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24-week Safety of Tenofovir When Administered According to Weight Band Dosing in HIV-infected Children ≥ 15 Kg as Part of a Once-daily HAART Regimen

Linda Aurpibul, M.D.
Research institute for health sciences,
Chiang Mai University, Chiang Mai, Thailand 50200.
E-mail: lindaa@rihes-cmu.org,
Tel: +66 53 945055 Fax: +66 53 894138

Linda Aurpibul MD.[1], Thition Narkbunnam MD.[2], Virat Sirisanthana MD.[1], Orasri Wittawatmongkol MD.[2], Wanatpreeya Phongsamart MD.[2], Tavitiya Sudjaritruk MD. [3], Tim R Cressey PhD. [4,5,6], Kulkanya Chokephaibulkit MD.[2]

[1]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand,[2]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, [4]Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand,[5]Harvard School of Public Health, Boston, MA,[6]Institut de Recherche pour le Développement (IRD), Marseille, France

Background

- ❖ Once-daily dosing is desirable for young children and adolescents to help maintain drug adherence.
- ❖ Tenofovir (TDF) is widely used as part of once-daily antiretroviral regimens. However, concerns have been raised about its effect on renal function and bone mineral density (BMD).
- ❖ Our objective was to evaluate the safety of TDF prescribed according to weight band dosing in treatment-experienced HIV-infected children.

Patients and Methods

- ❖ Phase II/III prospective, single arm, open label, multi-center study.
- ❖ HIV-infected children receiving a first line NNRTI-based regimen without tenofovir, aged between 3-18 years, weighing ≥15 kg, with virologic suppression were enrolled.
- ❖ At entry, the child's antiretroviral regimen was modified to tenofovir /lamivudine/efavirenz; TDF was prescribed according to weight band dosing (Table 1).
- ❖ A control group consisting of HIV-infected age-, gender-, and CD4- matched children receiving TDF-sparing regimens were also enrolled.
- ❖ Safety assessments were performed at entry and at week 24:
  - ☑ Urine analysis
  - ☑ Glomerular function: glomerular filtration rate (eGFR) was calculated using the Schwartz equation.
  - ☑ Tubular function: fractional excretion of calcium (FE_{Ca}) and phosphate (FE_P) were calculated. The cut-off values were set at 0.42 and 0.22 for ages < 6 years and ≥ 6 years, respectively. 24-hour urine collection was planned cases with high FE_{Ca} or FE_P to determine hypercalciuria.
  - ☑ Bone mineral density (BMD) was measured by Dual Energy Absorptiometry (DXA) at L2-L4 vertebrae; BMD z-score was calculated using age-matched normal Thai children references.
- ❖ Vitamin D level was measured in those with BMD z-score ≤ -1.5.

Table 1: Weight band dosing of tenofovir (PENTA2009)

Weight band (kg)	Total daily dose (mg)	Tenofovir (tab 300 mg)	Dose range (mg/kg)	Dose range (mg/m^2)
15-<22 kg	150	1/2	7.1-10.0	183-235
22-<33 kg	225	3/4	7.0-10.2	203-265
33-<44 kg	300	1	7.0-9.1	223-265
44 kg up	300	1	≤ 6.8	<220
Recommended dose 8 mg/kg (for age < 8years) or 210mg/m^2 (for age >8years)				
Acceptable range 90-125% is within 7-10 mg/kg or 189-263 mg/m^2				

Results

Eighty children were enrolled (40 per group); baseline characteristics were not different between the two groups

Efficacy

- ❖ The mean (SD) TDF dose prescribed was 8.1 (1.0) mg/kg (1.0) or 210 (30) mg/m^2
- ❖ During the 24-week follow-up, all remained clinically stable; 39 of 40 children in the TDF group remained

Table 2: Characteristics of study participants (n=80)

Characteristics	Total (n=80)	Study group (n=40)	Control group (n= 40)	*p*-value
Age, years (SD)	11.5(3.5)	11.7(3.5)	11.4(3.5)	0.785
Male gender (%)	35(44)	18(45)	17(43)	0.822
Body surface area, m^2 (SD)	1.13(0.26)	1.13(0.26)	1.13(0.26)	0.983
CD4 lymphocyte count prior to ART initiation, cells/mm^3 (SD)	617(798)	453(493)	785(1000)	0.067
HAART regimen prior to study enrollment				
Nevirapine-based	44(55)	23(58)	21(52)	
Efavirenz-based	25(31)	17(42)	8(20)	0.001
PI-based	11(14)	0(0)	11(28)	
Mean duration on HAART prior to study enrollment, years (SD)	7.0(3.0)	6.7(2.6)	7.4(3.3)	0.307
CD_4 lymphocyte count at the time of study entry, cells/mm^3 (SD)	911(462)	857(425)	947(516)	0.394
Number with HIV RNA level <400 copies/mL at study entry (%)	75(94)	38(95)	35(88)	0.055

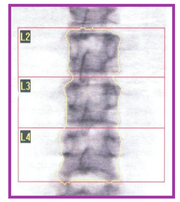
**2 participants in study group and 3 in the control groups had a plasma HIV RNA level > 400 copies/mL (between 96-635 copies/mL at entry)

Renal safety

- ❖ From baseline to week 24, there was no significant change in creatinine clearance, while there was an increase in fraction excretion of calcium in the TDF group (Table 3).
- ❖ There was no cases of hypocalcemia, hypophosphatemia, hypokalemia, hypouricemia, acidosis, proteinuria, or glucosuria

Table 3: Urine chemistry, proximal tubular function, and glomerular function

Variables	Study group			Control group			Compare between study and control group
	Baseline	week 24	*p*-value	Baseline	week 24	*p*-value	p-value
Urine creatinine (mg/dL)	104.81(70.54)	107.35(57.72)	0.816	101.89(74.66)	106.27(86.30)	0.795	0.948
Urine calcium (mg/dL)	5.01(5.13)	8.42(8.21)	0.015	5.86(5.68)	6.09(5.85)	0.806	0.147
Urine phosphate (mg/dL)	56.75(36.97)	53.86(29.00)	0.672	40.65(30.54)	41.76(35.60)	0.882	0.099
Urine calcium/creatinine ratio	0.06(0.05)	0.09(0.08)	0.011	0.06(0.05)	0.07(0.07)	0.444	0.240
Number of case with urine glucose positive	0	0	1.000	0	0	1.000	1.000
Fractional excretion of calcium (%)	0.26(0.23)	0.48(0.53)	0.019	0.32(0.26)	0.42(0.43)	0.094	0.621
Fractional excretion of phosphate (%)	5.91(2.63)	5.83(2.30)	0.829	4.84(2.56)	5.29(2.80)	0.377	0.340
Estimated glomerular filtration rate (mL/min/1.73m^2)	179(48)	168(54)	0.062	166(38)	156(29)	0.059	0.198
Data in mean (SD)							



Bone toxicity

- ❖ There was a significant decrease in mean BMD z-score among children in the TDF group from entry to week 24, but not in the control group (Table 4).
- ❖ Among children with normal baseline BMD, 3 in each group developed low BMD at week 24; all of them had normal vitamin D level (>20 ng/mL).

Table 4 Bone mineral density of children in study and control groups

Variables	Study group (n=39)			Control group (n=39)			Compared between study and control groups
	Baseline	week 24	p-value	Baseline	week 24	p-value	p-value
Mean BMD z-score (SD)	0.010(±1.311)	-0.681(±2.068)	0.032	-0.275(±1.280)	-0.111(±1.512)	0.107	0.168
Change in BMD z-score		-0.435 (0.813)			0.164 (0.621)		<0.001
Number of cases with z-score between <-1.5 to -2.0 (%)	3(8)	3(8)	1.000	5(13)	3(8)	0.455	1.000
Number of cases with z-score between <-2.0 to -2.5 (%)	0	2(5)	0.512	1(3)	3(8)	0.305	0.644
Number of cases with z-score between < -2.5 (%)	1(3)	2(5)	0.556	0	0	1	0.152

Children age <5 years old were excluded from analysis as there was no age-matched reference range

Discussion

- ❖ We demonstrate effect of TDF on renal tubular function (an increase In the fractional urine excretion of calcium), but not on glomerular function (no change in eGFR) which was in line with previous reported in adult and pediatric studies.[1-2] Although some pediatric studies reported no significant change in renal function.[3]
- ❖ A decrease in BMD was observed after 24 weeks of TDF-containing treatment which was in line with previous studies.[4-5] However, the study of Gafni et al.[4] reported no further decrease from week 24 to 48. There were some studies reported no significant change in BMD after longer (12-60 months) follow-up periods.[6-7]

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Conclusion

❖ TDF can be used safely as a part of once-daily antiretroviral regimen for children and adolescents; effects on renal function and BMD were observed after 24 weeks and needed long-term follow-up to see whether they become clinical significant.

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