

# Safety, tolerability, and clinical responses to tenofovir DF in combination with other antiretrovirals in heavily treatment-experienced HIV-infected children: Data through 48 weeks

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## ABSTRACT

Tenofovir DF (TDF) is a nucleoside analog HIV reverse transcriptase (RT) inhibitor approved for treatment of adults. We report safety and clinical responses through 48 weeks from a pediatric phase 1 study of TDF combined with other antiretrovirals (ARVs). **Methods:** 19 subjects had a median age (range) of 11.9 years (6.2-16.2). One subject was removed from the study prior to TDF dosing secondary to elevated transaminases. For the remaining 18 subjects, TDF was given alone for 6 days followed by the addition of optimized ARV background regimens. Patients were monitored by HIV RNA RT-PCR, flow cytometry, and chemistry and hematologic studies; monitoring for bone toxicity included measurement of lumbar spine bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA). **Results:** Subjects had extensive treatment experience: median (range) duration of prior ARV therapy was 9.7 years (4.8-13.5). Baseline resistance testing showed median (range) of 7 (2-8) major *rtR* mutations and 8 (1-10) major protease mutations. At baseline, median (range) CD4+ T cell count was 206 cells/mm<sup>3</sup> (0-766); median (range) log<sub>10</sub> HIV RNA was 5.4 (4.1-5.9). The only grade 3 or higher toxicities possibly or probably related to tenofovir DF were grade 3 elevated transaminases in 3 subjects (2 during the tenofovir DF monotherapy phase and 1 at week 18) and grade 3 BMD decreases in two subjects at 48 weeks. At week 24, the median (range) decrease in BMD Z-score was -0.38 (-1.2 to 0.52); 10 subjects had decreases in BMD from baseline. 7 of whom were virologic responders (decreased log<sub>10</sub> HIV RNA from -1.57 to -4.0). At week 48, the median (range) decrease in BMD Z-score from baseline was -0.31 (-2.9 to 0.21); 5 subjects had decreases in BMD from baseline, and all 5 had virologic responses (decreased log<sub>10</sub> HIV RNA from -2.15 to -4.0). Regimens were otherwise well-tolerated. At week 24, median (range) increase in CD4+ T cell count was 58 cells/mm<sup>3</sup> (-64 to 589); median (range) decrease in log<sub>10</sub> HIV RNA was -0.53 (-4.0 to 0.51). HIV RNA was <50 copies/ml in 4 children (<400 copies/ml in 6 children). At week 48, median (range) increase in CD4+ T cell count was 4 cells/mm<sup>3</sup> (-274 to 768); median (range) decrease in log<sub>10</sub> HIV RNA was -1.52 (-4.0 to 0.52). HIV RNA was <50 copies/ml in 4 children (<400 copies/ml in 6 children). **Conclusions:** TDF-containing combination antiretroviral therapy is virologically active for at least 48 weeks in heavily treatment-experienced children, but can be associated with decreased BMD. Further efficacy, toxicity, and tolerability studies are ongoing.

## INTRODUCTION

### Tenofovir disoproxil fumarate (TDF)

- Orally available prodrug of tenofovir, a nucleoside reverse transcriptase (RT) inhibitor, approved for adults in October 2001
- As potent as ritonavir, based upon nearly identical initial rates of viral load decline in treatment-naïve, HIV-infected adults (1)
- Addition to stable background antiretroviral regimen resulted in a durable viral load decrease of ~ 0.6 log<sub>10</sub> copies/ml in ART-experienced HIV-infected adults (2, 3)
- Retains activity against most HIV resistant to other RT inhibitors (4, 5)
- K65R mutation in RT associated with reduced susceptibility to TDF, but emerges only rarely *in vivo* (2, 4, 6)

### Pharmacokinetic studies (PK)

- Previously performed in both HIV-infected adults and children (7, 8). Latter report – data from current study
- After the first dose, tenofovir exposure over 30% lower in the children compared to that seen in HIV-infected adults
- Renal clearance in children approximately 1.5-fold higher
- At steady-state, tenofovir exposure approximately 13% lower in children but approached that seen in HIV-infected adults

### Objectives

- Primary objective: PK and safety of TDF in HIV-infected children
- Study also designed to provide potentially effective therapy for heavily-treatment experienced HIV-infected children with multidrug resistant virus

We now present data on the immunologic, virologic, and clinical effects of TDF administered to HIV-infected children alone and in combination with optimized background regimens, through 48 weeks.

## METHODS

- Single dose of TDF followed by 48 hours PK and 6 days of TDF monotherapy
- Addition of optimized HAART (based upon viral resistance testing and treatment history) on day 7
- Clinical and laboratory monitoring during first 9 days, and at weeks 4, 8, 12, 16, 24, 36, and 48
- Monitoring for bone toxicity: lumbar spine bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA) and measurements of bone resorption and formation markers at baseline and weeks 24 and 48

- Toxicity grading: The National Cancer Institute's Common Toxicity Criteria Version 2.0

## RESULTS

### Subject characteristics (Table 1)

- Extensive treatment experience
- Nine with history of treatment with lopinavir/ritonavir
- Sixteen with history of treatment with nevirapine or efavirenz
- No RT genotype with K65R at baseline
- Viral phenotypes demonstrated susceptibility to TDF except for 2 subjects with the *69* insertion complex, which has been shown previously to confer resistance to tenofovir (9)

TABLE 1. Baseline characteristics of the 18 subjects who received at least one dose of TDF.

Female-no. (%)	7 (39)
Race or ethnic group-no. (%)	
Non-Hispanic white	6 (33.3)
Non-Hispanic black	10 (55.5)
Hispanic (all races)	1 (5.5)
Other	1 (5.5)
Maternal transmission - no. (%)	18 (100)
CDC class- no. (%)	
Class A3	1 (5.5)
Class B2	1 (5.5)
Class B3	5 (28)
Class C2	2 (11)
Class C3	9 (50)
Age (years) (Mean ± SD)	12 ± 2.5
Median (range) prior ARVs	10 (4-13)
Median (range) prior ARV Rx (years)	9.7 (4.8-13.5)
Weight - z score (Mean ± SD)	-0.59 ± 1.46
Median (range) CD4 count (cells/mm <sup>3</sup> )	206 (0-766)
Median (range) log <sub>10</sub> HIV RNA	5.4 (4.1-5.9)
Median (range) major <i>rtR</i> mutations <sup>a</sup>	7 (3-9)
Median (range) major protease mutations <sup>b</sup>	8 (1-10)

<sup>a</sup> mutations at RT codons 41, 44, 62, 65, 67, 69, 70, 74, 75, 77, 115, 116, 118, 151, 184, 210, 215, 219  
<sup>b</sup> mutations at protease codons 10, 20, 24, 30, 32, 33, 46, 47, 50, 53, 54, 63, 71, 73, 82, 84, 90

### Adverse event profile

The regimens were generally well tolerated. The grade 3 or higher adverse events possibly or probably related to ARVs or requiring discontinuation of ARVs are shown in Table 3.

At baseline, the median lumbar spine BMD Z-score was -1.18. At week 24, the median (range) decrease in BMD Z-score was -0.38 (-1.2 to 0.52); 10 subjects had decreases in BMD from baseline, 7 of whom were virologic responders (decreased log<sub>10</sub> HIV RNA from -1.57 to -4.0). At week 48, the median (range) decrease in BMD Z-score from baseline was -0.31 (-2.9 to 0.21); 5 subjects had decreases in BMD from baseline, and all 5 had virologic responses (decreased log<sub>10</sub> HIV RNA from -2.15 to -4.0). Analysis of bone biomarker data suggests that the impaired bone mineral acquisition associated with TDF therapy was due to increased bone resorption (data not shown).

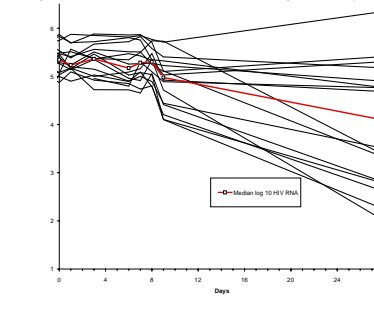
Table 3. Grade 3 or higher adverse events possibly or probably related to ARVs or requiring discontinuation of ARVs

Toxicity	Grade	Study Timepoint	TDF Action	Comment
Elevated transaminases	3	TDF monotherapy	Discontinued	Probably related to TDF
Elevated transaminases	3	TDF monotherapy	Discontinued	Possibly related to TDF
Confusion	2	Week 2	No change	Resolved with discontinuation of EFV
Rash	3	Week 2	No change	Possibly related to EFV or viral illness. Resolved without discontinuation of EFV
Hematuria	2	Week 12	Regimen interrupted	Resolved with discontinuation of IDV
Anemia (2 episodes)	3	After week 16	No change	Resolved with substitution of ZDV with d4T
Elevated transaminases	3	Week 18	Discontinued	Had grade 4 elevation probably related to oral contraceptives after TDF discontinuation
Intracranial hemorrhage	5	Week 34	Death	Unrelated to TDF
Disease progression	N/A	Week 43	Discontinued	Decrease in CD4 cell count
BMD decrease	3	Week 48	Discontinued	Possibly related to TDF
BMD decrease	3	Week 48	Discontinued	Possibly related to TDF

## Virologic and immunologic responses

- Figures 1 & 2. Viral load response during 6 days of TDF monotherapy not statistically significant (p=0.12, Wilcoxon signed rank test)

Figure 1. Individual and median viral load curves through initial 28 days.



child with EFV discontinuation

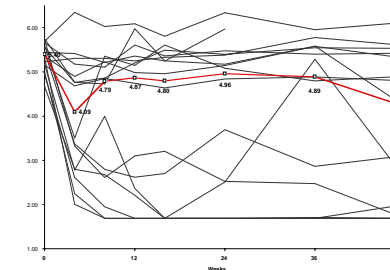


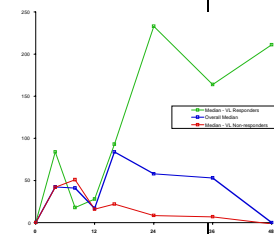
Figure 3. Change in CD4 count through 48 weeks for whole group and subsets of virologic responders and non-responders.

- Figure 3. Week 24 median (range) increase in CD4+ T cell count: 58 cells/mm<sup>3</sup> (-64 to 589)
- Week 48 median (range) increase in CD4+ T cell count: 0 cells/mm<sup>3</sup> (-274 to 768)

- Median (range) 4 (3-6) ARVs (Table 2) added to TDF on day 7
- Dramatic and sustained viral load decline in 7 of 16 who received TDF with HAART, evident by day 9

Figure 2. Individual and median viral load curves through 48 weeks.

- Viral load rebounded in 8<sup>th</sup>
- Viral load < 50 copies/ml in 4 subjects and < 400 copies/ml in 6 subjects at both 24 and 48 weeks
- One subject's resistance assay revealed the development of K65R and other RT mutations (V75I and F77L)
- Otherwise, lack of virologic response not associated with the development of significant RT mutations.



- Week 48 median increase in CD4+ T cell count among virologic responders (n=7): 211 cells/mm<sup>3</sup> and non-responders (n=8): -1.5 cells/mm<sup>3</sup>

Analysis to determine differences between the virologic responders versus the non-responders was limited by the small sample size, but several interesting trends were noted (Table 3). In view of the number of comparisons performed, we are requiring  $p < 0.01$  to declare a result to be significant while  $0.01 < p < 0.05$  would indicate strong trends. TDF exposure, as measured by area under the curve, exhibited a strong trend for being higher after the first dose ( $p = 0.0164$ , exact Wilcoxon rank-sum test) and at week 4 ( $p = 0.031$ , exact Wilcoxon rank-sum test) in the 7 virologic responders versus the 9 non-responders. Baseline BMD Z-score also exhibited a strong trend for being higher in the group of virologic responders ( $p = 0.012$ , exact Wilcoxon rank-sum test). The following observations lacked statistical support but may be worthy of evaluation in larger studies: virologic responders had less prior treatment, higher median weight Z-score, higher median CD4 count, less genotypic resistance, and were more likely to be treated with efavirenz.

TABLE 4. Comparison of virologic responders versus non-responders	Responders (n=7)	Non-responders (n=9)	P value
Median (range) number of prior ARTs	9 (4-13)	12 (8-13)	0.063
BL weight Z-score	-0.784	-0.961	0.14
BL BMD Z-score	-0.427	-1.467	0.012
BL height Z-score	-0.354	-1.649	0.25
Median (range) age (years)	10.4 (8.3-16.2)	13.2 (10.7-14.6)	0.24
Median (range) BL log10 HIV RNA	5.31 (4.61-5.69)	5.46 (4.6-6.44)	0.47
Median (range) BL CD 4 count	269 (2-605)	59 (0-649)	0.20
Median (range) major nRTI mutations	7 (4-8)	3 (3-9)	0.17
Median (range) major protease mutations	7 (5-8)	8 (1-10)	0.08
Presence of 69 insertion	0/7	2/9	0.48
Median (range) TDF dose (mg/m <sup>2</sup> )	208 (161-254)	207 (174-256)	1.00
Median (range) single dose TDF AUC	3290 (1910-3630)	1950 (1060-2670)	0.0164
Median (range) steady state TDF AUC	3800 (2020-5590)	2510 (1800-4160)	0.031
Study regimen included EFV	3/7	0/9*	0.0625
Study regimen included TDF	4/7	7/9	0.60
Study regimen included LPV	0/7	7/9	0.48

\* One subject received EFV for a short time but it was discontinued secondary to CNS toxicity.

## CONCLUSIONS

- Phase I studies of new ARVs in children conducted while administering an optimized background antiretroviral regimen can yield the necessary safety and dosing information while also providing potentially efficacious salvage treatment for heavily treatment-experienced HIV-infected children.
- Tenofovir DF-containing HAART was well tolerated.
- Tenofovir DF-containing HAART was associated with decreased BMD, which was more pronounced in the 7 virologic responders.
- Tenofovir DF-containing HAART produced durable suppression of HIV replication in 7 of 16 heavily-treatment experienced HIV-infected children with multidrug resistant virus.
- Development of RT mutation K65R was seen in only one subject and was associated with a lack of virologic response.
- Baseline BMD Z-score and TDF exposure exhibited a strong trend for being higher in the 7 virologic responders versus the 9 non-responders.

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