Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

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

Tablet: 150 mg, 200 mg, 250 mg, and 300 mg

Combination tablets:

- *With emtricitabine (FTC):* 200 mg FTC + 300 mg TDF (Truvada)
- *With FTC + efavirenz (EFV):* 200 mg FTC + 600 mg EFV + 300 mg TDF (Atripla)
- *With FTC + rilpivirine (RPV):* 200 mg FTC + 25 mg RPV + 300 mg TDF (Complera)
- *With FTC + elvitegravir (EVG) + cobicistat (COBI):* 200 mg FTC + 150 mg EVG + 150 mg COBI + 300 mg TDF (Stribild)

Dosing Recommendations

Neonate/infant dose:
Not FDA approved or recommended for use in neonates/infants aged <2 years.

Pediatric dose (aged ≥2 years to <12 years)*:

- 8 mg/kg/dose once daily.

Oral powder dosing table

Body Weight Kilogram (kg)	Oral Powder Once Daily Scoops of Powder
10–<12	2
12–<14	2.5
14–<17	3
17–<19	3.5
19–<22	4
22–<24	4.5
24–<27	5
27–<29	5.5
29–<32	6
32–<34	6.5
34–<35	7
≥35	7.5

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased bone mineral density (BMD)

Special Instructions

- Oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg TDF.
- Mix oral powder in 2–4 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 oral powder with liquid: the powder may float on the top even after vigorous stirring.
- TDF can be administered without regard to food, although absorption is enhanced when administered with a high-fat meal. Because Atripla also contains EFV, the combination tablet should be administered on an empty stomach.
- Given the potential for TDF-induced changes in renal tubular function, some panel members recommend monitoring for proteinuria and glycosuria every 6–12 months.

Tablets dosing table (aged ≥2 years and weight ≥17 kg)

Body Weight Kilogram (kg)	Tablets Once Daily
17–<22	150 mg
22–<28	200 mg
28–<35	250 mg
≥35	300 mg

Adolescent (aged ≥12 years and weight ≥35 kg)* and adult dose:

- 300 mg once daily

  * See text for concerns about decreased bone mineral density (BMD), especially in prepubertal patients and those in early puberty (Tanner Stages 1 and 2).

Combination Tablets

Truvada

- *Adolescent (aged ≥12 years and weight ≥35 kg) and adult dose:* 1 tablet once daily.

Atripla

- *Adolescent (aged ≥12 years and weight ≥40kg) and adult dose:* 1 tablet once daily.

Complera

- *Adult dose:* 1 tablet once daily in treatment-naive adults. Administer with a meal.

Stribild

- *Adult dose (aged ≥18 years):* 1 tablet once daily in treatment-naive adults. Administer with food

TDF in combination with didanosine (ddI):

- The combination of TDF and ddI should be avoided if possible. If used, ddI dose requires modification. See section on ddI.

TDF in combination with atazanavir (ATV):

- When ATV is used in combination with TDF, ATV should always be boosted with ritonavir (RTV).
- 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, monitor hepatic function for several months after therapy with TDF is stopped.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

Metabolism

- Renal excretion.
- Dosing of TDF in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. 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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir disoproxil fumarate (tenofovir).
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine serum concentrations are increased when the drug is co-administered with tenofovir and this combination should be avoided if possible because of increase in didanosine toxicity.
- *Protease inhibitors (PIs):* Tenofovir decreases atazanavir plasma concentrations. In adults, the recommended dosing for atazanavir co-administered with tenofovir is atazanavir 300 mg with ritonavir 100 mg and tenofovir 300 mg, all as a single daily dose with food. Atazanavir without ritonavir should not be co-administered with tenofovir. In addition, atazanavir and lopinavir/ritonavir increase tenofovir concentrations and could potentiate tenofovir-associated toxicity.
- *Use with 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):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density (BMD) have been reported in both adults and children taking tenofovir; the clinical significance of these changes is not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate, has been observed. Numerous case reports of renal tubular dysfunction have been reported in patients receiving tenofovir; patients at increased risk of renal dysfunction should be closely monitored.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/TDF.html).

Pediatric Use: Tenofovir is Food and Drug Administration (FDA) approved for use in children aged ≥2 years when used as a component of the two-NRTI backbone in combination antiretroviral therapy (cART).

The standard adult dose of tenofovir approved by the FDA for adults and children aged ≥12 years and weight ≥35 kg is 300 mg once daily; for children aged 2 to 12 years, the FDA-approved dose is 8 mg/kg/dose administered once daily, which closely approximates the dose of 208 mg/m^2/dose used in early studies in children.[1]

In adults, the recommended dose is highly effective.[2, 3]

In children aged 12 to <18 years, no difference in viral load response was seen between 2 treatment groups in a randomized, placebo-controlled trial of tenofovir 300 mg once daily or placebo, plus an optimized background regimen, in 87 treatment-experienced adolescents in Brazil and Panama.[4-6] Subgroup analyses suggest this lack of response was from imbalances in viral susceptibility to the optimized background regimens.

In children aged 2 to <12 years, tenofovir 8 mg/kg/ dose once daily showed non-inferiority to zidovudine- or stavurdine-containing cART over 48 weeks of randomized treatment using a snapshot analysis (product label). This was a switch study in children aged 2 to 12 years with viral load <400 copies/mL during treatment with zidovudine or stavudine as part of cART, randomized to continue their zidovudine or stavudine (N=49) or switch to tenofovir (N=48) while continuing other components of the regimen (Gilead study 352).[4]

Other pediatric studies have also shown that virologic success is related to prior treatment experience. In 115 pediatric patients treated with tenofovir, viral load decreased to <50 copies/mL at 12 months in 50% of patients on first-line therapy, 39% of patients on second-line therapy, and 13% of patients on third-line or subsequent therapy.[7] This cohort used a target dose of 8 mg/kg, but 18% of patients were dosed at greater than 120% of the target dose and 37% were dosed at less than 80% of the target dose.

Virologic success is also related to drug exposure. In a study using a median daily dose of 208 mg/m^2, [8] lower single-dose and steady-state area under the curve (AUC) were associated with inferior virologic outcome.

Pharmacokinetic (PK) studies in children receiving an investigational 75-mg tablet formulation of tenofovir showed that a median dose of 208 mg/m^2 of body surface area (range 161–256 mg/m^2 body surface area) resulted in a median single dose AUC and maximum plasma concentration (C_{max}) that were 34% and 27% lower, respectively, compared with values reported in adults administered a daily dose of 300 mg.[1, 9] Renal clearance of tenofovir was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure.[1] This lower exposure occurred even though participants were concurrently treated with ritonavir, which boosts tenofovir exposure. Lower-than-anticipated tenofovir exposure was also found in young adults (median age 23 years) treated with atazanavir/ritonavir plus tenofovir.[10]

Further studies are needed of tenofovir PK and clinical outcomes in children, especially when used in combinations that do not include lopinavir and/or ritonavir.

Decreases in BMD have been reported in both adult and pediatric studies. Younger children (Tanner Stages 1 and 2) may be at higher risk than children with more advanced development (Tanner Stage ≥3).[1, 11, 12] In a Phase I/II study of an investigational 75-mg formulation of tenofovir in 18 heavily pretreated children and adolescents, a >6% decrease in BMD measured by dual-energy x-ray absorptiometry (DXA) scan was reported in 5 of 15 (33%) children evaluated at Week 48.[1] Two of the 5 children who discontinued tenofovir at 48 weeks experienced partial or complete recovery of BMD by 96 weeks.[13] Among children with BMD decreases, the median Tanner score was 1 (range 1–3) and mean age was 10.2 years; for children who had no BMD decreases, the median Tanner score was 2.5 (range 1–4) and median age was 13.2 years.[8, 13] In a second study of 6 patients who received the commercially available, 300 mg formulation of tenofovir, 2 pre-pubertal children experienced >6% BMD decreases. One of the 2 children experienced a 27% decrease in BMD, necessitating withdrawal of tenofovir from her cART regimen with subsequent recovery of BMD.[14] Loss of BMD at 48 weeks was associated with higher drug exposure.[8]

In the industry-sponsored study that led to FDA approval of tenofovir in adolescents aged ≥12 years and weight ≥35 kg, 6 of 33 participants (18%) in the tenofovir arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with 1 of 33 participants (3%) in the placebo arm[4, 5] (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM209151.pdf).

In the Gilead switch study (352) in children aged 2 to 12 years over the 48 weeks of randomized treatment, total body BMD gain was less in the tenofovir group than in the zidovudine or stavudine group, but the mean rate of lumbar spine BMD gain was similar between groups. At 48 weeks all participants were offered tenofovir, and for the participants who were treated with the drug for 96 weeks, total body BMD *z* score declined by -0.338 and lumbar spine BMD *z* score declined by -0.012.[4]

Not all studies of tenofovir in children have identified a decline in BMD.[15, 16] No effect of tenofovir on BMD was found in a study in pediatric patients on stable therapy with undetectable viral load who were switched from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz.[17] All patients in this study remained clinically stable and virologically suppressed after switching to the new regimen.[18]

New onset or worsening of renal impairment has been reported in adults and children receiving tenofovir and may be more common in those with higher tenofovir trough plasma concentrations.[19] Possible tenofovir -associated nephrotoxicity manifest as Fanconi syndrome, reduced creatinine clearance (CrCl), and diabetes insipidus has been reported in a child receiving tenofovir as a component of salvage therapy including lopinavir/ritonavir and didanosine for 1 year.[20] Irreversible renal failure has been reported in an adolescent treated with tenofovir without didanosine.[21] Renal toxicity leading to discontinuation of tenofovir was reported in 3.7% (6 of 159) of HIV-1-infected children treated with tenofovir in the Collaborative HIV Pediatric Study (CHIPS) in the United Kingdom and Ireland.[7] Increased urinary beta-2 microglobulin suggesting proximal renal tubular damage was identified in 27% (12 of 44) of children treated with tenofovir compared with 4% (2 of 48) of children not treated with tenofovir.[22] An observational cohort study of 2,102 children with HIV in the United States suggested an increased risk of renal disease (increased creatinine or proteinuria) in children treated with tenofovir-containing cART.[23] Prospectively evaluated renal function was reported for a cohort of 40 pediatric patients on tenofovior-containing antiretroviral regimens from 5 Spanish hospitals. The patients ranged in age from 8 to 17 years (median age 12.5 years) and had received tenofovir for 16 to 143 months (median 77 months). The following observations were made: 18 patients had declines in CrCl after at least 6 months of therapy; 28 patients had decreases in tubular reabsorption of phosphate, which worsened with longer time on tenofovir; and 33 patients had proteinuria, including 10 patients with proteinuria in the nephrotic range.[24] However, no significant decrease in calculated glomerular filtration rate was found in 26 HIV-infected children treated with tenofovir for 5 years.[25] Of 89 participants who received tenofovir in Gilead study 352 (median drug exposure 104 weeks), 4 discontinued from the study for renal tubular dysfunction, and 3 of whom had hypophosphatemia and decrease in total body or spine BMD *z* score.[4]

Given the potential for BMD loss in children treated with tenofovir, some experts recommend obtaining a DXA before initiation of tenofovir therapy and approximately 6 months after start of tenofovir, especially in prepubertal patients and those early in puberty (Tanner Stages 1 and 2). Despite the ease of use of a once-daily drug and the efficacy of tenofovir, this potential for BMD loss during the important period of rapid bone accrual in early adolescence is concerning and favors judicious use of tenofovir in this age group.

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

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