Published in final edited form as:

Calcif Tissue Int. 2013 June ; 92(6): 557–565. doi:10.1007/s00223-013-9716-8.

Trabecular and cortical microarchitecture in postmenopausal HIV-infected women

Michael T. Yin¹, Aimee Shu¹, Chiyuan A. Zhang¹, Stephanie Boutroy¹, Donald J. McMahon¹, David C. Ferris², Ivelisse Colon¹, and Elizabeth Shane¹

¹Columbia University Medical Center, New York, NY

²St Lukes Roosevelt Hospital, New York, NY

Abstract

Objective—To assess the effects of HIV infection and antiretroviral therapy (ART) on trabecular and cortical microarchitecture in postmenopausal minority women.

Methods—A subgroup of 106 (46 HIV-infected, 60 uninfected) postmenopausal Hispanic and African American women from an established cohort had areal bone mineral density (aBMD) measured by dual-energy x-ray absorptiometry, and trabecular and cortical volumetric BMD (vBMD) and microarchitecture measured by high-resolution peripheral quantitative computed tomography (HRpQCT) at the radius and tibia.

Results—HIV-infected women were slightly younger (58 ± 1 versus 61 ± 1 yrs, $p=0.08$), and had lower body mass index (BMI, 28 ± 1 versus 32 ± 1 kg/m², $p<0.01$). BMI-adjusted aBMD Z scores were lower in HIV-infected women at the lumbar spine, total hip and ultradistal radius. Serum N-telopeptide and C-telopeptide levels were also higher in HIV-infected women. Trabecular and cortical vBMD were similar at the radius, but cortical area (105.5 ± 2.4 versus 120.6 ± 2.0 mm², $p<0.01$) and thickness (956 ± 33 versus 1075 ± 28 m, $p<0.01$) at the tibia were approximately 11–12% lower in HIV-infected women. Differences remained significant after adjusting for age, BMI and race/ethnicity. In contrast, cortical porosity was similar in both groups.

Conclusion—Although HIV-infected postmenopausal women had lower aBMD at the spine, total hip and ultradistal radius and higher levels of bone resorption markers, the only differences detected by HRpQCT were lower cortical thickness and area at the tibia.

Key Terms

HIV; microarchitecture; cortical structure; osteoporosis; postmenopausal women

INTRODUCTION

Low bone mineral density (BMD) has been associated with HIV-infection and its therapy [1] and recent data suggest that fracture rates may be higher in HIV-infected individuals [2–4]. As HIV-infected individuals live longer with effective antiretroviral therapy (ART), age-related bone loss will be superimposed upon bone loss already sustained related to HIV infection and its therapy.

Corresponding author: Michael T. Yin, MD, MS, Division of Infectious Diseases, Columbia University Medical Center, 630 West 168th street, PH8-876, NY, NY 10032, Tel. 212-305-7185, Fax. 212-305-7290, Mty4@columbia.edu.

Disclosure: We have no conflicts to disclose

M. Yin has a consultant/advisory role to Abbott and Gilead. All other authors have stated that they have no conflict of interest.

In the United States, older minority women represent a growing segment of those living with HIV [5]. We have previously reported that areal bone mineral density (aBMD) by dual energy xray absorptiometry (DXA) is lower at the lumbar spine and hip and bone turnover markers are higher in HIV infected than uninfected postmenopausal Hispanic and African American women [6]. In contrast to younger women and men on established ART [7–11], we also found that aBMD by DXA decreases more rapidly in HIV-infected women on established ART than uninfected controls, particularly at the distal forearm [12].

DXA is a powerful clinical tool for diagnosis of osteoporosis and prediction of fracture but estimates BMD based upon an areal projection rather than measuring true volumetric BMD (vBMD), and cannot distinguish between cortical and trabecular bone. High-resolution peripheral quantitative computed tomography (HRpQCT) is a noninvasive imaging technology that provides a 3-dimensional (3D) measurement of true vBMD at the distal radius and tibia, and permits separate assessment of cortical and trabecular bone and trabecular microarchitecture [13, 14]. We have reported that measurement of vBMD and microarchitecture by HRpQCT discriminates fragility fracture status in premenopausal women with unexplained osteoporosis, in postmenopausal women, and patients with chronic kidney disease [15–17].

HIV-infected individuals are at higher risk of fracture than the general population [18, 19], and we have reported lower aBMD in HIV-infected postmenopausal women [6]. We therefore performed HRpQCT scans in a subset of our original cohort, hypothesizing that HIV-infected women would have lower cortical and trabecular vBMD and greater microarchitectural deterioration than uninfected controls.

METHODS

Study Subjects

Between 2002 and 2007, 187 (92 HIV-infected, 95 HIV-uninfected) postmenopausal women were recruited from the infectious diseases and general internal medicine clinics at Columbia University Medical Center (CUMC) and the HIV clinic at Bronx-Lebanon Hospital Center (BLHC) in New York City into a longitudinal study. Our intention was to recruit HIV-uninfected controls similar to HIV-infected subjects with regard to other chronic medical illnesses and comorbidities[6]. Eligible subjects were over age 40, self-identified as Hispanic or African American race/ethnicity, and postmenopausal as defined by greater than one year of amenorrhea. In addition to amenorrhea, serum follicle-stimulating hormone (FSH) had to be either >30 mIU/ml, or >20 mIU/ml with a concomitant serum estradiol of <30 pg/ml. Women with metabolic bone disease, multiple myeloma, cancer, endocrinopathies, serum creatinine>1.5 mg/dl, celiac or inflammatory bowel disease, current glucocorticoid or anticonvulsant use, current hormone replacement therapy (HRT), and current or past treatment of osteoporosis were excluded. Characteristics of the cohort have been published previously [6, 12, 20]. We measured cortical and trabecular vBMD and microarchitecture by HRpQCT in an unselected subset of 46 HIV-infected and 60 HIV-uninfected postmenopausal women who were enrolled sequentially into the study after we acquired HRpQCT capability in 2006. These 106 subjects and their initial HRpQCT scans comprise the current analysis. Medical, surgical, and reproductive history, osteoporosis risk factors, current and past medication history, HIV and ART history were obtained by interview and chart review. For hysterectomized women, time since menopause was estimated as years since onset of menopausal symptoms; if none, menopausal age was set at 50. Control subjects met the same criteria; enzyme-linked immunosorbent assay (ELISA) testing verified HIV-uninfected status.

This study was approved by the Institutional Review Boards of CUMC and BLHC. All subjects provided written informed consent.

Bone Density Measurements

BMD of the lumbar spine (LS; L1-4), femoral neck (FN), total hip (TH), non-dominant 1/3 radius (DR), ultradistal radius (UDR), and body composition were measured by DXA on a QDR 4500 bone densitometer (Hologic, Inc., Bedford, MA) at CUMC. Short term in vivo precision is 0.68% for the LS, 1.36% for the TH, and 0.70% for the radius.

T-scores, which compare subjects to the peak bone mass of young individuals of the same sex and race, were derived for the hip from the National Health and Nutrition Examination Survey (NHANES III) or the manufacturer's normative database for spine and forearm. Osteoporosis and osteopenia were defined by World Health Organization criteria for postmenopausal Caucasian women: T-scores ≤ -2.5 represent osteoporosis; T-scores between -1.0 and -2.49 represent osteopenia [21]. Z-scores, comparing BMD to an age-, sex-, and ethnicity-matched reference population, were also calculated. Height and weight were measured by Harpenden stadiometer and balance beam scale, respectively.

Cortical and Trabecular Microarchitecture Measurements

vBMD and microarchitecture were assessed at the non-dominant distal radius and tibia using a single HRpQCT device (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland). This system allows for in vivo evaluation of bone at a nominal voxel size of 82 μm . The region of interest (ROI) at the radius consisted of an approximately 9 mm length of bone located from 9.5 to 18.5 mm proximal to the endplate. At the tibia, the ROI was located from 22 to 31 mm proximal to the endplate [13, 22]. The volume of interest was automatically separated into cortical and trabecular regions using a Gaussian filter and a threshold-based algorithm. Microarchitecture analysis was performed as previously described [13, 23–25]. The following parameters were reported: mean cortical thickness (Ct.Th; μm); cortical and trabecular bone density (Ct.vBMD and Tb.vBMD; $\text{mg HA}/\text{cm}^3$); trabecular number (Tb.N; mm^{-1}) thickness (Tb.Th; μm) and separation (Tb.Sp; μm). The standard deviation of Tb.Sp (Tb.Sp.SD; μm) was also measured to assess heterogeneity of the trabecular network.

Extended cortical parameters were measured with a newer algorithm incorporated in the manufacturer's analysis software (μCT Evaluation v6.0, Scanco Medical AG, Brüttisellen, Switzerland) [26–28]. This automated cortical analysis was first based on a dual threshold algorithm that permits segmentation of the dense cortical bone compartment and generates periosteal and endosteal contours that were visually validated. A second step consisted of segmentation of cortical porosity, where endosteal and periosteal voids, transcortical erosions and objects with a volume less than 0.003mm^3 (i.e. 5 connected voxels) were discarded. Finally, microarchitectural and density parameters were measured from the refined cortical ROI as the combination of segmented cortical bone compartment and cortical porosity. The outcome parameters were cortical vBMD ($\text{mg HA}/\text{cm}^3$) and tissue mineral density (Ct.TMD, $\text{mg HA}/\text{cm}^3$), which is the average mineral density within the cortical bone compartment after exclusion of all pore space and erosion of a 2-voxel thick layer on the periosteal and endosteal boundaries to minimize partial volume effects. Mean cortical thickness (Ct.Th; μm) was measured by direct 3D method [29] disregarding the presence of pores. Cortical porosity (Ct.Po, %) was calculated as the ratio of cortical pore volume (Ct.Po.V) over the cortical bone compartment volume. Mean and distribution (SD) of cortical pore diameter (respectively Ct.Po.Dm and Ct.Po.Dm.SD, μm) were measured by direct 3D method [29].

Laboratory Methods

Fasting morning serum, stored at -80°C , was batch-analyzed in the CUMC research laboratory for: parathyroid hormone (PTH; RIA; Corning-Nichols Laboratory, San Clemente, CA); serum 25-hydroxyvitamin D (25-OHD; RIA; Diasorin, Stillwater, MN); bone specific alkaline phosphatase (BAP; ELISA; Quidel Corp., San Diego, CA); osteocalcin (OC; RIA; Immotopics, San Clemente, CA); cross-linked N-telopeptide of type I bone collagen (NTx) by competitive-inhibition ELISA (Inverness Medical, Princeton, NJ). C-telopeptide of type I collagen (CTx) by sandwich ELISA (Serum Crosslaps, IDS Ltd, Fountain Hills, AZ). Tumor Necrosis Factor (TNF α) was measured by ELISA (Quantikine, R&D Systems, Minneapolis, MN) Interleukin-6 (IL-6) was measured by RIA (Diasorin, Stillwater, MN). CD4 counts were measured by flow cytometry (FACS Calibur, Becton Dickinson, San Jose, CA).

Statistical Analysis

All analyses were performed using SAS (version 9.2). Continuous data are presented as mean value $\pm$ standard deviation; categorical data are presented as percentage or absolute number. To reduce the number of microarchitectural parameters to those that differed most between HIV-infected and HIV-uninfected, means between groups were compared using Student's t-tests. Covariate-adjusted means between groups were compared by analysis of covariance. Between group differences in correlations between DXA and HRpQCT measures were tested with analysis of variance test of homogeneity of slopes. Categorical data were compared by odds ratios from chi-square, Fisher's exact, or Jonckheere-Terpstra test for trend. No adjustments were made for multiple comparisons during this data reduction analysis and tibial cortical area and thickness were identified for further analysis. A p-value < 0.05 was considered statistically significant.

Univariate associations of demographic, anthropometric, reproductive, medical and lifestyle variables with tibial cortical thickness and area were examined. These variables entered a stepwise multiple regression (p of 0.20 to enter and 0.05 to be retained in the model; SAS Proc REG, SAS Institute, Cary, NC) to identify variables independently related to cortical thickness and area. Collinearity was assessed, and model selected non-overlapping covariates retained for inclusion in final inferential models. Measures identified were subsequently entered into regression models to permit assessment of the independent contribution of HIV status to cortical thickness and area.

RESULTS

Characteristics of the Study Population

HIV-infected women were slightly although not significantly younger than uninfected, but had similar age at menopause. HIV-infected women had lower weight and BMI and were more likely to be HCV-infected, compared to HIV-uninfected women (Table 1). Fifty-four percent of HIV-infected women had a history of AIDS, 81% were currently receiving antiretroviral therapy (ART) and mean CD4 count was 553 ± 52 cells/mm³. Among HIV-infected women on ART, 12(26%) were on non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens, 22(48%) were on protease inhibitor (PI)-containing regimens, and 11(30%) were on tenofovir.

There were no between-group differences in the prevalence of radiographic vertebral fractures or history of fracture at any site. HIV-infected women had higher levels of bone resorption markers, NTx and CTx, and there was a trend for higher levels of TNF α in HIV+ women (p=0.08); group differences in TNF α reached statistical significance in the cross sectional analysis of the full cohort [6].

Bone Mineral Density by DXA

HIV-infected women had significantly lower mean T-scores at the LS, TH, FN and UDR (Table 1). After adjustment for age and BMI, absolute aBMD and T-scores remained lower in HIV+ women at the UDR but were no longer significant at the LS, TH and DR. HIV-infected women had lower mean Z-scores at the LS, TH, FN and DR, and UDR (Table 1); Z-scores remained lower in the HIV-infected group at the LS, TH, and UDR after adjustment for BMI.

Cortical and Trabecular Structure by HRpQCT

All HRpQCT measurements at the radius and most at the tibia were similar between the HIV-infected and uninfected women (Table 2). At the tibia, HIV-infected women had lower total vBMD, but the difference was not significant ($p=0.06$). Only cortical area and thickness were significantly lower (by 11–12%) in the HIV-infected women. With the extended algorithm method, which may include more trabecularized cortical bone from the endosteal surface of the cortex, tibial cortical area was approximately 8–10% higher and cortical thickness approximately 15% higher in both the HIV-infected and uninfected groups compared to the standard algorithm. With the extended algorithm, HIV-infected women also had 11–12% lower tibial cortical area and thickness than HIV-uninfected women (Table 3). These differences remained significant after adjustment for age and BMI ($p=0.03$ and $p=0.01$ respectively). HRpQCT images from two representative HIV-infected and uninfected women of similar age illustrate the observed group difference in tibial cortical thickness (Figure 1).

We also assessed whether group differences in tibial cortical area and thickness were due to differences in cortical porosity (Table 3). Cortical pore volume was lower in HIV-infected women, but cortical porosity, cortical pore diameter and the distribution of cortical pores diameters were similar in both groups. As both cortical pore volume and cortical thickness varied, the lower pore volume in HIV+ women likely reflects their lower cortical thickness (Table 3).

Subgroup Analyses by Ethnicity and Fracture History

To explore whether race/ethnicity was obscuring differences by HIV status, we stratified the analysis by Hispanic and African American race/ethnicity. In both race/ethnicity groups, the same HRpQCT pattern emerged: HIV-infected women had lower tibia cortical area and cortical thickness than uninfected women, but all other parameters were similar (data not shown).

To examine whether any HRpQCT parameters were associated with fracture history in our cohort, we grouped all 106 women together (46 HIV-infected + 60 HIV-uninfected). Subjects reporting a history of fracture ($N = 18$) had similar HRpQCT measurements to subjects without a history of fracture (data not shown). Similarly, HRpQCT parameters did not differ in women with ($N=6$) and without radiographic evidence of vertebral fracture.

Determinants of cortical thickness and area at the tibia

We used regression analysis to assess whether HIV status was an independent predictor of tibial cortical thickness and area after adjustment for potential confounders. (Table 4). In the model for cortical thickness, greater number of years since menopause, diabetes and HIV status were associated with lower thickness, while higher BMI was associated with greater thickness. In the model for cortical area, greater number of years since menopause, diabetes and HIV status were associated with lower area, while higher BMI and being Hispanic was associated with higher area. HIV status remained a significant predictor in the multivariate

cortical area model, while in the cortical thickness model, HIV status did not reach statistical significance ($p=0.06$).

Antiretroviral therapy and HRpQCT parameters

HRpQCT parameters did not differ in HIV-infected women on ($N = 37$) and off ART ($N = 9$). HRpQCT parameters also did not differ between groups on PI-, NNRTI- or tenofovir containing regimens. However, when we examined the correlations between cumulative use or class ART and HRpQCT parameters, we found a modest positive correlation between cumulative PI use and radial total ($r=0.339$, $p=0.02$) and trabecular ($r=0.306$, $p=0.04$) area as well as tibial total ($r=0.321$, $p=0.03$) and trabecular ($r=0.306$, $p=0.04$) area. In contrast, there was a negative correlation between cumulative tenofovir use and radial trabecular vBMD ($r=-0.286$, $p=0.056$) and trabecular number ($r=-0.343$, $p=0.02$) and a positive association with radial trabecular separation ($r=0.507$, $p=0.0004$) and heterogeneity of separation ($r=0.496$, $p=0.0005$). There were no significant correlations with cumulative NNRTI use and HRpQCT parameters.

CONCLUSIONS

HIV-infected women had lower age- and BMI-adjusted aBMD by DXA (Z scores) than postmenopausal uninfected women at central skeletal sites (LS, TH) and the UDR. In contrast, HIV-infected and uninfected women did not differ with regard to cortical and trabecular vBMD or trabecular microarchitecture at the distal radius or trabecular parameters at the tibia. At the tibia, cortical area and cortical thickness, estimated by both standard and extended algorithms, were 11–12% lower in HIV-infected women, while cortical porosity did not differ. Adjustment for age and BMI attenuated group differences for aBMD at all sites except the UDR, suggesting that lower body weight contributed to the differences in aBMD at the spine and hip. However, tibial cortical area and thickness remained lower in HIV-infected women after adjustment for age and BMI in both African American and Hispanic women, suggesting that the differences in cortical microarchitecture were independent of age and weight.

It is noteworthy that aBMD by DXA was lower but vBMD at the tibia and radius by HRpQCT did not differ between HIV-infected and uninfected women. Even at the UDR, where the sites measured by DXA and HRpQCT are closely aligned though not identical, HIV-infected women had lower aBMD by DXA but no discernible differences in either total, cortical or trabecular vBMD by HRpQCT. These results suggest that DXA may overestimate group differences in BMD in these women. As cross-sectional area (bone size) was similar between the groups, we cannot attribute this overestimation to smaller bone size in the HIV-infected women. It is also possible that the discrepancy we observed could be related to measurement site at least in part, as HRpQCT only assesses the peripheral skeleton. As yet, there are no other HRpQCT studies of HIV-infected individuals with which to compare our results. Of two published studies that utilized both DXA and central QCT to assess spine and hip aBMD and vBMD in HIV-infected and uninfected individuals, one found congruent results [30] and the other found discrepant results [31] by the two methodologies. Additional studies using both central and peripheral QCT are necessary to clarify the discrepancy between measurements of areal and volumetric BMD in these women.

The finding that HIV-infected women had similar cross-sectional area but lower cortical area and thinner cortices suggests that endocortical resorption may have been higher in HIV-infected women. This finding is characteristic of bone loss in late menopause, a time when accelerated endocortical resorption that is not balanced by periosteal apposition results in accelerated loss concentrated in cortical bone [32]. These results support the hypothesis that

bone loss in HIV-infected postmenopausal women is predominantly related to an augmentation of the endosteal remodeling associated with estrogen deficiency. As trabecular loss is typical of late perimenopause and early postmenopause [33], comparable amounts of trabecular losses may have already occurred in both groups. Since our study was cross-sectional and we compared the groups at one point later in menopause (mean years since menopause of 9–12 years), we cannot determine whether rate of trabecular loss was comparable or higher in HIV-infected women.

Among HIV-infected women, HRpQCT parameters did not differ among antiretroviral treatment groups, although there were modest associations with cumulative PI- or tenofovir exposure. The observed negative association between cumulative tenofovir use and trabecular parameters suggests that exposure to tenofovir may result in greater microarchitectural deterioration. This is consistent with many studies demonstrating decreased aBMD by DXA with tenofovir exposure in the setting of antiretroviral initiation [34, 35], switch [36], or utilization as pre-exposure prophylaxis in HIV-uninfected individuals[37]. Larger, longitudinal studies are necessary to define the acute and chronic impact of specific antiretrovirals on vBMD and microarchitecture.

Recent studies suggest that fracture incidence is higher in HIV-infected individuals, particularly older men and women, than population controls, even after adjustment for important predictors of fracture such as age, race, BMI and comorbidities [18, 19]. However, it is uncertain whether an isolated finding of lower cortical thickness at the tibia in HIV-infected women would ultimately contribute to higher fracture risk, particularly when volumetric BMD is not different. Other HRpQCT studies in HIV-uninfected individuals with and without fracture have reported differences in cortical thickness ranging from 12–33% [13, 38–41]. The cortical differences we report are clearly at the low end of this range and moreover, those studies also found differences in other cortical or trabecular parameters that we did not find in our study [16, 24, 42, 43]. In addition, HRpQCT assesses the peripheral skeleton, and isolated lower tibial cortical thickness may have no bearing on risk for the most clinically important fractures of the central skeleton, the spine and hip. It is possible that the higher fracture rates reported in HIV-infected postmenopausal women may be due to higher bone remodeling, a risk factor for fracture that is independent of BMD or to non-skeletal risks, such as increased falls among older HIV-infected individuals. It is also possible that bone microstructure of individuals of African American and Hispanic race/ethnicity differs from Caucasians and Asians, who constitute the bulk of studies examining microarchitecture in women with and without fractures.

To our knowledge, this is the first study to use HRpQCT to examine bone microarchitecture in HIV infected individuals. A major strength of our study is that the control group was similar in age and race/ethnicity and the participants were well-characterized. However, there are several limitations to our study. There were group differences in weight and BMI among African American women, requiring adjustment for these differences in analyses. The study was not powered to detect group differences in HRpQCT parameters in HIV-infected women by current ART regimen or by immunologic criteria such as CD4 or history of AIDS. We were not able to evaluate the central skeleton, where most important fractures occur. There were too few women with fractures to assess whether there were differences in DXA or HRpQCT parameters by fracture status. The large number of statistical tests performed raises the possibility that the differences in cortical area and thickness at the tibia were due to chance alone, although the fact that HIV status remained a significant predictor of cortical area, and a near-significant predictor of cortical thickness in the multivariate model suggests that the relationship is valid.

In conclusion, HIV-infected minority late postmenopausal women have lower aBMD by DXA at the hip and ultradistal radius, and 11–12% lower tibial cortical area and thickness, but no differences in trabecular or cortical vBMD or trabecular microarchitecture of the distal radius and tibia by HRpQCT. While the clinical significance of this isolated finding, with regard to fracture risk, is uncertain, our results are somewhat reassuring. Larger studies using central QCT and including fractured and non-fractured individuals are necessary to elucidate the microarchitectural characteristics of increased bone fragility in HIV infection.

References

1. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS*. 2006; 20:2165–2174. [PubMed: 17086056]
2. 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; 21:617–623. [PubMed: 17314524]
3. Prior J, Burdge D, Maan E, Milner R, Hankins C, Klein M, et al. Fragility fractures and bone mineral density in HIV positive women: a case-control population-based study. *Osteoporos Int*. 2007; 18:1345–1353. [PubMed: 17665239]
4. 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; 93:3499–3504. [PubMed: 18593764]
5. CDC. Diagnosis of HIV infection and AIDS in the United States and Dependent Areas, 2009. 2009; 19:1–63.
6. Yin MT, McMahon DJ, Ferris DC, Zhang CA, Shu A, Staron R, et al. Low bone mass and high bone turnover in postmenopausal human immunodeficiency virus-infected women. *J Clin Endocrinol Metab*. 2010; 95:620–629. [PubMed: 19965927]
7. 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; 67:270–275. [PubMed: 17547686]
8. Dolan SE, Kanter JR, Grinspoon S. Longitudinal analysis of bone density in human immunodeficiency virus-infected women. *J Clin Endocrinol Metab*. 2006; 91:2938–2945. [PubMed: 16735489]
9. Mondy K, Yarasheski K, Powderly WG, Whyte M, Claxton S, DeMarco D, 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]
10. Yin MT, Lu D, Cremers S, Tien PC, Cohen MH, Shi Q, et al. Short-term bone loss in HIV-infected premenopausal women. *Journal of acquired immune deficiency syndromes*. 2010; 53:202–208. [PubMed: 19890216]
11. Bolland MJ, Wang TK, Grey A, Gamble GD, Reid IR. Stable bone density in HAART-treated individuals with HIV: a meta-analysis. *The Journal of clinical endocrinology and metabolism*. 2011; 96:2721–2731. [PubMed: 21715534]
12. Yin MT, Zhang CA, McMahon DJ, Ferris DC, Irani D, Colon I, et al. Higher Rates of Bone Loss in Postmenopausal HIV-Infected Women: A Longitudinal Study. *The Journal of clinical endocrinology and metabolism*. 2012; 97:554–562. [PubMed: 22090266]
13. Boutroy S, Buxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab*. 2005; 90:6508–6515. [PubMed: 16189253]
14. Burghardt AJ, Kazakia GJ, Majumdar S. A local adaptive threshold strategy for high resolution peripheral quantitative computed tomography of trabecular bone. *Ann Biomed Eng*. 2007; 35:1678–1686. [PubMed: 17602299]
15. Burghardt AJ, Issever AS, Schwartz AV, Davis KA, Masharani U, Majumdar S, et al. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 95:5045–5055. [PubMed: 20719835]

16. Cohen A, Dempster DW, Muller R, Guo XE, Nickolas TL, Liu XS, et al. Assessment of trabecular and cortical architecture and mechanical competence of bone by high-resolution peripheral computed tomography: comparison with transiliac bone biopsy. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2010; 21:263–273. [PubMed: 19455271]
17. Rubin MR, Dempster DW, Kohler T, Stauber M, Zhou H, Shane E, et al. Three dimensional cancellous bone structure in hypoparathyroidism. *Bone*. 46:190–195. [PubMed: 19782782]
18. Hansen AB, Gerstoft J, Kronborg G, Larsen CS, Pedersen C, Pedersen G, et al. Incidence of low- and high-energy fractures in persons with and without HIV-infection: a Danish population-based cohort study. *AIDS*. 2011
19. Young B, Dao CN, Buchacz K, Baker R, Brooks JT. Increased rates of bone fracture among HIV-infected persons in the HIV Outpatient Study (HOPS) compared with the US general population, 2000–2006. *Clinical Infectious Diseases*. 2011; 52:1061–1068. [PubMed: 21398272]
20. Stein EM, Yin MT, McMahon DJ, Shu A, Zhang CA, Ferris DC, et al. Vitamin D deficiency in HIV-infected postmenopausal Hispanic and African-American women. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2011; 22:477–487. [PubMed: 20585939]
21. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet*. 2002; 359:1929–1936. [PubMed: 12057569]
22. Laib A, Hauselmann HJ, Rueggsegger P. In vivo high resolution 3D-QCT of the human forearm. *Technol Health Care*. 1998; 6:329–337. [PubMed: 10100936]
23. Liu XS, Zhang XH, Sekhon KK, Adams MF, McMahon DJ, Bilezikian JP, et al. High-resolution peripheral quantitative computed tomography can assess microstructural and mechanical properties of human distal tibial bone. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2010; 25:746–756. [PubMed: 19775199]
24. Stein EM, Liu XS, Nickolas TL, Cohen A, Thomas V, McMahon DJ, et al. Abnormal microarchitecture and reduced stiffness at the radius and tibia in postmenopausal women with fractures. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2010; 25:2572–2581. [PubMed: 20564238]
25. Nickolas TL, Stein E, Cohen A, Thomas V, Staron RB, McMahon DJ, et al. Bone mass and microarchitecture in CKD patients with fracture. *Journal of the American Society of Nephrology : JASN*. 2010; 21:1371–1380. [PubMed: 20395370]
26. Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK. Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. *Bone*. 2010; 47:519–528. [PubMed: 20561906]
27. Burghardt AJ, Kazakia GJ, Ramachandran S, Link TM, Majumdar S. Age- and gender-related differences in the geometric properties and biomechanical significance of intracortical porosity in the distal radius and tibia. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2010; 25:983–993. [PubMed: 19888900]
28. Nishiyama KK, Macdonald HM, Buie HR, Hanley DA, Boyd SK. Postmenopausal women with osteopenia have higher cortical porosity and thinner cortices at the distal radius and tibia than women with normal aBMD: an in vivo HR-pQCT study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2010; 25:882–890. [PubMed: 19839766]
29. Hildebrand T, Rueggsegger P. A new method for the model-independent assessment of thickness in three-dimensional images. *J Microsc*. 1997; 185:67–75.
30. Grund B, Peng G, Gibert CL, Hoy JF, Isaksson RL, Shlay JC, et al. Continuous antiretroviral therapy decreases bone mineral density. *AIDS*. 2009; 23:1519–1529. [PubMed: 19531929]
31. Pitukcheewanont P, Safani D, Church J, Gilsanz V. Bone measures in HIV-1 infected children and adolescents: disparity between quantitative computed tomography and dual-energy X-ray absorptiometry measurements. *Osteoporos Int*. 2005; 16:1393–1396. [PubMed: 15702261]

32. Lauretani F, Bandinelli S, Griswold ME, Maggio M, Semba R, Guralnik JM, et al. Longitudinal changes in BMD and bone geometry in a population-based study. *J Bone Miner Res.* 2008; 23:400–408. [PubMed: 17997708]
33. Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, et al. A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. *J Bone Miner Res.* 2008; 23:205–214. [PubMed: 17937534]
34. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA : the journal of the American Medical Association.* 2004; 292:191–201. [PubMed: 15249568]
35. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naïve persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. *The Journal of infectious diseases.* 2011; 203:1791–1801. [PubMed: 21606537]
36. Martin A, Bloch M, Amin J, Baker D, Cooper DA, Emery S, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2009; 49:1591–1601. [PubMed: 19842973]
37. Liu AY, Vittinghoff E, Sellmeyer DE, Irvin R, Mulligan K, Mayer K, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. *PloS one.* 2011; 6:e23688. [PubMed: 21897852]
38. Melton LJ 3rd, Christen D, Riggs BL, Achenbach SJ, Muller R, van Lenthe GH, et al. Assessing forearm fracture risk in postmenopausal women. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2010; 21:1161–1169. [PubMed: 19714390]
39. Melton LJ 3rd, Riggs BL, Keaveny TM, Achenbach SJ, Hoffmann PF, Camp JJ, et al. Structural determinants of vertebral fracture risk. *J Bone Miner Res.* 2007; 22:1885–1892. [PubMed: 17680721]
40. Sornay-Rendu E, Boutroy S, Munoz F, Delmas PD. Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased BMD measured by DXA: the OFELY study. *J Bone Miner Res.* 2007; 22:425–433. [PubMed: 17181395]
41. Vico L, Zouch M, Amirouche A, Frere D, Laroche N, Koller B, et al. High-resolution pQCT analysis at the distal radius and tibia discriminates patients with recent wrist and femoral neck fractures. *J Bone Miner Res.* 2008; 23:1741–1750. [PubMed: 18665795]
42. Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Buxsein ML, Delmas PD. Finite element analysis based on in vivo HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. *J Bone Miner Res.* 2008; 23:392–399. [PubMed: 17997712]
43. Sornay-Rendu E, Cabrera-Bravo JL, Boutroy S, Munoz F, Delmas PD. Severity of vertebral fractures is associated with alterations of cortical architecture in postmenopausal women. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2009; 24:737–743. [PubMed: 19113929]

Figure 1.
HRpQCT images in representative 61 year-old HIV+ and HIV- postmenopausal woman

Table 1

Subject characteristics, serum cytokines and DXA measures: HIV+ versus HIV– postmenopausal women

	HIV+ (N=46)	HIV– (N=60)	P value
Demographics and medical history			
Age (years)	58 ± 1	61 ± 1	0.08
Hispanic (%)	32	40	0.75
Years since menopause (years)	9 ± 1	12 ± 1	0.16
Weight (kg)	70 ± 2	79 ± 2	< 0.01
BMI (kg/m ²)	28 ± 1	32 ± 1	< 0.01
History of any clinical fracture (%)	9	9	0.54
Radiographic vertebral fracture (%)	4	2	0.26
Cigarette smoking, ever (%)	24	28	0.60
Alcohol use (1 drink/day) (%)	14	18	0.96
Diabetes (%)	10	11	0.66
Hepatitis C (%)	14	4	0.001
Serum biochemical markers			
PTH (pg/ml)	36.3 ± 2.0	38.3 ± 1.7	0.43
25-OH vitamin D (ng/ml)	23.2 ± 1.6	22.9 ± 1.4	0.88
C-telopeptide (ng/ml)	0.66 ± 0.05	0.43 ± 0.03	0.0004
N-telopeptide (nmol/BCE/liter)	19.1 ± 1.0	16.0 ± 0.7	0.01
Bone alkaline phosphatase (U/liter)	33.0 ± 1.9	30.2 ± 1.5	0.25
Osteocalcin (ng/ml)	6.0 ± 0.4	5.8 ± 0.3	0.7
Tumor Necrosis Factor α (pg/ml)	38.7 ± 2.7	33.0 ± 2.0	0.08
Interleukin-6 (pg/ml)	2.5 ± 0.4	2.5 ± 0.4	0.95
DXA measures			
LS T-score	−2.0 ± 0.2	−1.5 ± 0.2	0.03 / 0.21 *
LS Z-score	−0.7 ± 0.2	0.0 ± 0.2	<0.01 / 0.04 *
TH T-score	−1.0 ± 0.1	−0.5 ± 0.1	<0.01 / 0.11 *
TH Z-score	−0.2 ± 0.1	0.4 ± 0.1	<0.01 / 0.03 *
FN T-score	−1.4 ± 0.1	−0.9 ± 0.1	<0.02 / 0.23 *
FN Z-score	−0.3 ± 0.1	0.3 ± 0.1	<0.01 / 0.10 *
DR T-score	−0.8 ± 0.2	−0.5 ± 0.2	0.14 / 0.11 *
DR Z-score	0.3 ± 0.2	0.9 ± 0.1	0.03 / 0.12 *
UDR T-score	−1.2 ± 0.1	−0.7 ± 0.2	0.01 / 0.02 *
UDR Z-score	−0.4 ± 0.1	−0.3 ± 0.2	<0.01 / 0.01 *

Abbreviations: BMI, body mass index; PTH, parathyroid hormone; LS, lumbar spine; TH, total hip; FN, femoral neck, DR, 1/3 radius; UDR, ultradistal radius

* P values presented as unadjusted / adjusted. T-scores adjusted for age and BMI, Z-scores adjusted for BMI.

Table 2

HRpQCT measurements by site and HIV status (mean $\pm$ SEM)

	Radius		Tibia			
	HIV+ (N=46)	HIV- (N=60)	P value	HIV+ (N=46)	HIV- (N=60)	P value
Total bone parameters						
CSA (mm ²)	249 ± 7	256 ± 7	0.5	669 ± 18	673 ± 15	0.8
vBMD (mg HA/cm ³)	282 ± 9	289 ± 10	0.6	241 ± 7	260 ± 7	0.06
Cortical parameters						
Ct.Area (mm ²)	49 ± 2	50 ± 2	0.6	97 ± 3	110 ± 3	<0.01
Ct.vBMD (mg HA/cm ³)	868 ± 10	859 ± 12	0.6	845 ± 9	846 ± 8	0.9
Ct.Th (μm)	727 ± 26	737 ± 29	0.8	956 ± 33	1075 ± 28	<0.01
Trabecular parameters						
Tb.vBMD (mg HA/cm ³)	113 ± 5	119 ± 5	0.5	128 ± 5	134 ± 4	0.4
Tb.N (1/mm)	1.6 ± 0.1	1.7 ± 0.1	0.7	1.6 ± 0.1	1.6 ± 0.1	0.9
Tb.Th (μm)	58 ± 2	59 ± 2	0.6	68 ± 2	72 ± 2	0.1
Tb.Sp (μm)	595 ± 29	600 ± 33	0.9	592 ± 19	597 ± 20	0.8
Tb.Sp.SD (μm)	326 ± 39	332 ± 36	0.9	305 ± 22	320 ± 22	0.6

Abbreviations: vBMD, volumetric BMD; CSA, cross-sectional area; Ct., cortical; Ct.Th, cortical thickness; Ct.Area, cortical area; Tb., trabecular; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; Tb.Sp.SD, distribution of trabecular separation.

Table 3 Cortical parameters of tibia calculated with the extended algorithm (mean $\pm$ SEM)

	HIV+	HIV-		% difference
Cortical Area (mm ²)	106 $\pm$ 2	121 $\pm$ 2		-12.5% **
Cortical vBMD (mg HA/cm ³)	880 $\pm$ 12	873 $\pm$ 11		0.8%
Cortical TMD (mg HA/cm ³)	980 $\pm$ 6	979 $\pm$ 6		0.1%
Cortical Thickness (μ m)	1,102 $\pm$ 28	1,238 $\pm$ 23		-11.0% **
Cortical Pore Volume (mm ³)	62.5 $\pm$ 4.6	80.7 $\pm$ 6.1		-22.6% *
Cortical Porosity (%)	7.1 $\pm$ 0.5	7.8 $\pm$ 0.5		-8.9%
Cortical Pore Diameter (μ m)	212 $\pm$ 4	210 $\pm$ 4		1.1%
Cortical Pore Diameter Distribution (μ m)	100 $\pm$ 3	97 $\pm$ 3		2.8%

*
p<0.05,**
p<0.001**Abbreviations:** vBMD, volumetric Bone Mineral Density; TMD, Tissue Mineral Density

Table 4

Univariate and Multivariate models for cortical thickness and cortical area at the tibia for HIV+ and HIV– postmenopausal women (N=106)

Cortical thickness				
	Univariate Model		Multivariate model	
Variable	Parameter Estimate	p-value	Parameter Estimate	p-value
Intercept			0.786	<0.0001
Age	−0.0084	0.01		
Years Since Menopause	−0.0052	0.06	−0.005	0.043
BMI	0.015	<0.0001	0.014	<0.0001
Smoking Ever	−0.076	0.09		
Alcohol (≥ 1 drink)	−0.0006	0.99		
Race/ethnicity	0.071	0.13		
Diabetes	−0.104	0.059	−0.113	0.02
HCV	−0.057	0.33		
25OHD (<20 or ≥20)	−0.073	0.10		
HIV	−0.119	0.007	−0.075	0.06
Cortical area				
	Univariate Model		Multivariate Model	
Variable	Parameter Estimate	p-value	Parameter Estimate	p-value
Intercept			63.537	<0.0001
Age	−0.926	0.004		
Years Since Menopause	−0.566	0.03	−0.523	0.013
BMI	1.783	<0.0001	1.568	<0.0001
Smoking Ever	−7.944	0.06		
Alcohol (≥ 1 drink)	−0.293	0.95		
Race/ethnicity	14.079	0.002	8.743	0.015
Diabetes	−9.662	0.07	−9.345	0.026
HCV	−4.208	0.46		
25OHD (<20 or ≥20)	−9.523	0.03		
HIV	−12.774	0.003	−7.619	0.029