



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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## Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated April 27, 2017; last reviewed April 27, 2017)

For additional information see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Oral Powder:** 40 mg per 1 g of oral powder (1 level scoop = 1 g oral powder; supplied with dosing scoop)

**Tablets:** 150 mg, 200 mg, 250 mg, and 300 mg

### Fixed-Dose Combination Tablets

- *[Truvada low strength tablet]*
  - Emtricitabine 100 mg plus tenofovir disoproxil fumarate (TDF) 150 mg
  - Emtricitabine 133 mg plus TDF 200 mg
  - Emtricitabine 167 mg plus TDF 250 mg
- *[Truvada tablet]* Emtricitabine 200 mg plus TDF 300 mg
- *[Atripla]* Efavirenz 600 mg plus emtricitabine 200 mg plus TDF 300 mg
- *[Complera]* Emtricitabine 200 mg plus rilpivirine 25 mg plus TDF 300 mg
- *[Stribild]* Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TDF 300 mg

### Dosing Recommendations

#### Neonate/Infant Dose:

- Not Food and Drug Administration-approved or recommended for use in neonates/infants aged <2 years.

#### Pediatric Dose (Aged ≥2 Years to <12 Years)<sup>a</sup>:

- 8 mg/kg/dose once daily

#### TDF Oral Powder Dosing Table

Body Weight kg	TDF Oral Powder Once Daily Scoops of Powder
10 to <12	2 scoops (80 mg)
12 to <14	2.5 scoops (100 mg)
14 to <17	3 scoops (120 mg)
17 to <19	3.5 scoops (140 mg)
19 to <22	4 scoops (160 mg)
22 to <24	4.5 scoops (180 mg)
24 to <27	5 scoops (200 mg)
27 to <29	5.5 scoops (220 mg)
29 to <32	6 scoops (240 mg)
32 to <34	6.5 scoops (260 mg)
34 to <35	7 scoops (280 mg)
≥35	7.5 scoops (300 mg)

### Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased bone mineral density<sup>a</sup>

### Special Instructions

- Do not crush tablets; TDF oral powder formulation is available for patients unable to swallow tablets.
- TDF oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg TDF.
- Mix TDF oral powder in 2 to 4 oz of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the TDF oral powder with liquid. The powder may float on the top even after vigorous stirring.
- Although TDF can be administered without regard to food, food requirements vary depending on the other antiretroviral (ARV) drugs contained in a combination tablet.

**TDF Tablet Dosing Table**  
(Aged ≥2 Years and Weighing ≥17 kg)

Body Weight kg	TDF Tablet Once Daily
17 to <22	150 mg
22 to <28	200 mg
28 to <35	250 mg
≥35	300 mg

**Adolescent (Weighing ≥35 kg)<sup>a</sup> and Adult Dose:**

- TDF 300 mg once daily

**Combination Tablets**

[Truvada] Emtricitabine plus TDF

**Truvada Tablets Dosing Table**

Body Weight kg	FTC/TDF Tablet Once Daily
17 to <22	One FTC 100 mg/TDF 150 mg tablet
22 to <28	One FTC 133 mg/TDF 200 mg tablet
28 to <35	One FTC 167 mg/TDF 250 mg tablet
≥35 (Adolescent and Adult)	One FTC 200 mg/TDF 300 mg tablet

[Atripla] Efavirenz plus Emtricitabine plus TDF

**Adolescent (Aged ≥12 years and Weighing ≥40 kg) and Adult Dose:**

- 1 tablet once daily.

[Complera] Emtricitabine plus Rilpivirine plus TDF

**Adolescent (Weighing ≥35 kg) and Adult Dose:**

- 1 tablet once daily in treatment-naïve adults with baseline viral load <100,000 copies/mL or virologically suppressed adults, with no history of virologic failure, resistance to rilpivirine and other ARV drugs, and who are currently on their first or second regimen.
- Administer with a meal of at least 400 calories.

[Stribild] Elvitegravir plus Cobicistat plus Emtricitabine plus TDF

**Adolescent (Weighing >35 kg) and Adult Dose:**

- 1 tablet once daily in treatment-naïve adults or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild.
- Administer with food.

For Atripla (administer without food) and Complera (administer with a meal of at least 400 calories), refer to efavirenz or rilpivirine special instructions, respectively.

- Measure serum creatinine and urine dipstick for protein and glucose before starting a TDF-containing regimen and monitor serum creatinine and urine dipstick for protein and glucose at intervals (see [Table 13i](#)) during continued therapy. Measure serum phosphate if clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before use of TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, in patients with HBV infection, monitor hepatic function for several months after therapy with TDF is stopped.
- If using Stribild, please see the elvitegravir and cobicistat sections of the drug appendix for additional information.

**Metabolism/Elimination**

- Renal excretion
- Dosing of TDF in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function (creatinine clearance <50 mL/min). Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance (CrCl).
- Atripla and Complera (fixed-dose combinations) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Truvada (fixed-dose combination) should not be used in patients with CrCl <30 mL/min or in patients requiring dialysis.
- Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.

<sup>a</sup> See text for concerns about decreased BMD, especially in pre-pubertal patients and those in early puberty (Tanner Stages 1 and 2).

**Drug Interactions** (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#) and <http://www.hiv-druginteractions.org/>)

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of plasma tenofovir disoproxil fumarate (TDF).
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine serum concentrations are increased when the drug is co-administered with TDF and this combination should be avoided if possible because of increase in didanosine toxicity.
- *Protease inhibitors:* TDF decreases atazanavir plasma concentrations. Atazanavir without ritonavir should not be co-administered with TDF. In addition, atazanavir and lopinavir/ritonavir increase plasma tenofovir concentrations and could potentiate TDF-associated toxicity.
- *Use of Stribild:* If using Stribild, please see the Elvitegravir section of the drug appendix for additional information.

### **Major Toxicities**

- *More common:* Nausea, diarrhea, vomiting, and flatulence.
- *Less common (more severe):* TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking TDF; the clinical significance of these changes is not yet known. Renal toxicity, including increased serum creatinine, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate, has been observed. Patients at increased risk of renal glomerular or tubular dysfunction should be closely monitored. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

### **Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://iasusa.org/sites/default/files/tam/october\\_november\\_2015.pdf#page=10](http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

### **Pediatric Use**

#### **Approval**

TDF is Food and Drug Administration (FDA)-approved for use in children aged  $\geq 2$  years when used as a component of antiretroviral therapy (ART).

TDF has antiviral activity and efficacy against hepatitis B virus (HBV) and is FDA-approved for HBV treatment for children aged 12 years and older (reviewed in [Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Children](#)).

### **Efficacy in Clinical Trials in Adults Compared to Children and Adolescents**

The standard adult dose of TDF approved by the FDA for adults and children aged  $\geq 12$  years and weight  $\geq 35$  kg is 300 mg once daily; for children aged 2 to 12 years, the FDA-approved TDF dose is 8 mg/kg/dose administered once daily, which closely approximates the dose of 208 mg/m<sup>2</sup>/dose used in early studies in children.<sup>1</sup>

In adults, the recommended TDF dose is highly effective. In comparative clinical trials in adults, TDF when used with lamivudine or emtricitabine as a dual-NRTI backbone in combination with efavirenz was superior to zidovudine used with lamivudine and efavirenz in viral efficacy.<sup>2-4</sup> TDF with emtricitabine has been compared to abacavir in combination with lamivudine in several adult studies and meta-analyses with variable results.<sup>5-9</sup>

In children, the published efficacy data are mixed, but potency equal to that in adults is seen in pediatric patients aged 3 to 18 years with susceptible virus. In children aged 2 to  $<12$  years, TDF 8 mg/kg/dose once daily showed non-inferiority to twice-daily zidovudine- or stavudine-containing ART over 48 weeks of randomized treatment.<sup>10,11</sup> Virologic success is lower in treatment-experienced patients with extensive drug resistance.<sup>12-14</sup>

## **Pharmacokinetics**

### *Relationship of Drug Exposure to Virologic Response*

Virologic success is most closely related to intracellular tenofovir diphosphate (TFV-DP) concentrations, and for TDF, intracellular TFV-DP is linked to plasma TFV concentration.<sup>15</sup> A modeling study suggests that children and adolescents treated with TDF may have higher intracellular TFV-DP concentrations than adults<sup>16</sup> even though plasma TFV concentrations are lower in children and adolescents because renal clearance of TFV is higher in children than in adults.<sup>1,17,18</sup>

## **Formulations**

### *Special Considerations*

The taste-masked granules that make up the TDF oral powder give the vehicle (e.g., applesauce, yogurt) a gritty consistency. Once mixed in the vehicle, TDF should be administered promptly because, if allowed to sit too long, its taste becomes bitter.

## **Toxicity**

### *Bone*

TDF administration is associated with decreased BMD in both adults<sup>19,20</sup> and children.<sup>11,21-23</sup> When treated with TDF, younger children in Tanner Stages 1 and 2 may be at higher risk of decreased BMD than children with more advanced pubertal development (i.e., Tanner Stage  $\geq 3$ ).<sup>17</sup> Discontinuation of TDF results in partial or complete recovery of BMD.<sup>21</sup>

In the industry-sponsored study that led to FDA approval of TDF in adolescents aged  $\geq 12$  years and weight  $\geq 35$  kg, 6 of 33 participants (18%) in the TDF arm experienced a  $>4\%$  decline in absolute lumbar spine BMD in 48 weeks compared with 1 of 33 participants (3%) in the placebo arm.<sup>12</sup>

TDF administration disrupts vitamin D metabolism<sup>24</sup> and the decrease in BMD associated with TDF initiation was attenuated in adults with co-administration of high doses of vitamin D3 (4000 International Units [IU] daily) and calcium carbonate (1000 mg daily) for the first 48 weeks of TDF treatment.<sup>25</sup> During chronic TDF administration, in youth with HIV, supplementation with vitamin D3 (50,000 IU once monthly) was associated with decrease in serum parathyroid hormone;<sup>26</sup> the effect on BMD of vitamin D supplementation during chronic TDF administration is under study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01751646) identifier NCT01751646).

### *Monitoring Potential Bone Toxicity*

The Panel does not recommend routine dual-energy absorptiometry (DXA) monitoring for children or adolescents treated with TDF. Given the potential for BMD loss in children treated with TDF, some experts obtain a DXA before initiation of TDF therapy and approximately 6 months after starting TDF, especially in prepubertal patients and those early in puberty (i.e., Tanner Stages 1 and 2). If DXA results are abnormal, consider referral to a subspecialist in pediatric endocrinology or a related field.

Despite the ease of use of a once-daily drug and the efficacy of TDF, the potential for BMD loss during the important period of rapid bone accrual in childhood and early adolescence is concerning and favors use of abacavir (or possibly tenofovir alafenamide) in children in Tanner Stages 1–3, because children with perinatally acquired HIV are at risk for low peak bone mass.<sup>27,28</sup>

### *Renal*

New onset or worsening of renal impairment has been reported in adults<sup>29</sup> and children<sup>30,31</sup> receiving TDF, with renal toxicity leading to discontinuation of TDF reported in 3.7% (6 of 159) of children with HIV treated with TDF.<sup>14</sup> While TDF is clearly associated with a decline in glomerular filtration rate, the effect is generally small, and severe glomerular toxicity is rare.<sup>29,30</sup> Irreversible renal failure is quite rare but has been reported.<sup>32</sup>

The main target of TDF nephrotoxicity is the renal proximal tubule.<sup>30</sup> Case reports highlight the infrequent but most severe manifestations of renal Fanconi syndrome, hypophosphatemia, hypocalcemia, diabetes insipidus, myalgias, bone pain, and fractures.<sup>33,34</sup>



Subclinical renal tubular damage is more frequent. Increased urinary beta-2 microglobulin was identified in 27% (12 of 44) of children treated with TDF compared with 4% (2 of 48) of children not treated with TDF.<sup>35</sup> TDF-associated proteinuria or chronic kidney disease is more common with longer duration of treatment.<sup>36,37</sup> Of 89 participants aged 2 to 12 years who received TDF in Gilead study 352 (median drug exposure 104 weeks), 4 were discontinued from the study for renal tubular dysfunction, with the discontinuations occurring between 84 and 156 weeks on TDF therapy.<sup>10</sup>

### *Monitoring Potential Renal Toxicity*

Because of the potential for TDF to decrease creatinine clearance and to cause renal tubular dysfunction, measurement of serum creatinine and urine dipstick for protein and glucose prior to drug initiation is recommended. In asymptomatic individuals, the optimal frequency for routine monitoring of creatinine and renal tubular function (urine protein and glucose) is unclear. Many Panel members monitor creatinine with other blood tests every 3 to 4 months, and urinalysis every 6 to 12 months. Serum phosphate should be measured if clinically indicated; renal phosphate loss can occur in the presence of normal creatinine and the absence of proteinuria. Because nephrotoxicity increases with the duration of TDF treatment, monitoring should be continued during long-term therapy with the drug.

Because renal glomerular damage primarily increases urine concentration of albumin, and proximal renal tubular damage increases urine concentrations of low-molecular-weight proteins like beta-2 microglobulin, the dipstick urinalysis (measuring primarily urine albumin) may be a relatively insensitive marker for TDF-associated tubular damage. Measurement of urine albumin and urine protein, and calculation of the urine albumin to urine protein ratio, can be helpful in identifying the non-albumin proteinuria that is seen in TDF-associated nephrotoxicity.<sup>38,39</sup> While these more complex and expensive tests may be used in research settings, in clinical practice, renal tubular damage is perhaps easiest to identify by using a renal dipstick to identify normoglycemic glycosuria and proteinuria.

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