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Racial Differences in Bone Loss and Relation to Menopause Among HIV-infected and Uninfected Women

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Abstract

Objective—To characterize changes in bone mineral density (BMD) according to race among HIV-infected and uninfected women, and to evaluate the relationship between race and menopause-related bone loss.

Methods—Dual x-ray absorptiometry measured BMD on study entry and a minimum of 18 months later in 246 HIV-infected and 219 HIV-uninfected women in the Menopause Study. Linear regression analyses determined percent annual BMD change at total hip (TH), femoral neck (FN), and lumbar spine (LS) after adjusting for potential confounders. Race-stratified and HIV-infected subgroup analyses were performed.

Results—At baseline, mean age was 45 years, 19% of women were postmenopausal. HIV-infected women were more likely to be black (58% vs. 38%), and had lower BMI and less cigarette exposure when compared to HIV-uninfected women. Women who were perimenopausal at baseline and postmenopausal at follow-up had the greatest TH bone loss (−1.68%/yr, p<.0001) followed by those postmenopausal throughout (−1.02%/yr, p=.007). We found a significant interaction between HIV status and race in multivariate analyses of BMD change at the FN and TH. In race-stratified analyses, HIV infection was associated with TH BMD loss in non-black

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CONFLICT OF INTEREST

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women. Black women experienced greater menopause-associated decline in TH BMD compared with non-black women.

Conclusions—The association of HIV and BMD differs strikingly by race, as do the effects of the menopausal transition on bone. Determining the extent to which the effect of HIV on fracture risk varies by race will be crucial to identify HIV-infected women at greatest risk for osteoporotic fracture, particularly as they enter menopause.

Keywords

bone mineral density; menopause; HIV; race; women; osteoporosis

INTRODUCTION

Long-term consequences of HIV infection and its treatment, particularly disturbances of bone metabolism, are emerging concerns given the growing numbers of older adults living with HIV. Reduced bone mineral density (BMD) is common in persons living with HIV, who are estimated to be at over 3 times the risk for osteoporosis and almost 7 times the risk of osteopenia as their uninfected counterparts [1]. Emerging fracture data are worrisome, showing 30–70% higher fracture rates among HIV-infected persons compared with uninfected persons [2–4.] Although race and ethnicity are known to be important factors influencing osteoporosis and fracture risk in population based studies, few studies conducted in HIV-infected persons have specifically examined the contribution of race to osteoporosis. Additionally, studies focusing on BMD in HIV-infected women have generally lacked a seronegative comparison group with similar demographic characteristics and risk factors for osteoporosis, or have included either only premenopausal women [5–9] or only postmenopausal women [10]. In the general population, the most important risk factor for bone loss in middle-aged women is menopause. Yet there is wide variation in the rate of bone loss during the menopausal transition, with some women experiencing rapid bone loss and others having relatively stable BMD [11–13]. Patterns of bone loss during the menopausal transition may vary by race/ethnicity, which may in turn, contribute to differences in fracture rates. We undertook this study to evaluate racial and ethnic differences in risk for bone loss among middle-aged HIV-infected and uninfected women, and to investigate the relationship between race and bone loss associated with the menopausal transition among HIV-infected and at-risk women.

METHODS

Study Participants

Between August 2001 and July 2003, women over age 35 were recruited from methadone programs, primary care clinics, and community newsletters in the Bronx, New York, and enrolled in the Menopause Study cohort (MS) as previously described [14]. Enrollment was stratified so that 50% of the cohort was HIV-infected and 50% was uninfected, and within each strata 50% reported illicit drug use within 5 years, and 50% reported other high-risk behavior. Semiannual research visits included standardized interviews, phlebotomy, and height and weight measurements for body mass index (BMI) calculation. The current

analysis includes women who completed BMD measurement by dual x-ray absorptiometry (DEXA) on study entry and at a minimum of 18 months later. The MS was approved by the Institutional Review Boards of Montefiore Medical Center and Albert Einstein College of Medicine, and all participants provided written, informed consent.

Interview data

Standardized interviews were administered either in English or Spanish, using translated study instruments by trained research staff, and collected demographics, personal and family medical history, antiretroviral and other medication use, sexual history, reproductive and menstrual history, and exercise and dietary habits. Menopause status was based on self-report of bleeding pattern over the past year using menstrual diaries and defined according to World Health Organization (WHO) criteria [15]. Menopause was defined as at least 12 consecutive months of amenorrhea, and age at onset of menopause was determined as of the date of the last menstrual period, after WHO criteria were met. Women who reported amenorrhea for 12 months at their first visit were included. Perimenopause was defined as absence of menses in at least 3 cycles but for <12 months in the past year, and perimenopausal classification was retained until evidence of completion of menopause. For women who experienced onset of menopause at or just before the baseline interview, there was an average of 1 year of follow-up interviews for confirmation of menopause. Drug-use behaviors were measured at each visit, including drug type, route of administration, frequency, and methadone dose for subjects prescribed methadone replacement. The CAGE questionnaire was administered to screen for alcohol dependence [16], and amount and frequency of current alcohol use was also collected. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale [17], and depressive symptoms, drug use behaviors, and sexual history were assessed using audio computer-assisted self-interviewing technique, which enhances collection of stigmatic or sensitive information [18].

Laboratory Methods

Laboratory measures completed at each visit included HIV and Hepatitis C serologic testing, and for HIV-infected participants, CD4+ count and HIV viral load. Follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), estradiol (E2), and prolactin were collected annually, and during days 2–6 of the cycle for menstruating women. For women who had completed DEXA at two time points, using stored sera corresponding with time of the first DEXA, levels of 25-hydroxyvitamin D (25OHD) were assayed using ISYS automated immunoassay system (Immunodiagnostic Systems Inc.[IDS], Scottsdale, AZ); C-telopeptide of type 1 collagen (CTx) was analyzed using ELISA (Serum CrossLaps; IDS, Scottsdale, AZ); bone-specific alkaline phosphatase (BAP) was analyzed using the Ostase BAP EIA (IDS, Scottsdale, AZ); osteocalcin (OC) was analyzed using the N-Mid Osteocalcin ELISA (IDS, Scottsdale, AZ).

Bone Mineral Density Assessment

BMD (g/cm^2) of the total hip (TH), femoral neck (FN), and lumbar spine (LS, L2–L4) were measured at two time points using a Prodigy densitometer with GE Lunar software, version 6.8, with only one densitometer used for the entire study.

Statistical Analysis

Linear regression models examined the relationship between annual percent change in BMD at total hip (TH), femoral neck (FN), and lumbar spine (LS) and race in relation to menopause after adjusting for potential confounders (see below). Because race was strongly associated with BMD and there were unequal proportions of black women in the HIV-positive and HIV-negative groups, we constructed models stratified by race (black vs. non-black), and tested for an interaction between HIV status and race. Unique models were constructed for TH, FN, and LS for both race strata that included the same variables as in the combined models. Levels of bone turnover markers (CTx, OC, and BAP) were $\log_{10}$ transformed for analyses. Subgroup analyses assessed associations between HIV-specific factors and % change in BMD per year.

To avoid the problems associated with stepwise variable selection we first created two sets of independent variables for each of two groups: all women and HIV-infected women. One set was forced covariates included in all regressions for substantive reasons and another of covariates and independent variables that we were interested in assessing [19–21]. Forced covariates were: age, race, BMI, menopause status (at baseline and follow-up), smoking pack years, history of methadone use, HIV serostatus, Hepatitis C virus serostatus, FSH level, 25OHD level, and baseline BMD. Forced covariates for analyses restricted to HIV-infected women included history of AIDS diagnosis, duration of HIV diagnosis, CD4+ cell count, use of tenofovir, and use of antiretroviral therapy (ART) in addition to those covariates forced into analyses of the full cohort. Antiretroviral use was categorized as never use, initiation during the study period in ART naïve persons, use at first DEXA with subsequent discontinuation during the study period, reinitiation of antiretrovirals during the study period in non-naïve persons, and continuous use throughout the study. Tenofovir use was categorized similarly however no persons re-initiated tenofovir during the study. After performing multiple regressions with the forced covariates, we then performed multiple regressions with forced variables and other covariates of interest.

RESULTS

Study Participants

Participant characteristics are shown in Table 1. Of the 465 participants, 246 (53%) were HIV-infected. At baseline, 19% of women were postmenopausal, and an additional 10% of HIV-infected women and 6% of HIV-uninfected women became postmenopausal over the study period. HIV-infected women were younger and more likely to be black than were HIV-uninfected women, had lower BMI, less lifetime cigarette exposure, and were less likely to report a history of opioid exposure. Among HIV-infected women, 11% were antiretroviral therapy naïve, 85% reported past NRTI use, and 63% reported PI use. Tenofovir was initiated between the 2 DEXA measurements in 26% of HIV-infected women, 3% were on tenofovir at the time of the first DEXA and continued tenofovir throughout the study period, and 69% reported never using tenofovir. Cross-sectional and longitudinal BMD analyses have previously been published by our group, and the current analyses include new data on bone turnover markers and new regression analyses of the

effects of race, menopause, and initiation and discontinuation of antiretrovirals including tenofovir on bone mineral density [22, 23].

HIV-infected women had lower baseline BMD at the TH and FN when compared with HIV-uninfected women, in addition to higher levels of both bone formation and resorption markers. Median values of OC were higher in HIV-infected women compared with uninfected women [10.8 ng/mL for HIV+, (IQR 7.2–17.9) vs.9.4 ng/mL for HIV− (IQR 5.9–13.5); p=.001]. Median CTx level was also higher in HIV-infected women compared with uninfected women [0.19 ng/mL for HIV+, (IQR 0.13–0.31) vs. 0.17 ng/mL for HIV− (IQR 0.12–0.24); p =.02]. Mean time between the two DEXA scans was slightly lower for HIV-infected women (1.80 years + 0.28 for HIV+ vs.1.88 yrs + 0.34 for HIV−; p= 0.005). When comparing subjects who completed two DEXA scan to those who completed one, we found no significant differences between groups in terms of race, menopause status, opioid or methadone use, hepatitis C serostatus, history of corticosteroid use, FSH level, age, cigarette pack years, number of alcohol-containing drinks, or BMI. Baseline BMD at LS (1.20 g/cm^2 + 0.17 for one DXA, vs. 1.22 g/cm^2 + 0.17, p=0.23), and TH (1.03 g/cm^2 + 0.17 for one DEXA, vs. 1.06 g/cm^2 + 0.15, p=0.06) were similar between groups, however FN BMD was higher at baseline in those who completed both initial and follow-up DEXA when compared to those who had only one DEXA measure (0.99 g/cm^2 + 0.15 for one DEXA vs. 1.02 g/cm^2 + 0.14 for two DEXA, p=0.02).

Analysis of Annual % Change in Bone Mineral Density in the Full MS Cohort

In unadjusted analyses, mean annual % change in BMD was similar between HIV-infected and uninfected women at the TH (−0.34%/y HIV+ vs. −0.38%/y HIV−, p=0.88), FN (−0.47%/y HIV+ vs. −0.50%/y HIV−, p=0.88), and LS (−0.54%/y HIV+ vs. −0.17%/y HIV −, p=0.13). In multivariable analyses, we found a significant interaction between HIV status and race in analyses of change in BMD at FN and TH, showing that the combined effects of HIV and race on BMD vary, and we thus conducted race-stratified analyses. In analyses of the full MS cohort, when compared with women who remained premenopausal throughout the study period, women who were perimenopausal at baseline and postmenopausal at follow-up had the greatest amount of TH bone loss (−1.68%/yr, p<.0001), followed by those postmenopausal throughout (−1.02%/yr, p=.0066), and those pre-menopausal at baseline and perimenopausal at follow-up (−0.64%/yr, p=.024) or perimenopausal throughout (−0.58%/yr, p=.019) (Table 2.) BMI was positively associated with TH, FN, and LS BMD, while hepatitis C seropositivity was associated with FN BMD decline (−0.56%/yr, p=.019), and serum FSH level was associated with LS BMD decline (−0.020%/yr BMD change per IU/L of baseline FSH level, p=.014.

Race-stratified Analyses of Annual % Change in BMD

The association of HIV and change in BMD differed strikingly by race: although HIV infection was not associated with bone loss among black women, it was associated with −0.55% greater TH bone loss per year among non-black women, relative to non-black women who were HIV-uninfected (Table 3). Moreover, we found racial differences in bone loss associated with menopause. Among black women, we observed menopause-related bone loss at the TH in particular, such that when compared with black women who remained

premenopausal throughout the study period, those who were perimenopausal at baseline and postmenopausal at follow-up had the greatest amount of TH bone loss (−1.89%/yr, p=0.0017), followed by those postmenopausal throughout (−1.29%/yr, p=0.0033), and those pre-menopausal at baseline and perimenopausal at follow-up (−1.022%/yr, p=0.014) or perimenopausal throughout (−0.76%/yr, p=0.050). Among non-black women, compared with those who remained premenopausal throughout, menopause-related bone loss was significant for women transitioning from perimenopause to postmenopause, and at the TH only (−1.50%/yr, p=0.0047).

Annual % Change in BMD among HIV-infected Women Only

Table 4 shows sub-analyses performed in HIV-infected women. Although initiation of antiretroviral therapy in treatment-naive women was not associated with loss of BMD at any site, re-initiation of ART in treatment-experienced women was associated with loss of FN BMD. Tenofovir initiation was not associated with loss of BMD, whereas tenofovir discontinuation was associated with increases in FN and LS BMD. Other HIV-related factors such as CD4+ count, history of AIDS defining illness, and duration of HIV diagnosis were not associated with change in BMD at any site. The relationship between menopause and TH bone loss was similar in the subset of HIV-infected women to that observed in the overall cohort, although the magnitude of loss was slightly greater in HIV-infected women.

Differences in Bone Turnover Markers

Levels of baseline bone formation (BAP and OC) and resorption (CTX) markers correlated inversely with baseline BMD at all three sites among HIV-infected women ($p<.05$), but only BAP was significantly correlated with change in BMD over time, and only at the lumbar spine ($r=0.13$, $p<.05$) (data not shown). In multivariable, race-stratified analyses of baseline BMD which included BTMs, none of the BTMs were associated with baseline BMD at any site among black women. Among non-black women however, BAP was associated with reduced BMD at all sites, and CTX was associated with reduced baseline LS BMD. In longitudinal multivariable analyses, BTMs were not predictive of BMD change at any site among black women, and for non-black women, only osteocalcin was associated with increase in FN BMD (data not shown). None of the BTMs were associated with change in BMD at any site in the full Menopause Study cohort. In the subset of HIV-infected women, $\log_{10}$BAP was associated with higher BMD at the femoral neck only (1.81%/y for each 10-fold change in BAP in mcg/L; p=0.036, 95% CI: 0.12–3.50).

DISCUSSION

We observed significant racial differences in risks for bone loss in this cohort of middle-aged HIV-infected and at-risk women. In particular, we found that the effects of HIV infection on BMD over time were very different for black women and non-black women. Although HIV infection was associated with bone loss among non-black women, this was not the case among black women. In analyses of the entire Menopause Study cohort, HIV was not associated with change in BMD; however this is likely due to the differential effect of HIV among black vs. non-black women, which became evident only upon conducting race-stratified analyses and testing for an interaction between race and HIV status, which

was statistically significant. It is well known that race and ethnicity are important factors influencing the incidence of osteoporosis and osteoporotic fracture, yet studies conducted in HIV-infected persons have not specifically examined the contribution of race to bone loss.

Annual fractures and costs in the United States are projected to grow by 50% between 2005 and 2025, surpassing 3 million and $25 billion, respectively. Nonwhite populations will comprise a growing proportion of total osteoporosis fractures and related costs; in 2005, 12% of all fractures occurred in nonwhites, but by 2025, this percentage is expected to rise to 21% [24.] Rates of osteoporosis for white and hispanic women have declined, but not for African American women, according to data from Third National Health and Nutrition Examination Survey (NHANES) 1988–94, and NHANES 2005–06, although these differences are unexplained [25.] While the relative risk of fractures is lower in minority women compared with white women, their absolute risk of fracture is still significant [26]. Within 1 year in the Observational Study of the Women's Health Initiative, fractures were more common in minority women than myocardial infarction/coronary heart disease death, stroke, and breast cancer combined [27.] Consequences of osteoporotic hip fracture also differ by ethnicity and race, and mortality after hip fracture is higher for African American women compared with white women [28.] Although data on outcomes after hip fracture in non-white populations are limited, one study found the percentage of patients with hip fracture who were non-ambulatory at discharge was six times higher among African American women compared with white women [29.] Understanding racial and ethnic differences in risk for osteoporosis and fracture, as well as the health consequences of these fractures, will be crucial in order to develop interventions to reduce the burden of disease. For HIV-infected women, it will be important to determine whether the relationship between BMD and fracture varies by race, or differs from that observed in uninfected women, and what the consequences of osteoporotic fractures are in terms of pain, disability, and mortality as the HIV-infected population ages.

While BTMs were associated with baseline BMD in the Menopause Study cohort, they were not particularly predictive of BMD change, regardless of HIV status. Additionally, BTMs did not perform as well in black women compared with non-black women, and BTMs were neither associated with baseline BMD nor BMD change in black women. Our results differ somewhat from the findings of Yin et al, who conducted a small prospective cohort study of 128 (73 HIV+, 55 HIV−) postmenopausal Hispanic and African-American women and found that HIV status was associated with bone loss at the LS, TH, and ultra-distal radius (UDR), although age, race/ethnicity, and BMI were not associated with change in BMD at any site [10.] In that study, HIV-infected women had significantly higher levels of OC and CTx compared with uninfected women, and among HIV-infected women, serum NTx predicted bone loss at the distal radius and bone-specific alkaline phosphatase and serum NTx predicted bone loss at the UDR. Our study differed from Yin's in that we did not limit our study to postmenopausal women, nor to only racial and ethnic minority women; furthermore we recruited HIV-uninfected subjects to have similar behavioral risk factors as the HIV-infected subjects, rather than recruiting from general medical ambulatory clinics.

Our finding that HIV-infection was associated with bone loss in non-black women is somewhat surprising, as most published longitudinal studies in HIV-infected adults have

shown a decline in BMD within the first two years of HAART initiation, and stable BMD thereafter, and the majority of Menopause Study participants were antiretroviral treatment experienced and maintained on continuous therapy [30–33.] Initiation of HAART among antiretroviral naive women was not associated significantly with bone loss, however only 8 (3%) of the HIV-infected participants were antiretroviral therapy naive HAART initiators, and thus we were likely underpowered to observe effects of HAART on BMD in naive subjects, who would be expected to experience the greatest amount of antiretroviral therapy associated bone loss.

In this treatment experienced cohort, continuous antiretroviral therapy was not associated with bone loss, whereas re-initiation of ART was independently associated with reductions in BMD. Initiation of tenofovir during the study period was not associated with loss of BMD, unlike other reports associating tenofovir with accelerated BMD loss [34–38]. We found higher BMD at the FN and LS after tenofovir discontinuation, although our findings must be regarded with caution given the small numbers of HIV-infected women stopping tenofovir and unclear indications for its discontinuation. Others have described bone recovery after discontinuation of tenofovir, although these studies have been limited by non-randomized design [39] and small sample size [39, 40], and were conducted in predominantly white men [39, 40].

We were able to characterize not only the effect of the menopausal transition on BMD in HIV-infected and uninfected women, but also the influence of race. We found that the greatest amount of bone loss with menopause was seen at the total hip, particularly in black women. Bone loss was greatest for women as they transitioned from perimenopause to postmenopause, however postmenopausal women continued to lose more bone than women who remained premenopausal or perimenopausal throughout. These relationships were similar in the subset of HIV-infected women, who also had significant bone loss at the lumbar spine, associated with transition into perimenopause, or remaining in perimenopause. To our knowledge, this is the first study to evaluate the specific effect of the menopausal transition on BMD in HIV-infected women, or racial differences in bone loss with menopause. The Study of Women's Health Across the Nation (SWAN) Bone Study measured BMD at the LS and TH annually in a large multiethnic cohort of women and found little change in BMD during pre- or early perimenopause, marked acceleration of bone loss in late perimenopause and continued loss in postmenopause; however ethnic differences in rates of bone loss were largely eliminated after controlling for body weight [41.] Like SWAN, we found that the greatest amount of bone loss occurred as menopause approached, followed by the postmenopausal state. However unlike SWAN, we observed significant differences in bone loss by race despite adjusting for BMI, and in our study a greater amount of TH bone loss occurred than LS. A 10-year study in the SWAN found that annual transmenopausal (from 1 year before to 2 years after Final Menstrual Period) FN bone loss was greater in Asians and less in African Americans when compared with whites, and that African American women experienced less transmenopausal LS bone loss; however racial/ethnic differences in 10-year cumulative bone loss were small, and on the order of 1–2% [42]. Similar to our results, in that study, BMI independent racial/ethnic variation in bone loss were observed, and greater BMI and African American heritage were related to slower bone loss rates.

Our study has several limitations. Only a sub-set of the entire cohort had a repeat DEXA due to loss to follow-up, which may have resulted in a selection bias. Characteristics of those women who completed one DEXA and those who completed two DEXA scans were similar in terms of risk factors for osteoporosis, however. Because our data was collected as part of an observational study, our findings are subject to possible unmeasured confounding. Additionally because our cohort included only women with or at-risk for HIV infection, results are not generalizable to HIV-infected men, however because we were interested in understanding the relationship between menopause and bone loss, our study could only have been performed in a female population. Our study also has a number of strengths, particularly the inclusion of an HIV-uninfected comparison group with similar behavioral risk profiles and demographics to the HIV-infected group, and large number of women under study over five years. Lastly, the Menopause Study cohort was designed specifically to examine metabolic complications of HIV infection in women as they transition through menopause, and thus uniquely poised to evaluate the effects of menopause on bone mineral density, which has not previously been well characterized.

CONCLUSIONS

Significant racial differences in risks for bone loss exist among middle-aged HIV-infected and uninfected women. The effects of HIV infection on BMD over time are very different for black women and non-black women, as is the amount of bone loss associated with the menopausal transition. Determining the extent to which the effect of HIV on fracture risk varies by race will be crucial to identify HIV-infected women at greatest risk for osteoporotic fracture, particularly as they enter menopause. It is unclear whether current algorithms to evaluate fracture risk can accurately estimate the probability of fracture among HIV-infected women, and what the relative importance of race is in predicting fracture risk in HIV-infected women. Understanding racial and ethnic differences in risk for osteoporosis and fracture, as well as the health consequences of these fractures, will be crucial in order to develop interventions such as evidence-based screening recommendations, to reduce the burden of osteoporotic disease among HIV-infected women as they enter menopause.

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Highlights

- The association of HIV and bone mineral density differs strikingly by race.
- Menopause-associated bone loss was greater in black women than non-black women.
- HIV infection was associated with total hip bone loss in non-black women.
- Re-initiation of antiretrovirals was associated with reduced bone mineral density.
- Tenofovir discontinuation was associated with increase in bone mineral density.

Table 1

Menopause Study participant characteristics

Characteristic[a,b]	HIV− n=219	HIV+ n=246	P value[c]
Age at 1st exam (yrs), mean ± SD	48.0 ± 5.1	46.9 ± 4.9	.02
Race (%)			<.0001
Black	38.4	57.7	
Not Black (White, Hispanic, Other)	61.6	42.3	
Menopause status: visit 1 & 2 (%)			.57
Premenopausal (1) Premenopausal (2)	32.1	29.3	
Premenopausal (1) Perimenopausal (2)	16.0	14.2	
Perimenopausal (1) Perimenopausal (2)	26.4	25.9	
Perimenopausal (1) Postmenopausal (2)	6.1	10.3	
Postmenopausal (1) Postmenopausal (2)	19.3	20.3	
BMI at visit 1 (kg/m^2), mean ± SD	32.0 ± 7.1	28.2 ± 6.4	<.0001
Past estrogen therapy (%)	8.7	12.6	.17
Ever corticosteroid use (%)	10.5	9.0	.58
Smoking history (%)			.10
Nonsmoker	8.7	9.4	
Former smoker	21.0	29.3	
Current smoker	70.3	61.4	
Pack years at visit 1, mean ± SD	18.5 ± 15.9	14.4 ± 14.0	.003
Alcohol drinks per day, mean ± SD	0.39 ± 1.14	0.41 ± 0.09	.86
Opioid use ever (%)	54.3	31.3	<.0001
Methadone use ever (%)	46.1	21.6	<.0001
Hepatitis C Virus seropositivity (%)	47.7	51.5	.42
FSH level (IU/L), mean ± SD	46.1 ± 5.1	45.1 ± 4.2	.03
25OH vitamin D level (ng/mL), mean ± SD	18.8 ± 8.9	19.3 ± 9.6	.60
Log_{10} BAP (mcg/L), mean ± SD	1.26 ± 0.17	1.29 ± 0.20	.14
Log_{10} Osteocalcin (ng/mL), mean ± SD	0.94 ± 0.33	1.03 ± 0.36	.007
Log_{10} CTx (ng/mL), mean ± SD	−0.78 ± 0.23	−0.71 ± 0.30	.004
Total hip BMD (g/cm^2) (mean ± SD)	1.08 ± 0.14	1.04 ± 0.15	.002
Femoral neck BMD (g/cm^2) (mean ± SD)	1.04 ± 0.14	1.01 ± 0.14	.02

Characteristic[a,b]	HIV− n=219	HIV+ n=246	P value[c]
Lumbar spine BMD (g/cm^2) (mean ± SD)	1.23 ± 0.17	1.21 ± 0.17	.14
History of AIDS diagnosis	NA[d]	31.3	NA[d]
CD4 count (cells/ml), median (IQR)	NA[d]	486 (321, 697)	NA[d]
HIV RNA viral load (copies/ml), median (IQR)	NA[d]	141.3 (75.9, 4,265.8)	NA[d]
HIV RNA viral load (log_{10} copies/ml), median (IQR)	NA[d]	2.2 (1.9, 3.6)	NA[d]
Antiretroviral therapy use (%)			
Never use	NA[d]	11.4	NA[d]
Initiation (naive)	NA[d]	3.3	NA[d]
Discontinuation	NA[d]	5.3	NA[d]
Re-initiation	NA[d]	10.2	NA[d]
Continuous use	NA[d]	69.5	NA[d]
Tenofovir use (%)			
Never use	NA[d]	68.7	NA[d]
Initiation	NA[d]	25.6	NA[d]
Discontinuation	NA[d]	0.8	NA[d]
Continuous use	NA[d]	3.3	NA[d]
Time from HIV diagnosis (yrs, %)			
Unknown	NA[d]	1.6	NA[d]
< 5	NA[d]	19.9	NA[d]
5–9	NA[d]	36.6	NA[d]
≥10	NA[d]	41.9	NA[d]

[a] Abbreviations: HIV: human immunodeficiency virus; BMI: body mass index; BMD: bone mineral density; FSH: follicle-stimulating hormone; BAP: bone-specific alkaline phosphatase; OC: osteocalcin; CTx: C-telopeptide

[b] Values are expressed as mean ± SD for continuous variables and % for categorical variables

[c] Compares HIV− to HIV+ with independent samples t-test for continuous variables and with chi-square for categorical variables

[d] NA not applicable since only applies to HIV+

Menopause participant characteristics have been previously published (Sharma A, et al. Maturitas. 2011 Nov; 70(3): 295–301.)

Table 2

Factors Associated with % Annual Change in BMD (g/cm^2) in the Menopause Study Cohort

	Total Hip (p; 95% CI)	Femoral Neck (p; 95% CI)	Lumbar Spine (p; 95% CI)
Black race*HIV	**1.00 (0.0070; 0.27, 1.72)**	**1.30 (0.0032; 0.44, 2.16)**	0.43 (0.40; −0.58, 1.45)
Black race	−0.42 (0.13; −0.96, 0.12)	**−0.72 (0.032; −1.37, −0.064)**	0.028 (0.94; −0.74, 0.80)
HIV+ serostatus	−0.46 (0.080; −0.98, 0.054)	−0.49 (0.12; −1.10, 0.13)	−0.59 (0.11; −1.31, 0.13)
BMI (kg/m^2)	**0.044 (0.0026; 0.015, 0.073)**	**0.035 (0.040; 0.0016, 0.069)**	**0.096 (<0.0001; 0.058, 0.13)**
Menopause status (time 1 & 2)			
Pre-menopausal (1) Pre-menopausal (2)	Reference	Reference	Reference
Pre-menopausal (1) Peri-menopausal (2)	**−0.64 (0.024; −1.19, −0.086)**	**−0.68 (0.043; −1.34, −0.023)**	−0.68 (0.085; −1.46, 0.095)
Peri-menopausal (1) Peri-menopausal (2)	**−0.58 (0.019; −1.055, −0.097)**	−0.31 (0.29; −0.88, 0.27)	−0.22 (0.51; −0.90, 0.45)
Peri-menopausal (1) Post-menopausal (2)	**−1.68 (<0.0001; −2.43, −0.92)**	−0.79 (0.080; −1.68, 0.096)	−0.53 (0.32; −1.57, 0.52)
Post-menopausal (1) Post-menopausal (2)	**−1.020 (0.0066; −1.75, −0.29)**	−0.49 (0.27; −1.36, 0.38)	−0.53 (0.31; −1.56, 0.49)
HCV+ serostatus	−0.19 (0.33; −0.58, 0.20)	**−0.56 (0.019; −1.026, −0.095)**	−0.21 (0.45; −0.76, 0.34)
FSH level (per IU/L)	−0.0079 (0.20; −0.020, 0.0041)	−0.00029 (0.97; −0.014, 0.013)	**−0.020 (0.014; −0.036, −0.0042)**

Abbreviations: BMD: bone mineral density; CI: confidence interval; HIV: human immunodeficiency virus; BMI: body mass index. Models are adjusted for baseline BMD, age, race, BMI, menopause status at time 1 and 2 (reference value is premenopausal at time 1 and 2), smoking pack years, methadone use, HIV status, HCV status, FSH level, 25OH vitamin D

Table 3

Racial Differences in Factors Associated with % Annual Change in BMD (g/cm^2) in the Menopause Study Cohort

	Total Hip (p; 95% CI)		Femoral Neck (p; 95% CI)		Lumbar Spine (p; 95% CI)	
	Black Women	**Non-Black Women**	**Black Women**	**Non-Black Women**	**Black women**	**Non-Black Women**
HIV+ serostatus	0.58 (0.064; −0.033, 1.20)	**−0.55 (0.037; −1.064, −0.033)**	**0.81 (0.027; 0.095, 1.53)**	−0.53 (0.10; −1.17, 0.11)	−0.17 (0.63; −0.86, 0.53)	−0.63 (0.15; −1.49, 0.23)
BMI (kg/m^2)	0.040 (0.060; −0.0016, 0.082)	**0.054 (0.011; 0.013, 0.096)**	0.031 (0.21; −0.018, 0.080)	0.042 (0.089; −0.0065, 0.090)	**0.099 (<0.0001; 0.054, 0.15)**	**0.089 (0.0048; 0.028, 0.15)**
Menopause status (time 1 & 2)						
Pre-menopausal (1) Pre-menopausal (2)	Reference	Reference	Reference	Reference	Reference	Reference
Pre-menopausal (1) Peri-menopausal (2)	**−1.022 (0.014; −1.83, −0.21)**	−0.17 (0.67; −0.96, 0.61)	−0.80 (0.10; −1.76, 0.15)	−0.65 (0.18; −1.61, 0.30)	**−1.20 (0.011; −2.13, −0.28)**	−0.090 (0.89; −1.38, 1.20)
Peri-menopausal (1) Peri-menopausal (2)	**−0.76 (0.050; −1.52, −0.0013)**	−0.46 (0.15; −1.093, 0.17)	−0.67 (0.14; −1.56, 0.23)	−0.082 (0.84; −0.86, 0.69)	−0.12 (0.79; −0.98, 0.74)	−0.32 (0.54; −1.36, 0.72)
Peri-menopausal (1) Post-menopausal (2)	**−1.89 (0.0017; −3.057, −0.72)**	**−1.50 (0.0047; −2.53, −0.46)**	−0.73 (0.29; −2.08, 0.62)	−0.95 (0.13; −2.19; 0.28)	−0.35 (0.59; −1.66, 0.95)	−0.73 (0.39; −2.39, 0.93)
Post-menopausal (1) Post-menopausal (2)	**−1.29 (0.033; −2.47, −0.11)**	−0.84 (0.090; −1.81, 0.13)	−0.91 (0.20; −2.30, 0.49)	−0.29 (0.63; −1.46, 0.88)	−0.70 (0.30; −2.054, 0.64)	−0.33 (0.68; −1.90, 1.24)
FSH (IU/L)	−0.0058 (0.56; −0.025, 0.014)	−0.0096 (0.24; −0.026, 0.0064)	−0.00075 (0.94; −0.022, 0.020)	0.0024 (0.80; −0.016, 0.021)	**−0.029 (0.0057; −0.049, −0.0085)**	−0.012 (0.34; −0.037, 0.013)

Abbreviations: BMD: bone mineral density; CI: confidence interval; HIV: human immunodeficiency virus; BMI: body mass index. Models are adjusted for baseline BMD, age, BMI, menopause status at time 1 and 2 (reference value is premenopausal at time 1 and 2), smoking pack years, methadone use, HIV status, HCV status, FSH level, 25OH vitamin D

Table 4

Factors Associated with % Annual Change in BMD (g/cm^2) among HIV+ Women in the Menopause Study Cohort

	Total Hip (p value; 95% CI)	Femoral Neck (p value; 95% CI)	Lumbar Spine (p value; 95% CI)
Black race	**0.72 (0.016; 0.14, 1.30)**	**0.69 (0.029; 0.073, 1.30)**	0.58 (0.15; −0.21, 1.36)
BMI (kg/m^2)	**0.073 (0.0026; 0.026, 0.12)**	**0.072 (0.0043; 0.023, 0.12)**	**0.11 (0.0005; 0.046, 0.16)**
Serum 25OH vitamin D (ng/mL)	**0.033 (0.028; 0.0036, 0.062)**	0.024 (0.12; −0.0060, 0.054)	**0.044 (0.027; 0.0049, 0.082)**
Menopause status: (time 1 & 2)			
Pre-menopausal (1) Pre-menopausal (2)	Reference	Reference	Reference
Pre-menopausal (1) Peri-menopausal (2)	**−0.88 (0.039; −1.71, −0.046)**	−0.51 (0.27; −1.42, 0.40)	−1.054 (0.077; −2.22, 0.11)
Peri-menopausal (1) Peri-menopausal (2)	−0.63 (0.091; −1.35, 0.10)	−0.73 (0.071; −1.52, 0.062)	−0.99 (0.055; −1.99, 0.021)
Peri-menopausal (1) Post-menopausal (2)	**−1.70 (0.0015; −2.74, −0.66)**	−1.068 (0.059; −2.18, 0.042)	−0.88 (0.22; −2.29, 0.54)
Post-menopausal (1) Post-menopausal (2)	**−1.38 (0.011; −2.43, −0.33)**	−1.025 (0.077; −2.16, 0.11)	−1.21 (0.10; −2.67, 0.25)
Antiretroviral therapy use			
Never use	Reference	Reference	Reference
Initiation (naïve)	−1.39 (0.21; −3.57, 0.79)	−2.092 (0.063; −4.30, 0.12)	−0.37 (0.80; −3.20, 2.46)
Discontinuation	0.66 (0.31; −0.61, 1.93)	−0.083 (0.91; −1.49, 1.32)	−0.63 (0.49; −2.42, 1.17)
Re-initiation	−0.50 (0.39; −1.67, 0.66)	**−1.85 (0.0054; −3.15, −0.55)**	−0.12 (0.88; −1.75, 1.51)
Continuous use	0.48 (0.25; −0.35, 1.32)	−0.14 (0.76; −1.074, 0.79)	0.44 (0.47; −0.75, 1.62)
Tenofovir use			
Never use	Reference	Reference	Reference
Initiation	−0.19 (0.55; −0.82, 0.44)	−0.098 (0.77; −0.77, 0.57)	−0.66 (0.13; −1.52, 0.19)
Discontinuation	−0.67 (0.62; −3.30, 1.96)	**4.75 (0.0021; 1.74, 7.76)**	**4.03 (0.038; 0.22, 7.84)**
Continuous use	0.26 (0.73; −1.25, 1.77)	1.57 (0.070; −0.13, 3.28)	0.91 (0.41; −1.27, 3.094)

Abbreviations: BMD: bone mineral density; CI: confidence interval; HIV: human immunodeficiency virus; BMI: body mass index. Models are adjusted for baseline BMD, age, race, BMI, menopause status at time 1 and 2 (reference value is premenopausal at both times 1 and 2), smoking, methadone use, HCV status, FSH level, 25OH vitamin D level, AIDS history, CD4+ count, $\log_{10}$HIV RNA, length of HIV diagnosis, tenofovir use and HAART use