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High Prevalence of Low Bone Mineral Density and Substantial Bone Loss over 4 Years Among HIV-Infected Persons in the Era of Modern Antiretroviral Therapy

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Abstract

HIV-infected persons are living longer on combination antiretroviral therapy (cART) but experiencing more comorbidities including low bone mineral density (BMD). Using data from the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN Study), we determined the prevalence of low BMD (T-score below one standard deviation of the reference mean) and compared it with matched controls from the National Health and Nutrition Examination Survey (NHANES). We also assessed 4-year longitudinal BMD changes among participants virologically suppressed on cART. Of 653 participants included in this analysis (77% male, 29% black, median age 41 years, median $CD4^+$ cell count 464 cells/mm^3, 89% with HIV RNA <400 copies/ml), 51% and 10% had baseline osteopenia and osteoporosis, respectively. Low BMD at the femoral neck was significantly more prevalent than for the NHANES controls (47% versus 29%, $p < 0.001$). Lower body mass index, nonwhite race, longer tenofovir exposure, older age, being unemployed or retired, and lower apolipoprotein E were independently associated with baseline osteoporosis. Among 170 participants virologically suppressed on cART and with longitudinal BMD data, 31% experienced substantial bone loss (≥5% BMD decline from baseline) over 4 years. Female sex, current smoking, and longer stavudine use were more common among participants who had substantial bone loss, although these variables failed to reach statistical significance. Low BMD was highly prevalent among HIV-infected persons. One-third of participants experienced substantial bone loss despite cART, suggesting the need for monitoring and potential clinical interventions.

Introduction

With the advent of combination antiretroviral therapy (cART), survival has improved among HIV-infected persons with a marked reduction in AIDS-associated complications.[1] However, age-related comorbidities including osteoporosis occur with higher frequency as compared to the general population.[2,3] While there are substantial data on the prevalence of osteoporosis, longitudinal evaluations of changes in bone mineral density (BMD) over time among HIV-infected persons are limited.

Osteopenia and osteoporosis remain highly prevalent among HIV-infected persons, ranging from 40% to 62% and 14% to 42%, respectively.[4–6] Studies that assessed the progression of BMD among HIV-infected persons have yielded inconsistent results. Some studies demonstrated accelerated

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bone loss, while others showed stable or even increased BMD over time.[7–9] A meta-analysis reported that in studies that involved treatment-naive or untreated persons at baseline, BMD significantly declined at 1, 2, and 2.5 years after cART initiation. Conversely, in cohorts that involved cART-treated persons at baseline, BMD was stable over time.[10] One study documented a 2–6% decline in BMD within the first 2 years of cART initiation independent of antiretroviral regimen.[11]

In the setting of long-term viral suppression, understanding the complications of HIV infection and cART is paramount to successful HIV management. In the current analysis, we evaluated baseline BMD in a contemporary cohort of HIV-infected individuals to determine the prevalence of osteopenia and osteoporosis and then compared the findings to those from persons matched by age, sex, race, and body mass index (BMI) from the National Health and Nutrition Examination Survey (NHANES). We then assessed longitudinal BMD changes to determine the proportion of persons virologically suppressed on cART with progressive BMD decline over 4 years, and identified associated risk factors.

Materials and Methods

Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN Study)

This was a prospective, observational cohort funded by the Centers for Disease Control and Prevention (CDC) that monitored the clinical course of HIV-infected persons treated with cART at seven HIV specialty clinics in four cities in the United States: St. Louis, Missouri; Providence, Rhode Island; Minneapolis, Minnesota; and Denver, Colorado. Seven hundred HIV-infected persons were enrolled between March 2004 and June 2006 and were followed until June 2012. Informed consent was obtained from all study participants, and the study was approved and renewed annually by the institutional review boards of all participating institutions and the CDC. The cohort and detailed study methodology have been described elsewhere.[12]

Briefly, at baseline, comprehensive clinical and behavioral data were collected on all subjects including height and weight for calculating BMI, type and duration of all medications, behavioral risk data including alcohol, tobacco use, and substance abuse, comorbidities, and fasting laboratory data. Laboratory tests used for research only including insulin, adiponectin, leptin, highly-sensitive C-reactive protein, and 25-hydroxyvitamin D were performed by the Diabetes Research and Training Center Radioimmunoassay Core Laboratory, Washington University School of Medicine. Serum and plasma used for these tests were placed on ice immediately, centrifuged, and stored at −70°C until time of batched assay. At enrollment and annually for the following 4 years, whole-body and site-specific dual X-ray absorptiometry (DXA) scans, performed on Lunar or Hologic machines, were obtained by each study site on all participants and transmitted to central readers for interpretation.

National Health and Nutrition Examination Survey (NHANES)

The NHANES has been conducted annually by the National Center for Health Statistics since 1999.[13] Each year, NHANES surveys a nationally representative sample of approximately 5,000 persons from 15 counties across the United States. Each person is interviewed to collect demographic and socioeconomic data and examined to obtain medical and laboratory measures, including use of DXA scans on Hologic machines to evaluate femoral neck BMD. NHANES data are released in 2-year cycles and we used the 2007–2008 cycle to compare to our data, matching 1:1 based on age, sex, race, and BMI. Because NHANES releases only T-score data, this analysis was conducted using this measure.

Definitions

We used the World Health Organization (WHO) classification of BMD utilizing the difference between an individual's BMD and that of a young-adult reference population (T-score). In postmenopausal women and men at least 50 years, a T-score that is within one standard deviation (SD) of the reference BMD is classified as normal, 1 to 2.5 SD below the reference BMD as osteopenia, and greater than 2.5 SD below the reference BMD as osteoporosis.[14] The classification of low BMD includes all persons with either osteopenia or osteoporosis. We defined substantial BMD decline as ≥5% decrease from baseline at year 1 to 4 of follow-up at the femoral neck, total hip, or lumbar spine. Participants with <5% decrease or any percent increase in baseline BMD at years 1 to 4 were categorized as having stable and increased BMD, respectively. For the longitudinal analysis, we defined virologic suppression as HIV RNA below the limit of detection at all time points. Blips (i.e., HIV RNA between the limit of detection and <2,000 copies/ml that were followed by HIV RNA below the limit of detection on subsequent testing) were categorized as viral suppression. On the other hand, virologic nonsuppression was defined as any HIV RNA ≥2,000.

Statistical analysis

For univariate analysis, statistical associations between each outcome and categorical variables were tested using the chi-square test or Fisher's exact test. Associations with continuous variables were analyzed by either the Student's *t*-test or Wilcoxon rank-sum test for normally and nonnormally distributed variables, respectively. All tests of statistical significance were two-sided. Variables that were associated with osteoporosis versus no osteoporosis at any site, as indicated by $p < 0.10$ in univariate analysis, were then modeled using stepwise logistic regression.[15] Continuous variables were converted to quartile groups to facilitate interpretation of odds ratios. We determined the prevalence of low BMD and compared it with controls matched by age, sex, race, and BMI from NHANES using the paired *t*-test.

For assessment of longitudinal BMD change, we included participants who were virologically suppressed while taking cART for at least 2 years prior to baseline and had BMD data for 4 consecutive years during study follow-up. Baseline demographic and laboratory data were used as variables to determine significant associations with BMD loss from baseline. We used the chi-square test, the Student's *t*-test, and the Wilcoxon rank-sum test to compare differences between participants who did and did not have substantial BMD decline. All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, NC).[16]

Results

Baseline BMD

A total of 653 SUN Study participants had DXA and clinical data available for analysis. Twenty-nine percent were African American, 10% were Hispanic, and 23% were female, and the median age was 41 years. The median $CD4^+$ cell count was 464 cells/mm^3 with 523 (79%) persons currently on cART, among whom 89% had HIV RNA <400 copies/ml. At the lumbar spine, 46% had low BMD (38% with osteopenia and 8% with osteoporosis). At the femoral neck, 46% had low BMD (42% with osteopenia and 4% with osteoporosis). At the total hip, 28% had low BMD (26% with osteopenia and 2% with osteoporosis). At any site, 61% had evidence of low BMD (51% with osteopenia and 10% with osteoporosis). Additional characteristics of the study subjects are shown in Table 1.

In multivariate logistic regression, the following factors were independently associated with osteoporosis: age >46 years [odds ratio (OR) 2.27; 95% confidence interval (CI) 1.26–4.07; $p=0.006$]; nonwhite race (OR 2.58; 95% CI 1.45–4.65; $p=0.001$); BMI <22.8 kg/m^2 (OR 3.96; 95% CI 2.23–7.07; $p=<0.001$); being unemployed or retired (OR 2.16; 95% CI 1.16–3.94; $p=0.013$); time on tenofovir >1 year (OR 2.47; 95% CI 1.35–4.48; $p=0.003$); and apolipoprotein E <4.8 mg/liter (OR 1.97; 95% CI 1.10–3.59; $p=0.023$) (Table 2). Of note, markers of bone turnover [i.e., cross-linked C-telopeptide of type 1 collagen (CTx), osteocalcin, alkaline phosphatase) were significantly elevated among participants with low BMD but were not independently associated with osteoporosis by multivariate analysis. Furthermore, persons with low BMD had a median 25-hydroxyvitamin D that did not statistically differ from those with normal BMD.

Comparison with NHANES subjects

Femoral neck BMD measurements of the 462 SUN participants whose DXA scan was performed on a Hologic scanner were compared to data from NHANES to determine relative rates of osteopenia and osteoporosis. The mean T-score at the femoral neck was −0.81 for the SUN cohort versus −0.33 for the NHANES group ($p<0.001$) (Fig. 1). Low BMD at the femoral neck was significantly more prevalent in the SUN group than the NHANES group (47% versus 29%) ($p<0.\ 001$), with osteopenia found in 45% versus 28% ($p<0.001$) and osteoporosis found in 3.5% versus 0.9% ($p=0.005$).

Longitudinal BMD change

There were 170 SUN Study participants who were virologically suppressed at baseline with at least 2 years of cART and with 4-year longitudinal BMD data available. Over this 4-year period, BMD was stable in 35% of participants at the femoral neck, 49% at the total hip, and 29% at the lumbar spine; BMD increased in 50% at the femoral neck, 35% at the total hip, and 54% at the lumbar spine. The proportion of participants who had ≥5% decline in BMD from baseline increased over time such that at year 4, 15% had substantial bone loss at the femoral neck, 15% at the total hip, 17% at the lumbar spine, and 31% at any site (Fig. 2). In univariate analysis, certain parameters were more common in those with substantial bone loss including female sex, current smoking, and longer stavudine use; however, these failed to reach statistical significance (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/aid). The BMI of participants who had substantial bone loss at any site also did not significantly change over 4 years. The majority of subjects remained in the same WHO BMD classification at 4 years and the prevalence of WHO-defined osteopenia or osteoporosis also remained stable over time. We found a modest negative correlation between lower BMD at baseline and increased BMD over time at the total hip ($r=-0.19$, $p=0.015$) but not at other sites.

Discussion

Consistent with several other studies, the prevalence of osteopenia or osteoporosis was high (61%) in this cohort of HIV-infected persons with mostly well-controlled viremia and high $CD4^+$ cell counts.[4–6] In comparison to controls from NHANES matched by age, sex, race, and BMI, our cohort had significantly lower T-scores at the femoral neck with almost twice as many persons with osteopenia and osteoporosis. These findings confirm other data regarding the robust association of HIV infection with low BMD. Furthermore, a significant number of persons on cART continue to experience bone loss despite suppressed viremia.

The mechanism of bone loss associated with HIV infection is multifactorial. Previous studies have highlighted the high prevalence of osteopenia and osteoporosis among cART-naive persons and those with poorly controlled HIV infection (low $CD4^+$ cell count and detectable HIV-RNA), suggesting direct (increased osteoclastic activity and decreased bone formation caused by HIV-associated proteins) or indirect (aberrant B cell activation with stimulation of osteoclast activity) viral effects in reducing BMD.[5,17–19] Chronic immune activation and inflammation, in turn, have been linked with bone loss associated with HIV infection.[20]

In this analysis, we did not find an independent association of osteoporosis with metabolic risk factors that have been previously associated with osteoporosis in HIV-infected persons (e.g., vitamin D deficiency).[21] We also did not find an independent association with markers of chronic inflammation, including high-sensitivity C-reactive protein (hs-CRP) and bone turnover determined by cross-linked CTx and osteocalcin. However, we identified several traditional risk factors associated with osteoporosis, including older age, lower BMI, and in the HIV-infected population, longer use of tenofovir. The association of tenofovir has been reported not only among HIV-infected treatment-naive persons started on tenofovir but also among HIV-uninfected persons receiving tenofovir for preexposure prophylaxis.[7,22] Longer cumulative exposure to tenofovir has also been independently associated with an increased risk of osteoporotic fracture.[23]

We also found novel associations of osteoporosis with being unemployed or retired and with lower serum apolipoprotein E. To our knowledge, the independent association with being unemployed or retired has not previously been reported in the HIV literature, although, a link between the level of education and low BMD has been seen in a cohort of HIV-infected persons in Ireland.[24] In the general population, the association of unemployment with risk of osteoporotic fracture has been described.[25] Low socioeconomic status, as evidenced by unemployment and low income, is strongly

Table 1. Baseline Characteristics of Participants by Bone Mineral Density Classification, the SUN Study, (N=653), 2004–2012

	All participants (n=*653*)	*Normal BMD* (n=*254*)	*Osteopenia* (n=*336*)	*Osteoporosis* (n=*63*)
Characteristic				
Age (years)[a]	41 (35–47)	40 (33–44)	42 (35.5–48)[b]	45 (38–51)[b]
Gender[c]				
Men	505 (77)	169 (67)	282 (84)[b]	54 (86)[b]
Women	148 (23)	85 (33)	54 (16)	9 (14)
Race/ethnicity[c]				
White, non-Hispanic	386 (59)	145 (57)	214 (64)	27 (43)
Black, non-Hispanic	188 (29)	83 (33)	82 (24)	23 (37)
Hispanic	64 (10)	21 (8)	31 (9)	12 (19)
Other/unknown	15 (2)	5 (2)	9 (3)	1 (2)
BMI (kg/m^2)[a]	25.5 (22.8–28.4)	26.9 (24.3–30.5)	24.7 (22.6–27.4)[b]	22.6 (20.7–25.1)[b]
VAT (kg)[a]	115.6 (77.0–158.6)	117.8 (83.0–160.8)	118.1 (74.9–163.4)	100.8 (61.4–136.3)[b]
SAT (kg)[a]	192.4 (129.4–301.8)	231.6 (154.1–375.4)	179.5 (118.2–263.6)[b]	149.3[a] (100.1–227.1)
VAT/SAT[a]	0.57 (0.39–0.82)	0.51 (0.33–0.74)	0.62[a] (0.43–0.88)[b]	0.61 (0.47–0.98)[b]
Any resistance training/exercise[c]	248 (40)	108 (46)	121 (37)[b]	19 (33)
Any aerobics/exercise[c]	296 (48)	107 (45)	169 (52)	20 (34)
Employed full-time[c]	302 (48)	127 (52)	158 (48)	17 (27)[b]
Tobacco smoking, ever	426 (67)	164 (67)	218 (66)	44 (71)
Tobacco smoking, current	280 (44)	111 (45)	134 (40)	35 (56)
History of substance abuse[c]	451 (69)	172 (68)	240 (71)	39 (62)
Alcohol use in last 30 days[c]	444 (70)	171 (70)	230 (69)	43 (69)
Postmenopausal[c,d]	22 (18)	10 (14)	11 (25)	1 (20)
HIV-related factors				
Time since HIV diagnosis in years[a]	4.8 (2.2–8.0)	4.5 (2.2–7.3)	5.1 (2.2–8.1)	6.6 (2.5–11.0)[b]
History of opportunistic infection[c]	155 (24)	57 (22)	78 (23)	20 (32)
Nadir CD4 count (cells/mm^3)[a]	204 (89–316)	205 (98–338)	213.5 (92–309)	139.5 (34–269)[b]
CD4 count (cells/mm^3)[a]	464.5 (332–673)	470.5 (334.5–707.5)	476 (328–651)	413 (242–595)[b]
ART naïve[c]	76 (12)	28 (11)	42 (12)	6 (10)
cART, current	515 (79)	203 (80)	259 (77)	53 (84)
Length of any ART (months) (IQR)[a]	32.6 (13.3–65.1)	29.7 (10.9–60.0)	34.5 (14.0–70.7)	35.3 (18.0–72.6)
On ART[c]				
HIV RNA <400 copies/ml	455 (89)	177 (88)	230 (89)	48 (91)

(*continued*)

TABLE 1. (CONTINUED)

	All participants (n = *653*)	*Normal BMD* (n = *254*)	*Osteopenia* (n = *336*)	*Osteoporosis* (n = *63*)
ART use[c]				
Any use of PI	367 (56)	136 (54)	197 (59)	34 (54)
Any use of NNRTI	362 (55)	141 (56)	182 (54)	39 (62)
Any use of NRTI	574 (88)	225 (89)	292 (87)	57 (90)
Any use of stavudine	171 (26)	52 (20)	96 (29)[b]	23 (37)[b]
Any use of tenofovir	297 (45)	117 (46)	146 (43)	34 (54)
Current use tenofovir	257 (39)	103 (41)	122 (36)	32 (51)
Duration of ART use in months[a]				
Any PI	3.7 (0–24.9)	1.8 (0–20.7)	6.1 (0–27.9)	2.5 (0–34.9)
Any NNRTI	3.2 (0–26.4)	2.5 (0–22.7)	3.2 (0–27.2)	9.4 (0–34.3)
Any NRTI	25.7 (7.5–59.0)	22.1 (5.8–55.2)	27.8 (7.9–64.8)	33.5 (11.3–60.9)
Laboratory parameters				
Hepatitis C antibody-reactive[c]	78 (13)	21 (9)	42 (13)	15 (26)[b]
eGFR by sMDRD (ml/min)[a]	96.6 (83.0–110.6)	96.9 (83.1–110.7)	95.3 (82.8–109.7)	97.9 (84.1–114.0)
TSH (mU/liter)[a]	1.6 (1.1–2.3)	1.7 (1.2–2.4)	1.6 (1.1–2.2)	1.5 (1.1–2.6)
Free testosterone (ng/dl)[a,e]	20.8 (13.5–89.1)	20.7 (13.9–93.7)	21.1 (13.0–89.1)	20.7 (12.1–73.0)
Fasting insulin (mU/liter)[a]	8.5 (5.3–13.6)	8.5 (5.8–13.8)	8.7 (5.1–13.5)	8.1 (4.3–13.2)
Adiponectin (μg/ml)[a]	8,152.5 (5,225–12,410)	7,730 (4,980–10,720)	8,162.5 (5,327.5–13,070)	9,815 (5,775–13,230)[b]
Leptin (ng/ml)[a]	4.3 (2.2–9.2)	5.6 (2.6–13.6)	3.7 (2.0–7.0)[b]	3.0 (1.6–6.1)[b]
Highly sensitive C-reactive protein (mg/liter)[a]	1.8 (0.8–4.5)	1.9 (0.8–5.0)	1.7 (0.7–4.2)	1.6 (0.7–3.4)
25-hydroxyvitamin D (ng/ml)[a]	23.5 (15.5–31.4)	23.2 (15.4–31.3)	24.3 (16.1–31.9)	21.5 (13.6–29.3)
CTX (ng/ml)[a]	302 (190–438)	284 (172–406)	311 (214–441.5)[b]	355 (201–483)[b]
Osteocalcin (ng/ml)[a]	2.3 (1.4–3.5)	2.0 (1.1–2.6)	2.7 (1.6–4.1)[b]	3.2 (2.0–5.8)
Alkaline phosphatase (IU/liter)[a]	80.5 (66.0–101.5)	77.5 (64.5–98.0)	81 (67–100)	88 (77–115)[b]
Apolipoprotein E (mg/l)[a]	4.8 (3.9–5.8)	4.7 (3.8–5.8)	4.9 (4.0–5.8)	5.7 (4.4–5.1)

[a]Median (IQR).
[b]Denotes p value < 0.05; normal BMD versus osteopenia, normal BMD versus osteoporosis.
[c]n (%).
[d]Women only.
[e]Men only.

SUN Study, Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy; BMD, bone mineral density; IQR, interquartile range; BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; ART, antiretroviral therapy; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; eGFR, estimated glomerular filtration rate; sMDRD, simplified Modification of Diet in Renal Disease; TSH, thyroid-stimulating hormone; CTX, cross-linked C-telopeptide of type 1 collagen.

linked to poorer health outcomes, including increased all-cause mortality.[26] The association we found between nonwhite race and osteoporosis was not expected. It may have been a result of unmeasured variables that influence outcome that are different among racial groups (i.e., socioeconomic factors such as annual income and geographic location, family history of osteoporosis, use of calcium and other supplements).

The independent association of osteoporosis with lower serum apolipoprotein E is intriguing. Apolipoprotein E, an essential component of lipoproteins, plays an important role in bone metabolism by facilitating vitamin K-dependent carboxylation of bone proteins. In the general population, apolipoprotein $\varepsilon 4$, a gene that encodes for apolipoprotein E, is a risk factor for coronary artery disease, Alzheimer's disease, low BMD, and increased fracture risk.[27–30] To our knowledge, there are no previously published data that correlated serum apolipoprotein E with risk of bone loss in the HIV-infected population. Further studies are needed to explore whether this biomarker is also linked with several inflammatory diseases, including Alzheimer's disease and atherosclerosis, among HIV-infected persons.

Similar to other studies, we found that the majority of our participants on at least 2 years of cART had stable BMD over time.[8] However, we identified an increasing proportion of participants with ≥5% BMD decline over 4 years, though without a change in proportions of WHO-defined osteopenia/osteoporosis. The magnitude of bone loss in these relatively young individuals is compelling and is similar to that associated with a year of corticosteroid treatment and greater than that seen among HIV-uninfected perimenopausal or postmenopausal women and older men.[31–34] Among these participants, bone loss was more common among female subjects, current smokers, and those with longer stavudine use. Unfortunately, the smaller sample size of this longitudinal cohort limited statistical power. Nonetheless, this trend is not surprising since female sex and tobacco use are traditional risk factors for osteoporosis and stavudine use has been associated with bone loss in several clinical trials.[35,36] Further studies with long-term follow-up and larger numbers of participants are needed to investigate whether this degree of bone loss will lead to osteopenia and osteoporosis over time.

Baseline BMD influences the rate of bone loss among premenopausal and postmenopausal women in the general population.[37] Studies conducted among HIV-infected women show varying results.[6] We found a significant, albeit modest, correlation between lower baseline BMD and subsequent gain in BMD at the total hip, with baseline total hip BMD accounting for only 3.6% of the variance in the total hip BMD change over time. We may be limited by the fact that our baseline DXA scans do not reflect a true baseline for the participants, as the median time since HIV diagnosis was 4.8 years and all had at least 2 years of suppressive cART exposure at time of first DXA scan.

Table 2. Multivariate Logistic Regression Analysis of Factors Associated with Osteoporosis at Any Anatomical Site, at Baseline, in the SUN Study ($N=653$), 2004–2012

	Univariate analysis		*Multivariate analysis*	
Characteristic	*Odds ratio (95% CI)*	p *value*	*Odds ratio (95% CI)*	p *value*
Age >46 years[a]	2.39 (1.40–4.06)	0.001	2.27 (1.26–4.07)	0.006
Male gender	1.85 (0.89–3.84)	0.099		
Nonwhite race	2.07 (1.23–3.51)	0.007	2.58 (1.45–4.65)	0.001
BMI <22.8 kg/m^2[b]	3.99 (2.33–6.86)	<0.001	3.96 (2.23–7.07)	<0.001
SAT <302.4 kg[a]	3.92 (1.54–9.97)	0.004		
Any exercise	0.58 (0.34–0.99)	0.048		
Resistance training	0.70 (0.40–1.22)	0.210		
Aerobic activity	0.54 (0.31–0.94)	0.031		
Unemployed or retired	2.76 (1.60–4.78)	<0.001	2.16 (1.16–3.94)	0.013
Current smoking	1.75 (1.03–2.97)	0.038		
Alcohol use in last 30 days	0.99 (0.56–1.74)	0.966		
Time since HIV diagnosis >8.1 years[a]	0.47 (0.27–0.81)	0.006		
Nadir CD4$^+$ <89 c/mm^3[b]	1.90 (1.10–3.30)	0.022		
Baseline CD4$^+$ count <323 c/mm^3[b]	2.16 (1.26–3.73)	0.006		
Ever used stavudine	1.72 (1.00–2.96)	0.052		
Time on tenofovir >1 year[c]	2.12 (1.23–3.63)	0.007	2.47 (1.35–4.48)	0.003
Hepatitis C antibody-reactive	2.75 (1.44–5.23)	0.002		
Adiponectin >8,025 μg/ml[d]	0.52 (0.30–0.89)	0.018		
Leptin <2.2 ng/ml[b]	1.79 (1.03–3.09)	0.038		
25-Hydroxyvitamin D <10 ng/ml[e]	2.43 (1.19–4.98)	0.015		
Apolipoprotein E <4.8 mg/liter[b]	1.76 (1.03–3.00)	0.038	1.97 (1.10–3.59)	0.023
Apolipoprotein A1				
>180 mg/dl for men, 205 mg/dl for women	2.75 (1.14–6.64)	0.025		

[a]Upper quartile.
[b]Lower quartile.
[c]Cut off decided by investigators.
[d]Median.
[e]Definition of severe vitamin D deficiency.
SUN Study, Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy; CI, confidence interval; BMI, body mass index; SAT, subcutaneous adipose tissue.

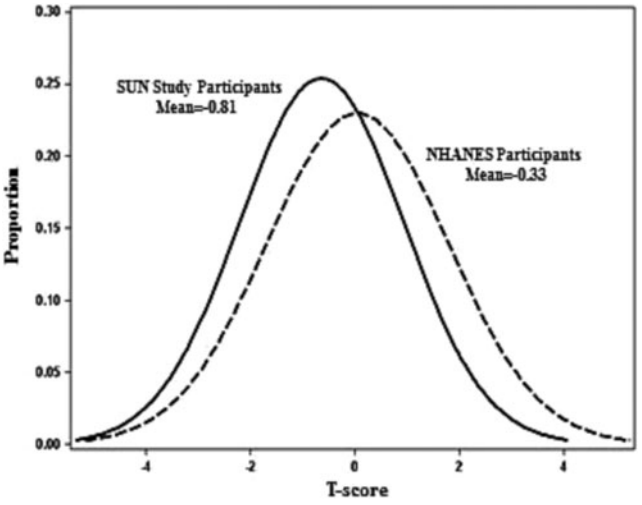

FIG. 1. Comparison of femoral neck bone mineral density (BMD) between HIV-infected Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN) study participants and matched controls from the National Health and Nutrition Examination Survey (NHANES) ($n=462$), 2004–2012. The distribution of femoral neck BMD (as measured by calculated T-scores) for 462 HIV-infected individuals from the SUN (*solid line*) and 462 control subjects matched for age, sex, race, and body mass index is demonstrated. The data for both groups are normally distributed but demonstrate a significant decrement in BMD among the HIV-infected cohort compared to the NHANES cohort (mean T-score −0.81 vs. −0.33, $p<0.001$).

The high prevalence of osteopenia and osteoporosis in our cohort and the identification of an increasing proportion of participants who continued to experience substantial bone loss over four years can better be contextualized by the increased fracture risk associated with low BMD. Higher fractures rates have been consistently reported among HIV-infected persons compared to the general population.[38,39] Moreover, HIV-infected persons often have risk factors for falling, such as multimorbidity, polypharmacy, peripheral neuropathy, and frailty, which lead to the development of fragility fracture at much younger ages.[39–41]

Our study was subject to several limitations. The SUN Study was conducted in only four U.S. cities; therefore, data presented here may not be generalizable to all HIV-infected persons in care in the United States. Our cohort is also heterogeneous with regard to antiretroviral exposure and other risk factors for low BMD. We also did not match subjects in the NHANES for tobacco use. As noted previously, our longitudinal analysis was limited by the small number of subjects and the short duration of follow-up that reduced statistical power. Furthermore, we did not have longitudinal data regarding participants' use of vitamin D, calcium supplements, bisphosphonates, or corticosteroids.

In conclusion, we found a high prevalence of osteopenia and osteoporosis among a cohort of HIV-infected persons that was significantly higher than that among matched controls from NHANES. Additionally, we found novel associations between baseline osteoporosis and low serum apolipoprotein E and being unemployed or retired. We also identified an increasing proportion of participants who continued to have a substantial degree of bone loss over 4 years, suggesting the

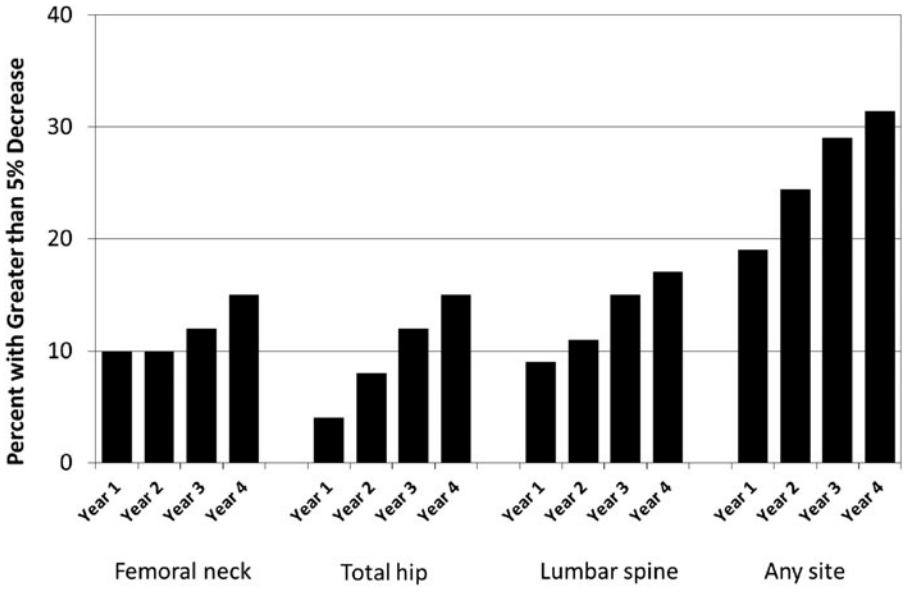

FIG. 2. Proportion of participants with at least 5% loss in bone mineral density over 4 years of follow-up ($n=170$), the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN) Study 2004–2012. The increasing proportion of participants in the SUN Study with ≥5% decline in bone mineral density (BMD) at key sites for osteoporotic fractures (femoral neck, total hip, and lumbar spine) as measured by annual dual X-ray absorptiometry (DXA) scan is demonstrated. Data are also included from 170 persons who maintained virologic suppression for ≥2 years on antiretroviral therapy prior to the baseline DXA. At the 4-year DXA scan, ≥5% loss of BMD was identified in 15% of subjects at the femoral neck, 15% at the total hip, and 17% at the lumbar spine. The proportion of subjects with ≥5% decline in BMD at any of these sites is also demonstrated, showing that by 4 years, 31% of all persons had experienced ≥5% BMD decline at one or more relevant sites.

need for monitoring and potential clinical interventions. Further studies are warranted to determine effective measures to prevent fragility fractures as our population ages.

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