

**LOW BONE MASS IN BEHAVIORALLY HIV-INFECTED YOUNG MEN ON ANTIRETROVIRAL THERAPY: ADOLESCENT TRIALS NETWORK (ATN) STUDY 021B**

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Summary: We report evidence of low bone mass in behaviorally HIV-infected young men on antiretroviral therapy with a relatively recent diagnosis of HIV infection, compared with seronegative controls.

## ABSTRACT

**Background:** Peak bone mass is achieved in adolescence/early adulthood and is the key determinant of bone mass in adulthood. We evaluated the association of bone mass with HIV infection and antiretroviral therapy (ART) during this critical period among behaviorally HIV-infected young men and seronegative controls.

**Methods:** HIV-positive men (N=199) and HIV-negative controls (N=53), ages 14-25 years, were studied at 15 ATN sites. HIV-positive participants were recruited on the basis of ART status: ART-naïve (N=105) or on a regimen containing a non-nucleoside reverse transcriptase inhibitor (NNRTI; N=52) or protease inhibitor (PI; N=42). Bone mineral density (BMD) and content (BMC) and body composition were measured by dual-energy X-ray absorptiometry (DXA). Results were compared across groups by linear modeling. Bone results were adjusted for race, BMI, and type of DXA (Hologic/Lunar).

**Results:** The HIV-positive and HIV-negative groups had comparable median age (21 years) and racial/ethnic distribution. Median times since HIV diagnosis were 1.3, 1.9, and 2.2 years in the ART-naïve, NNRTI, and PI groups, respectively (P=0.01). Total and regional fat were significantly lower in the ART-naïve group, compared with seronegative controls. Mean BMD and Z-scores were generally lower among HIV-positive participants on ART, particularly in the PI group. Average Z-scores for the spine were below zero in all four groups, including controls.

**Conclusion:** Young men on ART with a relatively recent diagnosis of HIV infection have lower bone mass than controls. Longitudinal studies are required to determine the impact of impaired accrual or actual loss of bone during adolescence on subsequent fracture risk.

## BACKGROUND

Low bone mineral density (BMD) is frequently observed in persons with HIV infection [1, 2]. Studies have reported increasing fracture rates among older HIV-infected adults [3-5]. Risk factors for low BMD or fractures include initiation and use of antiretroviral therapy (ART) [6-9], specific antiretrovirals [7, 8, 10], inflammation [11], and hepatitis B or C virus co-infection [12], as well as conventional lifestyle factors such as cigarette smoking, alcohol or drug use, age, low body weight, white race, and inactivity [2]. Some studies suggest that the risk of low BMD in HIV-infected adult men may be similar to or greater than the risk in HIV-infected women [13, 14]. Perinatally HIV-infected males in the final stage of pubertal development have shown more evidence of low bone mass than HIV-infected females [15].

Peak bone mass is achieved or approached during adolescence [16]. Failure to accrue bone during this critical period of growth could confer greater risk for fracture later in life. This risk is likely to be exacerbated in HIV-infected youth, who face extended exposure to HIV, ART, and other HIV-related comorbidities during adulthood. In the current study, we examined the effects of HIV infection and ART on bone density in behaviorally HIV-infected young men and seronegative controls.

## METHODS

HIV-positive young men (N=199), ages 14-25 years, were enrolled in this cross-sectional study between April, 2006 and July, 2007 at 15 clinical sites on behalf of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) in the United States and Puerto Rico. Recruitment was based on current use of ART as follows: antiretroviral naïve (ART-naïve; N=105); on an ART regimen that contained a non-nucleoside reverse transcriptase inhibitor (NNRTI) for  $\geq 3$  months (NNRTI; N=52); or on an ART regimen that included a PI for  $\geq 3$  months (PI; N=42). Participants in the NNRTI group had not received  $>6$  months of PI in total and must have received none in the preceding year. Likewise, participants in the PI group had not received  $>6$  months of NNRTI and must have received none in the preceding year. A

seronegative control group (N=53) from the same age range was recruited at the same clinical sites. Recruitment of this latter group was initiated after the first 50 HIV-infected participants were enrolled and monitored throughout the recruitment period to assure that the distributions of sociodemographic characteristics were similar to those of HIV-positive participants. All HIV-infected participants had acquired HIV infection through risk behavior (i.e., not acquired perinatally or from transfusion of blood products), were Tanner stage 4 or 5, and had accessible medical and medication histories. Exclusion criteria for all participants included type 1 diabetes mellitus and use of androgens or systemic glucocorticoids. Transgender youth were excluded. The institutional review board at each clinical site approved the study, and appropriate written informed consent/assent was obtained before enrollment.

### **Assessments**

Height and weight were measured following standard protocols. Separate dual-energy X-ray absorptiometry (DXA) scans of the left hip, spine, and whole-body were performed with central analysis at Tufts University by readers who were blinded to HIV status and ART regimen. A standard phantom was scanned on each DXA instrument used in the study. Machine-generated Z-scores for spine (L1-L4) and hip BMD were used. Z-scores for total body bone mineral content (BMC) were calculated using norms developed at Baylor University [17]. These latter norms have been validated only up to age 22 years and, thus, could be applied to only 66% of participants. Total and regional fat and lean body mass (LBM) were obtained from the whole-body scans.

All participants underwent detailed medical histories, including documentation of substance use, and, in HIV-positive participants, age at HIV diagnosis, ART and HIV disease histories, current and peak HIV-1 RNA, and current and nadir CD4+ T cell measures. All participants completed food frequency (Block Dietary Systems, NutritionQuest, Berkeley, CA) and lifestyle questionnaires that included questions about smoking, alcohol use, and regular exercise (defined as exercising more than once weekly).

## Statistical Analyses

Demographic characteristics and HIV disease-related history were compared between and among groups using bivariate analyses - Fisher Exact test for categorical characteristics and nonparametric testing (Kruskal-Wallis test) for continuous measures. The race-adjusted least squares estimated means ( $\pm$ SE) from linear regression models are presented for height, weight, BMI, LBM, and fat, with the overall p-values for differences among all four groups and among HIV-infected groups, and pairwise contrasts obtained using ANOVA. Similarly, for BMC, BMD, and Z-score outcomes, least squares estimated means ( $\pm$ SE) are reported along with p-values obtained from regression models adjusted for race, BMI, and type of DXA scanner (Lunar or Hologic). Significance tests for pairwise comparisons of HIV-infected groups on ART to HIV-negative and among HIV-infected, comparisons to ART-naïve controls were also obtained from linear regression models.

All analyses were performed using the SAS Software System, Version 8.0. There was no imputation for missing values, nor were any adjustments made for multiple comparisons.

## RESULTS

### Demographic and Lifestyle Characteristics

The median age was 21 years in both HIV-positive and HIV-negative groups ( $P=0.13$ ; Table 1). By design, the racial and ethnic distribution within the two groups was balanced, with the majority of participants being African American and 28% of Hispanic ethnicity. More than two-thirds of participants in each group reported alcohol use. Cigarette smoking was reported by more than 30% of participants in each group, and slightly more than half reported some kind of regular exercise. There was significantly more cocaine use among HIV-positive than HIV-negative participants ( $P=0.01$ ). There were trends toward greater use of amphetamines and cannabinoids among HIV-positive participants, but these were not statistically significant. Self-reported vitamin D intake was significantly higher in the HIV-positive group, but median levels of

vitamin D intake in both groups were below the current level recommended by the Institute of Medicine [18]. Median calcium intake did not differ between groups.

### **HIV Disease-Related Data**

Among the HIV-positive groups, the median reported time since HIV diagnosis ranged from 1.3 years in ART-naïve to 2.2 years in the PI group ( $P=0.01$ ; Table 2). Current CD4 measures did not differ significantly among groups. However, among those on ART, nadir CD4 (both absolute count and percent) and current HIV RNA were lower, and peak HIV RNA levels higher, compared with the ART-naïve group. Virologic suppression, defined as an HIV RNA level  $\leq 400$  copies/mL, was seen in 92% and 74% of participants in the NNRTI and PI groups, respectively, but in only 5% of ART-naïve participants ( $P<0.001$ ). CDC staging differed significantly among HIV-positive groups ( $P<0.001$ ), with a greater proportion of ART-naïve participants classified in stage A/none and a smaller proportion in stage C, than among the groups receiving ART. Two participants, both in the PI group, were hepatitis C virus (HCV) antibody positive. Among participants in the NNRTI group, 96% were using efavirenz, 4% nevirapine, 71% emtricitabine, 63% tenofovir, 27% lamivudine, 25% zidovudine, 12% didanosine, and 2% abacavir. Among participants in the PI group, 90% were on a ritonavir-containing regimen (either as lopinavir/ritonavir or other use of ritonavir in boosting or therapeutic doses); 57% were using atazanavir, 33% lopinavir, 7% fosamprenavir, 2% nelfinavir, 79% tenofovir, 69% emtricitabine, 21% lamivudine, 19% zidovudine, 12% abacavir, 7% didanosine, and 2% stavudine. Use of tenofovir did not differ significantly between the NNRTI and PI groups ( $P=0.12$ ).

### **Body Composition**

Average height did not differ significantly among groups (Table 3). Weight, BMI, and total LBM were significantly lower in the ART-naïve and NNRTI groups, compared with the HIV-negative controls. Total body fat and trunk fat were lower in the ART-naïve group, both when compared with the HIV-negative group and when compared with each HIV-infected group on

ART. Arm and leg fat were lower in both the ART-naïve and NNRTI groups, compared with HIV-negative controls. Among the three HIV-infected groups, the ART-naïve group had significantly less arm fat than either of the two groups on ART, and leg fat in the ART-naïve group was significantly lower than in the PI group.

### **Bone Mass**

Both total body BMD and Z-scores for total BMC differed significantly among groups, whereas total body BMC did not (Table 4). In pairwise comparisons, the PI group had lower total body BMD than both seronegative and HIV-infected ART-naïve controls, and both groups on ART had lower total body BMC Z-scores than seronegative controls. In the total hip, BMD was significantly lower in both groups on ART relative to the seronegative controls, and BMD in the PI group was also lower relative to the HIV-positive, ART-naïve group. Total hip BMD Z-scores in the PI group were significantly lower than those in both the seronegative and the HIV-positive ART-naïve groups. In the femoral neck, BMD and BMD Z-scores were significantly lower only in the PI group, relative to both the HIV-negative and HIV-positive ART-naïve groups. Results for other hip regions (trochanter, Ward's) followed similar patterns, with BMD and BMD Z-scores in each of these subregions being significantly lower in the PI group, compared with the HIV-negative and ART-naïve controls (data not shown). Spine (L1-L4) BMD tended to be lower in the groups on ART, but differences did not achieve a level of statistical significance when results in all four groups were considered ( $P=0.083$ ). Among the three HIV-infected groups, spine BMD was significantly lower in the PI group compared with the ART-naïve group. The spine Z-scores were below zero in all four groups and were significantly lower only in the PI group, compared with both HIV-negative and HIV-positive ART-naïve controls. In post-hoc analyses, we found no statistically significant association of low bone mass with current tenofovir use, regular exercise, or use of alcohol, amphetamines, cocaine, or marijuana (data not shown). Likewise, excluding the two HCV-infected participants in the PI group from the analysis did not materially affect the results.

## CONCLUSIONS

We report evidence of low bone mass in behaviorally HIV infected young men on ART, particularly those on ART regimens that include a PI. Our results are consistent with those of other cross-sectional studies reporting lower bone density in groups of HIV-positive adults [1] and lower bone density or content and/or quality in perinatally HIV infected children [15, 19-22], when compared with HIV-negative controls. However, the adults and youth in these other studies had longer reported durations of HIV infection and, as a result, longer exposure to ART. To our knowledge, this is the first report of low bone mass among youth who acquired HIV infection relatively recently, presumably after the onset of sexual debut during late stages of puberty, and have relatively less exposure to ART.

Peak bone mass is approached or achieved during adolescence and early adulthood and is the major determinant of bone mass during adulthood [16]. It is likely that many of our participants had not yet achieved peak bone mass. It is critically important to maintain bone health during this period to optimize an individual's chances of achieving his or her genetically determined potential for peak bone mass. Factors that interfere with achieving this potential during adolescence may further increase subsequent fracture risk, even if bone loss during adulthood is minimized. Although low bone mass observed in people with HIV infection has not yet been directly related to fractures, there is increasing evidence that older persons with HIV infection have higher fracture rates than are seen in HIV-negative populations [3-5, 23]. Currently available fracture risk assessment tools such as FRAX cannot be applied to young persons [24]. However, it is reasonable to expect that bone loss or impaired accrual of bone mass among HIV-infected youth on ART may place them at greater risk for fractures in adulthood.

A unique feature of this study is the inclusion of a sizeable HIV-infected but ART-naïve group, which allowed us to examine the potential separate contributions of untreated HIV infection and use of ART on bone mass. In the ART-naïve group, total and regional fat were

lower than both seronegative controls and HIV-infected participants on ART, consistent with the known effects of untreated HIV infection [25]. However, we saw little evidence of loss or impaired accrual of bone mass in this group. Thus, in these youth who had acquired HIV infection relatively recently, the effect of HIV infection *per se* on bone mass appeared to be minimal. We should point out that although we adjusted our DXA results for race, our population was predominantly non-white, and our results may not apply to young men from other racial/ethnic groups.

The role of ART in bone loss is not fully understood. Studies in ART-naïve HIV-infected adults have consistently shown a statistically significant decrease in BMD over the first 6-12 months after ART initiation that typically averages between 4 and 6% [6-8, 26] and appears to stabilize or partially reverse after that time [7, 26, 27]. Although decreases in BMD have been reported with initiation of any ART regimen, the magnitude of the decrease is consistently greater in groups initiating regimens that contain tenofovir [7, 8, 26] and, in most cases, is greater with initiation of regimens containing a PI, when compared with those that contain an NNRTI but no PI [8, 10]. Longitudinal studies performed in HIV-infected persons on ART are less consistent, with some showing stability of BMD [28-30] and others showing continuing loss [9, 14, 31]. Likewise, the effect of cumulative exposure to tenofovir is unclear, with some studies showing continuing loss and others relative stability [9, 27, 29]. The mechanisms by which ART induces bone loss are as yet unknown.

Mean spine Z-scores were below zero in all four groups, including the seronegative control group. The latter was an unexpected finding, since one would expect the average Z-scores among this healthy group of young men to be zero. A similar result was reported in preliminary results of analysis of baseline DXA scans in an international HIV pre-exposure prophylaxis (PrEP) study in seronegative men with a median age of 25 years [32]. In addition, Liu et al. [33] reported a higher than expected prevalence of low bone mass among adult men in the U.S. (median age 48) who underwent screening or baseline testing for another PrEP study.

Finally, Grijzen et al. [34] reported a high prevalence of low bone density among 33 Dutch men (mean age 38) with primary HIV infection. The authors speculated that their findings may reflect an acute effect of immune activation on bone mass but acknowledged that low bone mass in their population may also have predated the acquisition of HIV. Although we cannot exclude the possibility that the normative data used to generate the standard deviations (T- or Z-scores) do not represent the current distribution of BMD among healthy younger men, these findings warrant further investigation. They are also of particular relevance given recent successes with pre-exposure prophylaxis as an HIV prevention intervention among at-risk populations of young men (e.g. [35]).

We acknowledge the well-described shortcomings of the use of DXA, which provides a two-dimensional measure of bone density that may be more prone to misinterpretation in younger populations that are still undergoing linear growth [36]. We also acknowledge the resulting challenges of characterizing bone mass in a population that spans the dynamic developmental period of adolescence and early adulthood (14-25 years). Accordingly, we would urge particular caution in interpreting the hip data and all Z-scores reported here, in accordance with the explicit caveat from the International Society for Clinical Densitometry that the diagnosis of osteoporosis cannot be made on the basis of BMD results alone in this age group [37]. In the U.S., a large longitudinal study of bone mass in children has been initiated and has already provided valuable normative data for use of DXA in individuals up to age 20 [38], and the anticipated availability of additional normative data in years to come will greatly enhance the ability of researchers and clinicians to characterize bone mass in individuals during this critical stage in bone development. Techniques such as quantitative CT would no doubt provide more accurate assessment of bone mass, but limited availability and substantial expense for research in large groups of participants, as well as radiation exposure, make this technology less suitable for multicenter use in an adolescent population.

This group had a relatively high prevalence of several known risk factors for low bone mass, including use of tobacco and alcohol. Only 52% of the HIV-infected young men reported some form of regular exercise. Median vitamin D intake was far below currently recommended levels, and median calcium intake was close to the currently recommended level, suggesting that about half of the participants had insufficient calcium intake. Although we did not measure serum vitamin D levels in this study, other studies have demonstrated a high prevalence of vitamin D deficiency/insufficiency in HIV-infected adolescents [39, 40]. Overall, there is ample opportunity to mitigate bone loss by addressing modifiable risk factors.

In summary, we report evidence of low bone mass in behaviorally HIV-infected young men on ART. Although the clinical significance and potential impact on peak bone mass and subsequent fracture risk are not known and will require longitudinal studies, risk reduction through changes in diet and lifestyle is warranted.

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**Table 1. Demographic Characteristics and Lifestyle Factors that Affect BMD**

<b>Characteristic</b>	<b>HIV-negative (n = 53)</b>	<b>HIV-positive (n = 199)</b>	<b>p-value<sup>a</sup></b>
Age (years): Median [range]	21 [14 - 25]	21 [17 - 25]	0.13
Race: n (%)			
Black, non-Hispanic	31 (58.5)	119 (59.8)	0.97
Hispanic	15 (28.3)	56 (28.1)	
Other	7 (13.2)	24 (12.1)	
Drink alcohol: n (%)	36 (67.9)	153 (76.9)	0.21
Currently smoke cigarettes: n (%)	16 (30.2)	84 (42.2)	0.12
Exercise regularly: n (%)	30 (56.6)	103 (51.8)	0.54
Ever or currently using drugs: n (%)	31 (58.5)	132 (66.3)	0.29
Ever used amphetamines	3 (5.7)	27 (13.6)	0.15
Ever used cocaine	4 (7.6)	45 (22.6)	<b>0.01</b>
Ever used marijuana/hash/THC	24 (45.3)	113 (56.8)	0.16
Vitamin D intake (IU/D): Median [range]	201 [55-1011]	323 [17-2209]	<b>0.01</b>
Calcium intake (mg/d): Median [range]	1074 [307-4205]	1124 [153-5678]	0.49

<sup>a</sup> P-values were obtained from Fisher's Exact test for categorical characteristics and the nonparametric Kruskal-Wallis test for continuous measures.

**Table 2. HIV Disease Characteristics**

HIV disease characteristic		Type of Antiretroviral Regimen			p-value <sup>a</sup>
		ART naïve (n=105)	NNRTI/Non-PI containing regimen (n=52)	PI/Non-NNRTI containing regimen (n=42)	
Years since HIV diagnosis	Median [Range]	1.3 [0.02 – 8.4]	1.9 [0.2 – 6.9]	2.2* [0.3 – 6.1]	<b>0.01</b>
Current CD4 count, cells/μL	Median [Range]	466 [7 – 1,362]	433 [105 – 1,335]	398 [15 – 1,430]	0.59
Nadir CD4 count, cells/μL	Median [Range]	412 [7 – 980]	204.5* [23 - 571]	215* [1 – 682]	<b>&lt;0.001</b>
Current CD4 percent	Median [Range]	27.0 [1.3 – 51.0]	29.0 [9.0 – 52.0]	23.8 [2.3 – 51.0]	0.09
Nadir CD4 percent	Median [Range]	22.0 [1.3 – 50.0]	14.0* [2.0 – 41.8]	14.0* [0.04 – 33.6]	<b>&lt;0.001</b>
Current HIV RNA, copies/mL	Median [Range]	9,963 [<400 - 498,593]	<400* [<400 - 4,436]	<400* [<400 - 258,108]	<b>&lt;0.001</b>
Current HIV RNA levels: n (%)					
≤ 400 copies/mL		5 (4.8)	47 (92.2)*	31 (73.8)*	<b>&lt;0.001</b>
> 400 copies/mL		99 (95.2)	4 (7.8)	11 (26.2)	
Peak HIV RNA, copies/mL	Median [Range]	36,700 [50 - 750,000]	78,892* [400 - 5,087,379]	138,892* [400 - 1,417,974]	<b>0.001</b>
CDC Stage from medical chart review: n (%)					
A/none		96 (91.4)	37 (71.2)*	26 (61.9)*	<b>&lt;0.001</b>
B		6 (5.7)	10 (19.2)	8 (19.0)	
C		3 (2.9)	5 (9.6)	8 (19.0)	

<sup>a</sup> P-values were obtained from the Fisher's Exact test for categorical measures and the F-test for the contribution of study group to linear regression modeling of continuous measures of disease characteristics.

\* P<0.05 using HIV-infected, ART naïve participants as the comparison group; analyses restricted to HIV positive participants

**Table 3. Anthropometric and Body Composition Data<sup>a</sup>**

	HIV-Positive by Type of Antiretroviral Regimen				p-value <sup>b</sup>	
	HIV-negative (n=53)	ART naïve (n=105)	NNRTI/Non-PI containing regimen (n=52)	PI/Non-NNRTI containing regimen (n=42)	Overall (n=252)	HIV+ only (N=199)
Height, cm	176.9 (1.1)	174.8 (0.8)	175.1 (1.1)	174.9 (1.2)	0.43	0.96
Weight, kg	79.7 (2.0)	70.1 (1.4)*	72.8 (2.0)*	74.1 (2.3)	<b>0.002</b>	0.22
BMI, kg/m <sup>2</sup>	25.5 (0.6)	22.9 (0.4)*	23.6 (0.6)*	24.1 (0.7)	<b>0.006</b>	0.18
Total lean body mass, kg/m	44.5 (1.1)	39.8 (0.8)*	41.3 (1.1)*	41.9 (1.2)	<b>0.005</b>	0.20
Total body fat, kg/m	9.3 (0.6)	6.4 (0.5)*	7.9 (0.7) <sup>†</sup>	8.5 (0.7) <sup>†</sup>	<b>0.001</b>	<b>0.013</b>
Total body fat, %	19.6 (1.0)	15.2 (0.7)*	18.5 (1.0) <sup>†</sup>	19.1 (1.2) <sup>†</sup>	<b>0.001</b>	<b>0.002</b>
Trunk fat, kg/m	4.3 (0.4)	3.0 (0.2)*	3.8 (0.4) <sup>†</sup>	4.2 (0.4) <sup>†</sup>	<b>0.004</b>	<b>0.009</b>
Arm fat, kg/m	0.9 (0.06)	0.6 (0.05)*	0.7 (0.06) <sup>*†</sup>	0.8 (0.07) <sup>†</sup>	<b>&lt;0.001</b>	<b>0.023</b>
Leg fat, kg/m	3.6 (0.2)	2.4 (0.2)*	2.9 (0.2)*	3.1 (0.3) <sup>†</sup>	<b>0.001</b>	<b>0.049</b>

<sup>a</sup> Body composition measured by dual-energy X-ray absorptiometry; data are least squares estimated means (SE), adjusted for race.

<sup>b</sup> P-values obtained from the F-test for the contribution of study group to linear regression models fit to the data for anthropometric and body composition measures.

\* P<0.05 using HIV-negative participants as the comparison group

<sup>†</sup> P<0.05 using HIV-infected, ART naïve participants as the comparison group; analyses restricted to HIV positive participants

**Table 4. Bone Mineral Content and Density<sup>a</sup>**

	HIV-Positive by Type of Antiretroviral Regimen				p-value <sup>b</sup>	
	HIV-negative (n=53)	ART naïve (n=105)	NNRTI/Non-PI containing regimen (n=52)	PI/Non-NNRTI containing regimen (n=42)	Overall (n=252)	HIV+ only (n=199)
Total body BMD, g/cm <sup>2</sup>	1.21 (0.01)	1.21 (0.01)	1.18 (0.01)	1.17 (0.01)* <sup>†</sup>	<b>0.035</b>	<b>0.019</b>
Total body BMC, g	2876 (53)	2830 (38)	2734 (53)	2723 (60)	0.118	0.103
Total body BMC Z-score <sup>c</sup>	0.08 (0.18)	-0.33 (0.12)	-0.72 (0.16)*	-0.69 (0.22)*	<b>0.005</b>	0.076
Total hip BMD, g/cm <sup>2</sup>	1.12 (0.02)	1.11 (0.01)	1.06 (0.02)*	1.03 (0.02)* <sup>†</sup>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Total hip BMD Z-score <sup>d</sup>	-0.05 (0.15)	-0.01 (0.10)	-0.39 (0.14)	-0.68 (0.15)* <sup>†</sup>	<b>0.001</b>	<b>&lt;0.001</b>
Femoral neck BMD, g/cm <sup>2</sup>	1.07 (0.02)	1.06 (0.01)	1.03 (0.02)	0.98 (0.02)* <sup>†</sup>	<b>0.003</b>	<b>0.003</b>
Femoral neck BMD Z-score <sup>d</sup>	0.03 (0.18)	0.04 (0.12)	-0.35 (0.17)	-0.67 (0.18)* <sup>†</sup>	<b>0.005</b>	<b>0.003</b>
Spine (L1-L4) BMD, g/cm <sup>2</sup>	1.11 (0.02) <sup>e</sup>	1.12 (0.01)	1.09 (0.02)	1.07 (0.02) <sup>†</sup>	0.083	<b>0.025</b>
Spine (L1-L4) BMD Z-score	-0.57 (0.15)	-0.67 (0.10)	-0.95 (0.14)	-1.19 (0.16)* <sup>†</sup>	<b>0.013</b>	<b>0.015</b>

<sup>a</sup> Data are least squares estimated means (SE), adjusted for race, BMI and DXA scanner type (Hologic or Lunar).

<sup>b</sup> P-values obtained from the F-test for the contribution of study group to linear regression models fit to the data for bone mineral content and density measures

<sup>c</sup> Numbers per group for whole-body Z-scores are 35, 71, 39, and 21, respectively

<sup>d</sup> Numbers per group for total hip and femoral neck Z-scores are 32, 77, 38, and 34, respectively.

<sup>e</sup> N for HIV-negative is 51. One participant in this group had spine data for L1-L3 only and thus was excluded from the analysis

\* P<0.05 using HIV-negative participants as the comparison group

<sup>†</sup> P<0.05 using HIV-infected, ART-naïve participants as the comparison group; analyses restricted to HIV positive participants