

# Bone Mineral Density in Adolescents Infected with HIV Perinatally or in Early Childhood - Data from the NIH Intramural Program

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## ABSTRACT

**Background:** Altered bone health is a potential complication associated with HIV and ARVs. In 2 previous studies of tenofovir DF (TDF)-containing salvage therapy, we found low mean baseline bone mineral density (BMD) overall and absolute BMD declines of ~6% in 7 of 21 subjects. We designed this study to measure BMD in a larger cohort of stable ARV-experienced HIV-infected adolescents who acquired HIV in infancy or childhood that includes 6 of the 7 subjects in whom we previously documented BMD declines associated with TDF.

**Methods:** Subjects are enrolled in a prospective observational study that includes dual-energy x-ray absorptiometry (DXA) scans of the lumbar spine (LS). Baseline data and retrospective longitudinal data from 2 subjects are presented. Z-scores were calculated using appropriate standards. Laboratory measurements include viral load and vitamin D levels.

**Results:** From March 2007 to July 2008, 37 HIV+ subjects (34 perinatally-infected, 3 transfusion-acquired) enrolled. 51% were male, 59% non-black, mean (+/- SD) age 16 ± 3.4 years, mean (+/- SD) cumulative ARV exposure 13.9 ± 2.7 years. Mean (+/- SD) height Z-score, BMI Z-score, and LS BMD Z-score were -0.47 ± 1.3, -0.02 ± 1.1, and -0.43 ± 1.1. Mean (+/- SD) variability between repeated LS BMD measurements was 0.88 ± 0.7%. 51.4% had vitamin D insufficiency (25-OH D <30 ng/mL), 38% of the subjects were currently on TDF, and 46% had <50 HIV RNA copies/mL, but there were no significant associations between vitamin D status, current treatment with TDF, or VL with LS BMD. Data from 2 subjects who experienced BMD declines associated with TDF are shown in the graph in relation to the normal BMD for age. Both subjects first received TDF when they were pre-pubertal, had durable virologic responses, entered puberty before the age of 13 years (normal), and subsequently discontinued TDF for renal toxicity. Subject #1 then experienced a partial recovery resulting in absolute BMD 42% higher than his baseline with a Z-score 0.99 lower. Subject #2 experienced full recovery while still on TDF, resulting in absolute BMD 51% higher than baseline and the same Z-score.

**Conclusions:** BMD was not affected by current TDF therapy in this cohort. BMD improved over time in 2 subjects with a history of BMD declines associated with TDF. The impact of TDF-containing HAART on BMD in HIV-infected children appears to diminish as patients progress through puberty.

## Introduction

- Decreased bone mineral density (BMD) is an emerging metabolic complication in HIV-infected adults and children and may impact the quality of life of HIV-infected children as they survive well into adulthood<sup>1-4</sup>.
- Dual energy X-ray absorptiometry (DXA) measurements of BMD are used to define osteoporosis in adults. Osteopenia and osteoporosis are common in HIV-infected adults, occurring in 23%-46% of patients, and HIV-infected adults have a higher prevalence of fractures than uninfected patients<sup>5-7</sup>.
- In children, osteoporosis is a clinical diagnosis, but DXA is the preferred method for assessing BMD<sup>8</sup>.
- Data on BMD in HIV-infected children and youth are limited but demonstrate a lower BMD than normal<sup>9, 10</sup>.
- The decreased BMD in HIV-infected patients is multifactorial, related to HIV infection, its treatment, comorbidities and factors unrelated to HIV<sup>2, 3, 5, 10, 11</sup>.
- Tenofovir DF (TDF) has been associated with mild BMD loss in HIV-infected adults<sup>9</sup> and severe BMD loss in some<sup>2, 12, 13</sup> but not all<sup>14</sup> HIV-infected children.
- Vitamin D status may have an impact on bone health in this population<sup>15</sup>.

## Methods

- Subjects were evaluated through the Intramural Program of the NIH between March 2007 and July 2008 in a study investigating long-term complications of HIV.
- Evaluations included DXA (Hologic, QDR 4500A) scans of the lumbar spine (LS) and laboratory measurements, including viral load and vitamin D levels.
- 2 DXA scans were performed on the same day, and percent variance between the 2 BMD measurements were calculated.
- Z-scores were calculated using a standard formula and reference population data from Hologic, Inc. for both children and adults.
- Z-score =  $\frac{BMD_{patient} - BMD_{mean\ of\ reference\ population\ same\ age\ and\ sex\ as\ patient}}{Standard\ deviation\ of\ reference\ population\ same\ age\ and\ sex\ as\ patient}$
- Retrospective longitudinal data from 2 subjects who had low mean BMD overall and absolute BMD declines in our previous studies were included.

## Results

TABLE 1. General and HIV Disease Characteristics (N=37)

Age – years (mean +/- SD)	18 +/- 3.42
Male sex – no. (%)	19 (51%)
Race or ethnic group – no. (%)	0
Non-black	22 (59%)
Black	15 (41%)
Perinatally-acquired HIV – no. (%)	34 (92%)
Transfusion-acquired HIV – no. (%)	3 (8%)
HIV-1 RNA – copies/mL (mean +/- SD)	52,593 +/- 156,274
<50 copies/mL – no. (%)	17 (46%)
CD4+ lymphocyte count – cells/mm <sup>3</sup> (mean +/- SD)	662 +/- 426
Cumulative ARV exposure – years (mean +/- SD)	13.9 +/- 2.7
Current TDF exposure – no. (%)	14 (38%)

TABLE 2. Growth and Bone Characteristics

Height Z-Score (mean +/- SD)	-0.47 +/- 1.27
Weight Z-Score (mean +/- SD)	-0.22 +/- 1.16
BMI Z-Score (mean +/- SD)	-0.02 +/- 1.08
Vitamin D (25-OH D) – ng/mL (mean +/- SD)	28.0 +/- 11.8
Vitamin D insufficient (<30 ng/mL) – no. (%)	18 (51.4%)
LS BMD Z-Score (mean +/- SD)	-0.43 +/- 1.06
LS BMD Percentage Variance (mean +/- SD)	0.88 +/- 0.69%

FIGURE 1. Longitudinal BMD changes associated with TDF for 2 adolescents

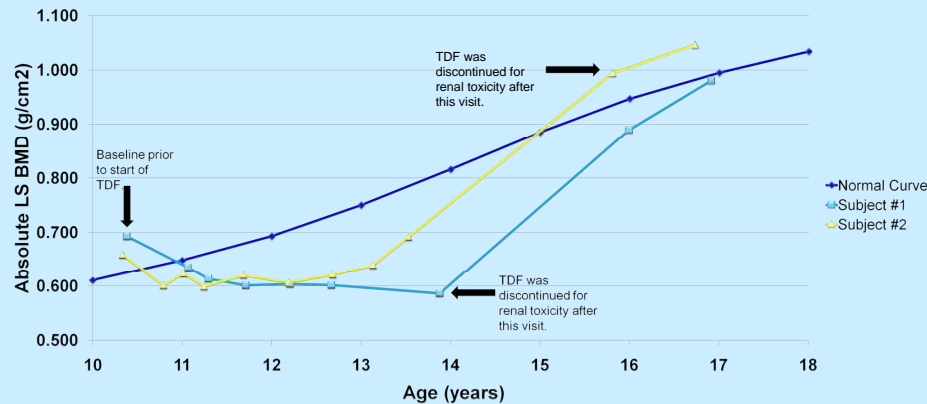
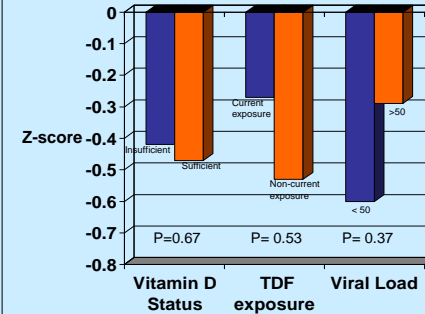


FIGURE 2. BMD Z-score comparisons at baseline visit



- No significant associations were present between vitamin D status, current TDF exposure, or viral load with LS BMD Z-score.

## Conclusions

- BMD was not affected by current TDF therapy in this cohort.
- The older age of our cohort suggests that previously reported metabolic bone abnormalities associated with TDF-containing HAART may diminish as HIV-infected adolescents progress through puberty.
- BMD improvements over time in 2 adolescents with previous pre-pubertal BMD declines also suggest the diminishing impact of TDF-containing HAART on BMD through puberty.
- These findings warrant careful monitoring in these adolescents as they continue to progress through puberty into early adulthood.

## References

- Glesby MJ. Bone disorders in human immunodeficiency virus infection. *Clin Infect Dis*. 2003;37 Suppl 2:S91-95.
- Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics*. Dec 2005;116(6):e846-854.
- Jacobson DL, Spiegelman DL, Duggan C, et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. *J Pediatr Gastroenterol Nutr*. Sep 2005;41(3):338-346.
- Mora S, Sala N, Bricalli D, Zun G, Chiurlo G, Vignano A. Bone mineral loss through increased bone turnover in HIV-infected children treated with highly active antiretroviral therapy. *AIDS*. Sep 28 2001;15(14):1823-1829.
- Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs zidovudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA*. Jul 14 2004;292(2):191-201.
- Moody K, Tebas P. Emerging bone problems in patients infected with human immunodeficiency virus. *Clin Infect Dis*. Apr 1 2003;36(Suppl 2):S101-105.
- Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab*. Sep 2008;93(9):3499-3504.
- Gordon GM, Bachrach LK, Carpenter TO, et al. Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. *J Clin Densitom*. Jan-Mar 2008;11(1):43-58.
- Mora S, Zampronio I, Beccio S, Bianchi R, Giacomini V, Vignano A. Longitudinal changes of bone mineral density and metabolism in antiretroviral-treated human immunodeficiency virus-infected children. *J Clin Endocrinol Metab*. Jan 2004;88(1):24-28.
- Lewis A, Engleton ES, Wang J, Heymsfield SB, Kotler DP. Equivalent osteopenia in HIV-infected individuals studied before and during the era of highly active antiretroviral therapy. *AIDS*. Jan 26 2001;15(2):278-280.
- Tebas P, Yarasheski K, Henry K, et al. Evaluation of the virological and metabolic effects of switching protease inhibitor combination antiretroviral therapy to nevirapine-based therapy for the treatment of HIV infection. *AIDS Res Hum Retroviruses*. Jun 2004;20(6):589-594.
- Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics*. Sep 2006;118(3):e711-718.
- Purdy JB, Gafni RI, Reynolds JC, Zeichner S, Hazra R. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. *J Pediatr*. Apr 2008;152(4):685-684.
- Giacomini V, Mora S, Martelli L, Merlo M, Scianambio M, Vignano A. A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children. *J Acquir Immune Defic Syndr*. Dec 1 2005;40(4):448-450.
- Stephensen CB, Marquis GS, Krulich LA, Douglas SD, Alrovand GM, Wilson CM. Vitamin D status in adolescents and young adults with HIV infection. *Am J Clin Nutr*. May 2006;83(5):1135-1141.

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