ± 1.22 mg·hr/mL, respectively. Tenofovir population pharmacokinetics were assessed in 47 HIV-infected patients 8 to 18 years of age participating in a multicentre protocol (IMPAACT). Apparent tenofovir plasma clearance was slightly higher in this population compared to adults (96.2 L/hr vs. 90.9 L/hr) and affected by creatinine clearance. Differences in rate of absorption were likely due to concomitant food intake. Age, sex, Tanner stage and concomitant medications did not affect tenofovir clearance or volume of distribution.[King J et al. 2010]. In a retrospective analysis of HIV-infected Thai adults who initiated tenofovir-based cART, ABCC4 3463 AG/GG variants were associated with higher tenofovir exposure. No SNPs were associated with significant (>25% change from baseline) decreases in Clcr over time.[Cressey et al. HIVPK 2013, O_06]
CSF (% of serum)	Not available. 2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	Not a substrate of CYP450 enzymes.
Excretion	32% ± 10% unchanged in the urine; undergoes glomerular filtration and active tubular secretion
Dosing – Adult	Viread® (tenofovir 300 mg): one tablet with or without food. Truvada® (tenofovir 300 mg/emtricitabine 200 mg): one tablet once daily with or without food. Complera® (emtricitabine 200 mg/rilpivirine 25 mg/tenofovir 300 mg): one tablet daily with a meal.

<table>
<tr><td></td><td>Viread® (tenofovir) oral powder formulation: For adults unable to swallow VIREAD tablets, the oral powder formulation (7.5 scoops once daily) may be used.

Recommended Dose in Adolescents (≥12 Years of Age and ≥35 kg/77 lb): 300 mg once daily taken orally, without regard to food.</td></tr>
<tr><td>Dosing – Pediatric</td><td>Tenofovir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older.

Recommended Dose (ages 2 to <18 years of age):
• 8 mg of tenofovir disoproxil fumarate/kg body weight (up to a maximum of 300 mg) once daily as oral powder or tablets.

<table>
<tr><th>Body Weight (kg)</th><th>Oral Powder QD (# scoops)</th><th>Tablets QD</th></tr>
<tr><td>10 to <12</td><td>2</td><td rowspan="3">Use tablets if child weighs ≥17 kg</td></tr>
<tr><td>12 to <14</td><td>2.5</td></tr>
<tr><td>14 to <17</td><td>3</td></tr>
<tr><td>17 to <19</td><td>3.5</td><td rowspan="2">17 to <22 kg:
150 mg</td></tr>
<tr><td>19 to <22</td><td>4</td></tr>
<tr><td>22 to <24</td><td>4.5</td><td rowspan="3">22 to <28 kg:
200 mg</td></tr>
<tr><td>24 to <27</td><td>5</td></tr>
<tr><td>27 to <29</td><td>5.5</td></tr>
<tr><td>29 to <32</td><td>6</td><td rowspan="3">28 to <35 kg:
250 mg</td></tr>
<tr><td>32 to <34</td><td>6.5</td></tr>
<tr><td>34 to <35</td><td>7</td></tr>
<tr><td>≥ 35</td><td>7.5</td><td>300 mg</td></tr>
</table>

Neonatal/Infant: unknown</td></tr>
<tr><td>Special instructions for pediatric patients</td><td><u>Tenofovir oral powder</u> should be measured only with the supplied dosing scoop. One level scoop delivers 1 g of powder which contains 40 mg of tenofovir disoproxil fumarate. The oral powder should be mixed in a container with 2 to 4 ounces of soft food not requiring chewing (e.g., applesauce, baby food, yogurt). The entire mixture should be ingested immediately to avoid a bitter taste. Do not administer tenofovir oral powder in a liquid as the powder may float on top of the liquid even after stirring.

Tenofovir tablets may be split or chewed (bitter taste).
May dissolve tenofovir tablets in water, grape juice, or grapefruit juice. Once dissolved, take immediately.

Crushing Atripla® tablets: Bioequivalence of Atripla tablet and compounded oral liquid formulation in HIV-negative volunteers was not demonstrated. The 90% CI for FTC Cmax and AUC fell</td></tr>
</table>

	within the range of 0.8-1.25 thus, bioequivalence was met, but the 90% CI for efavirenz Cmax fell below the range of bioequivalence while efavirenz AUC∞ fell slightly above the range and tenofovir Cmax and AUC∞ fell above the range. Tenofovir Cmax and AUC∞ were approximately 40% and 20% higher, respectively with the liquid formulation. The clinical implications of these data are unknown.[Kiser et al. CROI 2010, #605].
Adjust in Liver Dysfunction	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.
Adjust in Renal Failure/ Dialysis [a] CrCl (mL/min) for men: (140 - age) (wt) x 60 (Scr) (50) *CrCl (mL/min) for women: as above multiplied by 0.85	Reduce dose based on CrCl[a]: ≥ 50mL/min: 300 mg q 24 hours 30-49 mL/min: 300 mg q 48 hours 10-29 mL/min: 300 mg q72-96 hours Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. 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. In 20 HIV-infected subjects with moderate renal impairment (median Clcr 42 mL/min) on lopinavir/ritonavir-based ART, equivalent tenofovir exposures were observed with administration of either tenofovir 300 mg q48h or tenofovir 150 mg daily. Tenofovir Cmax was significant lower ($p<0.01$) and Clast (i.e. C48h vs. C24h) significantly higher ($p<0.01$) with daily TDF dosing. All subjects remained virologically suppressed and no drug-related adverse events were reported.[Cressey et al. CROI 2014].
Toxicity	Nausea, diarrhea, vomiting, flatulence, asthenia, headache **Lactic acidosis**, 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] **Pancreatitis** 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] **Nephrotoxicity:** 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, Rollot 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. **Bone toxicity:** osteomalacia and reduced bone density seen in animals at high doses. Decreases in bone mineral density, via increased bone turnover, have been observed in adolescents and adults. Assessment of bone mineral density (BMD) should be considered for adults and adolescents who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. Severe acute exacerbations of **HBV** have been reported in patients who have discontinued tenofovir. Monitor hepatic function closely for several months upon discontinuation.
Pregnancy & Lactation	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. Secreted into the breast milk of lactating rats. In a phase I trial, 36 pregnant women received a single dose of 900 mg tenofovir at the onset of labour or 4 hours prior to caesarean section, and their newborns received tenofovir 6 mg/kg for 3 doses (after birth, 72 hours and 120 hours). Median tenofovir cord blood concentration was 123 ng/mL, with a median cord blood:maternal plasma concentration ratio of 0.59.[Mirochnick et al. 2010] In a trial, of HIV-infected pregnant women and their infants, women received a single dose of either 600 mg TDF, 900 mg TDF, or 900 mg TDF-600 mg FTC at labor onset or prior to a cesarean section. Infants received no drug or a single dose of TDF at 4 mg/kg of body weight or of TDF at 4 mg/kg plus FTC at 3 mg/kg as soon as possible after birth. All regimens were safe and well tolerated. Maternal areas under the serum concentration-time curve (AUC) and concentrations at the end of sampling after 24 h (C_{24}) were similar between the two doses of TDF. The median ratio of the TFV concentration in cord blood to that in the maternal plasma at delivery was 0.73 (range, 0.26 to 1.95). [Flynn PM et al. 2011] In 34 HIV-infected pregnant women on tenofovir-containing cART, tenofovir exposures were ~25% lower in the 3rd trimester compared to post-partum; these results were independent of concomitant use of boosted PIs. The median (range) ratio of cord blood:maternal blood was 0.82 (0.64–1.10; n=14) for tenofovir.[Colbers et al. 2013]
Drug Interactions	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.
Baseline Assessment	CBC/diff, electrolytes, serum creatinine, blood urea, anion gap, serum bicarbonate, LFTs, serum phosphate, uric acid, urinalysis
Routine Labs	CBC/diff, electrolytes, serum creatinine, blood urea, anion gap, serum bicarbonate, LFTs, serum phosphate, uric acid, urinalysis (glucosuria, proteinuria, uricosuria, phosphaturia, and/or calcuria) every 3 months. Consider monitoring bone mineral density (BMD) in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss. 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. **D/C drug:** Sx of lactic acidosis, serum lactate > 5 mmol/L, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, serum creatinine >175 mmol/L or grade 3 clinical or laboratory events (e.g., serum potassium < 2.5 mmol/L, serum phosphorus < 0.48 mmol/L)
Dosage Forms	Viread® (tenofovir) tablets: • 300 mg (light blue, almond-shaped); DIN 02247128 • 150 mg, 200 mg and 250 mg tablets *(available in U.S.)* Viread® (tenofovir) oral powder: *(available in U.S.)* • 40 mg per 1 gram of oral powder formulation **Combination formulations:** • Truvada®: tenofovir 300 mg/emtricitabine 200 mg, DIN 02274906 • Atripla®: efavirenz 600 mg/emtricitabine 200 mg/tenofovir 300 mg tablet, DIN 02300699 • Complera®: Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir DF 300 mg tablet, DIN 02374129 • Stribild®: Elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/ tenofovir DF 300 mg tablet
Storage	Store tablets and powder at room temperature.

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