Published in final edited form as:
Maturitas. 2011 November ; 70(3): 295–301. doi:10.1016/j.maturitas.2011.08.003.

Prospective Evaluation of Bone Mineral Density among Middle-Aged HIV-Infected and Uninfected Women: Association between Methadone Use and Bone Loss

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Abstract

Objective—We undertook a prospective study to assess the impact of HIV infection on BMD in a cohort of HIV-infected and uninfected women that included illicit drug users, and to measure the contribution of traditional risk factors as well as HIV-related factors to loss of BMD over time.

Methods—We analyzed BMD at baseline and after ≥18 months in 245 middle-aged HIV-infected and 219 uninfected women, and conducted linear regression analysis to determine factors associated with annual BMD change at the femoral neck, total hip and lumbar spine.

Results—HIV-infected women had lower baseline BMD at the femoral neck and total hip compared with controls; unadjusted rates of BMD change did not differ by HIV status at any site. In multivariable analyses, we found that HIV seropositivity without protease inhibitor (PI) use was associated with BMD decline at the lumbar spine (−.009 gm/cm^2 per year, p=.03.) Additional

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Disclosure Statement. All authors: no conflicts of interest.

List of contributors and their role in the paper
Anjali Sharma: Concept and planning of the study, statistical analysis, and preparation of the manuscript..
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Competing Interest
All authors: no competing interests or conflict of interest

factors associated with BMD decline were: postmenopausal status, lower BMI, and methadone use at the lumbar spine; postmenopausal status and hepatitis C seropositivity at the femoral neck; and postmenopausal status, age, smoking, and lower BMI at the total hip (all p<.05). Among HIV-infected women, ≥3 years of PI use was associated with an increase in lumbar spine BMD (.013 gm/cm^2 per year, p=.008.)

Conclusions—Bone loss among HIV–infected middle-aged women was modest, and possibly mitigated by PI use. Methadone use was associated with BMD decline, and should be considered when evaluating women for osteoporosis risk.

Keywords

osteopenia; osteoporosis; bone mineral density; HIV; women

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. Studies focusing on bone mineral density (BMD) in HIV-infected women have generally lacked a seronegative comparison group with similar risk factors for osteoporosis, and have instead used either healthy or historical controls, or have excluded women who engaged in illicit drug use [1-4]. To our knowledge, there has been only one published longitudinal study of BMD among HIV-infected women which included HIV-uninfected women with lifestyle risk factors predisposing to bone loss, and that study included only premenopausal women [5]. We undertook a prospective study to assess the impact of HIV infection on BMD in a cohort of HIV-infected and uninfected women that included illicit drug users, and to measure the contribution of traditional risk factors as well as HIV-related factors to loss of BMD over time.

METHODS

Study Participants

Between August 2001 and July 2003, 620 women over age 35, with or at-risk for HIV infection were enrolled in the Menopause Study cohort (MS). This longitudinal analysis includes women who completed BMD measurement by dual x-ray absorptiometry (DEXA) on study entry and at a minimum of 18 months later. Participant recruitment and study design have been described elsewhere [6]. In brief, subjects from the MS were recruited from methadone maintenance clinics, primary care clinics, community newsletters, and by word-of-mouth, in the Bronx, New York. Enrollment was guided so that 50% of the cohort was infected with HIV and 50% was uninfected. In both strata, 50% reported illicit drug use within the past 5 years, and 50% reported other high-risk behavior. Participants underwent semiannual research visits, which included standardized interviews, phlebotomy, and height and weight measurements for calculation of body mass index (BMI). 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 administered either in English or Spanish by trained research staff collected demographic characteristics, personal and family medical history, use of antiretrovirals and other medication, 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 criteria (i.e., after 12 months of amenorrhea, the date of the LMP is

established) [7]. 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 [8], and amount and frequency of current alcohol use was also collected. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale (CES-D), a 20-item scale on which a score of 16 or more has been used as a criterion for significant depressive symptoms, and a cutoff score of 23 has been used to indicate more severe levels of depressive symptoms [9]. Depressive symptoms, drug use behaviors, and sexual history were assessed using audio computer-assisted self-interviewing (A-CASI) [10].

Laboratory Methods

Laboratory measures completed at each visit and included HIV serologic testing, and for HIV-infected participants, CD4+ lymphocyte count, complete blood count, and HIV viral load.

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 (GE Healthcare). Osteopenia was defined as BMD >1.0 SD and <=2.5 SD below the average peak bone mass in young adult women at any of the three sites examined (T-score between −1.0 and −2.5), osteoporosis was defined as a T-score < −2.5, and normal BMD was defined as a T-score > −1.0 at all three sites [11].

Data Analysis

Analysis of Variance was used to compare differences in means of BMD at baseline and follow-up at the TH, FN, and LS as well as mean change in BMD at each of the three sites by protease inhibitor (PI) use history and HIV status. Multivariable linear regression analysis was conducted to determine factors independently associated with change in BMD per year at each bone site after adjusting for baseline BMD. Separate regression models were constructed for the HIV-infected subset. In the analyses, CESD score was dichotomized, so that a score ≥23 was compared with below 23, with higher scores indicating greater depressive symptomatology. Women who reported a history of ever smoking were compared with non-smokers. Women who reported any alcohol intake within 6 months were compared with those who reported none. Menstrual status was dichotomized as post-menopausal status vs. else. Women who reported performing either moderate or strenuous exercise at least 2 days per week were classified as physically active. We categorized HIV status and PI exposure as: HIV−, HIV+ with PI exposure, and HIV+ without PI exposure in analyses with HIV− as reference. We tested for interactions between HIV serostatus and methadone use, and for methadone use and menopausal status. Race, baseline BMD, menopausal status, smoking history, BMI, HIV+, HIV status + with PI exposure, and methadone use were forced into regression models. Age, CESD ≥23, hepatitis C virus serostatus, exercise habits, heroin use within 5 years, alcohol use, change in menopausal status, change in BMI or weight, and prior use of estrogen or corticosteroids were allowed to enter in a forward stepwise procedure with $p < .10$ as criterion for entry. Similar models were constructed in the subset of HIV-infected women. For models restricted to HIV-infected women, AIDS diagnosis, duration of HIV diagnosis, CD4+ cell count, prior use of tenofovir, nucleoside analog reverse transcriptase inhibitors (NRTIs), non-nucleoside analog reverse transcriptase inhibitors (NNRTIs), PIs as well as duration of use for PIs, NRTIs, and NNRTIs were also allowed to enter in a forward stepwise procedure with $p < .10$ as criterion for entry. Because we observed a potentially protective effect of PI

use on BMD, exploratory analyses were conducted to evaluate the relationship between duration of PI use and change in BMD.

RESULTS

Study Participants

Participant characteristics are shown in Table 1. Of the 464 participants, 245 (53%) were HIV-infected. At baseline, 19% of women were postmenopausal, and an additional 8% became postmenopausal over the study period (9.8% HIV+ vs. 5.9% HIV−). HIV-infected women were younger and more likely to be black than were HIV-uninfected women, and also had lower BMI, lower lifetime cigarette exposure, less depressive symptomatology, and were less likely to report a history of opioid exposure. Among HIV-infected women, 53% reported PI use at some point. At baseline, women with a history of methadone use were more likely to be postmenopausal than women without methadone use (27% methadone users vs. 15% methadone nonusers, p=.001.) Cross-sectional BMD analyses from the MS have been published [12].

Differences in Mean Bone Mineral Density

Mean interval between baseline and follow-up DEXA was 21.8 ± 3.1 months for HIV-infected women and 22.5 ± 3.9 months for HIV-uninfected women (p=.03.) HIV-infected women had lower baseline BMD at FN, (1.01 ±.14 vs. 1.04 ±.14 g/cm^2, p= .02) and TH (1.04 ±.15 vs. 1.08 ±.14 g/cm^2, p< .01) compared with HIV-uninfected controls. Women with a history of methadone use had lower BMD at LS at both baseline (1.20 ± .17 vs. 1.24 ± .17 g/cm^2, p= .02) and follow-up visits (1.18 ±.17 vs. 1.23 ±.17 g/cm^2, p= .002) compared with those who had never used methadone.

Unadjusted Analysis of Change in Bone Mineral Density

Change in BMD over time was not significantly different between HIV-infected and uninfected women at FN, TH, or LS in unadjusted analyses. Mean annual decline in BMD at LS was .002 g/cm^2 for HIV-uninfected women, .005 g/cm^2 for HIV-infected women with a history of PI use, and .011 g/cm^2 for HIV-infected women with no history of PI use (p for trend =.04). Overall, mean annual decline in BMD at FN was .005 g/cm^2 and for the TH it was .004 g/cm^2, and was not significantly different between HIV-uninfected women, HIV-infected women with PI use, and HIV infected women without PI use. Among HIV-infected women with a history of tenofovir use, mean annual decline in BMD was .006 g/cm^2 at FN, .007 g/cm^2 at TH and .005 g/cm^2 at LS, and was not significantly different when compared with HIV-infected women without a history of tenofovir use (mean annual decline .004 g/cm^2 at FN, .005 g/cm^2 at TH and .002 g/cm^2 at the LS.) Mean annual decline in LS BMD was greater among methadone users than non-users (.009 g/cm^2 vs. .003 g/cm^2, p=.01).

Multivariable Analysis of Change in Bone Mineral Density

Factors associated with annual change in BMD at FN, TH, and LS are shown in Table 2. Higher baseline BMD was significantly associated with greater loss of BMD at all three sites (p <.001). At FN, loss of BMD was associated with postmenopausal status (p=.002) and hepatitis C virus seropositivity (p=.004). At TH, postmenopausal status (p=.001), age (p=.03), smoking history (p=.001), and lower BMI (p=.01) were associated with BMD decline. At LS, factors associated with loss of BMD were post-menopausal status (p<.001), lower BMI (p<.001), methadone use (p=.04), and HIV seropositivity without PI use (p=.03). In the subset of HIV-infected women, as with the group as a whole, higher baseline BMD and postmenopausal status were associated with greater decline in BMD at all three sites,

and additionally lower BMI was associated with loss of BMD at all three sites (Table 3). Smoking was associated with BMD loss at TH (p=.02). Use of PIs for three or more years was associated with an increase in LS BMD when compared with no history of PI use, despite adjusting for duration of HIV diagnosis and CD4+ count (p=.008). There was no significant difference in the rate of decline in LS BMD when comparing HIV-infected women with PI use for less than three years to PI naïve subjects. Other HIV-related factors such as CD4+ cell count, HIV viral load, AIDS diagnosis, or other antiretroviral use were not associated with change in BMD (data not shown).

Prevalence of osteoporosis and osteopenia

At baseline 25.8% of HIV-infected women had osteopenia compared to 18.9% of HIV-uninfected women (p=.09). At visit 2, these proportions were 27.0% and 21.0% respectively (p=.14). At baseline 2.7% of HIV-infected women had osteoporosis compared to 2.4% of HIV-uninfected women (p=.88) and at the visit 2 these proportions were 4.1% and 2.3% respectively (p=.26).

DISCUSSION

In this sample of middle-aged women we found that overall, HIV-infected women had similar rates of decline in BMD as those who were HIV-uninfected. However, at the lumbar spine, HIV-infected women without a history of PI use had a greater decline in BMD than HIV-uninfected women or HIV-infected women who had received PIs, suggesting that PIs may mitigate the deleterious effects of HIV infection on bone. Furthermore, among HIV-infected women, longer duration of PI use appeared protective, and was associated with a gain in BMD at the LS, despite adjusting for duration of HIV infection and CD4+ cell count in addition to osteoporosis risk factors. We found no association with change in BMD and use of other antiretroviral classes or other HIV-associated factors such as CD4 count, duration of HIV infection, or AIDS diagnosis. It is unclear what accounts for the higher initial prevalence of low BMD among HIV infected women, and it is possible that bone loss earlier in the course of HIV disease may have occurred, HIV-related inflammation may play a role in bone disease, or that baseline differences in illicit drug use may account for these cross-sectional findings. Our study suggests that traditional risk factors for reduced BMD, such as age, menopausal status, lower BMI and tobacco use have greater impact on BMD decline than HIV status, especially among women treated with PI. Additionally, methadone use was associated with a heightened decline in BMD.

Our findings are generally similar to those reported in the two other longitudinal studies of BMD in HIV-infected women, with some specific differences [4, 5]. Dolan et al reported that rates of change in BMD were not different between HIV-infected women and healthy controls at the LS, FN, or TH, and that among HIV-infected women, duration of NRTI use was associated with bone loss, as well as CD4+ count, weight, FSH, and baseline BMD, with no effect of PI found on bone [4]. Yin et al found similar rates of bone loss at LS and FN in premenopausal HIV-infected and uninfected women, however inferences could not be drawn about the effects of antiretrovirals on BMD due to the study's small sample size [5]. Taken together, our results along with those of Yin and Dolan suggest that ongoing bone loss in women with HIV is multifactorial, and that the direct effect of HIV upon BMD is less significant than that of other osteoporosis risk factors which are often prevalent among HIV-infected persons. Nolan et al. reported an increase in BMD among male HIV-infected patients treated with indinavir and stable BMD in those receiving nelfinavir [13]. Although some cross-sectional studies have reported a relationship between PI use and low BMD [14, 15], lack of an effect of PIs on BMD, along with stable BMD among patients on established HAART has been reported in longitudinal analyses [4, 16, 17] with the exception of the recent SMART substudy, which reported an association between continuous ART and

decline in BMD when compared to intermittent HAART [18]. In HAART naïve patients, loss of BMD has been observed in the first 1-2 years after HAART initiation, with subsequent stabilization [19-23]. In our cohort, the association between PI use and BMD was only observed at the lumbar spine, which consists mainly of trabecular bone and may be more sensitive to early changes in BMD in contrast to the femoral neck, which is composed primarily of cortical bone. Our findings may also reflect a wide variability, lack of a strong effect, or heterogeneous response to protease inhibitors in treatment experienced women. Further prospective studies are needed to better determine whether protease inhibitor use is associated with change in bone density in women with chronic HIV infection and in which direction the change occurs, and whether specific protease inhibitors have different effects on bone metabolism.

Our findings suggest an *independent* association between methadone use and bone loss, among women with or at risk for HIV infection. We found an association between methadone use and menopause in this cohort, both of which were independently associated with bone loss. These data extend the cross-sectional findings in this cohort [12] and in a similar cohort of aging men [24], which reported an association between reduced BMD in the lumbar spine and methadone use. To our knowledge this is the first longitudinal study of HIV-infected and at-risk women to evaluate the contribution of methadone use on BMD. Prior studies focusing on HIV-positive women did not consider opioid use and comparison groups consisted of either healthy women or historical controls, or excluded women who engaged in substance use [1-4]. Opioid users possess multiple risk factors for osteopenia, such as tobacco use, alcohol use, lack of physical activity, and malnutrition. Multiple endocrine and metabolic abnormalities, including central hypogonadism have been described in HIV-infected patients, and opiate use may contribute to these problems [25]. Although opioid users, particularly those infected with HIV, appear to be at increased risk for reduced BMD, the epidemiology and pathogenesis of bone loss in this population is virtually unexplored. In the Third National Health and Nutrition Examination Survey, prescription opioid users, including methadone users had significantly reduced TH BMD compared with nonusers, yet data on illicit opioid use was unavailable [26]. A cross-sectional study conducted in a methadone maintenance program found that more than three quarters of the patients had reduced BMD, including an unexpectedly high proportion of the male sample [27]. While the median age in that study was substantially younger than expected for the degree of osteoporosis observed (42 years), many participants had risk factors for osteoporosis including history of tobacco use, heavy alcohol use, persistent amenorrhea, and HIV infection, which likely contributed to the prevalence of low BMD. Pedrazzoni et al. found reduced LS BMD in heroin users compared with non-drug dependent controls and former drug addicts; although 60% of current and former heroin users were HIV-infected, the contribution of HIV to BMD was not evaluated [28].

Our findings are subject to some limitations. We had no evidence regarding the mechanism of the observed associations. Additionally, osteoporosis and osteopenia were defined based on the use of T-scores, although the cohort included both premenopausal and postmenopausal women. Information about drug use was obtained by self-report, which may be subject to bias; however drug use behaviors were queried using ACASI technique, which enhances collection of potentially stigmatic information [10]. Additionally, we did not have data on duration or therefore cumulative dose of methadone. Although alcohol and steroid use and lack of physical activity are known risk factors for osteoporosis, these were not observed to be associated with BMD change in this sample. Finally, we cannot exclude the possibility that the observed association between protease inhibitor non-use and BMD decline may have been a type I error, however the nature of the association and the site of bone loss are biologically plausible. The small absolute BMD loss found is likely related to the short follow up time, and the ultimate clinical relevance of bone loss of this magnitude

over longer periods of time cannot be assessed by this study. Our study also has several strengths. Our cohort represents a large, ethnically diverse group of middle-aged, HIV-infected women and a control group of HIV-uninfected women with similar behavioral risk factors. The inclusion of women with a history of opioid use allowed us to demonstrate the role of methadone use in bone loss, in contrast to other studies of BMD in HIV-infected women.

In conclusion, we found that middle-aged women with HIV infection are likely to have lower bone density than HIV-negative women, although the use of protease inhibitors may confer a protective effect against loss of BMD in this population. Additionally, methadone use was independently associated with bone loss. Knowledge of whether methadone use is associated with adverse effects on BMD has important implications for risk assessment for osteopenia among opioid users, perhaps requiring more intensive risk-reduction interventions. HIV-infected women in methadone maintenance programs may be at higher risk for bone disease, particularly as they enter the menopausal transition, and screening for osteopenia may be prudent. Furthermore, since other pathologies known to accelerate bone loss are prevalent in HIV-infected individuals and drug users, special attention to these factors are warranted. Fractures may occur more frequently in HIV-infected individuals [29], and continuous antiretroviral therapy may be associated with higher fracture risk [30]. Thus, as more women with HIV infection and opioid use survive to older ages, there is an increasing need to better identify those women at risk for fracture, and to examine whether current therapeutic interventions to prevent fractures will be helpful in these special sub-populations of women.

Acknowledgments

Role of the Funding Source. This study was supported by the National Institute on Drug Abuse (RO1 DA13564 to Dr. Schoenbaum). Dr. Sharma is supported by the Robert Wood Johnson Foundation Physician Faculty Scholars Program and SUNY Downstate Medical Center Dean's Initiative in Research Investment. The study sponsors did not play a role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication

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Ethical approval, consent or animal equivalent

The Menopause Study was approved by the Institutional Review Boards of Montefiore Medical Center and Albert Einstein College of Medicine, and all participants provided written, informed consent.

Table 1

Menopause Study participant characteristics

Characteristic[a, b]	HIV − n=219	HIV+ n=245	P value[c]
Age at 1st exam (yrs)	46.1±5.1	45.0±4.8	.02
Age at 2nd exam (yrs)	48.0±5.1	46.8±4.8	.01
Race (%)			<.001
White	14.6	5.7	
Black	38.4	57.6	
Hispanic	42.5	31.4	
Other	4.6	5.3	
Post-menopausal at 1st exam (%)	18.7	18.8	.99
Post-menopausal at 2nd exam (%)	24.7	28.6	.34
Smoking history (%)	75.8	69.8	.15
Any current alcohol use (%)	55.7	52.2	.46
Physically active (%)	21.5	18.8	.47
CESD ≥ 23 (%)	30.6	20.0	.01
BMI at visit 1(kg/m^2)	32.0 ± 7.1	28.2 ± 6.4	<.001
BMI ever < 25 kg/m^2 (%)	21.5	42.0	<.001
Past estrogen therapy (%)	8.7	12.2	.21
Past prednisone use (%)	13.7	11.8	.55
Opioid or cocaine use ever (%)	60.3	44.9	.001
Methadone use ever (%)	46.1	21.6	<.001
Hepatitis C virus seropositive (%)	32.9	35.5	.55
CD4+ count in cells/ mm^3 (%)			
<200	NA[d]	10.3	NA[d]
200-499	NA[d]	43.4	NA[d]
≥500	NA[d]	46.3	NA[d]
Past protease inhibitor use (%)	0	53.1	NA[d]
Past non-PI based ART (%)	0	30.2	NA[d]
Past NNRTI use (%)	0	60.0	NA[d]

Characteristic[a, b]	HIV − n=219	HIV+ n=245	P value[c]
Past NRTI use (%)	0	87.8	NA[d]
Past tenofovir use (%)	0	31.4	NA[d]
Time from HIV diagnosis (yrs)			
Unknown	NA[d]	1.6	NA[d]
< 5	NA[d]	20.0	NA[d]
5-9	NA[d]	36.3	NA[d]
≥10	NA[d]	42.0	NA[d]

[a] Abbreviations: HIV: human immunodeficiency virus; CESD: Center for Epidemiologic Studies Depression Scale; BMI: body mass index

[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+

Table 2

Multivariable linear regression analysis of factors associated with change in BMD[a] per year at three sites over time among MS study participants

Characteristic[b]	Femoral neck			Total hip			Lumbar Spine[e]		
	BMD change per year[c]	95% CI[d]	P value	BMD change per year	95% CI	P value	BMD change per year	95% CI	P value
Black	−.002	−.008, .004	.57	.004	−.003, .011	.26	.002	−.007, .010	.70
Hispanic	−.002	−.008, .004	.56	.000	−.007, .007	.10	−.002	−.010, .006	.66
White/other	ref	-	-	ref	-	-	ref	-	-
Post-menopausal	−.007	−.012, −.003	.002	−.010	−.016, −.004	.001	−.012	−.018, −.006	<.001
Methadone use	.000	−.005, .004	.82	−.001	−.006, .004	.69	−.007	−.013, .000	.04
Baseline BMD	−.034	−.050, −.019	<.001	−.051	−.068, −.034	<.001	−.027	−.044, −.011	.001
Age				.000	−.001, .000	.03			
CESD ≥23	−.004	−.009, .001	.09						
Smoking history	.000	−.005, .004	.73	−.009	−.015, −.004	.001	−.002	−.008, .004	.49
BMI	.000	.000, .001	.10	.000	.000, .001	.01	.001	.001, .001	<.001
Hepatitis C	−.006	−.011, −.002	.004						
HIV+ with PI use	.001	−.004, .006	.68	.001	−.005, .006	.77	.000	−.007, .006	.81
HIV+ no PI use	.000	−.007, .005	.79	−.002	−.009, .004	.47	−.009	−.017, −.001	.03
HIV−	ref	-	-	ref	-	-	ref	-	-

[a] Abbreviations: BMD: Bone mineral density; HIV: human immunodeficiency virus; CESD: Center for Epidemiologic Studies Depression Scale ; BMI: body mass index; PI: protease inhibitor

[b] Blank cells indicate variable did not enter that model.

[c] Values less than zero indicate loss of BMD. Units are gm/cm^2 per year

[d] 95% Confidence Interval

$e_{\text{Lumbar spine (L2-4)}}$

Table 3

Multivariable linear regression analysis of factors associated with change in BMD per year among HIV-infected MS study participants

Characteristic[b]	Femoral neck			Total hip			Lumbar Spine[e]		
	BMD change per year[c]	95% CI[d]	P value	BMD change per year[c]	95% CI	P value	BMD change per year[c]	95% CI	P value
Black	.002	−.007, .011	.72	.006	−.006, .018	.31	.006	−.007, .019	.39
Hispanic	−.003	−.012, .006	.53	−.002	−.015, .010	.72	.003	−.010, .017	.63
White/other	ref	-	-	ref	-	-	ref	-	-
Post-menopausal status	−.007	−.014, .00	.05	−.016	−.024, −.008	<.001	−.010	−.019, −.001	.02
Methadone use	−.003	−.009, .004	.45	−.005	−.014, .004	.25	−.008	−.018, .001	.09
Baseline BMD	−.039	−.060, −.018	<.001	−.078	−.106, −.050	<.001	−.034	−.058, −.010	.006
Age	.000	−.001, .000	.07						
Smoking history	.000	−.006, .006	.94	−.010	−.018, −.002	.02	−.005	−014, .004	.29
BMI	.001	.000, .001	.003	.001	.000, .001	.002	.001	.000, .002	.002
Time from HIV diagnosis									
<5 yrs	.001	−.006, .009	.74	−.002	−.012, .008	.66	.001	−.010, .011	.92
5-9 yrs	−.005	−.011, .001	.12	.000	−.009, .008	.86	−.003	−.012, .006	.45
≥ 10 yrs	ref	-	-	ref	-	-	ref	-	-
CD4+ count < 200 c/mm^3	.002	−.008, .011	.70	.007	−.006, .020	.30	.000	−.014, .014	.95
CD4+ count 200-500 c/mm^3	−.001	−.007, .005	.71	−.005	−.013, .003	.24	−.001	−.010, .007	.88
CD4+ count ≥ 500 c/mm^3	ref	-	-	ref	-	-	ref	-	-
PI use ≥ 3yrs	.004	−.003, .010	.27	.007	−.001, .016	.09	.013	.003, .022	.008
PI use < 3yrs	.002	−.005, .008	.62	.006	−.003, .015	.17	.006	−.003, .016	.21
No PI use	ref	–	–	ref	–	–	ref	–	–

[a] Abbreviations: BMD: Bone mineral density; CESD: Center for Epidemiologic Studies Depression Scale ; BMI: body mass index; PI: protease inhibitor

[b] Blank cells indicate variable did not enter that model.

[c] Values less than zero indicate loss of BMD. Units are gm/cm^2 per year

[d] 95% Confidence Interval

[e] Lumbar spine (L2-4)