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The Place of Tenofovir Disoproxil Fumarate in Pediatric Antiretroviral Therapy

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In this issue the Journal continues its leadership in publication of high-impact articles concerning all aspects of pediatric HIV infection, with the inclusion of 4 manuscripts discussing the use of tenofovir disoproxil fumarate (TDF) in children and youth with HIV. TDF was first United States (US) Food and Drug Administration (FDA)-approved for use in adults in 2001. Fourteen years later, the 2015 publication of the registrational trial in children ages 2–12 years[1] is occurring at the same time as a topic review [2]. This demonstrates the difficulty of performing clinical trials in children with HIV, and is a testament to the determination of Gilead, the drug's manufacturer, to generate and publish the data required for FDA approval for use of TDF in children.

Each of the trials published in this issue of the Journal evaluates TDF for efficacy and for the major toxicities that have been associated with its use. As detailed in the excellent topic review[2], these toxicities are 1) renal glomerular toxicity, manifest by a rise in serum creatinine and fall in glomerular filtration rate (GFR); 2) renal tubular toxicity, manifest by proteinuria, normoglycemic glycosuria, and phosphate wasting with hypophosphatemia; and 3) bone toxicity, measured as decreased bone mineral density (BMD) determined by dual-energy X-ray absorptiometry (DXA). We will briefly summarize each article from these 3 perspectives.

Gilead Study: Ages 2–12 years

In children ages 2–12 years, TDF did not reach the prespecified non-inferiority margin for efficacy when compared to zidovudine (ZDV) or stavudine (D4T)[1]. This was a switch study, which by design may favor the baseline drug (ZDV or D4T). However, TDF is

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Conflicts of Interest

RH: none declared.

supplied as “taste-masked granules”, while ZDV and D4T are administered as liquids. It is not clear if palatability of the TDF formulation contributed to the disappointing virologic outcome in this study.

Late occurrence (study week 84 to 156) of renal tubular dysfunction manifested by proteinuria, glycosuria, and rise in serum creatinine led to TDF discontinuation in 4/79 (5%) participants in the study extension phase [1]. As reviewed elsewhere in this issue of the Journal[2], this is consistent with findings of other pediatric TDF studies showing that longer duration of TDF use is associated with presence of proteinuria [3]. These late-occurring renal toxicities demonstrate the importance of long-term studies of the effects of combination antiretroviral therapy (cART) for children with HIV.

While bone toxicity was not specifically addressed in that study, 3 fractures were reported in the 79 extension phase participants, all said to be related to high impact trauma[1].

Gilead Study: Ages 12–17 years

For children ages 12–17 years[4], the current publication expands on the previously reported 48-week data from a randomized trial of tenofovir versus optimized background treatment in heavily pretreated HIV infected youth.[5]. In this open label extension phase, lasting up to 144 weeks, demonstration of antiretroviral efficacy was hampered by resistance to TDF as well as to many of the antiretrovirals included in the background regimens. Only 44/81 (54%) study participants had full genotypic susceptibility to TDF at study baseline. Given this high rate of resistance, low antiviral effectiveness would be expected, and only 30 to 39% of participants had HIV RNA<50 copies/mL between study weeks 96 and 240.

An important contribution of this report is demonstration of the long-term safety of TDF, but a full understanding of late TDF treatment effects is obscured by the number of study discontinuations prior to 144 weeks. Of the 81 participants who started the study, 60 entered the extension phase and only 2 completed the 3rd extension[4]. Medication adherence of >95% was documented in fewer than half of participants, which might act to underestimate toxicity. The median estimated GFR declined from 167 mL/min/1.73M² to 142 mL/min/1.73M² between baseline (N=81) and week 144 (N=25), but renal tubular dysfunction was uncommon, with proteinuria in 2 and acute renal failure in one participant[4]. The apparent long-term falling GFR is concerning for safety for the treatment duration needed in children. However, the results need to be interpreted cautiously because of the large change in the number of study participants from baseline to week 144.

While median DXA-measured spine BMD and total body less head (TBLH) BMD both increased over the course of the study, the age-adjusted spine BMD Z-score showed a statistically significant decline from baseline through week 96 and the age-adjusted TBLH BMD showed a statistically significant decline from baseline through week 192. A >4% decrease in spine and/or TBLH BMD was seen in 13/81 (16%) study participants[4]. This is similar to a prior study showing a decrease in spine BMD of >6% in 5 of 15 study participants treated with TDF and followed for 48 weeks.[6]

Thai Study: Ages 3–18 years

In an open label switch study of TDF use in children and youth ages 3–18 years with viral suppression on their first antiretroviral (ARV) regimen in Thailand[7], weight band dosing resulted in a median TDF administered dose and plasma drug exposures similar to those in early reports[8] and in studies using the FDA recommended TDF dose of 8 mg/kg[2]. Efficacy was excellent, with 39/40 (98%) TDF arm participants maintaining viral suppression to 96 weeks. The excellent efficacy observed here matches that seen in adults[9], and is the reason that TDF is the “recommended” nucleoside component of cART in the US Department of Health and Human Services (DHHS) guidelines for antiretroviral therapy of adults[10].

In this study, efavirenz was used concurrently with TDF, compared to other pediatric studies in which lopinavir/ritonavir was most commonly used as a part of cART. Lopinavir/ritonavir slows tenofovir clearance which leads to increased tenofovir plasma concentrations[11] and resultant toxicity[12]. With efavirenz instead of lopinavir/ritonavir included as a part of cART, there was no evidence of increased renal glomerular or renal tubular toxicity in the TDF group over the 96 weeks of this study. However, bone toxicity persisted as a problem, with statistically significant decrease in spine BMD Z-score in the TDF group but not in the control group. The greatest declines in spine BMD were seen in the first 6 months of the study, with smaller changes in the later study months[7]. Since 6 months of viral suppression was required for study entry, this suggests a TDF-specific effect rather than just the decline in BMD observed with cART initiation[13].

The place of tenofovir disoproxil fumarate in pediatric cART

Given these data, what decisions can be made about the most appropriate use of TDF in treatment of children with HIV infection? Clearly TDF is only used as one component of cART, as part of a “backbone” with a nucleoside analogue reverse transcriptase inhibitor (NRTI) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or integrase strand transfer inhibitor (INSTI)[14]. The choice of the NRTI backbone needs to incorporate information on drug efficacy, toxicity, formulation, acceptability/ease of use, and potential for drug interactions. For children and youth, the relative impact of each of these factors may vary by age and country and be controlled by availability and cost[14–16].

Current US DHHS pediatric guidelines recommend TDF for initial use as the preferred agent only in persons in Tanner stage 4 or 5, recommend it as an alternative agent for those in Tanner stage 3, and provide the lowest level of recommendation (“use in special circumstances”) for those in Tanner stage 1 or 2; TDF use is not recommended for children age <2 years[14] (Table). World Health Organization (WHO) guidelines recommend TDF as the preferred regimen for adults and children age ≥10 years and body weight ≥35 kg, recommend it as an alternative (to the preferred agent abacavir) for children ages 3 to 10 years and body weight <35 kg, and do not recommend TDF use for children age <3 years. [15]. Paediatric European Network for the Treatment of AIDS (PENTA) guidelines recommend TDF as the preferred starting NRTI for children age >12 years with viral load

>100,000 copies/mL (but recommend abacavir as the preferred NRTI for children age >12 years with viral load <100,000 copies/mL), recommend TDF as an alternative NRTI component of cART for ages 3 to 12 years, and do not recommend its use for children age < 3 years[16]

Compared to stavudine, zidovudine, and didanosine, TDF has less mitochondrial toxicity and so confers less metabolic damage[7], making TDF preferable to those NRTIs. Abacavir does not have the bone and renal toxicities of TDF, an important consideration when choosing a drug that will be used for many years in successful cART in children. TDF should not be used with didanosine because of increased didanosine toxicity[2]. Both abacavir and tenofovir select for the K65R mutation, and while safe, that combination is not commonly used. TDF is most commonly paired with lamivudine or emtricitabine to form the NRTI component of cART, a combination that improves the activity of both drugs even in the setting of partial drug resistance[2].

In adults and older adolescents, TDF and abacavir can both be used once daily and readily available fixed dose combinations (FDCs) allow low pill burden for many drug combinations. TDF plus emtricitabine was shown to be more potent than abacavir plus lamivudine when combined with efavirenz or ritonavir-boosted atazanavir in adults with baseline HIV-1 RNA concentration >100,000 copies/mL [17], data that have influenced the PENTA guideline recommendations[16]. However, this difference in efficacy between TDF and abacavir is not found when combined with an INSTI, and now either TDF- or abacavir-based combinations are recommended with equal strength for initial cART when combined with a second NRTI and an INSTI[10, 18]. This recommendation may be applicable for children age 12 years and older and weighing at least 35 kg (for elvitegravir, which is coformulated with TDF, emtricitabine and cobicistat) or 40 kg (for dolutegravir, which is coformulated with abacavir and lamivudine). Given equal efficacy of TDF and abacavir when combined with an INSTI, the favorable toxicity profile of abacavir compared to TDF perhaps favors the abacavir-lamivudine-dolutegravir regimen in children >40 kg. However, for smaller children or in circumstances where insurance will not pay for the abacavir-lamivudine-dolutegravir combination, the TDF-containing regimen would be favored.

For use in children who cannot swallow pills, the abacavir liquid formulation may be more palatable and easier to use than the TDF taste masked granules, but a comparison study is lacking. Abacavir is FDA-approved for use in children as young as age 3 months, while TDF is only FDA-approved to age 2 years. In the US, TDF is co-formulated with emtricitabine and can be used in children with body weight ≥ 35 kg, and triple combinations with efavirenz or rilpivirine are also available, but only for children with body weight >40 kg. Co-formulated abacavir plus lamivudine can be combined with a third ARV in children with body weight of at least 30 kg. In many countries abacavir is coformulated with lamivudine in formulations available for younger children [15], but TDF is not available in such “child-friendly” FDCs[2]. In these younger children, US, PENTA, and World Health Organization guidelines all favor abacavir over TDF[14–16], with the recommendation in the US to avoid TDF until patients are in Tanner stage 4 or 5.

TDF is a highly potent antiretroviral with an excellent record of safe and effective use worldwide. Its broader use in pediatrics is constrained by the lack of available coformulations for young children, and concerns about long term bone and renal toxicities. While the renal toxicities are relatively rare they can occur late in therapy; optimal clinical and laboratory monitoring recommendations are not well established, especially in resource limited settings. The evidence for decreased BMD with TDF is well established, although there are conflicting reports on the magnitude of this toxicity. The clinical consequences of this BMD decrease are uncertain. Only long term surveillance studies of children and adolescents treated with TDF will answer this question. With the ongoing Gilead program for development of tenofovir alafenamide (TAF)[19], the excellent efficacy of the intracellular drug can be maintained while the toxicities are limited because of the lower plasma tenofovir concentrations seen with TAF compared to TDF[20]. Studies of TAF are currently open for adolescents (<http://www.clinicaltrials.gov/ct2/show/NCT02276612>), and will recruit for children as young as age 6 years (<http://www.clinicaltrials.gov/ct2/show/NCT02285114>). We can hope for rapid pediatric development of TAF, with a focus on FDC formulations appropriate for younger patients, to further expand the safety and efficacy of regimens available for antiretroviral therapy of children.

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Table 1

Place of Tenofovir Disoproxil Fumarate as Preferred or Alternative First-Line Antiretroviral Therapy for Infants, Children, Adolescents and Adults: Comparison of US DHHS, PENTA and WHO Guidelines

US DHHS Adult[10] and Pediatric[14]		PENTA[16]		WHO[15]		TDF recommendation
Age group	TDF recommendation	Age group	TDF recommendation	Age group	TDF recommendation	
Adults[10]	preferred	-	-	Adults		preferred
>12 years and Tanner stage 4–5	preferred	>12 years	preferred [/] alternative	10 to 19 years and body weight ≥ 35 kg		preferred
12 years and Tanner stage 3	alternative					
6 years or Tanner stage 1–2	special circumstances	6 to 12 years	alternative	3 years to <10 years or older age but body weight <35 kg		alternative
2 years to <6 years	special circumstances	3 to 6 years	alternative			
<2 years	not recommended	<3 years	not recommended			
				< 3 years		not recommended

[/] PENTA guidelines state “TDF/FTC is preferred [to ABC/3TC] in older children with viral load >100,000 copies/mL. Some clinicians would advocate deferring the use of TDF until after puberty.”

Key to Acronyms: PENTA = Paediatric European Network for the Treatment of AIDS; TDF = tenofovir disoproxil fumarate; US DHHS = United States Department of Health and Human Services; WHO = World Health Organization