Published in final edited form as:

AIDS. 2010 September 24; 24(15): 2337–2345. doi:10.1097/QAD.0b013e32833d7da7.

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

Anjali Sharma¹, Peter L. Flom², Jeremy Weedon^{2,3}, and Robert S. Klein⁴

¹Department of Medicine, Division of Infectious Diseases, State University of New York Downstate Medical Center, Brooklyn, New York

²Department of Scientific Computing Center, State University of New York Downstate Medical Center, Brooklyn, New York

³Department of Epidemiology, State University of New York Downstate Medical Center, Brooklyn, New York

⁴Department of Medicine, Division of Infectious Diseases, Mount Sinai School of Medicine, New York, New York

Abstract

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—Prospective cohort study among 230 HIV-infected and 159 HIV-uninfected men aged ≥ 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 (PYAR) was 2.6 for HIV-uninfected men and 7.2 for HIV-infected men; osteoporosis incidence was 2.2/100 PYAR 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 gm/cm²). Hepatitis C virus seropositivity was also associated with femoral neck bone loss ($p=.04$). The interaction between AIDS and heroin use also was associated with bone loss at the total hip, as was current methadone use ($p<.01$).

Conclusions—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.

Keywords

osteopenia; osteoporosis; bone mineral density; HIV; men; aging

Address correspondence and requests for reprints to: Anjali Sharma, M.D., M.S., SUNY Downstate Medical Center, 450 Clarkson Avenue, Box 1240, Brooklyn, NY 11203, Ph: 718-270-1281; Fax: 718-270-3386, anjali.sharma@downstate.edu.

Potential conflicts of interest. All authors: no conflicts

Introduction

As a result of the decline in mortality among HIV-infected individuals associated with widespread use of highly active antiretroviral therapy (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 and/or AIDS. 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 U.S. will be over the age of 50 [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 60s [7]. These trends imply that more HIV-infected persons will live to experience co-morbid conditions associated with aging and drug use. HIV-infected persons and opioid users possess multiple risk factors for osteopenia, such as hypogonadism, tobacco use, alcohol use, lack of physical activity, low body weight, and poor nutrition. In a cross-sectional study 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) [8]. 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, have 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 Cohort of HIV At-Risk Men's Prospective Study (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. 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, subjects from the CHAMPS were community-dwelling men aged 49 or older who either had documented HIV infection or were at risk for HIV through injection drug use 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 study 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 semi-annual 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 subjects 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 (A-CASI) 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 ($\text{L}_1\text{--}\text{L}_4$) were measured at two time points by dual x-ray absorptiometry (DEXA) using a Prodigy densitometer with GE Lunar software, version 6.8 (GE Healthcare). In accordance with World Health Organization T-score criteria, osteopenia was defined as $\text{BMD} > 1.0 \text{ SD}$ and $\leq 2.5 \text{ SD}$ 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 < -2.5 . Normal BMD was defined as a T-score > -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 CESD score ≥ 16 . Alcoholism was defined as CAGE score ≥ 2 . Men who had reported a history of current, former, or never smoking were compared. Independent variables tested included age, race/ethnicity, body mass index (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 last 5 years or no heroin use in last 5 years). We looked at HIV status as a 3- category variable (HIV-negative, HIV-positive but not AIDS, and AIDS) combined with the 2- 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 which 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-nucleoside analog reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) as well as duration of use for PIs, NRTIs, and NNRTIs. All analysis was performed in SAS 9.2 (SAS Institute, Inc. Cary, North Carolina).

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 body mass index (BMI) at the time of first DEXA was 26.6 g/m², and 58% of subjects 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 c/mL (IQR 264-571). Risk factors for bone disease were common in the cohort; 88% reported use of either cocaine or opioids in their 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/cm², $p = .02$), total hip (1.01 vs. 1.06 g/cm², $p < .01$) and lumbar spine (1.15 vs. 1.19 g/cm², $p = .03$) when compared with HIV-uninfected controls. Mean interval ($\pm$ SD) between DEXA at time 1 and time 2 was 32 months ($\pm$ 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/cm², $p = .03$), total hip (0.99 vs. 1.03 g/cm², $p = .02$), and lumbar spine 1.15 vs. 1.19 g/cm², $p = .02$) 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 3 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 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 bone mineral density included at 1) the femoral neck: race, current methadone use, ever use of corticosteroids, ever use of testosterone, and hepatitis C serostatus, 2) total hip: race, smoking, current methadone use, ever use of testosterone, and hepatitis C serostatus, and 3) the lumbar spine: smoking, and hepatitis C serostatus (data not shown.) Higher baseline BMD was associated with bone loss at the femoral neck ($p = .05$) and higher BMI was associated with increase in BMD at the lumbar spine ($p < .01$).

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 yrs) 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 gm/cm²), 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 femoral neck bone loss ($p=.04$). 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 ($p<.01$), 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 ($p=.04$) while the association with current methadone use was of borderline significance ($p=.06$), (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, PI), duration of antiretroviral therapy, or CD4 cell count at any of the 3 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 bone mineral density. 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 which 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 co-morbid 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 percent 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 bone mineral density. 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 bone mineral density in patients with opioid dependence has received limited attention. Prescription opioid users had reduced total hip BMD compared with nonusers in the 3rd NHANES, with a nonsignificant trend toward longer-term opioid users having lower BMD than shorter term users. Data on illicit opioid use was not available in that study [15]. A cross-sectional study 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%) [16]. Many participants had risk factors for osteoporosis including history of tobacco use (95%), heavy alcohol use (52%),

persistent amenorrhea (32% of females), 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 (GnRH), luteinizing hormone, estrogen, and testosterone [17]. Cross-sectional studies in HIV-negative heroin and methadone users have shown decreased levels of gonadotropins [18-20] 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 injection drug use, hepatitis C virus seropositivity, high body mass index, 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, glucocorticoid 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. While history of testosterone replacement was associated with a lower rate of bone loss in univariate analyses, compared to those men who did not report testosterone use, this association was no longer significant in multivariable analyses. Thus while 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 bone mineral density by directly interfering with bone formation. Studies have documented large concentrations of opioid receptors in osteoblasts [26,27], inhibition of the growth of human osteoblast 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. found a reduction in lumbar bone mineral density in heroin users compared with non-drug dependent control subjects 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 PTH, 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 on calcium regulating hormones in opioid users focused on the finding of higher levels of serum calcitonin [30-33].

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 were associated with increased overall fracture risk in a case-control study using Denmark's National Health Registry [37]. While 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 bone mineral density

was assessed [35,36]. When measured in one study of older women, the risk of falls was no different between opioid users and nonusers [38]. 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 under-recognized problem in men, whether or not they are infected with HIV. While several longitudinal studies of BMD have been conducted in HIV-infected, HAART-treated patients [39-47], 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 found that compared with HIV-uninfected controls, HIV-infected patients had a 6.4-fold increased odds of reduced BMD [48]. Many studies in the general population indicate that for each SD reduction in BMD as measured by DEXA, the risk of fracture doubles [49,50]. 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 is 30% [52], similar to the lifetime risk of developing prostate cancer [53]. Studies have shown that the fracture-related mortality rate is higher in men than in women [54-56], 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 suggests that fractures may occur more frequently in HIV-infected individuals [61] and that continuous antiretroviral therapy may be associated with higher fracture risk [62].

Our study is subject to some limitations. We had no evidence regarding the mechanism of the observed associations, including that of opioid use on bone mineral density. 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 audio computer-assisted interviewing (ACASI) technique, which has been shown to enhance collection of potentially stigmatizing information [12]. Finally, due to 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 bone mineral density 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 bone mineral density 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 bone mineral density.

Acknowledgments

This study was supported by the National Institute on Drug Abuse (R01 DA14998). 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.

Financial support: This study was supported by the National Institute on Drug Abuse (R01 DA14998), grant to Dr. Klein. 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.

References

1. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. EuroSIDA study group. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003 Jul 5; 362(9377):22–9. [PubMed: 12853195]
2. Lima VD, Hogg RS, Harrigan PR, Moore D, Yip B, Wood E, et al. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. *AIDS*. 2007; 21:685–692. [PubMed: 17413689]
3. Walensky RP, Paltiel AD, Losina E, Mercincavage LM, Schackman BR, Sax PE, et al. The survival benefits of AIDS treatment in the United States. *Journal of Infect Dis*. 2006; 194:11–9. [PubMed: 16741877]
4. Lohse N, Hansen AE, Pedersen G, Kronborg G, Gerstoft J, Sorensen HT, et al. Survival of Persons with and without HIV infection in Denmark, 1995–2005. *Ann Intern Med*. 2007; 146:87–95. [PubMed: 17227932]
5. Bhaskaran K, Hamouda O, Sannes M, Boufassa F, Johnson AM, Lambert PC, et al. CASCADE Collaboration. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA*. 2008 Jul 2; 300(1):51–9. [PubMed: 18594040]
6. Medical Management of Older Patients with HIV/AIDS (R01). [January 14, 2010]. [on-line]. Available at <http://grants.nih.gov/grants/guide/pa-files/PA-09-017.html>
7. Hartel DM, Schoenbaum EE, Lo Y, Klein RS. Gender differences in illicit substance use among middle-aged drug users with or at risk for HIV infection. *Clin Infect Dis*. 2006; 43:525–31. [PubMed: 16838244]
8. Arnsten JH, Freeman R, Howard AA, Floris-Moore M, Lo Y, Klein RS. Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. *AIDS*. 2007 Mar 12; 21(5):617–23. [PubMed: 17314524]
9. Klein RS, Lo Y, Santoro N, Dobs AS. Androgen levels in older men who have or who are at risk of acquiring HIV infection. *Clin Infect Dis*. 2005; 41:1794–1803. [PubMed: 16288406]
10. Mayfield DG, McCleod G, He YD. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psych*. 1974; 131:1121–1123.
11. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977; 1:385–401.
12. Metzger DS, Koblin B, Turner C, Navaline H, Valenti F, Holte S, et al. Randomized controlled trial of audio computer-assisted self-interviewing: utility and acceptability in longitudinal studies. HIVNET Vaccine Preparedness Study Protocol Team. *Am J Epidemiol*. 2000; 152:99–106. [PubMed: 10909945]
13. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of WHO study group. *World Health Org Tech Rep Ser*. 1994; 843:1–129.
14. Arnsten JH, Freeman R, Howard AA, Floris-Moore M, Santoro N, Schoenbaum EE. HIV infection and bone mineral density in middle-aged women. *Clin Infect Dis*. 2006; 42:1014–20. [PubMed: 16511769]

15. Kinjo M, Setoguchi S, Schneeweiss S, Solomon DH. Bone mineral density in subjects using central nervous system-active medications. *Am J Med.* 2005; 118:1414.e7–1414.e12. [PubMed: 16378792]
16. Kim TW, Alford DP, Malabanan A, Holick MF, Samet JH. Low bone density in patients receiving methadone maintenance treatment. *Drug Alcohol Depend.* 2006 Dec 1; 85(3):258–62. [PubMed: 16860495]
17. Cooper OB, Brown TT, Dobs AS. Opiate drug use: a potential contributor to the endocrine and metabolic complications in human immunodeficiency virus disease. *Clin Infect Dis.* 2003; 37(2Suppl):S132–6. [PubMed: 12942387]
18. Brambilla F, Sacchetti E, Brunetta M. Pituitary-gonadal function in heroin addicts. *Neuropsychobiology.* 1977; 3:160–6. [PubMed: 331136]
19. Celani MF, Carani C, Montanini V, Baraghini GF, Zini D, Simoni M, et al. Further studies on the effects of heroin addiction on the hypothalamic-pituitary-gonadal function in man. *Pharmacol Res Commun.* 1984; 16:1193–203. [PubMed: 6522443]
20. Mendelson JH, Meyer RE, Ellingboe J, Mirin SM, McDougale M. Effects of heroin and methadone on plasma cortisol and testosterone. *J Pharmacol Exp Ther.* 1975; 195:296–302. [PubMed: 1185598]
21. Mendelson JH, Ellingboe J, Kuehnle JC, Mello NK. Heroin and naltrexone effects on pituitary-gonadal hormones in man: interaction of steroid feedback effects, tolerance, and supersensitivity. *J Pharmacol Exp Ther.* 1980; 214:503–6. [PubMed: 7400959]
22. Dobs AS, Dempsey MA, Ladenson PW, Polk BF. Endocrine disorders in men infected with human immunodeficiency virus. *Am J Med.* 1988; 84:611–6. [PubMed: 3348269]
23. Rietschel P, Corcoran C, Stanley T, Basgoz N, Kilbanski A, Grinspoon S. Prevalence of hypogonadism in men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy. *Clin Infect Dis.* 2000; 31:1240–4. [PubMed: 11073758]
24. Wahlstrom JT, Dobs AS. Acute and long term effects of AIDS and injection drug use on gonadal function. *J Acquir Immune Defic Syndr.* 2000; 25(Suppl 1):S27–S36. [PubMed: 11126423]
25. Ebeling PR. Osteoporosis in men: new insights into aetiology, pathogenesis, prevention and management. *Drugs Aging.* 1998; 13:421–34. [PubMed: 9883398]
26. Elhassan AM, Lindgren JU, Hultenby K, et al. Methionine-enkephalin in bone and joint tissues. *J Bone Miner Res.* 1998; 13:88–95. [PubMed: 9443794]
27. Pérez-Castrillón JL, Olmos JM, Gómez JJ, Barrallo A, Riancho JA, Perera L, et al. Expression of opioid receptors in osteoblast-like MG-63 cells, and effects of different opioid agonists on alkaline phosphatase and osteocalcin secretion by these cells. *Neuroendocrinology.* 2000; 72:187–194. [PubMed: 11025413]
28. Rico H, Costales C, Cabranes JA, Escudero M. Lower serum osteocalcin levels in pregnant drug users and their newborns at the time of delivery. *Obstet Gynecol.* 1990; 75:998–1000. [PubMed: 2342747]
29. Pedrazzoni M, Vescovi PP, Maninetti L, Michelini M, Zaniboni G, Pioli G, et al. Effects of chronic heroin abuse on bone and mineral metabolism. *Acta Endocrinol.* 1993; 129:42–5. [PubMed: 8351958]
30. Tagliaro F, Capra F, Dorizzi R, Luisetto G, Accordini A, Renda E, et al. High serum calcitonin levels in heroin addicts. *J Endocrinol Invest.* 1984; 7:331–3. [PubMed: 6501805]
31. Tagliaro F, Dorizzi R, Lafisca S, Maschio S, Marigo M. Calcitonin serum levels in heroin addicts: Effects of methadone and clonidine detoxication treatments. *Drug Alcohol Depend.* 1987; 70:143–148.
32. Spagnoli W, Torboli P, Mattarei M, De Venuto G, Marcolla A, Miori R. Calcitonin and prolactin serum levels in heroin addicts: study on a methadone treated group. *Drug Alcohol Depend.* 1987; 70:143–8. [PubMed: 3678052]
33. Spagnoli W, De Venuto G, Mattarei M, Dal Piaz A, Merz O, Miori R. Immunoheterogeneity of serum calcium in heroin addicts. *Drug Alcohol Depend.* 1988; 32:1960–1966.
34. Shorr RI, Griffin MR, Daugherty JR, Ray WA. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. *J Gerontol.* 1992; 47:M111–15. [PubMed: 1624693]

35. Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. *Am J Epidemiol.* 1998; 148:887–892. [PubMed: 9801019]
36. Ensrud KE, Blackwell T, Mangione CM, Bowman PJ, Bauer DC, Schwartz A, et al. Study of Osteoporotic Fractures Research Group. Central nervous system active medications and risk for fractures in older women. *Arch Intern Med.* 2003; 163:949–57. [PubMed: 12719205]
37. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associate with the use of morphine and opiates. *J Intern Med.* 2006; 260:76–87. [PubMed: 16789982]
38. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC, et al. Study of Osteoporotic Fractures Research Group. Central nervous system active medications and risk for falls in older women. *J Am Geriatr Soc.* 2002; 50:1629–37. [PubMed: 12366615]
39. Bolland MJ, Grey AB, Horne AM, Briggs SE, Thomas MG, Ellis-Pegler RB, et al. Bone mineral density remains stable in HAART-treated HIV-infected men over 2 years. *Clin Endocrinol (Oxf).* 2007 Aug; 67(2):270–5. [PubMed: 17547686]
40. Dolan SE, Kanter JR, Grinspoon S. Longitudinal analysis of bone density in human immunodeficiency virus-infected women. *J Clin Endocrinol Metab.* 2006; 91(8):2938–2945. [PubMed: 16735489]
41. Fernández-Rivera J, García R, Lozano F, Macías J, García-García JA, Mira JA, et al. Relationship between low bone mineral density and highly active antiretroviral therapy including protease inhibitors in HIV-infected patients. *HIV Clin Trials.* 2003 Sep-Oct; 4(5):337–46. [PubMed: 14583850]
42. Grund B, Peng G, Gibert CL, Hoy JF, Isaksson RL, Shlay JC, et al. INSIGHT SMART Body Composition Substudy Group. Continuous antiretroviral therapy decreases bone mineral density. *AIDS.* 2009 Jul 31; 23(12):1519–29. [PubMed: 19531929]
43. Jacobson DL, Spiegelman D, Knox TK, Wilson IB. Evolution and predictors of change in total bone mineral density over time in HIV-infected men and women in the nutrition for healthy living study. *J Acquir Immune Defic Syndr.* 2008 Nov 1; 49(3):298–308. [PubMed: 18845956]
44. Madeddu G, Spanu A, Solinas P, Calia GM, Lovigu C, Chessa F, et al. Bone mass loss and vitamin D metabolism impairment in HIV patients receiving highly active antiretroviral therapy. *Q J Nucl Med Mol Imaging.* 2004 Mar; 48(1):39–48. [PubMed: 15195003]
45. Mondy K, Yarasheski K, Powderly WG, Whyte M, Claxton S, DeMarco D, et al. Longitudinal evolution of bone mineral density and bone markers in HIV-infected individuals. *Clin Infect Dis.* 2003; 36:482–490. [PubMed: 12567307]
46. Nolan D, Upton R, McKinnon E, John M, James I, Adler B, et al. Stable or increasing bone mineral density in HIV-infected patients treated with nelfinavir or indinavir. *AIDS.* 2001; 15:1275–80. [PubMed: 11426072]
47. Yin MT, Lu D, Cremers S, Tien PC, Cohen MH, Shi Q, et al. Short-Term Bone Loss in HIV-Infected Premenopausal Women. *J Acquir Immune Defic Syndr.* 2009 Nov 3.
48. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS.* 2006 Nov 14; 20(17):2165–74. [PubMed: 17086056]
49. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ.* 1996 May; 312(7041):1254–9. [PubMed: 8634613]
50. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, et al. Predictive value of BMD for hip and other fractures. *J Bone Miner Res.* 2005 Jul; 20(7):1185–94. [PubMed: 15940371]
51. Kanis JL, Melton LJ, Christiansen C, Johnston CC, Khaltav N. The diagnosis of osteoporosis. *J Bone Miner Res.* 1994; 9:1137–1141. [PubMed: 7976495]
52. Melton LJ 3rd, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective. How many women have osteoporosis? *J Bone Miner Res.* 1992; 7:1005. [PubMed: 1414493]
53. Merrill RM, Weed DL, Feuer EJ. The lifetime risk of developing prostate cancer in white and black men. *Cancer Epidemiol Biomarkers Prev.* 1997; 6:763. [PubMed: 9332756]
54. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet.* 1999; 353:878. [PubMed: 10093980]

55. Hasserijs R, Karlsson MK, Nilsson BE, Redlund-Johnell I, Johnell O, European Vertebral Osteoporosis Study. Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study. *Osteoporos Int.* 2003; 14:61. [PubMed: 12577186]
56. Olszynski WP, Shawn Davison K, Adachi JD, Brown JP, Cummings SR, Hanley DA, et al. Osteoporosis in men: epidemiology, diagnosis, prevention, and treatment. *Clin Ther.* 2004 Jan; 26(1):15–28. [PubMed: 14996514]
57. Greenspan SL, Myers ER, Maitland LA, Resnick NM, Hayes WC. Fall severity and bone mineral density as risk factors for hip fracture in ambulatory elderly. *JAMA.* 1994 Jan 12; 271(2):128–33. [PubMed: 8264067]
58. Greenspan SL, Myers ER, Maitland LA, Kido TH, Krasnow MB, Hayes WC. Trochanteric bone mineral density is associated with type of hip fracture in the elderly. *J Bone Miner Res.* 1994 Dec; 9(12):1889–94. [PubMed: 7872054]
59. Karlsson MK, Johnell O, Nilsson BE, Sernbo I, Obrant KJ. Bone mineral mass in hip fracture patients. *Bone.* 1993 Mar-Apr; 14(2):161–5. [PubMed: 8334034]
60. Nguyen T, Sambrook P, Kelly P, Jones G, Lord S, Freund J, et al. Prediction of osteoporotic fractures by postural instability and bone density. *BMJ.* 1993 Oct 30; 307(6912):1111–5. [PubMed: 8251809]
61. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab.* 2008 Sep; 93(9):3499–504. [PubMed: 18593764]
62. Grund B, Peng G, Gibert CL, Hoy JF, Isaksson RL, Shlay JC, et al. Continuous antiretroviral therapy decreases bone mineral density. *AIDS.* 2009 Jul 31; 23(12):1519–29. [PubMed: 19531929]

Table 1
Participant Characteristics of 389 Men Studied

Characteristic	HIV - n=159	HIV+ n=230	P
Age at 1st exam (yrs); mean $\pm$ SD	56.4 $\pm$ 5.64	55.0 $\pm$ 4.13	.008
Race (%)			.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	<.001
Heroin use last 5 years (%)	39.0	23.5	.001
Opioid or cocaine use ever (%)	91.2	85.2	.08
Injection drug use ever (%)	57.9	57.0	.86
Smoking history (%)			.008
Nonsmoker	11.9	10.9	
Former smoker	17.0	30.9	
Current smoker	71.1	58.3	
Pack years visit 1; mean $\pm$ SD	21.1 $\pm$ 23.1	20.7 $\pm$ 24.3	.87
Alcoholism (%)	45.9	48.0	.68
Hepatitis C seropositivity (%)	67.5	65.8	.72
Depressive symptoms at visit 1 (%)	50.3	41.9	.10
BMI at visit 1(kg/m2); mean $\pm$ SD	27.5 $\pm$ 5.1	25.9 $\pm$ 4.5	.001
BMI visit 2 (kg/m2); mean $\pm$ SD	27.4 $\pm$ 5.2	25.3 $\pm$ 4.7	<.001
Testosterone level (ng/dL); mean $\pm$ SD	347.3 $\pm$ 368.4	358.1 $\pm$ 282.6	.74
Low testosterone (<300 ng/dL); (%)	49.1	46.1	.56
Past testosterone replacement (%)	5.7	26.2	<.001
Current testosterone replacement (%)	2.5	17.0	<.001
Past corticosteroid use (%)	1.9	5.2	.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

Characteristic	HIV - n=159	HIV+ n=230	P
Current non-PI based ART use (%)	0	34.8	NA
Current PI 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/ml), (%)			
0-200	NA	17.4	NA
201-500	NA	49.6	NA
>500	NA	33.0	NA

Table 2
Multivariable linear regression analysis of factors associated with annual change in BMD^a at three sites among CHAMPS study participants

Variable	Femoral neck		Total hip		Lumbar Spine	
	Parameter estimate ^c	95% CI ^d	Parameter estimate	95% CI	Parameter estimate	95% CI
Heroin use within 5 yrs	.0031	-.0039, .0101	.0017	-.0049, .0084	.0015	-.0060, .0089
History of AIDS diagnosis	-.0014	-.0077, .0049	-.0020	-.0080, .0040	.0038	-.0029, .0106
HIV+	.0036	-.0021, .0094	.0005	-.0050, .0060	.0002	-.0060, .0064
AIDS and heroin use ^b	-.0150	-.0267, -.0033	-.0109	-.0218, -.0000	-.0092	-.0214, .0030
HIV+ and heroin use ^b	-.0016	-.0120, .0089	-.0072	-.0174, .0030	-.0059	-.0171, .0053
Baseline BMD at site	-.0187	-.0326, -.0048	-.0179	-.0306, -.0051	.0037	-.0081, .0161
Age at 1 st exam	-.0001	-.0006, .0003	-.0001	-.0006, .0003	.0002	-.0003, .0006
Black	-.0039	-.0103, .0026	.0028	-.0032, .0089	.0011	-.0057, .0078
Hispanic	.0001	-.0068, .0069	.0051	-.0015, .0117	.0023	-.0051, .0097
Other	-.0101	-.0204, .0023	-.0028	-.0127, .0070	.0040	-.0071, .0150
White	Reference		Reference		Reference	
Body Mass Index (kg/m ²)	.0001	-.0004, .0005	.0003	-.0001, .0008	.0003	-.0001, .0008
Ever use of corticosteroids	.0090	-.0020, .0199				
Family history of spine fracture	.0048	-.0128, .0223	.0026	-.0142, .0194	.0026	-.0142, .0194
Current methadone use	-.0036	-.0091, .0020	-.0085	-.0138, -.0032	-.0085	-.0138, -.0032
Hepatitis C virus seropositivity	-.0050	-.0002, -.0097	-.0034	-.0079, .0011	-.0034	-.0079, .0011

^aBMD: Bone mineral density

^bFor 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.

c 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 gm/cm^2 per year

d 95% Confidence Interval for parameter estimate

Parameter estimates with blank cells indicate variable did not enter that model.

Table 3
Multivariable linear regression analysis of factors associated with annual change in BMD^a at three sites among HIV + CHAMPS study participants

Variable	Femoral neck		Total hip		Lumbar Spine	
	Parameter estimate ^c	95% CI ^d	Parameter estimate	95% CI	Parameter estimate	95% CI
Heroin use	-.0056	-.0138, .0027	.0003	-.0102, .0108	-.0063	-.0163, .0037
AIDS diagnosis	-.0048	-.0109, .0011	-.0007	-.0085, .0072	.0051	-.0023, .0125
AIDS and heroin use ^b	-.0062	-.0187, .0063	-.0122	-.0279, .0035	-.0016	-.0169, .0138
Baseline BMD	-.0045	-.0220, .0129	-.0469	-.0681, -.0257	-.0041	-.0242, .0160
Age at 1 st exam	-.0003	.0009, .0004	-.0002	-.0010, .0006	-.0002	-.0010, .0006
Black	-.0116	-.0120, -.0033	.0063	-.0044, .0170	.0068	-.0033, .0169
Hispanic	-.0065	-.0156, .0026	.0114	-.0003, .0231	.0063	-.0047, .0174
Other	-.0183	-.0324, -.0042	.0022	-.0162, .0205	.0178	.0005, .0351
White	Reference		Reference		Reference	
Body Mass Index (kg/m ²)	.0002	-.0005, .0008	.0004	-.0004, .0012	.0008	-.0000, .0016
Ever use of corticosteroids	.0097	-.0021, .0216	-.0003	-.0158, .0152	-.0053	-.0199, .0093
Family history of spine fracture	.0242	-.0025, .0510	.0089	-.0258, .0436	.0107	-.0220, .0435
Family history of hip fracture	.0053	-.0046, .0151			-.0068	-.0194, .0058
Current methadone use			-.0078	-.0172, .0017		
CD4+ cell count (c/mL)						
0-200	-.0056	-.0132, .0021			-.0086	-.0183, .0010
201-500	.0027	-.0132, .0085			.0025	-.0046, .0096
>500	Reference		Reference		Reference	

Variable	Femoral neck		Total hip		Lumbar Spine	
	Parameter estimate ^c	95% CI ^d	Parameter estimate	95% CI	Parameter estimate	95% CI
Length of HIV diagnosis						
<1 year					-.0036	-.0307, .0234
1-2 years					.0201	.0005, .0397
3-4 years					.0081	-.0084, .0246
5-9 years					.0049	-.0019, .0116
10+ years					Reference	
Ever use of protease inhibitors						
					-.0071	-.0160, .0017
No NRTI use						
					-.0098	-.0220, .0024
Previous NRTI use						
					-.0071	-.0161, .0020
Current NRTI use						
					Reference	

^a Abbreviations: BMD: Bone mineral density; NRTI: nucleoside analog reverse transcriptase inhibitor

^b 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.

^c 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 gm/cm² per year

^d 95% Confidence Interval for parameter estimate

Parameter estimates with blank cells indicate variable did not enter that model.