Prospective study of bone mineral density changes in aging men with or at risk for HIV infection

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Objective: To investigate rates and predictors of change in bone mineral density (BMD) in a cohort of aging men with or at risk for HIV infection.

Design: A prospective cohort study among 230 HIV-infected and 159 HIV-uninfected men aged at least 49 years.

Methods: Longitudinal analyses of annual change in BMD at the femoral neck, total hip, and lumbar spine.

Results: At baseline, 46% of men had normal BMD, 42% had osteopenia, and 12% had osteoporosis. Of those men with normal BMD, 14% progressed to osteopenia and 86% continued to have normal BMD. Of the men initially with osteopenia, 12% progressed to osteoporosis and 83% continued to have osteopenia. Osteopenia incidence per 100 person-years at risk was 2.6 for HIV-uninfected men and 7.2 for HIV-infected men; osteoporosis incidence was 2.2 per 100 person-years at risk among men with osteopenia, regardless of HIV status. In multivariable analysis of annual change in BMD at the femoral neck, we found a significant interaction between heroin use and AIDS diagnosis, such that the greatest bone loss occurred with both AIDS and heroin use (adjusted predicted mean annual bone loss 0.0196 g/cm^2). Hepatitis C virus seropositivity was also associated with femoral neck bone loss ($P = 0.04$). The interaction between AIDS and heroin use also was associated with bone loss at the total hip, as was current methadone use ($P < 0.01$).

Conclusion: We found an association of heroin use and AIDS with BMD change, suggesting that heroin users with AIDS may be at particular risk for bone loss.

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Introduction

As a result of the decline in mortality among HIV-infected individuals associated with widespread use of HAART, the life expectancy of the HIV-infected population in developed nations now approaches that of the general population [1–5]. The survival benefit of HAART, along with a growing number of HIV cases newly diagnosed in older persons, has led to a dramatic increase in the number of older persons with HIV infection, AIDS, or both. The number of older people with HIV/AIDS is expected to increase even further during the next decade, and it is projected that, by 2015, more than half of all HIV-infected individuals in the United States will be over the age of 50 years [6]. Long-term consequences of chronic HIV infection and HAART exposure, including disturbances of bone metabolism, are emerging concerns, given the growing numbers of older adults living with HIV.

A relatively high proportion of middle-aged substance users with or at risk for HIV infection continue to use illicit drugs into their sixties [7]. These trends imply that more HIV-infected persons will live to experience

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comorbid conditions associated with aging and drug use. HIV-infected persons and opioid users possess multiple risk factors, such as hypogonadism, tobacco use, alcohol use, lack of physical activity, low body weight, and poor nutrition, for osteopenia. In a cross-sectional study [8] conducted in the Cohort of HIV-at risk Aging Men's Prospective Study (CHAMPS), we found an independent association between methadone therapy and reduced spine bone mineral density (BMD). Although HIV-infected opioid users appear to be at increased risk for osteopenia, there is presently little known about the epidemiology or pathogenesis of osteopenia in this population. Most studies of BMD in HIV-infected men have focused on younger men, lacked an HIV-negative comparison group with similar drug-use behaviors, and been cross-sectional.

We undertook this prospective study to investigate rates and predictors of change in BMD over time in a cohort of aging men with or at risk for HIV infection.

Methods

Study participants

Between August 2002 and December 2003, participants were enrolled in the CHAMPS, a study of selected medical outcomes in older men with or at risk for HIV infection enrolled from the community in the Bronx, New York, USA. This longitudinal analysis includes men who completed BMD measurement by dual X-ray absorptiometry (DEXA) on study entry and again at a minimum of 18 months later. Participant recruitment and study design have been described elsewhere [9]. In brief, participants from the CHAMPS were community-dwelling men aged 49 years or older who either had documented HIV infection or were at risk for HIV through injection drug use (IDU) or high-risk sexual behavior. Men were excluded if they were unable to participate in a detailed standardized interview or unable to provide a blood specimen. Participants underwent semiannual research visits, which included standardized interviews, phlebotomy for HIV serology, T-lymphocyte subsets, and height and weight measurements. Serum testosterone levels and bone density evaluations were done at the second study visit, and bone density was repeated at a subsequent follow-up visit. The CHAMPS was approved by the Institutional Review Board of Montefiore Medical Center and Albert Einstein College of Medicine, and all participants provided written, informed consent.

Interview data

During semiannual research visits, participants underwent a standardized interview administered either in English or Spanish by trained research staff, which collected demographic characteristics, personal and family medical history, use of antiretrovirals and other medication, sexual history, and exercise and dietary habits. Drug-use behaviors were measured at each visit, including drug type, route of administration, frequency, and methadone dose for participants prescribed methadone replacement. The CAGE questionnaire was administered to screen for alcohol dependence [10], 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 cutoff score of 16 or more has been used as a criterion for significant depressive symptoms [11]. Depressive symptoms, drug-use behaviors, and sexual history were assessed using the audio computer-assisted self-interviewing (ACASI) technique, which enhances collection of potentially stigmatic or otherwise sensitive information [12].

Bone mineral density assessment

BMD (g/cm^2) of the total hip, femoral neck, and lumbar spine (L_1–L_4) were measured at two time points by DEXA, using a Prodigy densitometer with GE Lunar software, version 6.8 (GE Healthcare, Waukesha, Wisconsin, USA). In accordance with WHO T-score criteria, osteopenia was defined as BMD between 1 and 2.5 SD below the average peak bone mass in young adult men at any of the three sites examined (T-score between -1.0 and -2.5), and osteoporosis was defined as a T-score below -2.5. Normal BMD was defined as a T-score above -1.0 at all three sites [13].

Statistical analysis

Associations with independent variables of median change in BMD per year at the total hip, femoral neck, and lumbar spine as well as greatest median change in BMD per year at any of the three sites were determined using Wilcoxon rank sum tests for categorical variables and Spearman correlation coefficients for continuous variables. Depressive symptoms were defined as CES-D score of at least 16. Alcoholism was defined as CAGE score of at least 2. Men who had reported a history of current, former, or never smoking were compared. Independent variables tested included age, race/ethnicity, BMI in kg/m^2, current or ever use of calcium supplements, alcoholism, depressive symptoms, current or ever use of corticosteroids, diabetes, serum testosterone level, current or ever use of testosterone supplements, hepatitis C serostatus, current methadone use, smoking history, cigarettes pack years, and family history of osteoporosis, hip fracture, or spine fracture. We also tested interactions between HIV clinical group (HIV negative, HIV positive without AIDS, and AIDS) and heroin use (heroin use in past 5 years or no heroin use in past 5 years). We looked at HIV status as a three-category variable (HIV-negative, HIV-positive but not AIDS, and AIDS) combined with the two-category variable of heroin use. Thus for the heroin use and HIV clinical group interactions, the reference groups would be the categories

in which heroin was not used (no heroin and any HIV status) plus that of heroin use and HIV seronegative.

Multivariable linear regression analysis was conducted to determine factors independently associated with annual changes in BMD at the total hip, femoral neck, and lumbar spine and with greatest change at any site after adjusting for age, race/ethnicity, BMI, and baseline BMD. We first examined a relatively simple multivariable model, with each dependent variable regressed on heroin use, HIV clinical status (HIV negative, HIV positive without AIDS, and AIDS), the interaction of these two, baseline level of BMD at the site, age, race, and BMI. We used this regression to predict the BMD change at each site for each combination of heroin use and HIV clinical group. We also used these relatively simple models to check for outliers. In order to decide which variables to include in a more complex model, we then examined the effect of adding each of the independent variables to the model. Covariates that made large differences in the predicted values were included in the final multiple regression models for each outcome. Separate analyses were also conducted for the HIV-infected subset of men using the same analytic approach, along with testing of the following variables: duration of HIV diagnosis, $CD4^+$ cell count, use of tenofovir, nucleoside analog reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), protease inhibitors, as well as duration of use for protease inhibitors, NRTIs, and NNRTIs. All analysis was performed in SAS 9.2 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

Study participants

Participant characteristics are shown in Table 1. Of the 389 men, 230 (59%) were HIV infected. Mean age was 55.6 years; mean BMI at the time of first DEXA was 26.6 g/m^2; and 58% of participants were black, 22% hispanic, and 14% white. Among HIV-infected men, 54% reported being diagnosed with HIV for over 10 years and 77% reported previous or current protease inhibitor use (median duration of use was 24 months). Median $CD4^+$ cell count was 398 cells/μl (interquartile range 264–571). Risk factors for bone disease were common in the cohort: 88% reported use of either cocaine or opioids in their

Table 1. Participant characteristics of 389 men studied.

Characteristic	HIV−, $n=159$	HIV+, $n=230$	P
Age at first examination (years), mean ± SD	56.4 ± 5.64	55.0 ± 4.13	0.008
Race (%)			0.27
White	17.6	11.7	
Black	54.1	61.3	
Hispanic	21.4	22.2	
Other	6.9	4.8	
Current methadone use (%)	35.8	16.1	<0.001
Heroin use in past 5 years (%)	39.0	23.5	0.001
Opioid or cocaine use ever (%)	91.2	85.2	0.08
Injection drug use ever (%)	57.9	57.0	0.86
Smoking history (%)			0.008
Nonsmoker	11.9	10.9	
Former smoker	17.0	30.9	
Current smoker	71.1	58.3	
Pack years visit 1, mean ± SD	21.1 ± 23.1	20.7 ± 24.3	0.87
Alcoholism (%)	45.9	48.0	0.68
Hepatitis C seropositivity (%)	67.5	65.8	0.72
Depressive symptoms at visit 1 (%)	50.3	41.9	0.10
BMI at visit 1(kg/m^2), mean ± SD	27.5 ± 5.1	25.9 ± 4.5	0.001
BMI at visit 2 (kg/m^2), mean ± SD	27.4 ± 5.2	25.3 ± 4.7	<0.001
Testosterone level (ng/dl), mean ± SD	347.3 ± 368.4	358.1 ± 282.6	0.74
Low testosterone (<300 ng/dl), (%)	49.1	46.1	0.56
Past testosterone replacement (%)	5.7	26.2	<0.001
Current testosterone replacement (%)	2.5	17.0	<0.001
Past corticosteroid use (%)	1.9	5.2	0.09
Protease inhibitor use ever (%)	0	76.5	NA
Past tenofovir use (%)	0	26.5	NA
Tenofovir use in prior 6 months (%)	0	23.5	NA
Current non-protease inhibitor-based ART use (%)	0	34.8	NA
Current protease inhibitor-based ART use (%)	0	46.5	NA
NNRTI use ever (%)	0	53.9	NA
NRTI use ever (%)	0	90.8	NA
History of AIDS diagnosis	0	42.2	NA
$CD4^+$ cell count (cells/μl, %)			
0–200	NA	17.4	NA
201–500	NA	49.6	NA
>500	NA	33.0	NA

ART, antiretroviral therapy; NNRTI, non-NRTI; NRTI, nucleoside analog reverse transcriptase inhibitor.

lifetime, 64% were current smokers, 47% showed evidence of alcoholism, and 47% had low serum testosterone levels (<300 ng/dl).

Differences in mean bone mineral density

At the time of the first DEXA, HIV-infected men had lower BMD at the femoral neck, (0.98 vs. 1.02 g/cm^2, $P = 0.02$), total hip (1.01 vs. 1.06 g/cm^2, $P < 0.01$), and lumbar spine (1.15 vs. 1.19 g/cm^2, $P = 0.03$) when compared with HIV-uninfected controls. Mean interval (±SD) between DEXA at time 1 and time 2 was 32 months (±2.8) and was not significantly different by HIV status. At follow-up, HIV-infected men again had lower BMD at the femoral neck, (0.96 vs. 1.00 g/cm^2, $P = 0.03$), total hip (0.99 vs. 1.03 g/cm^2, $P = 0.02$), and lumbar spine (1.15 vs. 1.19 g/cm^2, $P = 0.02$) when compared with HIV-uninfected controls.

Prevalence and incidence of osteoporosis and osteopenia

At the time of the first DEXA measurement, 46.1% ($n = 175/380$) of men had normal BMD at all three sites, 41.6% had osteopenia ($n = 158/380$), and 12.4% ($n = 47/380$) had osteoporosis at least at one site. Of those men initially with normal BMD at all sites, 13.7% progressed to osteopenia ($n = 24/175$) and 86.3% continued to have normal BMD ($n = 151/175$) at all sites; none progressed to osteoporosis. Among men with normal BMD, the incidence of osteopenia for HIV-uninfected men was 0.026 [2.6 per 100 person-years at risk (PYAR)], whereas for HIV-infected men, the incidence of osteopenia was 0.072 (7.2 per 100 PYAR). Of the men initially with osteopenia, 12% ($n = 19/158$) progressed to osteoporosis and 83% ($n = 131/158$) continued to have osteopenia at follow-up. Among men with osteopenia, for both HIV-uninfected and HIV-infected men, the incidence of osteoporosis was 0.022 (2.2 per 100 PYAR).

Univariate analysis of annual change in bone mineral density

Factors (categorical variables) significantly associated in univariate analysis with change in BMD included at the femoral neck: race, current methadone use, ever use of corticosteroids, ever use of testosterone, and hepatitis C serostatus; total hip: race, smoking, current methadone use, ever use of testosterone, and hepatitis C serostatus; and the lumbar spine: smoking and hepatitis C serostatus (data not shown.) Higher baseline BMD was associated with bone loss at the femoral neck ($P = 0.05$) and higher BMI was associated with increase in BMD at the lumbar spine ($P < 0.01$).

Multivariable analysis of annual change in bone mineral density

In multivariable analysis of annual change in BMD at the femoral neck, we found a significant interaction between heroin use (within 5 years) and AIDS diagnosis, such that the greatest amount of bone loss was seen in persons with both AIDS and heroin use (adjusted predicted mean annual bone loss of 0.0196 g/cm^2), after adjusting for age, race/ethnicity, BMI, baseline BMD, use of corticosteroids, family history of vertebral fracture, and current methadone use (Table 2). In this model, hepatitis C virus seropositivity was also significantly associated with

Table 2. Multivariable linear regression analysis of factors associated with annual change in bone mineral density at three sites among Cohort of HIV-at risk Aging Men's Prospective Study participants.

	Femoral neck		Total hip		Lumbar spine	
Variable	Parameter estimate[a]	95% CI[b]	Parameter estimate	95% CI	Parameter estimate	95% CI
Heroin use within 5 years	0.0031	−0.0039 to 0.0101	0.0017	−0.0049 to 0.0084	0.0015	−0.0060 to 0.0089
History of AIDS diagnosis	−0.0014	−0.0077 to 0.0049	−0.0020	−0.0080 to 0.0040	0.0038	−0.0029 to 0.0106
HIV+	0.0036	−0.0021 to 0.0094	0.0005	−0.0050 to 0.0060	0.0002	−0.0060 to 0.0064
AIDS and heroin use[c]	−0.0150	−0.0267 to −0.0033	−0.0109	−0.0218 to −0.0000	−0.0092	−0.0214 to 0.0030
HIV+ and heroin use[c]	−0.0016	−0.0120 to 0.0089	−0.0072	−0.0174 to 0.0030	−0.0059	−0.0171 to 0.0053
Baseline BMD at site	−0.0187	−0.0326 to −0.0048	−0.0179	−0.0306 to −0.0051	0.0037	−0.0081 to 0.0161
Age at first examination	−0.0001	−0.0006 to 0.0003	−0.0001	−0.0006 to 0.0003	0.0002	−0.0003 to 0.0006
Black	−0.0039	−0.0103 to 0.0026	0.0028	−0.0032 to 0.0089	0.0011	−0.0057 to 0.0078
Hispanic	0.0001	−0.0068 to 0.0069	0.0051	−0.0015 to 0.0117	0.0023	−0.0051 to 0.0097
Other	−0.0101	−0.0204 to 0.0023	−0.0028	−0.0127 to 0.0070	0.0040	−0.0071 to 0.0150
White		Reference		Reference		Reference
BMI (kg/m^2)	0.0001	−0.0004 to 0.0005	0.0003	−0.0001 to 0.0008	0.0003	−0.0001 to 0.0008
Ever use of corticosteroids	0.0090	−0.0020 to 0.0199				
Family history of spine fracture	0.0048	−0.0128 to 0.0223	0.0026	−0.0142 to 0.0194	0.0026	−0.0142 to 0.0194
Current methadone use	−0.0036	−0.0091 to 0.0020	−0.0085	−0.0138 to −0.0032	−0.0085	−0.0138 to −0.0032
Hepatitis C virus seropositivity	−0.0050	−0.0002 to −0.0097	−0.0034	−0.0079 to 0.0011	−0.0034	−0.0079 to 0.0011

BMD, bone mineral density; CI, confidence interval.
[a]Parameter estimates reflect the difference in annual rate of change in BMD, such that estimates less than zero indicate loss of BMD. Units for parameter estimates are g/cm^2 per year.
[b]95% CI for parameter estimate. Parameter estimates with blank cells indicate variable did not enter that model.
[c]For these interactions, the reference groups are the categories in which heroin was not used (no heroin and any HIV status) plus that of heroin use and HIV-seronegative.

femoral neck bone loss ($P = 0.04$). At the total hip, the interaction between AIDS diagnosis and heroin use remained significantly associated with loss of BMD in the multivariable model, as was current use of methadone ($P < 0.01$), as shown in Table 2. Only BMI was associated with change in BMD at the lumbar spine in multivariable analysis (Table 2.) In a multivariable analysis of factors associated with greatest annual decline in BMD at any site (femoral neck, total hip, or lumbar spine), the interaction between AIDS diagnosis and heroin use was associated with greater bone loss ($P = 0.04$), whereas the association with current methadone use was of borderline significance ($P = 0.06$) (data not shown). Multivariable analyses of annual change in BMD at the femoral neck, total hip, and lumbar spine for the subset of HIV-infected men are shown in Table 3. There were no significant associations found between BMD change and HAART use, class of antiretrovirals uses (NRTI, NNRTI, and protease inhibitor), duration of antiretroviral therapy (ART), or CD4 cell count at any of the three sites.

Discussion

In this prospective study of older men with or at risk for HIV infection, we found that the combination of heroin use and AIDS diagnosis was associated with a substantial decline in BMD. This was evident at both the femoral neck and total hip, as well as in analyses of the greatest decline in BMD at any of the femoral neck, total hip, or lumbar spine. Hepatitis C seropositivity and methadone use, factors that are prevalent among HIV-infected opioid users, were also associated with bone loss in this cohort. Taken together, these data suggest that HIV-infected opioid-using men may be at particular risk of bone loss as they age, as a result of comorbid disease such as hepatitis C infection, opioid substitution treatment with methadone, ongoing heroin use, progression to AIDS, or a combination of these factors. The lack of an independent association of BMD loss with cigarette smoking might be due in part to the fact that nearly 90% of participants in the cohort were current or former smokers.

These longitudinal data extend the cross-sectional findings previously reported in this cohort [8], and in a similar cohort of middle-aged women with or at risk for HIV infection [14], which reported an association between reduced BMD in the lumbar spine and methadone use. To our knowledge, this is the first longitudinal study in HIV-infected men to evaluate the association of opioid use with changes in BMD. Like HIV-infected individuals, opioid users possess multiple risk factors for osteopenia, including hypogonadism, tobacco use, alcohol use, lack of physical activity, and malnutrition. Yet BMD in patients with opioid dependence has received limited attention. Prescription opioid users had reduced total hip BMD compared with nonusers in the third National Health and Nutrition Examination Survey , with a nonsignificant trend toward longer term opioid users having lower BMD than shorter term users. Data on illicit opioid use were not available in that study [15]. A cross-sectional study [16] in a methadone maintenance treatment program found that more than three quarters of the patients met the WHO criteria for osteoporosis or osteopenia despite a median age of only 42 years, including an unexpectedly high proportion of the 33 men studied having osteopenia (36%) and osteoporosis (61%). Many participants had risk factors for osteoporosis including history of tobacco use (95%), heavy alcohol use (52%), persistent amenorrhea (32% of women), and HIV infection (28%), which likely contributed to the high prevalence of low BMD.

Multiple endocrine and metabolic abnormalities have been described in patients infected with HIV, and opiate use may contribute to these problems. Opioid use has been associated with central hypogonadism, resulting in diminished secretion of gonadotropin-releasing hormone, luteinizing hormone (LH), estrogen, and testosterone [17]. Cross-sectional studies [18–20] in HIV-negative heroin and methadone users have shown decreased levels of gonadotropins, which may be dose dependent [20], and partially reversible with the administration of naltrexone, an opiate antagonist [21]. Hypogonadism is also common in men with AIDS-related wasting syndrome [22], and has been reported in 21% of men with HIV-related weight loss on HAART [23]. Androgen deficiency is prevalent in our cohort; previously, we reported that among this cohort, HIV infection was not associated with androgen deficiency, whereas IDU, hepatitis C virus seropositivity, high BMI, and use of psychotropic medications were [9]. To date, most studies examining hypogonadism in HIV infection have used non-IDU HIV patients, and HIV-infected drug users remain a largely understudied group [24]. Osteoporosis in men often has secondary causes, the most common of which are alcohol abuse, glucocortoicoid excess, and hypogonadism [25]. In our cohort, despite the high prevalence of hypogonadism, we did not find an association between serum testosterone level and loss of BMD over time. Although history of testosterone replacement was associated with a lower rate of bone loss in univariate analyses; compared with those men who did not report testosterone use, this association was no longer significant in multivariable analyses. Thus, although hypogonadism has been associated with both HIV infection and opioid use, as well as osteoporosis, this association was not significant in our cohort and does not explain the combined effect of HIV clinical status and heroin use on BMD observed.

Opioids may contribute to lowered BMD by directly interfering with bone formation. Studies [26,27] have documented large concentrations of opioid receptors in osteoblasts; inhibition of the growth of human osteoblast

Table 3. Multivariable linear regression analysis of factors associated with annual change in bone mineral density at three sites among HIV-positive Cohort of HIV-at risk Aging Men's Prospective Study participants.

	Femoral neck		Total hip		Lumbar spine	
Variable	Parameter estimate[a]	95% CI[b]	Parameter estimate	95% CI	Parameter estimate	95% CI
Heroin use	−0.0056	−0.0138 to 0.0027	0.0003	−0.0102 to 0.0108	−0.0063	−0.0163 to 0.0037
AIDS diagnosis	−0.0048	−0.0109 to 0.0011	−0.0007	−0.0085 to 0.0072	0.0051	−0.0023 to 0.0125
AIDS and heroin use[c]	−0.0062	−0.0187 to, 0.0063	−0.0122	−0.0279 to 0.0035	−0.0016	−0.0169 to 0.0138
Baseline BMD	−0.0045	−0.0220 to 0.0129	−0.0469	−0.0681 to −0.0257	−0.0041	−0.0242 to 0.0160
Age at first examination	−0.0003	0.0009–0.0004	−0.0002	−0.0010 to 0.0006	−0.0002	−0.0010 to 0.0006
Black	−0.0116	−0.0120 to −0.0033	0.0063	−0.0044 to 0.0170	0.0068	−0.0033 to 0.0169
Hispanic	−0.0065	−0.0156 to 0.0026	0.0114	−0.0003 to 0.0231	0.0063	−0.0047 to 0.0174
Other	−0.0183	−0.0324 to −0.0042	0.0022	−0.0162 to 0.0205	0.0178	0.0005–0.0351
White	Reference		Reference		Reference	
BMI (kg/m^2)	0.0002	−0.0005 to 0.0008	0.0004	−0.0004 to 0.0012	0.0008	−0.0000 to 0.0016
Ever use of corticosteroids	0.0097	−0.0021 to 0.0216	−0.0003	−0.0158 to 0.0152	−0.0053	−0.0199 to 0.0093
Family history of spine fracture	0.0242	−0.0025 to 0.0510	0.0089	−0.0258 to 0.0436	0.0107	−0.0220 to 0.0435
Family history of hip fracture	0.0053	−0.0046 to 0.0151			−0.0068	−0.0194 to 0.0058
Current methadone use			−0.0078	−0.0172 to 0.0017		
CD4$^+$ cell count (cells/μl)						
0–200	−0.0056	−0.0132 to 0.0021			−0.0086	−0.0183 to 0.0010
201–500	0.0027	−0.0132 to 0.0085			0.0025	−0.0046 to 0.0096
>500	Reference				Reference	
Length of HIV diagnosis (years)						
<1					−0.0036	−0.0307 to 0.0234
1–2					0.0201	0.0005–0.0397
3–4					0.0081	−0.0084 to 0.0246
5–9					0.0049	−0.0019 to 0.0116
10+					Reference	
Ever use of protease inhibitors					−0.0071	−0.0160 to 0.0017
No NRTI use					−0.0098	−0.0220 to 0.0024
Previous NRTI use					−0.0071	−0.0161 to 0.0020
Current NRTI use					Reference	

BMD, bone mineral density; CI, confidence interval; NRTI, nucleoside analog reverse transcriptase inhibitor.
[a]Parameter estimates reflect the difference in annual rate of change in BMD, such that estimates less than zero indicate loss of BMD. Unit for parameter estimates is g/cm^2 per year.
[b]95% CI for parameter estimate. Parameter estimates with blank cells indicate variable did not enter that model.
[c]For these interactions, the reference groups are the categories in which heroin was not used plus that of heroin use and HIV-seropositive without AIDS.

tissue cultures by small concentrations of opioids [26]; prevention of this inhibition by opioid antagonists [26]; lowered serum levels of osteocalcin, a bone formation marker, in heroin addicts [28]; and inhibition of osteocalcin production by morphine in osteoblast tissue cultures, which was abolished when osteoblastic cells were incubated simultaneously with naloxone [27]. An effect of opiates on calcium-regulating hormones has also been reported, in addition to other mechanisms relating to altered bone metabolism. Pedrazzoni *et al.* [29] found a reduction in lumbar BMD in heroin users compared with nondrug-dependent control participants and former drug addicts. Heroin users had higher levels of serum calcium, urinary excretion of calcium, and urinary excretion of hydroxyproline and lower levels of parathyroid hormone, LH, and testosterone. Levels of bone-specific alkaline phosphatase and osteocalcin were normal [29]. Of note, although 60% of current and former heroin users were HIV infected, the contribution of HIV serostatus to bone and mineral metabolism and bone mass was not evaluated. Prior to that study, reports [30–33] on calcium-regulating hormones in opioid users focused on the finding of higher levels of serum calcitonin.

Opioid analgesics have been associated with hip fracture in hospitalized [34] and community-dwelling [35] elderly patients and with nontraumatic, nonvertebral fractures in community-dwelling older women [36]. Use of morphine, methadone, oxycodone, nicomorphine, ketobemidone, tramadol, and codeine, but not buprenorphine, was associated with increased overall fracture risk in a case–control study [37] using Denmark's National Health Registry. Although the assumption in these studies was that the higher risk of fracture was due to an increased risk of falls from impaired alertness and neuromuscular function among older individuals using opioids, neither the number of falls [35] nor BMD was assessed [35,36]. When measured in one study [38] of older women, the risk of falls was no different between opioid users and nonusers. Prospective studies of the associations between opioid use and neuromuscular function, fall risk, changes in sex steroids, markers of bone turnover, and rates of bone loss are needed to demonstrate the causality of these relationships.

Osteoporosis is a common, yet underrecognized, problem in men, whether or not they are infected with HIV. Although several longitudinal studies [39–47] of BMD have been conducted in HIV-infected, HAART-treated patients, they have generally lacked a suitable comparison group of HIV-negative persons with similar risk factors for osteoporosis, and either have used healthy controls [39,40] did not include HIV-uninfected controls [41–46], or focused on specific groups such as premenopausal women [47] or men with normal or above average BMD [39]. A recent meta-analysis [48] found that compared with HIV-uninfected controls, HIV-infected patients had a 6.4-fold increased odds of reduced BMD. Studies [49,50] in the general population indicate that for each SD reduction in BMD as measured by DEXA, the risk of fracture doubles. The gradient of risk between BMD and fracture is continuous, suggesting that men with osteopenia may be at increased risk of developing osteoporosis when compared with men with higher BMD [13,51]. In the general population, it is estimated that the lifetime risk of experiencing an osteoporotic fracture in men over the age of 50 years is 30% [52], similar to the lifetime risk of developing prostate cancer [53]. Studies [54–56] have shown that the fracture-related mortality rate is higher in men than in women, and that fractures occur at higher BMD levels in men than in women [57–60]. Considering the risk of fracture in men with low BMD and the increased prevalence of low BMD in HIV-infected adults at younger than expected ages, HIV-infected men may be at even greater risk for fragility fractures as they age. In fact, recent data suggest that fractures may occur more frequently in HIV-infected individuals [61] and that continuous ART may be associated with higher fracture risk [42].

Our study is subject to some limitations. We had no evidence regarding the mechanism of the observed associations, including that of opioid use on BMD. We did not include measures of vitamin D, calciotropic hormones, or biochemical markers of bone formation or resorption. Additionally, data collection and analyses were structured on patient interview data. 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 has been shown to enhance collection of potentially stigmatizing information [12]. Finally, because of the limited number of incident cases of osteopenia and osteoporosis, we were unable to do multivariable analysis regarding factors affecting differences in these outcomes by HIV status. Our study also has several strengths. Our cohort represents a large, ethnically diverse group of older, HIV-infected men and a control group of HIV-uninfected men with similar behavioral risk factors. The inclusion of a comparison group with similar drug use, in particular, allowed us to demonstrate the potential role of opioid use in bone loss, in contrast to other studies of BMD in HIV-infected men, which lacked comparison groups that could address the novel role of drug use in bone disease.

Our findings suggest that there is an association of heroin use and AIDS with decreased BMD, and that heroin users with AIDS may be at particular risk for bone loss. An improved understanding of factors associated with ongoing bone loss and fracture risk is needed to help guide thresholds for assessment of BMD and for osteopenia treatment in HIV-infected persons and opioid users. The degree to which opioid use and advanced HIV disease affect the risk of osteopenia will inform the need

for treatment efforts and programs to prevent bone loss among drug users with HIV infection. Furthermore, for drug users who are treated with methadone, it is imperative to determine whether treatment adversely affects BMD, and if so, to develop ways to prevent or attenuate any adverse effect of opioids on BMD.

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