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

Published in final edited form as:
J Acquir Immune Defic Syndr. 2008 November 1; 49(3): 298–308. doi:10.1097/QAI.0b013e3181893e8e.

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

DL Jacobson[1], **D Spiegelman**[1,2], **TK Knox**[3], and **IB Wilson**[4]

[1]Department of Biostatistics, Harvard School of Public Health, Boston, MA.

[2]Department of Epidemiology, Harvard School of Public Health, Boston, MA.

[3]Department of Public Health and Family Medicine, Tufts University School of Medicine, Boston, MA.

[4]Institute for Clinical Research and Health Policy Studies and the Department of Medicine, Tufts-New England Medical Center, Boston, MA.

Abstract

Background—Osteopenia is common in the era of effective antiretroviral therapy (ART), yet the etiology is unclear. We evaluated the association of host factors, disease severity and ART to changes in total body bone mineral density (Total BMD) over time in HIV-infected men (n=283) and women (n=96).

Methods—Total BMD was measured annually by whole body dual energy absorptiometry (DXA) and medical, dietary and behavioral history was collected. The median time from first to last DXA was 2.5 years (range 0.9 to 6.8). Using a repeated measures regression model, we identified variables independently associated with percent change in Total BMD between consecutive DXA exams (n=799 intervals), adjusted for age, race, sex, menopause and smoking. We estimated percent change in Total BMD over an average interval (one year) standardized for representative levels of each determinant in males, pre- and post-menopausal women.

Results—Median baseline age, CD4 and viral load were 42 years, 364 cells/mm^3 and 2.7 $\log_{10}$ copies/ml, respectively. The estimated change in Total BMD for those not on ART was −0.37%/yr (95%CI −0.76, −0.02) for men, −0.08%/yr (95%CI −0.49, 0.33) for pre-menopausal women and −1.07%/yr (95%CI −1.86, −0.28) for post-menopausal women. Greater loss of Total BMD was associated with lower albumin, lower BMI, prednisone/hydrocortisone use, tenofovir use and longer duration of ddI. Strength training and long duration of d4T and saquinavir prevented or mitigated bone loss. For those on ART for 3 years (not including the above agents), the rate of loss was −0.57%/yr (95%CI −1.00, −0.14) for men, −0.28% (95%CI −0.71, 0.15) for pre-menopausal women and −1.27% (95%CI −2.07, −0.47) for post menopausal women. Post-menopausal women had greater loss than pre-menopausal women and men.

Please address all correspondence to Denise L. Jacobson, PhD MPH, Department of Biostatistics, Center for Biostatistics and AIDS Research, Harvard School of Public Health, 655 Huntington Avenue 02115. Phone (617)-432-3266, fax (617)-432-3163, jacobson@sdac.harvard.edu.

This was presented as an abstract at the 12th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 2005.

Conclusion—Low body weight, low albumin, catabolic steroid use and menopause may accelerate bone loss, and strength training may be protective. Tenofovir and ddI may also have a deleterious effect on BMD.

INTRODUCTION

Low bone mineral density is frequently observed among HIV-infected adults and children [1, 2] . The etiology is poorly understood and probably multifactorial. The long-term clinical outcomes are not known. Most cases of bone loss in HIV-infected individuals result in mild osteopenia; osteoporosis is less prevalent [3-6] . As HIV-infected patients live longer due to more effective anti-retroviral therapy (ART), they are exposed to numerous factors over time which may have an impact on bone mineral density (BMD), including traditional risk factors (aging, genetic predisposition, menopause, low calcium and vitamin D intake and low sun exposure, lack of weight-bearing exercise, smoking, catabolic steroid use, weight change) and HIV-associated factors (chronic HIV infection, various and changing treatment regimens).

Cross-sectional studies in HIV-infected adults show conflicting results regarding the association of low BMD with ART [3, 7-14] . Most of these studies selected specific patient groups based on current treatment regimen, wasting or lipodystrophy status, making it difficult to compare across studies or to generalize across HIV-infected subgroups. In addition, the cross-sectional design of these studies makes it impossible to know for certain if the risk factors preceded the bone loss.

Our understanding of the independent effects of host factors, medications and HIV disease factors is limited by the lack of prospective studies in men and women with careful control for confounding by host factors. Few studies have a baseline measure of BMD before treatment. In one clinical trial, ART naïve patients randomized to tenofovir-based highly active antiretroviral therapy (HAART) had a greater decrease in lumbar spine BMD over time compared to patients on d4T based HAART [13] . A few other studies examined change in BMD or bone mineral content (BMC) over time. Mondy et al. followed patients for 72 weeks and found an overall increase in lumbar spine (2.6%) and hip (2.4%) BMD among those with undetectable HIV viral load and with greater increases in CD4 count, but no difference by protease inhibitor (PI) - compared to non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART [15] . Other studies have found decreasing BMD in patients on dual nucleoside reverse transcriptase inhibitor (NRTI) [16] , stable BMD among patients using nelfinavir-containing HAART [13] and slightly increasing BMD among patients using indinavir-containing HAART [13] . Dolan et al. found lower baseline BMD in HIV–infected compared to HIV-negative persons, but a similar rate of change over time between the groups [17] . McDermott et al. found decreases in extremity BMC in PI-based HAART users and increases in those on nelfinavir. Decreases in trunk BMC were observed among those on zidovudine and increases in those on d4T [18] . Finally, tenofovir is associated with bone loss [19, 202122] .

To better understand the evolution and predictors of change in BMD over time, we followed a heterogeneous cohort of HIV-infected men and women in the Nutrition for Healthy Living Study (NFHL) for a median of 2.5 years (range 0.9 to 6.8). We performed annual assessments of Total Body BMD by dual energy x-ray densitometry (DXA) and semi-annual measurements of demographics, disease severity, body mass index (BMI), physical activity, steroid use, ART and dietary intake.

METHODS

Study Participants

NFHL is a longitudinal cohort of HIV-infected adults (18 years or older) living in Massachusetts or Rhode Island, USA as previously reported[23-25, 26, 27] . Those included in this analysis were seen between August 1996 and September 2003. The Institutional Review Boards at Tufts University School of Medicine and Miriam Hospital, Rhode Island approved this study and written informed consent was obtained from each participant. Participants were seen semi-annually for all data collection except DXA which was annual.

Interview Data

Data on demographics, dietary intake, HIV-related clinical events, ART and steroid use (prednisone/hydrocortisone, testosterone and growth hormone) were collected by trained interviewers and nutritionists [28] . Doses were not collected on medications. Participants were able to select more than one category to define their race. If at least one of the selected categories was black, they were categorized as African American. If they only selected white they were categorized as “white”. All other categories were combined as “other”. Injection drug use (IDU) was dichotomized as ever vs. never and smoking was defined as current vs. not current. We determined which participants were living below the U.S. Federal poverty level (yes/no) based on household income [29] . Daily caloric intake, protein, calcium and vitamin D consumption, including supplements, were determined from three-day food records using the Minnesota Nutrition Data System Version 4.06_34. If a three-day food record was not kept, a 24-hour food recall was obtained by a trained nutritionist. We assessed strength training over the past 7 days using the Physical Activity Recall instrument [30] . “Strength training” was defined as any strength training in the last week.

Laboratory Data

HIV RNA (log10 copies/ml) was measured by the Roche Amplicor Monitor reverse transcriptase PCR assay (Roche Molecular Systems, Somerville, NJ), with a lower detection limit of 400 copies/ml.

Physical Examination

Subjects were weighed (kg) fully dressed, but without shoes, heavy clothing or objects, before eating or drinking (minimum 5 hour fast). Height (cm) was measured without shoes by stadiometer. BMI was calculated as weight divided by height squared (kg/m^2). Wasting was defined as: BMI <20 kg/m^2, weight loss > 10% body weight since enrollment or weight loss > 5% body weight maintained at least 6 months. Ever wasting was any episode of wasting since entering the study.

Dual X-ray absorptiometry (DXA)

Yearly DXA scans were performed on the Hologic QDR-2000 machine (Hologic, Waltham, MA). Hologic 2000 software computed total body bone mineral density (Total BMD, gm/cm^2).

Analysis

Baseline analysis: Baseline characteristics are described using the median (25^{th}, 75^{th}) for continuous variables and the number (%) for categorical variables by sex. Total BMD at baseline was calculated at the median age for men, pre-menopausal women, and menopausal women by race (Caucasian/Asian, African American).

Interval analysis

Unit of analysis - DXA interval: For each participant, consecutive DXA visits were paired to form DXA intervals. For example, first to second DXA, second to third DXA, etc. The length of time within each DXA interval was determined. For this analysis, all intervals ranging from 9 to 24 months were included on all participants, and longer or shorter intervals were excluded. Thus, each participant with >1 DXA interval (at least two DXA visits) that conformed to the above criteria was included. Two intervals were excluded because strength training was missing. We report participant characteristics at the beginning of the first DXA interval (Baseline) in Tables 1a and 1b.

Dependent variable (outcome): The dependent variable was the percent change in total BMD across a DXA interval. It was calculated as: (Total BMD at the end of the interval minus Total BMD at the beginning of the interval)/Total BMD at the beginning of the interval.

Independent variables: We evaluated several variables for their relationship to the outcome (percent change in Total BMD). These variables were measured at the beginning of a DXA interval. The variables were menopause (pre and post menopausal), disease severity (HIV viral load, CD4, albumin), dietary intake (calcium, vitamin D) with and without supplements, body composition (BMI, weight loss), exercise (strength training), prednisone/hydrocortisone, testosterone/growth hormone and use of HAART or any ART. Each woman was asked “Have you been through menopause (the change of life).” If the answer was “yes” she was categorized as post-menopausal, if the answer was “no” she was categorized as pre-menopausal. She was also asked if she had had a hysterectomy (yes/no). We made two dummy variables to compare males to pre-menopausal women and to compare post-menopausal women to pre-menopausal women. Thus, pre-menopausal women were the reference group. Each ART agent was examined as months of continuous use up until the beginning of the interval. The beginning of continuous use of an ART agent may have begun before the baseline visit and thus continuous use is the total of use from baseline until the beginning of the interval plus use before the study began if it was uninterrupted at baseline. HAART was defined as use of at least three medications from two or more classes (NRTI, NNRT, PI).

Repeated Measures Analysis of Change in Total BMD: We evaluated the association between each independent variable and the outcome using generalized estimating equations (GEE) for repeated measures regression analysis because there are multiple records per person. The Toeplitz 2 covariance structure was used because the outcome is change. The basic models contained the determinant of interest and they were adjusted for the dummy variables of male and post-menopausal women (pre-menopausal women was the reference group) and time in interval (time between DXA visits). The robust variance was used to calculate 95% confidence intervals (95% CI). Significant variables at $P<0.20$ in the basic models were entered into multivariate models. The final multivariate model included significant variables at $P<0.05$ plus time between DXA visits, age, race, the male and menopause dummy variables, smoking and number of years on “other ART”. “Other ART” indicates the maximum time of all the other ART agents that a participant was taking, not including the ones in the multivariate model. This term was included because patients are rarely on one agent alone. All analyses were performed in SAS 9.2 (SAS Institute, Carey NC). The assumption of linearity between each continuous determinant (CD4, viral load, albumin, BMI, duration of each ART) and the outcome (percent change in Total BMD) was assessed using restricted cubic splines [31] . Since none of these variables had large deviations from normality there were used as continuous variables. A missing indicator was used for albumin and menopause, for which there were 35 and 18 intervals missing, respectively.

Two additional variables were included, one for catabolic steroid use (hydrocortisone, prednisone) and one for anabolic steroids (testosterone, growth hormone).

Estimates of change in Total BMD: For the basic models, we estimated the percent change in Total BMD over 12 months at selected levels of the determinant of interest. For example, the estimate for strength training in males from the basic model is %change in Total BMD = intercept + $\beta_1$time in interval + β_2 Male + $\beta_3$strength training. For the multivariate model, we estimated the percent change in Total BMD for selected levels of all variables of interest in the model, adjusted for age, race and smoking, the male and post-menopausal women dummy variables and time on other ART. All estimates assume three years of "other ART" use and were calculated separately for males, pre-menopausal women, and post-menopausal women. Age, BMI and albumin were mean-centered at 45 years, 25 kg/m^2 and 4.0 g/dl, respectively, so that the intercept for each model reflects the mean value, not zero, for each of these variables. For example the estimate for a male on d4T would be %change in Total BMD = intercept + β_1(time in interval=1 year) + β_2 age + β_3African American + $\beta_4$male + $\beta_5$smoker + $\beta_6$albumin + $\beta_7$strength training + β_8BMI + β_9 Time on d4T + β_{10} Time on Other ART. For race, smoking status and strength training we used the values for Caucasian (African American =0), smoker=0, strength training=0 for all estimates, except when we made estimates for strength training we then used the value 1 for strength training. For estimates of men, pre-menopausal females and post-menopausal females, age was specified as 45, 40 and 51, respectively, based on the median age in each group over all of the intervals. The p-values given in Tables 2 and 3 test the hypothesis that there is no association between change in total BMD and the continuous or categorical row variable, using the robust Wald test. For some ART agents, strength training and types of steroid use, there were few or no pre-menopausal or post-menopausal women who used the agent or practiced strength training. In those cases, no estimate was given in Tables 2 or 3 for the variable.

RESULTS

Participant characteristics

A total of 799 intervals were available for 379 individuals. The median (25th, 75th) number of intervals included per person was 2 (1,3), range 1-6. The date at the beginning of the first interval ranged from August 1996 until August 2002. The median (25th, 75th) number of months within the DXA intervals was 12.8 [12.0, 16.5]. The median total time of follow-up from first DXA visit to last DXA visit was 2.5 years (IQR 1.2, 3.8; range 0.9, 6.8).

There were 283 men, 76 pre-menopausal women and 20 post-menopausal women in the study with a median age of 43, 38 and 49, respectively. Three of the 20 post-menopausal women became post-menopausal during follow-up and 8 of 20 reported ever having a hysterectomy. Nine pre-menopausal women reported ever having a hysterectomy. Compared to women in this study, men were older, more likely to be white, less likely to be obese, reported higher intakes of calories, calcium and vitamin D and had lower CD4 cell counts (Table 1a). Intake was inadequate for vitamin D (< 10mcg) and calcium (< 1000 mg) for 43% and 46% of men, 63% and 71% of pre-menopausal women and 53% and 82% of post-menopausal women, respectively. At the end of follow-up (data not shown), the median age of the post-menopausal women, premenopausal women and men in our cohort was 51, 41, and 46 years, respectively. Use and duration of use until the beginning of the first DXA interval is shown in Table 1b for different ART agents and HAART regimens, stratified by sex,

Total BMD at baseline by sex, race and menopausal status

At baseline, the estimated total BMD was 1.12 gm/cm^2 for Non-African American men (includes Caucasian, Hispanic and Asian) and 1.20 gm/cm^2 for African American men ($P < 0.0001$) data not shown . For pre-menopausal women, total BMD was 1.09 gm/cm^2 for Non-African American women and 1.13 gm/cm^2 for African American women (P=0.04). Finally, among post-menopausal women total BMD was 1.04 for Non-African American women and 1.08 gm/cm^2 for African American women (P=0.41).

Estimates of percent change in Total BMD over DXA intervals by sex and menopausal status

Basic estimates—Estimates of the percent change in Total BMD over one year are shown in Table 2 for each selected level of the determinant in each basic model. They are presented for men, pre-menopausal women and post-menopausal women separately.

Multivariate Estimates—Estimates of the percent change in Total BMD over one year for selected levels of each determinant in the multivariate model adjusted for time in interval, age, race, smoking and the sex and menopausal dummy variables, are shown in Table 3. Total BMD did not vary significantly by age, race, and time in the interval after adjusting for other variables. Pre-menopausal women tended to have less bone loss than men (P=0.065) while post-menopausal women lost almost three times the BMD than pre-menopausal women (P=0.012). For example, for participants on “other ART” for at least three years, on average men lost −0.57% (95% CI −1.00, −0.14), pre-menopausal women lost −0.28%/yr (95% CI −0.71, −0.15) and post-menopausal women lost −1.27%/yr (95% CI −2.07, −0.47). P values for all other variables of interest are shown in Table 3. There were no significant interactions between sex or menopausal status and other terms in the model.

The adjusted estimates described in this paragraph are for men and the estimates for women can be seen in Table 3. Higher albumin, higher BMI and strength training were associated with less bone loss, after adjusting for other determinants of change in BMD. For example, the estimated one year percent change in total BMD in a male with an albumin level of 3.5 mg/dL was −0.76%/yr (95% CI −1.23, −0.30) and −0.57%/yr (95% CI −1.00, −0.14) for a albumin of 4.0 mg/dL. For men with BMI of 20, 25 and 30, the estimated percent change in Total BMD was −0.78%/yr (95% CI −1.21, −0.36), −0.57%/yr (95% CI −1.00, −0.14) and −0.36%/yr (95% CI −0.85, 0.13), respectively. On average, men who practiced strength training had stable BMD (−0.15%/yr , 95%CI −0.52, 0.21) while those who did not practice strength training had a decrease in Total BMD (−0.57%/yr, 95%CI −1.00%, −0.14%). Men on no ART had a decline in BMD −0.37%/yr (95% CI −0.76%, −0.02%). Men on prednisone/hydrocortisone lost two times the amount of BMD than non-users. Decreases in Total BMD were greater with increasing time on ddI and with tenofovir use. Use vs. non-use of tenofovir (P=0.003) was included in the model as it was more significant than duration of use (P=0.10). The estimated percent change in Total BMD in men was −0.84%/yr (95% CI −1.32, −0.35) for men on ddI for one year and −1.37%/yr (95% CI −2.10, −0.64) for men on ddI for 3 years. The estimated change in Total BMD for men on tenofovir was −2.04% (95% CI −3.00, −1.08). In contrast, long durations of d4T and saquinavir were associated with less loss in Total BMD.

Most participants who were on these agents at the beginning of the interval, were on it throughout the interval (Percent on throughout interval): d4T (65%), tenofovir (77.3%), saquinavir (71.3%), ddI (69.4%). There was no significant difference in the percent change in Total BMD by CD4 cell count, HIV viral load, years known HIV-infected, smoking, testosterone/growth hormone, calcium or vitamin D intake, hormonal contraceptive use or other individual ART.

DISCUSSION

In this study, we followed an ethnically diverse group of HIV-infected men and women to study the effect of various treatment regimens on change in Total Body BMD over time with detailed adjustment for known risk factors. There were three main findings. First, post-menopausal women had more bone loss than pre-menopausal women or men. Second, higher albumin, higher BMI and strength training were all associated with less bone loss. Third, use of tenofovir, ddI or catabolic steroids was associated with more loss and use of d4T or saquinavir was associated with less loss, compared with non-users. Markers of HIV disease severity (lower CD4 cell count, higher HIV viral load), history of wasting, dietary intake of calcium, testosterone/growth hormone, smoking and race were not independently associated with changes in bone mineral density.

Many of the important risk factors for loss of BMD in our cohort are established risk factors for bone loss in the general population. These include menopause, low BMI, lack of strength training and prednisone/hydrocortisone use. In the general population, peak bone mass is achieved between 20 and 25 years of age in both sexes [32] and decreases slowly after 35 years of age [33] with accelerated loss during the peri-menopausal years [33, 34] . Menopausal women had greater loss than pre-menopausal women and men in our cohort. In contrast, men tended to have more loss than women who had not reached menopause and less bone loss than post-menopausal women. With larger numbers of pre-and post-menopausal women we would have had more power to detect differences. The reasons for suggested differences are not clear. The premenopausal women were on average five years younger than the men. Many of these are probably not peri-menopausal. Age was not an independent risk factors and the rate of change over time did not differ across race. For each sex, total BMD was higher in African Americans compared to other races. This corresponds to population surveys, in which blacks have higher BMD than other races. Blacks also have a lower rate of hip fracture than whites, Hispanics and Asians [35] . We did not have data on fractures.

A recent meta-analysis in HIV, showed that much of the difference in BMD between HIV-positives and HIV-negatives disappeared after adjustment for weight[36] . In the general population, positive correlations of BMD with weight, frame size [37] or BMI [33, 38] are thought to be largely due to the effect of mechanical force on bone formation. Within our HIV-infected patients, BMI was an important factor for bone loss, but a past episode of wasting did not predict future bone loss. While wasting still occurs in HAART users [39, 40] , episodes of wasting are less severe and may explain the lack of association in our study [41] .

Exercise training of various types among persons with HIV, including aerobic exercise and resistance exercise, has been shown to improve muscle mass [42, 43] , strength [44, 45] , physical functioning [43, 46, 47] and a variety of cardiovascular and metabolic parameters [48] . This is the first report that we are aware of that indicates that strength training may also reduce bone loss in HIV-infected patients. Maintaining adequate weight and engaging in physical activity may help to preserve and perhaps improve BMD in HIV-infected patients.

Participants who used catabolic steroids such as prednisone or hydrocortisone also had greater bone loss than those who did not, while testosterone and growth hormone did not explain gain in BMD. Vitamin D insufficiency is an important risk factor for osteoporosis [49] . In our cohort, 43% of men, 63% of pre-menopausal women and 53% of post-menopausal women had inadequate vitamin D intake. Low vitamin D intake was not a significant predictor of bone loss in men (P=0.77) or women (p=0.11). Dietary and supplement intake may not adequately reflect body levels, as HIV patients may have other complications, such as malabsoprtion or chronic diarrhea, which may prevent absorption of dietary nutrients, and renal disease may inhibit 1,25 vitamin D production. Moreover, there

may not be enough variation in intake in either males or females in our cohort to detect an effect on bone.

Common markers of HIV disease severity, including CD4 and viral load, were not predictive of bone loss in our cohort of HIV-infected adults. However, our patients with low albumin were at increased risk of bone loss. This has been observed by others [50] . While the mechanism is unclear, low albumin predicts decreasing CD4, development of AIDS and death [51-56] and probably reflects a combination of factors including poor nutrition, liver disease, concurrent infections and proinflammatory cytokines.

There are few relevant animal studies or clinical trials showing the affect of specific antiretroviral agents on bone mineralization. Our finding that participants on tenofovir had greater decreases in Total BMD over time is supported by previous studies [19, 202122] . To our knowledge there are no other reports of the potentially deleterious effects of ddI or the potentially protective effects of saquinavir on BMD. There are a few studies on the association between d4T and BMD. In a previous study in our cohort, McDermott et al. observed increases in trunk BMC in those on d4T [18] . Gallant et al. reported decreases of 1.0% in the spine and 2.4% in the hip over three years[21] in antiretroviral naïve patients who began d4T based HAART. The authors did not comment on the statistical significance of these estimates. We estimate a rate of approximately 0.3% increase over three years in total body BMD in men using d4t for at least three years. In contrast, to the former study, our participants were not anti-retroviral naïve. In addition, we could not determine why each individual started, continued or discontinued a particular treatment. Finally, total body BMD, which is primarily cortical bone, is less metabolically active and less sensitive to acute changes in medication and health, compared to the spine BMD. Total BMD reflects the longer term impact of risk factors and may change more slowly. Thus, factors associated with hip and spine may differ from those that affect total BMD [57-59] . Future studies are needed to understand how each bone site predicts fractures and health outcomes in this population.

Longitudinal studies offer a unique opportunity to examine changes in BMD over time. Nevertheless, in contrast to a clinical trial, it is not always possible to disentangle the affects of HIV disease and therapy in treatment-experienced patients. That is, patients may continue an agent or switch to another agent based on CD4, viral load, viral resistance, agent-related symptoms, metabolic disturbances or interaction with concomitant medications. Also, there are counteracting effects. Sicker patients may be less physically active, have more weight loss, increased cytokine activity and hypogonadism, while healthier patients may experience the metabolic side effect of specific ART, including mitochondrial toxicity. We measured agent use prior to changes in BMD so we feel that temporal bias is unlikely to explain our findings. In addition, in contrast to many studies in HIV we included variables for disease activity, diet, exercise and steroid use. Some of the regimens in our analysis may not be used to treat HIV disease today. Similar analyses in current cohorts will shed light on the new ART agents. Finally, we lacked biochemical measures such as estrogen or testosterone levels, markers of bone mineralization and chronic inflammation that may further explain our findings.

Our findings suggest that in the context of HIV infection, maintaining adequate weight and nutritional status and performing strength training exercises may help to combat HIV-associated bone loss. Overall, we observed small changes in total BMD and the risk of fractures is not known. Further study is needed to assess the effects of individual anti-retroviral medications on bone health, especially among post-menopausal women, and to assess fracture rates. Patients on specific agents, such as tenofovir, ddI or catabolic steroids may require close monitoring of BMD.

Acknowledgments

This paper is dedicated to the memory of Abby Shevitz, MD MPH. We wish to thank Jinyong Huang for his contributions to the data analysis, Sally Skinner for checking the programs and Christine Wanke for her valuable comments on HIV disease and treatment.

All authors on this paper had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Support: National Institute of Diabetes and Digestive and Kidney Diseases (P01DK45734); General Clinical Research Center, funded by the National Center for Research Resources (M01RR00054); Lifespan/Tufts/Brown Center for AIDS Research (P30A142853); National Institute of Allergy and Infectious Diseases (1K24 A1055293). National Institute of Drug Abuse (1P30DA13868); National Heart, Lung, and Blood Institute of the National Institute of Health (R01HL65947); National Centers for Research Resources (K24 RR020300).

REFERENCES

1. Glesby MJ. Bone disorders in human immunodeficiency virus infection. Clin Infect Dis. 2003; 37:S91–S95. [PubMed: 12942380]
2. Thomas J, Doherty SM. HIV infection - A risk factor for osteoporosis. Jaids-Journal of Acquired Immune Deficiency Syndromes. 2003; 33:281–291.
3. Fairfield WP, Finkelstein JS, Klibanski A, Grinspoon SK. Osteopenia in eugonadal men with acquired immune deficiency syndrome wasting syndrome. J Clin Endocrinol Metab. 2001; 86:2020–2026. [PubMed: 11344201]
4. Moore AL, Vashisht A, Sabin CA, et al. Reduced bone mineral density in HIV-positive individuals. AIDS. 2001; 15:1731–1733. [PubMed: 11546951]
5. Knobel H, Guelar A, Vallecillo G, Nogues X, Diez A. Osteopenia in HIV-infected patients: Is it the disease or is it the treatment? AIDS. 2001; 15:807–808. [PubMed: 11371701]
6. Loiseau-Peres S, Delaunay C, Poupon S, et al. Osteopenia in patients infected by the human immunodeficiency virus. A case control study. Joint Bone Spine. 2002; 69:482–485. [PubMed: 12477232]
7. 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; 42:1014–1020. [PubMed: 16511769]
8. Brown TT, Ruppe MD, Kassner R, et al. Reduced bone mineral density in human immunodeficiency virus-infected patients and its association with increased central adiposity and postload hyperglycemia. J Clin Endocrinol Metab. 2004; 89:1200–1206. [PubMed: 15001610]
9. Carr A, Miller J, Eisman JA, Cooper DA. Osteopenia in HIV-infected men: Association with asymptomatic lactic acidemia and lower weight pre-antiretroviral therapy. AIDS. 2001; 15:703–709. [PubMed: 11371684]
10. Huang JS, Wilkie SJ, Sullivan MP, Grinspoon S. Reduced bone density in androgen deficient women with acquired immune deficiency syndrome wasting. J Clin Endocrinol Metab. 2001; 86:3533–3539. [PubMed: 11502775]
11. Huang JS, Rietschel P, Hadigan CM, Rosenthal DI, Grinspoon S. Increased abdominal visceral fat is associated with reduced bone density in HIV-infected men with lipodystrophy. AIDS. 2001; 15:975–982. [PubMed: 11399979]
12. McDermott AY, Shevitz A, Knox T, Roubenoff R, Kehayias J, Gorbach S. Effect of highly active antiretroviral therapy on fat, lean, and bone mass in HIV-seropositive men and women. Am J Clin Nutr. 2001; 74:679–686. [PubMed: 11684538]
13. Nolan D, Upton R, McKinnon E, et al. Stable or increasing bone mineral density in HIV-infected patients treated with nelfinavir or indinavir. AIDS. 2001; 15:1275–1280. [PubMed: 11426072]
14. Tebas P, Yarasheski K, Henry K, et al. Evaluation of the virological and metabolic effects of switching protease inhibitor combination antiretroviral therapy to nevirapine-based therapy for the treatment of HIV infection. AIDS Res Hum Retrovir. 2004; 20:589–594. [PubMed: 15242534]

15. Mondy K, Yarasheski K, Powderly WG, et al. Longitudinal evolution of bone mineral density and bone markers in human immunodeficiency virus-infected individuals. Clin Infect Dis. 2003; 36:482–490. [PubMed: 12567307]
16. Tsekes G, Chrysos G, Douskas G, et al. Body composition changes in protease inhibitor-naive HIV-infected patients with two nucleoside reverse transcriptase inhibitors. HIV Medicine. 2002; 3:85–90. [PubMed: 12010354]
17. Dolan SE, Kanter JR, Grinspoon S. Longitudinal analysis of bone density in HIV-infected women. J Clin Endocrinol Metab. 2006
18. McDermott AY, Terrin N, Wanke C, Skinner S, Tchetgen E, Shevitz AH. CD4+ cell count, viral load, and highly active antiretroviral therapy use are independent predictors of body composition alterations in HIV-infected adults: A longitudinal study. Clin Infect Dis. 2005; 41:1662–1670. [PubMed: 16267741]
19. Van Rompay KKA, Brignolo LL, Meyer DJ, et al. Biological effects of short-term or prolonged administration of 9-[2-(phosphonomethoxy)propyl]adenine (tenofovir) to newborn and infant rhesus macaques. Antimicrobial Agents Chemother. 2004; 48:1469–1487.
20. Castillo AB, Tarantal AF, Watnik MR, Martin RB. Tenofovir treatment at 30 mg/kg/day can inhibit cortical bone mineralization in growing rhesus monkeys (macaca mulatta). Journal of Orthopaedic Research. 2002; 20:1185–1189. [PubMed: 12472227]
21. Gallant JE, Staszewski S, Pozniak AI, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients. J Am Med Assoc. 2004; 292:191–201.
22. Guest JL, Rimland D, Patterson BY, deSilva KE. Tenofovir-induced nephrotoxicity in the first year of therapy. Denver, CO: Conference on Retroviruses and Opportunistic Infections. 2006
23. Shevitz AH, Knox TA, Spiegelman D, Roubenoff R, Gorbach SL, Skolnik PR. Elevated resting energy expenditure among HIV-seropositive persons receiving highly active antiretroviral therapy. AIDS. 1999; 13:1351–1357. [PubMed: 10449288]
24. Silva M, Skolnik PR, Gorbach SL, et al. The effect of protease inhibitors on weight and body composition in HIV-infected patients. AIDS. 1998; 12:1645–1651. [PubMed: 9764784]
25. Wilson IB, Roubenoff R, Knox TA, Spiegelman D, Gorbach SL. Relation of lean body mass to health-related quality of life in persons with HIV. J Acquir Immune Defic Syndr. 2000; 24:137–146. [PubMed: 10935689]
26. Forrester JE, Spiegelman D, Tchetgen E, Knox TA, Gorbach SL. Weight loss and body-composition changes in men and women infected with HIV. Am J Clin Nutr. 2002; 76:1428–1434. [PubMed: 12450913]
27. Knox TA, Spiegelman D, Skinner SC, Gorbach S. Diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. American Journal of Gastroenterol. 2000; 95:3482–3489.
28. Jacobson DL, Knox TA, Spiegelman D, Skinner S, Gorbach SL, Wanke C. Prevalence, evolution and risk factors for fat atrophy and fat deposition in a cohort of HIV-infected men and women. Clin Infect Dis. 2005; 40:1837–1845. [PubMed: 15909274]
29. Register, F., editor. The 1998 HHS Poverty Guidelines. 1998.
30. Sallis JF, Haskell WL, Wood PD, et al. Physical activity assessment methodology in the five-city project. Am J Epidemiol. 1985; 121:91–106. [PubMed: 3964995]
31. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med. 1989; 8:551–561. [PubMed: 2657958]
32. Nguyen TV, Maynard LM, Towne B, et al. Sex differences in bone mass acquisition during growth: The fels longitudinal study. J Clin Densitom. 2001; 4:147–157. [PubMed: 11477308]
33. Riggs, BL.; Melton, LJ. Osteoporosis: Etiology, Diagnosis and Management. Vol. Vol Second. Lippincott-Raven; Philadelphia: 1995.
34. Favus, MJ. Primer on the Metabolic Bone Disorders and Disorders of Mineral Metabolism. No. 5th. Favus, MJ., editor. American Society for Bone and Mineral Research; Washington: 2003.
35. Cooper, C. Epidemiology of osteoporosis. In: Favus, MJ., editor. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. Vol. Vol 5th. American Society for Bone and Mineral Research; Washington,D.C.: 2003. p. 311

36. Bolland MJ, Grey AB, Gamble GD, Reid IR. Clinical review: Low body weight mediates the relationship between HIV infection and low bone mineral density: A meta-analysis. J Clin Endocrinol Metab. 2007; 92:4522–4528. [PubMed: 17925333]
37. Chumlea WC, Wisemandle W, Guo SS, Siervogel RM. Relations between frame size and body composition and bone mineral status. Am J Clin Nutr. 2002; 75:1012–1016. [PubMed: 12036807]
38. Bakker I, Twisk JW, Van Mechelen W, Kemper HC. Fat-free body mass is the most important body composition determinant of 10-yr longitudinal development of lumbar bone in adult men and women. J Clin Endocrinol Metab. 2003; 88:2607–2613. [PubMed: 12788863]
39. Wanke CA, Silva M, Knox TA, Forrester J, Spiegelman D, Gorbach SL. Weight loss and wasting remain common complications in individuals infected with human immunodeficiency virus in the era of highly active antiretroviral therapy. Clin Infect Dis. 2000; 31:803–805. [PubMed: 11017833]
40. Tang AM, Jacobson DL, Spiegelman D, Knox TA, Wanke C. Increasing risk of 5% or greater unintentional weight loss in a cohort of HIV-infected patients, 1995 to 2003. J Acquir Immune Defic Syndr. 2005; 40:70–76. [PubMed: 16123685]
41. Lawal A, Engelson ES, Wang J, Heymsfield SB, Kotler DP. Equivalent osteopenia in HIV-infected individuals studied before and during the era of highly active antiretroviral therapy. AIDS. 2001; 15:278–280. [PubMed: 11216941]
42. Driscoll SD, Meininger GE, Lareau MT, et al. Effects of exercise training and metformin on body composition and cardiovascular indices in HIV-infected patients. AIDS. 2004; 18:465–473. [PubMed: 15090799]
43. Shevitz AH, Wilson IB, McDermott AY, et al. A comparison of the clinical and cost-effectiveness of 3 intervention strategies for AIDS wasting. J Acquir Immune Defic Syndr. 2005; 38:399–406. [PubMed: 15764956]
44. Dolan SE, Frontera W, Librizzi J, et al. Effects of a supervised home-based aerobic and progressive resistance training regimen in women infected with human immunodeficiency virus: A randomized trial. Arch Intern Med. 2006; 166:1225–1231. [PubMed: 16772251]
45. Perez-Moreno F, Camara-Sanchez M, Tremblay JF, Riera-Rubio VJ, Gil-Paisan L, Lucia A. Benefits of exercise training in spanish prison inmates. Int J Sports Med. 2007
46. Roubenoff R, Wilson IB. Effect of resistance training on self-reported physical functioning in HIV infection. Med Sci Sports Exerc. 2001; 33:1811–1817. [PubMed: 11689729]
47. Fillipas S, Oldmeadow LB, Bailey MJ, Cherry CL. A six-month, supervised, aerobic and resistance exercise program improves self-efficacy in people with human immunodeficiency virus: A randomised controlled trial. Aust J Physiother. 2006; 52:185–190. [PubMed: 16942453]
48. Driscoll SD, Meininger GE, Ljungquist K, et al. Differential effects of metformin and exercise on muscle adiposity and metabolic indices in human immunodeficiency virus-infected patients. J Clin Endocrinol Metab. 2004; 89:2171–2178. [PubMed: 15126538]
49. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006; 84:18–28. [PubMed: 16825677]
50. Fernandez-Rivera J, Garcia R, Lozano F, et al. Relationship between low bone mineral density and highly active antiretroviral therapy including protease inhibitors in HIV-infected patients. Hiv Clinical Trials. 2003; 4:337–346. [PubMed: 14583850]
51. Melchior JC, Niyongabo T, Henzel D, Durack-Bown I, Henri SC, Boulier A. Malnutrition and wasting, immunodepression, and chronic inflammation as independent predictors of survival in HIV-infected patients. Nutrition. 1999; 15:865–869. [PubMed: 10575662]
52. Brechtl JR, Patrick PA, Visintainer P, Brand DA. Predictors of death within six months in patients with advanced AIDS. Palliat Support Care. 2005; 3:265–272. [PubMed: 17039981]
53. Olawumi HO, Olatunji PO. The value of serum albumin in pretreatment assessment and monitoring of therapy in HIV/AIDS patients. HIV Med. 2006; 7:351–355. [PubMed: 16903978]
54. Mehta SH, Astemborski J, Sterling TR, Thomas DL, Vlahov D. Serum albumin as a prognostic indicator for HIV disease progression. AIDS Res Hum Retroviruses. 2006; 22:14–21. [PubMed: 16438640]

55. Bonarek M, Morlat P, Chene G, et al. Prognostic score of short-term survival in HIV-infected patients admitted to medical intensive care units. Int J STD AIDS. 2001; 12:239–244. [PubMed: 11319975]

56. Afessa B, Green B. Clinical course, prognostic factors, and outcome prediction for HIV patients in the ICU. the PIP (pulmonary complications, ICU support, and prognostic factors in hospitalized patients with HIV) study. Chest. 2000; 118:138–145. [PubMed: 10893371]

57. Blake GM, Fogelman I. The role of bone density measurements in the evaluation of new treatments for osteoporosis. Curr Pharm Des. 2002; 8:1885–1905. [PubMed: 12171529]

58. Blake GM, Herd RJ, Patel R, Fogelman I. The effect of weight change on total body dual-energy X-ray absorptiometry: Results from a clinical trial. Osteoporos Int. 2000; 11:832–839. [PubMed: 11199186]

59. Blake GM, Knapp KM, Spector TD, Fogelman I. Predicting the risk of fracture at any site in the skeleton: Are all bone mineral density measurement sites equally effective? Calcif Tissue Int. 2006; 78:9–17. [PubMed: 16362461]

Table 1a

Baseline characteristics of 379 HIV-infected men and women

	Men (n=283)			Women (n=96)		
	Median	**(25th, 75th)**	**%**	**Median**	**(25th, 75th)**	**%**
Demographics						
Age (years)	42.7	(37.9, 47.6)		39.4	(35.3, 44.1)	
Race						
White			59.4			34.4
African American			25.4			51.0
Other			15.2			14.6
Current smoker (%yes)			43.3			66.7
Ever injected drugs (%yes)			32.2			44.8
Years known HIV-positive	7.7	(4.4, 10.6)		7.7	(3.7, 10.1)	
Clinical						
Menopause						17.7
Hysterectomy						12.5
On Depo Provera or Norplant						2.1
On oral contraceptives						6.2
Prednisone/hydrocorticone use			3.2			1.0
Testosterone *			17.1			2.7
Strength training last week (%yes)			30.0			11.6
Body composition						
BMI kg/m^2						
< 20			5.0			7.3
20-24.9			49.1			35.4
25-29.9			36.4			28.1
≥30			9.5			29.2
Dietary intake						
Calories (kcal/kg/day)	36.2	(26.9, 44.3)		28.6	(23.8, 39.7)	
Calcium (mg/day) †	1064	(682, 1534)		778	(501, 1019)	
Vitamin D (mcg/day)†	11.8	(5.5, 17.5)		6.9	(4.0, 13.0)	
HIV disease severity						
CD4 count (cells/mm^3)	334	(207, 551)		439	(271, 662)	
HIV viral load ($\log_{10}$ copies/ml)	2.8	(2.3, 4.0)		2.3	(2.3, 3.8)	

* There were 61 males and 22 females who were missing data on testosterone. Two males were on testosterone and hydrocortisone.

† Includes diet and supplement intake

Table 1b

Frequency of anti-retroviral use at baseline in 379 HIV-infected men and women

ART	Men (n=283)			Women (n=96)		
	Users	Continuous months of use among users		Users	Continuous months of use among users	
	%	median	(25th, 75th)	%	median	(25th, 75th)
HAART REGIMENS						
HAART	69.2	15	(8, 28)	60.6	12	(6, 24)
PI-based HAART	44.4	17	(8, 26)	37.2	12	(6, 24)
NNRTI-based HAART	13.3	12	(6, 24)	13.8	9	(7, 16)
MIXED HAART	8.6	6	(5, 16)	4.3	8	(6, 13)
NRTI-based HAART	2.9	2	(1, 19)	5.3	4	(2, 9)
INDIVIDUAL MEDICATIONS						
NRTI/NtRTI						
abacavir	10.2	11	(8, 17)	7.3	6	(6, 8)
AZT	31.1	22	(11, 36)	31.2	17	(12, 28)
d4T	37.4	17	(8, 30)	30.2	16	(9, 24)
DDC	1.4	19	(10, 30)	5.2	12	(12, 48)
ddI	10.9	12	(6, 23)	13.5	12	(6, 24)
Tenofovir	1.8	2	(1,2)	2.1	2	(1, 3)
3tC	59.7	20	(11, 36)	47.9	16	(9, 26)
NNRTI						
Efavirenz	12.7	13	(6, 24)	10.4	7	(6, 18)
Nevirapine	10.9	10	(6, 16)	9.4	9	(8, 14)
Delavirdine	1.1	6	(6, 26)	1.0	15	-
PI						
Amprenavir	3.9	18	(16, 24)	3.1	6	(4, 6)
Indinavir	17.7	13	(7, 24)	19.8	12	(5, 24)
Kaletra	1.4	12	(10, 15)	2.1	5	(4,6)
Nelfinavir	20.1	12	(6, 24)	12.5	15	(7, 24)
Ritonavir	14.1	11	(5, 21)	4.2	13	(10, 14)
Saquinavir	12.4	12	(6, 23)	8.3	15	(13, 26)

Table 2

Basic Models – Estimated Percent Change in Total BMD Over One-Year Intervals at Selected Levels of Each Determinant: by Sex and Menopausal Status

Determinant in Basic Model [*,†]	Level for estimation	P value [‡]	Males N=283, 603 intervals		Pre-menopausal females N=76, 156 intervals [*]		Post-menopausal females N=20, 40 intervals	
			Mean	95% CI	Mean	95% CI	Mean	95% CI
Demographics								
Post menop vs. Pre-menop women	n/a	0.02 [**]	−0.19	−0.41, 0.02	0.12	−0.16, 0.41	−1.00	−1.67, −0.34
Men vs. Pre-menop women		0.08						
Age[‡] (yrs)	35	0.55	−0.14	−0.44, 0.16	−0.03	−0.34, 0.28		
	45		−0.19	−0.41, 0.02	−0.05	−0.34, 0.23		
	51		−0.22	−0.44, −0.003			−1.00	−1.67, −0.34
Race/ethnicity	Af.Amer.	0.03	−0.42	−0.71, −0.13	−0.19	−0.51, 0.14	−1.10	−1.80, −0.40
	Not Af. Amer.		−0.12	−0.34, 0.10	0.11	−0.19, 0.41	−0.80	−1.51, −0.09
Current smoker	Yes	0.38	−0.17	−0.39, 0.06	−0.03	−0.33, 0.28	−0.99	−1.66, −0.32
	No		−0.30	−0.60, 0.007	−0.16	−0.49, 0.18	−1.12	−1.85, −0.40
Clinical								
Albumin (gm/dL) [‡]	3.5	0.003	−0.47	−0.76, −0.18	−0.24	−0.55, 0.06	−1.16	−1.86, −0.46
	4.0		−0.22	−0.43, −0.002	0.007	−0.26, 0.28	−0.91	−1.60, −0.22
CD4 count (cells/mm^3)	200	0.28	−0.25	−0.50, −0.0001	−0.14	−0.45, 0.18	−1.05	−1.77, −0.34
	500		−0.17	−0.37, 0.04	−0.06	−0.34, 0.23	−0.97	−1.65, −0.29
HIV (copies/ml)	< 400	0.55	−0.14	−0.41, 0.13	0.004	−0.31, 0.32	−0.88	−1.57, −0.19
	≥ 400		−0.23	−0.47, 0.005	−0.85	−0.39, 0.22	−0.97	−1.73, −0.20
Known years HIV + (yrs)	5	0.16	−0.10	−0.35, 0.15	0.03	−0.29, 0.34	−0.92	−1.59, −0.25
	10		−0.21	−0.43, −0.003	−0.08	−0.37, 0.20	−1.04	−1.70, −0.37
Ever wasted since entry	Yes	0.12	−0.54	−1.04, −0.04	−0.38	−0.89, 0.13	−1.32	−2.17, −0.47
	No		−0.16	−0.37, 0.06	0.0004	−0.29, 0.29	−0.94	−1.60, −0.28
Any testosterone/growth hormone	Yes	0.50	−0.08	−0.49, 0.33				
	No		−0.22	−0.44, 0.006				
Any prednisone/hydrocortisone	Yes	0.01	−0.99	−1.64, −0.35				
	No		−0.19	−0.41, −0.02				

Determinant in Basic Model *†	Level for estimation	P value ‡	Males N=283, 603 intervals		Pre-menopausal females N=76, 156 intervals *		Post-menopausal females N=20, 40 intervals	
			Mean	95% CI	Mean	95% CI	Mean	95% CI
Strength training last week	Yes	0.002	0.16	−0.11, 0.43	0.38	0.04, 0.72		
	No		−0.36	−0.61, −0.11	−0.14	−0.44, 0.16		
BMI (kg/m^2) ‡	20	0.01	−0.39	−0.65, −0.14	−0.32	−0.64, 0.002	−1.29	2.00, −0.57
	25		−0.19	−0.40, 0.02	−0.12	−0.40, 0.17	−1.09	−1.74, −0.43
	30		0.008	−0.27, 0.28	0.08	−0.25, 0.42	−0.88	−1.52, −0.25
Diet plus supplements								
Calcium (mg/day)	500	0.38	−0.26	−0.51, −0.002	−0.09	−0.39, 0.21	−1.03	−1.70, −0.36
	1000		−0.22	−0.44, −0.0005	−0.05	−0.33, 0.23	−0.99	−1.65, −0.33
Vit D (mcg/day)	5 mcg	0.06	−0.32	−0.59, −0.05	−0.13	−0.45, 0.19	−1.08	−1.76, −0.41
	20 mcg		−0.08	−0.29, 0.14	0.12	−0.17, 0.40	−0.84	−1.51, −0.17
Vit D supplement only (mcg/day)	0	0.48	−0.25	−0.52, 0.03	−0.10	−0.46, 0.26	−1.04	−1.71, −0.37
	10		−0.15	−0.37, 0.07	−0.0006	−0.27, 0.27	−0.94	−1.62, −0.27
Continuous ART use (yrs)	yrs							
Maximum continuous ART	0	0.15	−0.33	−0.65, −0.02	−0.17	−0.53, 0.19	−1.11	−1.81, −0.41
	1		−0.28	−0.54, −0.02	−0.12	0.44, 0.20	−1.05	−1.73, −0.38
	3		−0.17	−0.37, 0.04	−0.008	−0.28, 0.27	−0.94	−1.61, −0.28
NRTI/NtRTI								
Abacavir	1	0.39	−0.27	−0.51, −0.03	−0.13	−0.44, 0.19	−1.08	−1.75, −0.42
	2		−0.37	−0.77, 0.04	−0.22	−0.68, 0.24	−1.18	−1.91, −0.44
AZT	1	0.24	−0.20	−0.41, 0.01	−0.06	−0.34, 0.22	−1.01	−1.67, −0.35
	3		−0.26	−0.49, −0.03	−0.12	−0.42, 0.17	−1.07	−1.74, −0.41
d4T	1	0.005	−0.15	−0.35, 0.05	0.03	−0.25, 0.31	−0.87	−1.53, −0.20
	3		0.25	−0.07, 0.57	0.43	0.03, 0.83	−0.47	−1.20, 0.26
DDI	1	0.14	−0.28	−0.53, −0.04	−0.16	−0.48, 0.17		
	3		−0.51	−0.99, −0.04	−0.39	−0.93, 0.16		
Tenofovir	1	0.09	−0.86	−1.68, −0.05	−0.72	−1.51, 0.07		
	2		−1.54	−3.12, 0.04	−1.40	−2.93, 0.14		
3TC	1	0.39	−0.21	−0.42, −0.0009	−0.06	−0.35, 0.22	−1.02	−1.68, −0.36
	3		−0.15	−0.40, 0.09	−0.004	−0.32, 0.31	−0.96	−1.63, −0.29

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2014 February 21.

Determinant in Basic Model *†	Level for estimation	P value ‡	Males N=283, 603 intervals		Pre-menopausal females N=76, 156 intervals *		Post-menopausal females N=20, 40 intervals	
			Mean	95% CI	Mean	95% CI	Mean	95% CI
NNRTI								
Efavirenz	0.1 to 0.99	0.02	0.75	0.02, 1.49	0.87	0.15, 1.60	−0.02	−1.0, 0.96
	≥ 1	0.52	−0.40	−0.82, 0.02	−0.28	−0.77, 0.21	−1.17	−1.9, −0.45
Nevirapine	1	0.94	−0.21	−0.50, 0.09	−0.07	−0.44, 0.30		
	2		−0.22	−0.71, 0.28	−0.08	−0.64, 0.49		
PI								
Amprenavir	1	0.85	−0.24	−0.76, 0.28				
	2		−0.29	−1.28, 0.70				
Indinavir	1	0.08	−0.14	−0.36, 0.08	0.003	−0.29, 0.30	−0.96	−1.61, −0.31
	3		0.04	−0.30, 0.37	0.18	−0.21, 0.56	−0.78	−1.46, −0.10
Kaletra	1	0.81	−0.08	−1.10, 0.94				
	2		0.05	−1.99, 2.09				
Nelfinavir	<3	0.65	−0.11	−0.49, 0.27	0.04	−0.40, 0.48		
	≥3	0.046	−0.81	−1.43, −0.19	−0.66	−1.29, −0.04		
Ritonavir	1	0.90	−0.19	−0.43, 0.04	−0.05	−0.37, 0.27	−1.0	−1.67, −0.33
	3		−0.17	−0.66, 0.32	−0.03	−0.59, 0.54	−0.98	−1.76, −0.19
Saquinavir	1	0.08	−0.11	−0.33, 0.11	0.02	−0.29, 0.33	−0.92	−1.59, −0.25
	3		−0.11	−0.27, 0.50	0.25	−0.22, 0.72	−0.69	−1.43, 0.04

* All models include days in interval and sex and menopausal status. † All variables are the value at the beginning of each interval except antiretroviral use which is continuous use up until the beginning of the interval. For some ART agents, there were few or no pre-menopausal or post-menopausal women who used them. In that case, no estimate was given in the above table.

‡ Robust Wald P value for the determinant in the model, adjusted for time in interval, sex and menopause.

** For sex, the p value is for the difference between pre-menopausal and post-menopausal females (P = 0.02). The P value for difference between males and pre-menopausal females is P=0.08.

Table 3

Estimated Percent Change in Total BMD for Predictors in Multivariate Model: By Sex and Menopausal Status

			Percent Change in Total BMD Over One-Year Intervals					
Determinants in Model		**P value**	**Males N=283, 603 intervals**		**Pre-Menopausal Females N=76, 156 intervals**		**Post-menopausal Females N=20, 40 intervals**	
	Level		**Mean**	**95%CI**	**Mean**	**95%CI**	**Mean**	**95%CI**
Post-menop vs. pre-menop female **	n/a	0.012						
Male vs. Pre-menop female **	n/a	0.065						
Age	35	0.98	−0.57	−1.03, −0.12	−0.28	−0.71, 0.15		
	45		−0.57	−1.00, −0.14	−0.28	−0.71, 0.15		
	51		−0.57	−1.02, −0.13			−1.27	−2.07, −0.47
Race/Ethnicity	Af.Amer.	0.11	−0.79	−1.27, −0.30	−0.49	−0.96, −0.03	−1.48	−2.31, −0.65
	Not Af.Amer.		−0.57	−1.00, −0.14	−0.28	−0.71, 0.15	−1.27	−2.07, −0.47
Albumin mg/dL	3.5	0.031	−0.76	−1.23, −0.30	−0.47	−0.92 −0.02	−1.46	−2.27, −0.64
	4.0		−0.57	−1.00, −0.14	−0.28	−0.71, −0.15	−1.27	−2.07, −0.47
Current Smoker	Yes	0.16	−0.36	−0.72, −0.01	−0.07	−0.45, 0.31	−1.06	−1.80, −0.31
	No		−0.57	−1.00, −0.14	−0.28	−0.71, 0.15	−1.27	−2.07, −0.47
BMI kg/m^2	20	0.009	−0.78	−1.21, −0.36	−0.49	−0.93, −0.06	−1.48	−2.32, −0.64
	25		−0.57	−1.00, −0.14	−0.28	−0.71, −0.15	−1.27	−2.07, −0.47
	30		−0.36	−0.85, 0.13	−0.07	−0.54, 0.41	−1.06	−1.85, −0.26
Strength training	Yes	0.009	−0.15	−0.52, 0.21	−0.14	−0.25, 0.52		
	No		−0.57	−1.00, −0.14	−0.28	−0.71, −0.15		
Prednisone/hydrocortisone	Yes	0.014	−1.31	−2.02, −0.61				
	No		−0.57	−1.00, −0.14				
No ART	0 yrs	0.051	−0.37	−0.76, −0.02	−0.08	−0.49, 0.33	−1.07	−1.86, −0.28
Other ART only	3 yrs		−0.57	−1.00, −0.14	−0.28	−0.71, 0.15	−1.27	−2.07, −0.47
Other ART plus …								
d4T	1 yr	0.001	−0.33	−0.68, 0.02	−0.04	−0.41, 0.34	−1.02	−1.80, −0.25
	3 yrs		0.16	−0.21, 0.53	0.45	0.01, 0.89	−0.54	−1.35, 0.28
ddI	1 yr	0.004	−0.84	−1.32, −0.35	−0.55	−1.03, −0.06		
	3 yrs		−1.37	−2.10, −0.64	−1.08	−1.81, −0.34		

Percent Change in Total BMD Over One-Year Intervals								
Determinants in Model		**P value**	**Males N=283, 603 intervals**		**Pre-Menopausal Females N=76, 156 intervals**		**Post-menopausal Females N=20, 40 intervals**	
	Level		**Mean**	**95%CI**	**Mean**	**95%CI**	**Mean**	**95%CI**
Tenofovir	Yes	0.003	−2.04	−3.00, −1.08	−1.74	−2.67, −0.81		
	No		−0.57	−1.00, −0.14	−0.28	−0.71, 0.15		
Saquinavir	1 yr	0.009	−0.40	−0.81, - 0.002	−0.11	−0.53, 0.30	−1.10	−1.88, −0.31
	3 yrs		−0.07	−0.52, 0.39	0.23	−0.27, 0.72	−0.76	−1.57, 0.05

*The p value is the Robust Wald p value for the coefficient in the multivariate model.

†Estimates are calculated from the multivariate repeated measures model, which includes age, race, smoker, sex, menopausal status, strength training, albumin, BMI, prednisone/hydrocortisone and years of continuous use of d4T, ddI, saquinavir, tenofovir yes/no and any other ART. All estimates were calculated for Caucasian, non-smoker, and 12.0 months between DXA visits. The estimates for albumin is also calculated for BMI =25 and non-strength training. Similarly the estimate for BMI is calculated for albumin=4.0 mg/dL and non-strength training. Finally, the estimates for strength training are also for albumin = 4.0 mg/dL and BMI=25. Demographic variables were retained in the model even if they were not significant to adjust for confounding. All other variables were included in the model if they were significant at $P \leq 0.05$. Maximum cumulative time on other ART was included to estimate percent change among those on ART but not on the ART variables that were significant and included in the multivariate model.

‡"Other ART" includes any ART except d4T, ddI, tenofovir or saquinavir.. Other ART was assumed to be 3 years of use. NA- No estimates were made for tenofovir, ddI or strength training among the post-menopausal women there were too few or no women who used those agents or practiced strength training.

**Separate estimates were calculated for men, pre-menopausal women and post-menopausal women. The age for each of these groups was 45 years old for males, 40 years old for pre-menopausal women and 51 years old for menopausal women. No estimates are shown for the dummy variables sex-menopause because they are shown below for selected levels of the other variables in the model.

The p value for the difference between men and post-menopausal women is 0.065.