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Bone and Renal Safety at 96 weeks of TDF-containing in HIV-infected Thai children

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INTRODUCTION

- Tenofovir (TDF) is currently recommended in first- and second-line ART regimens for children above 2 years of age[1,2].
- Renal dysfunction and bone demineralization are the most concerning toxicity of TDF.
- Limited studies in HIV-infected children reported a decrease in BMD particularly at 24-48 weeks after commencement of a TDF-based regimen in children[3,4]. However, its clinical significance is not well understood.
- HIV-infected children receiving TDF have twice the risk of renal impairment compared to non-TDF containing regimen[5]. A decrease in glomerular function and proximal tubular dysfunction were identified in majority of children receiving TDF in a Spainish cohort[6]. In addition, renal dysfunction relates to higher TDF plasma concentrations[7].
- This study was aimed at determining the impact of TDF on bone mineral density (BMD) and renal function among HIV-infected adolescents over 96 weeks.

OBJECTIVES

- To assess the effect of TDF on renal function and bone mineral density in HIV-infected children receiving TDF-containing regimen.
- To describe the relationship between TDF mid-dose concentration and renal toxicity.

METHODS

- HIV-infected children on TDF-containing regimens were recruited for efficacy and safety assessments over 96 weeks.
- Renal toxicity criteria were based on glomerular filtration rate (GFR), spot urine protein, glucose, calcium and uric acid, tubular reabsorption of phosphate (TRP) and beta-2 microglobulin levels (Table 1).
- BMD was assessed yearly using dual-energy x-ray absorptiometry (DEXA).
- Cross-sectional renal toxicity assessments and mid-dose plasma TDF concentrations analysis at 10-14 hours after dosing were performed as a part of sub-study.
- Regression models were used to assess the overall change of renal and bone parameters. Geometric means for mid-dose TDF concentration are presented with coefficient of variation percentage (%CV).

Table 1: Criteria determine renal dysfunction

Glomerular dysfunction criteria
- Glomerular filtration rate (GFR) <90 mL/min/1.73 m^2

Proximal renal tubular dysfunction criteria
- Spot urine protein >2+
- Spot urine sugar ≥1+
- Urine calcium ≥0.2
- Urine uric acid ≥1.0
- Tubular reabsorption of phosphate < 80%
- Beta-2 microglobulin levels >300 mcg/L

RESULTS

- Sixty-two HIV-infected children were on TDF-containing regimens; 35 children had CD4, HIV-RNA, BMD and renal function assessments over 96 weeks (Table 2).
- Fifty of these 62 children had cross-sectional renal toxicity assessments and mid-dose plasma TDF concentrations measured 10-14 hours after dosing.

Table 2: Baseline demographics of 35 children with follow-up to 96 weeks

Characteristics	Values
Median (IQR) age, years	15.7 (14.1-16.9)
Male, n (%)	11 (31%)
Median (IQR) body weight, kgs	42.5 (38.4-47.4)
Tanner stage, n (%)	
Stage 3	4 (11.43)
Stage 4	7 (20.00)
Stage 5	24 (68.57)
Median (IQR) duration on ARV, years	7 (3-10)
Median (IQR) duration on TDF, months	5 (2-15)
Median (IQR) TDF dosage, mg/m^2	217.4 (205.5-234.4)
Antiretroviral (ARV) regimen, n (%)	
TDF plus NVP or EFV	11 (31)
TDF plus LPV/r or ATV/r	19 (54)
TDF plus DRV/r	4 (11)

Efficacy (Table 3)
- The majority (83%) remained virologically suppressed and 9% developed virological failure over 96 weeks.

Renal Safety
- Over 96 weeks, 20 (57%) developed ≥1 criteria for renal toxicity over 96 weeks. including proteinuria ≥2+ (6%), glucosuria ≥1+ (9%), hypercalciuria (3%), hyperuricosuria (6%) and urine beta-2 microglobulin >300 (24%) mcg/L. None had clinically significant renal toxicity. Although none of these symptoms of proximal renal tubular dysfunction were clinically significant, glomerular function decreased significantly from baseline to week 96 (P<0.001; Table 3).
- In a multivariate regression model, protease inhibitor (PI) use (p=0.02), female sex (p <0.01) and longer duration on TDF (p <0.01) were associated with GFR reduction (Table 4).

Table 3: Efficacy and renal function results at baseline and week 96

	Baseline	Week 96
Median (IQR) CD4, cells/mm^3	694 (558-1123)	667 (366-1199)
Median (IQR) CD4, percentage	28 (23-35)	18 (21-38)
%HIV RNA <50 copies/ml	92% (n=32)	83% (n=29)
Median (IQR) Serum creatinine, mg/dl*	0.6 (0.5-0.7)	0.68 (0.62-0.74)
Median (IQR) GFR, mL/min/1.73 m^2*	101.8 (90.2-120.1)	91.9 (87.7-104.4)

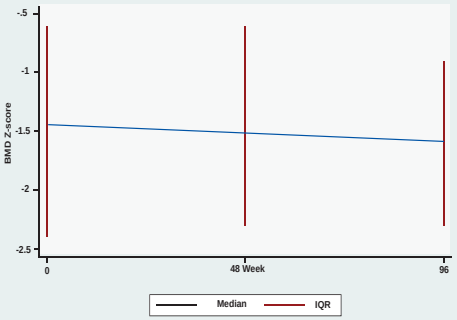
* p value <0.05

Table 4: Regression analysis of risk factors for GFR reduction over 96 weeks

	Univariate			Multivariate		
	Coef	95%CI	p-value	Coef	95%CI	p-value
Age	0.63	(-0.66,1.92)	0.340			
Gender: female	6.26	(0.29,12.23)	**0.040**	7.77	(2.26,13.29)	**0.006**
BSA	1.21	(-15.39,17.80)	0.887			
Current ARV regimen			**0.025**			**0.002**
PI-based	-5.89	(-11.03,-0.74)		-5.71	(-10.51,-0.91)	
NNRTI-based	1	1				
Duration on TDF	-4.11	(-7.19,-1.02)	**0.009**	-4.42	(-7.35,-1.48)	**0.003**
Detectable HIV-RNA (>50 copies/ml)	3.96	(-1.86,9.79)	0.182			
CD4%	-0.12	(-0.47,0.24)	0.518			

Bone safety
- Half (17/35) had BMD z-score >-1.5 at baseline. The median BMD z-score decreased from -1.5 (-2.4 to -0.6) to -1.6 (-2.3 to -0.9) (p=0.13) (Figure 1).

Figure 1: Change in BMD Z-score at baseline, 48 and 96 weeks of follow-up



TDF plasma concentration vs. renal dysfunction
- Among 50 children who had mid-dose TDF concentrations available, median duration of TDF use was 16 (8-24) months and TDF dose was 219 (203-235) mg/m^2. Cross-sectional evaluation revealed 18 (36%) children with ≥1 renal toxicity criterion. The geometric mean (% CV) mid-dose TDF concentration among children with renal toxicity (108.8 [42%] ng/mL) was significantly higher than those without renal toxicity (87.7 [29%] ng/mL; p=0.03) (Table 5).

Table 5: Geometric means mid-dose (C10-14) TDF plasma concentrations with % coefficient of variation (%CV)

Group	N	Geometric means for TDF mid-dose (C12) plasma concentration (ng/mL)		
		Mean	GSD	%CV
Children with normal renal tubular function	32	87.7	1.33	29.25
Children with at least 1 criterion of proximal renal tubular dysfunction	18	108.8	1.50	42.15
Total	50	94.8	1.41	35.64

GSD: geometric standard deviation; %CV: % coefficient of variation

DISCUSSION

- Similar to previous reports[3-7], HIV-infected children receiving TDF developed renal impairment and had a decrease in BMD.
- About one-third of children had at least one abnormal parameter of proximal renal tubular function and glomerular function decreased significantly over 96 weeks.
- Longer duration of TDF treatment, concomitant PI use and higher mid-dose TDF concentrations were associated with renal abnormalities.
- However, no one developed Fanconi syndrome or bone fractures. The long-term clinical significance of these laboratory abnormalities needs to be determined.

CONCLUSIONS

HIV-infected children receiving TDF-containing regimen are at risk of renal dysfunction and developing bone demineralization. Long-term monitoring of renal and bone toxicity is suggested in children receiving TDF-containing regimen.

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