

Exposure During Gestation to Highly Active Antiretroviral Treatment (HAART) Including Tenofovir does not Impair Bone Status and Metabolism in HIV-uninfected Children Born to HIV-infected Mothers.

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ABSTRACT

Background: Recent works demonstrated the applicability of Quantitative Ultrasound (QUS) in newborn, children and adolescents. Bone toxicity due to fetal exposure to TDF has been shown in animal models. Fetal risks associated to the use of TDF during pregnancy in HIV-infected women became an urgent priority. The aim of the study was to assess bone status and metabolism in seroreverter (SR) children in-uterus exposed to TDF.

Methods: This is a multicenter observational prospective cross-sectional study. We enrolled 51 SR children, in-uterus exposed to a Protease Inhibitor (PI)-based HAART regimen, including TDF in 27 cases (TDF+) and not including TDF in 24 cases (TDF-). Since bone formation occurs mostly in the middle and late pregnancy, a TDF exposure at least in the third trimester of pregnancy was the main inclusion criteria. Neonatal parameters and duration of HAART exposure were recorded; at enrollment anthropometric measurements, tibial speed of sound (SOS) by QUS, serum level of bone alkaline phosphatase (BAP) and C-terminal telopeptide of type I collagen (CTX) were assessed. SOS data were expressed as absolute values and z-scores. Comparisons between TDF+ and TDF- cases were made by Wilcoxon tests.

Results: TDF+ and TDF- cases were similar for mean gestational age (36.6 vs 37.2 weeks), mean birth weight (2694 vs 2701 g), mean birth length (46.7 vs 46.2 cm) and duration of HAART-exposure (mean exposure 27.1 vs 30.8; median exposure [range] 25[6-38] vs 34[20-38] weeks). At enrollment, they were also comparable for age (mean age 29.7 vs 36.5 months; median age [range] 23.2 [13-16.2] vs 35.4 [17.5-77.9]), mean weight (12.7 vs 13.9 Kg), mean height (88.9 vs 92.8 cm). Although absolute tibial SOS values were lower in TDF+ than in TDF- cases (3471 vs 3558 m/s; p=0.038), tibial SOS z-scores were similar in the two groups (0.6 vs 0.9; p=0.45).

Similarly, no differences between groups were detected in serum concentration of BAP (mean value 145.8 vs 139.1 U/l) and CTX (mean value 1.41 vs 1.57 ng/ml).

Conclusions: Our study showed that exposure to TDF during the second and third trimesters of gestation, when bone formation occurs, does not impair bone mass and bone metabolism in seroreverter children born to HIV-infected women.

INTRODUCTION

Quantitative Ultrasound (QUS) is a technique of recent introduction to assess bone health with the following characteristics: low costs, easiness of use in different skeletal regions, non-invasivity, absence of ionizing radiations, and applicability in children < 5 years.

The high clinical efficacy and the favorable resistant profile have led to a frequent TDF clinical use in adults and also in pregnant women. In a macaque model, perinatal exposure to TDF resulted in bone toxicity in some offspring. To our knowledge, fetal risks possibly associated with the use of TDF during pregnancy in HIV-infected women have not been described yet.

Aims of the present study were: **1)** to assess the tibial speed of sound (SOS) by QUS and its Z-score obtained from the comparison with normal values for age and gender provided by densitometer's software; **2)** to estimate bone metabolism markers; **3)** to compare tibial SOS and its Z-score, and bone metabolism markers in HIV-uninfected children, by maternal TDF use.

STUDY DESIGN

This was a multicenter observational prospective cross-sectional study.

We enrolled 51 HIV-uninfected children, aged from 13 to 76 months, born to HIV-infected mothers, exposed at least in the third trimester of pregnancy to **1)** a PI-based HAART regimen, including TDF and **2)** a PI-based HAART regimen not including TDF. HIV infection was excluded in all subjects according to Public Health Service recommendations. **TABLE 1** and **TABLE 2** show demographic and anthropometric data at birth and at enrollment.

METHODS

At birth and at enrollment patients underwent clinical and anthropometrical assessment. At enrollment tibial SOS was measured in all cases: SOS measurements were performed at half tibial length by QUS (Sunlight Omnisense 7000 p) and data were expressed as absolute values and Z-score. Concomitantly, blood samples from all of the children were assessed for bone alkaline phosphatase (BAP) concentrations [Metra™ BAP EIA kit, Quidel Corp., San Diego, CA]; C-terminal telopeptide of type I collagen (CTX) values [Serum CrossLaps® ELISA, Immunodiagnostic Systems Ltd, UK], Calcium, Phosphate and Albumin. Results are shown in **TABLE 3**.

Values are presented as median (range). Comparisons between groups have been performed by Chi Square test (nominal variables) and Wilcoxon test (continuous variables).

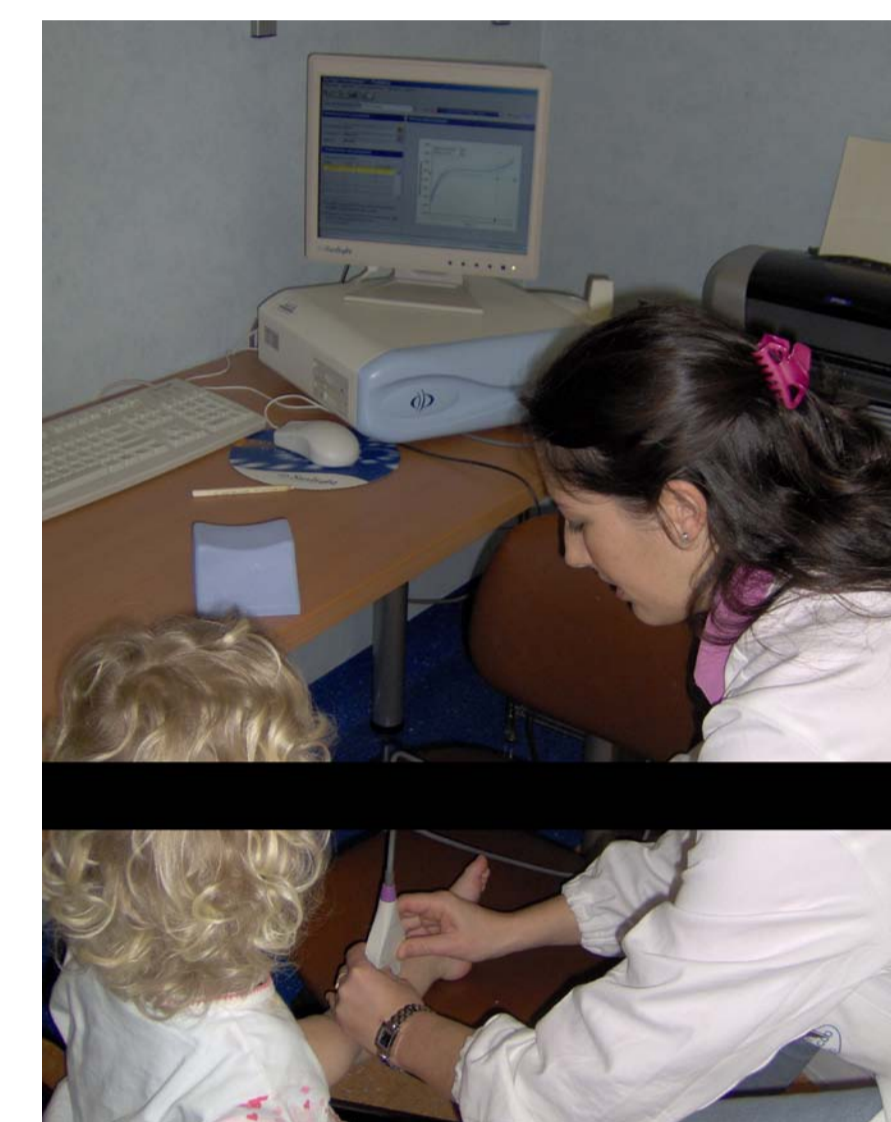


TABLE 1. HIV-uninfected infants demographics and anthropometrics at birth grouped by maternal HAART.

Variables	PI –based HAART with TDF	PI-based HAART without TDF	Paired analysis
NUMBER	27	24	
GENDER			
Male, n	18	13	P = 0.36
Female, n	9	11	
RACE			
White, n	19	22	P = 0.08
Black, n	6	1	
Hispanic, n	2	1	
DURATION OF IN-UTERO EXPOSURE TO HAART, weeks	25 (6 – 38)	34 (20 – 38)	P = 0.31
GESTATIONAL AGE, weeks	37 (34 – 38)	37 (34 – 39)	P = 0.07
WEIGHT, kg	2.8 (1.3 – 3.8)	2.7 (1.8 – 3.7)	P = 0.83
LENGTH, cm	47 (37 – 59)	46 (10 – 51.5)	P = 0.40
HEAD CIRCUMFERENCE, cm	33 (28 – 35)	33 (30 – 37.5)	P = 0.31

TABLE 2. HIV-uninfected children demographics and anthropometrics at enrollment grouped by maternal HAART.

Variables	PI –based HAART with TDF	PI-based HAART without TDF	Paired analysis
AGE, months	23.2 (13.0 – 76.2)	35.4 (17.5 – 77.9)	P = 0.15
WEIGHT, kg	12.1 (9.1 – 21.0)	13.2 (8.9 – 20.0)	P = 0.20
HEIGHT, cm	86.5 (76 – 109)	91.7 (77.5 – 111.0)	P = 0.17

RESULTS

At birth, cases exposed and not exposed to TDF were matched for gestational age, birth weight, birth length and duration of HAART-exposure. Both groups were also comparable for age, weight and height at enrollment.

SOS measurements

Children in-utero exposed to a PI-based HAART regimen with TDF showed a similar Z-score of tibial SOS than children in-utero exposed to a PI-based HAART regimen without TDF (**TABLE 3**), (**FIGURE 1**).

Biochemical markers of bone metabolism

Serum total calcium, phosphate and corrected calcium were similar in children in-utero exposed to a PI-based HAART with and without TDF (**TABLE 3**), (**FIGURE 2**).

The higher serum phosphate concentration observed in children in-utero exposed to a PI-based HAART with TDF is of little clinical significance, because only one value in the group was outside of the reference normal values.

TABLE 3. SOS-tibia values and blood samples results in HIV-uninfected children grouped by maternal HAART.

Variables	PI –based HAART with TDF	PI-based HAART without TDF	Paired analysis
SOS Tibia, Z-score	0.5 (-2.4 - 2.6)	0.85 (-2.1 - 4.1)	P = 0.45
Total Calcium, mg/dl	9.7 (4.9 - 10.9)	9.9 (4.8 - 10.8)	P = 0.92
Total Calcium			
Low	9	5	P=0.32
Normal	18	19	
Serum Phosphate, mg/dl	5.4 (3.4 - 6.7)	5.1 (4.2 - 5.9)	P = 0.048
Serum Phosphate			
Low	1	0	P = 0.35
Normal	26	24	
Corrected Calcium, mg/dl	9.7 (4.7 - 10.7)	9.9 (4.6 - 10.7)	P = 0.64
BAP, U/l	147.6 (82.8 - 215.8)	127.1 (94.2 - 222.4)	P = 0.35
CTX, ng/ml	1.40 (0.26 - -3.52)	1.25 (0.28 - 3.80)	P = 0.79

FIGURE 1. Z-score of SOS Tibia measurements collected in cases exposed and not exposed to TDF.

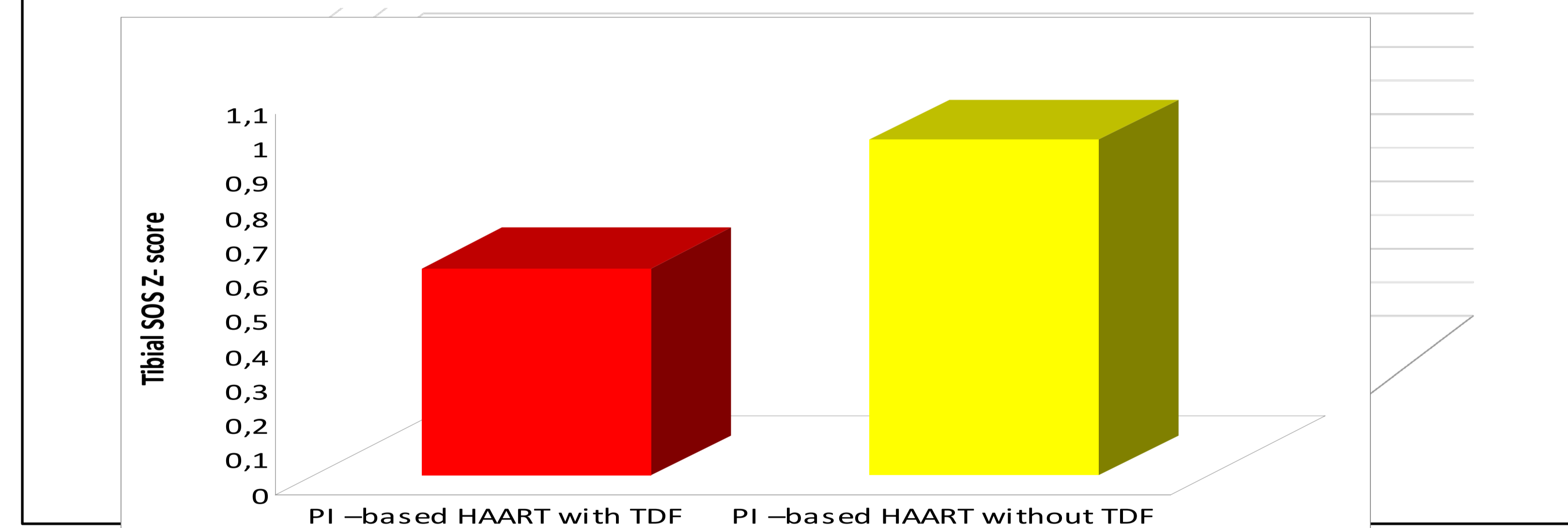
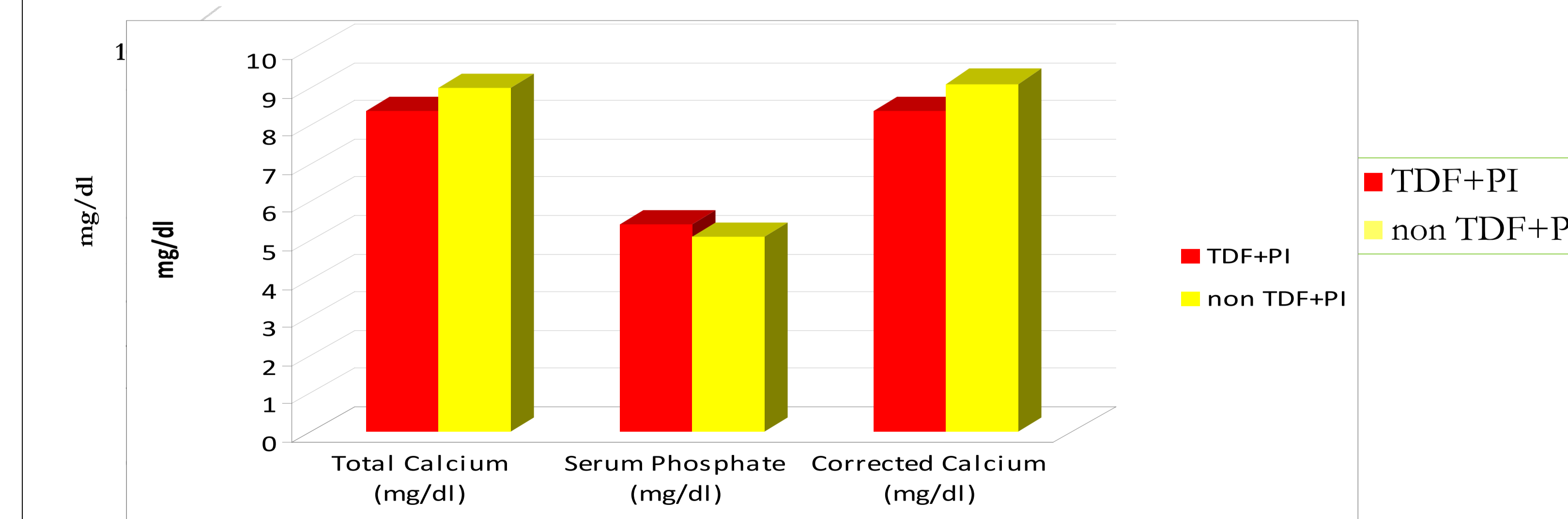


FIGURE 2. Comparison between serum total Calcium, Serum Phosphate and Corrected Calcium in cases exposed and not exposed to TDF.



CONCLUSION

Our study showed that exposure to a PI-based HAART to TDF during the second and third trimester of gestation, when bone formation occurs, does not impair bone mass and metabolism in HIV-uninfected children born to HIV-infected mothers.