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HIV Infection is Associated with Abnormal Bone Microarchitecture: Measurement of Trabecular Bone Score in the Women's Interagency HIV Study

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Abstract

Objectives—We compared skeletal microarchitecture using Trabecular Bone Score (TBS) and evaluated relationships between change in TBS and lumbar spine (LS) bone mineral density (BMD) in women with and without HIV.

Methods—Dual energy X-ray absorptiometry (DXA) was performed on 319 women with and 118 without HIV in the Women's Interagency HIV Study (WIHS) at baseline and 2 and 5 years, to measure regional BMD and lean and fat mass. TBS was extracted from LS DXA images and examined continuously and categorically [normal (≥1.35), intermediate (1.20–1.35), or degraded (≤1.20) microarchitecture]. Pearson correlation and linear regression examined associations of TBS with regional BMD at baseline and over time.

Results—Women with HIV were older (43 vs. 37 yrs), more likely to be post-menopausal (27% vs. 4%), have lower baseline total fat mass, trunk fat and leg fat than uninfected women, degraded microarchitecture (27% vs. 9%, p=0.001), and lower baseline mean TBS (1.3±0.1 vs. 1.4±0.1, p<0.001). After adjusting for age, race, menopause status, and BMI, TBS remained lower in

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women with HIV (p<0.0001). Annual change in TBS correlated with LS BMD change among women with HIV (r=0.36, p<0.0001) and without HIV (r=0.26, p=0.02); however mean % annual TBS change did not differ by HIV status (−1.0%/yr±2.9% for HIV+ vs. −0.8%/yr±1.7% for HIV−, p=0.42).

Conclusions—Women with HIV have worse bone microarchitecture than uninfected women, but annual percent change in LS BMD or TBS was similar. Use of TBS as an adjunct to BMD to improve prediction of fragility fractures in women with HIV merits further study.

Keywords

bone microarchitecture; bone mineral density; trabecular bone score; HIV; women

INTRODUCTION

As the survival of persons with HIV in the United States approaches that of uninfected persons, people living with HIV (PLWH) are experiencing an excess burden of comorbid conditions typically associated with advanced age, including osteopenia and osteoporosis. It is estimated that PLWH have over 3 times the risk of osteoporosis and almost 7 times the risk of osteopenia compared with their uninfected counterparts.[1] Moreover, several large cohort studies have found a higher fracture incidence in PLWH compared with uninfected persons. [2–4] Middle-aged women with HIV had higher fracture incidence than uninfected women over a 10 year follow up period in the Women's Interagency HIV Study (WIHS).[3] As women with HIV age and transition through menopause, their risk of sustaining a fracture is expected to further increase.

Osteoporosis, a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, results in increased bone fragility and susceptibility to fracture.[5] Bone strength reflects both bone density and bone quality, including bone microarchitecture. Loss of bone mass and deterioration of microstructure both lead to compromised bone strength and increased fracture risk. Currently, there is no accurate measure of overall bone strength. Bone mineral density (BMD) is measured using dual X-ray absorptiometry (DXA) in clinical settings, and used to operationally define osteoporosis.[6] However about one-half of incident fractures occur in persons with BMD above the diagnostic threshold of osteoporosis.[7–10] Although BMD is frequently used as a proxy measure for bone strength, it accounts for only 70% of bone strength.[11]

Until recently, bone microarchitecture could not be measured using standard DXA. Trabecular bone score (TBS) is a noninvasive, indirect evaluation of the skeletal microarchitecture that can be derived from high-quality DXA images, as well as performed retrospectively and extracted from existing spine DXA images.[12–14] TBS has been shown to predict hip and major osteoporotic fractures independent of BMD and other clinical risk factors in older individuals, but has not been well studied in HIV-infected individuals. [15–18] We undertook this study to evaluate and compare TBS, an indirect marker of bone microarchitecture, in women with and without HIV, and to investigate relationships between change in TBS and lumbar spine (LS) BMD by HIV status.

METHODS

Study Population

The WIHS is an ongoing, multicenter observational study of HIV infection in women that initially enrolled HIV-infected and uninfected women in 1994–95 at six sites nationally (Bronx/Manhattan NY, Brooklyn NY, Chicago IL, Washington DC, San Francisco CA, and Los Angeles, CA), with additional enrollment in 2001–02 and 2011–12. In 2014–15, the WIHS closed its Los Angeles site and added four southern U.S. sites: Atlanta GA, Chapel Hill NC, Miami FL, and Birmingham AL/Jackson MS. WIHS methods and baseline cohort characteristics have been described previously.[19,20] Briefly, semiannual visits include an interviewer-administered questionnaire, physical examination, and collection of laboratory specimens. Between 2003 and 2006, 319 HIV-infected and 118 HIV-uninfected women with similar age, ethnicity, and risk behaviors from three WIHS sites (San Francisco, Bronx and Chicago) enrolled in a 5-year Metabolic Substudy, and underwent dual X-ray absorptiometry (DXA) scanning for bone density and fat distribution at baseline and at follow up visits 2 and 5 years later. Eligibility criteria have been published previously, and included women age ≤65 years old, weight <264 pounds, height less < 6′1″, who were not pregnant or breast feeding in the past six months. Exclusion criteria included type I diabetes, use of corticosteroids, use of exogenous hormones including growth hormone and hormonal contraceptives in the past 12 months, and drugs used to treat osteoporosis.[21] The institutional review boards of participating institutions approved the study protocol, and all participants provided informed consent.

Bone Mineral Density and Body Composition Assessment

Bone mineral density (BMD) of the lumbar spine (LS), total hip (TH), and femoral neck (FN) and regional fat mass in the trunk and leg and were measured by DXA (GE/Lunar Prodigy, Madison, WI, USA) at the index visit and subsequent 2-year and 5 year follow-up visits. Established instrument calibration and quality control procedures were used for accurate comparisons of BMD data between subjects measured at different times. The precision of the DXA operators are within acceptable limits. The visit when the first DXA scan was performed was referred to as the index visit. Body composition at index visit and subsequent visits included trunk fat and leg fat which were measured in kilograms by DXA. Fat free mass (FFM), total body fat (TBF), and percent body fat (PBF) were calculated based on height, weight, resistance and reactance which were measured by bioimpedance analysis (BIA) (RJL Systems, Inc, Detroit, MI, USA).[22,23]

Estimation of Skeletal Microarchitecture Using the Trabecular Bone Score

TBS is a new gray-level textural metric that can be extracted from the 2-dimensional lumbar spine DXA image to estimate trabecular microstructure, and provides information about bone microarchitecture that is not captured in the standard BMD measurement. Based upon experimental variograms of projected DXA images, TBS can discern differences in 3-dimensional microarchitecture between 2-dimensional DXA images that are similar to each other.[13] An elevated TBS value correlates with better skeletal texture (a reflection of better micro-architecture) and a low TBS value correlates with weaker skeletal texture (a reflection of degraded microarchitecture). The relationship between TBS texture parameters and 3D

micro-architecture parameters has been documented by several studies correlating TBS and microstructural parameters of bone assessed by micro-CT.[13,24] In the current study, previously measured, anonymized anterioposterior spine DXA image files were uploaded and TBS at lumbar spine L1–L4 regions was analyzed using TBS iNsight software by Med-Imaps (http://www.medimapsgroups.com/tbs-inisight).

Statistical Analysis

The primary outcome of interest was TBS measured at the lumbar spine, at the index visit and 2-year and 5 year follow-up visits. TBS was categorized as normal (≥1.35), intermediate (1.20–1.35), or degraded (≤1.20) and was analyzed as a categorical variable as well as a continuous variable.[15,25] The primary exposure of interest was HIV status. HIV infection was defined as a positive HIV EIA confirmed by Western Blot. Covariates included: Hepatitis C virus (HCV) infection, defined as positive HCV antibody and positive HCV RNA at baseline enrollment; lumbar spine (L1–L4) BMD; normal T- score at the lumbar spine (i.e. T-score > −1, representing normal BMD based on WHO criteria);[6] **demographics** including age, race/ethnicity (African American, Hispanic, Caucasian, and other), and WIHS study site; menopause status at index visit and subsequent visit, defined by self-reported menopause at 2 consecutive visits for women aged ≥45 years old; **substance use** including self-report of: cigarette smoking status (never smoked, current smoking and ever smoked); current alcohol: abstainer, light (<3 drinks/week), moderate (3–13 drinks/week) and heavy (≥14 drinks/week); and ever opiate use (including methadone) before index visit; and **body composition** measurements at index visit and subsequent visits, which included trunk fat, leg fat, FFM, TBF, and PBF.

In analyses limited to women with HIV, the following factors were also included in the model: self-reported AIDS status at index and subsequent visits; plasma HIV-RNA viral load and CD4 cell count at index and subsequent visit, and nadir CD4 count prior to index visit; time dependent antiretroviral therapy (ART) use, and cumulative exposure to ART (in unit of person-visit) prior to index visit; the type of ART was categorized as protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), or other. We tested for an interaction between (time-dependent) ART use and time, to determine whether being on or off ART was associated with change in TBS over time.

The basic characteristics of women with and without HIV were compared at the index visit. Binary and categorical characteristics in women with and without HIV were compared by chi-squared tests; continuous covariates were compared by 2-sample t test if they were normally distributed or by Wilcoxon rank sum test if they were not normally distributed. The association of TBS with LS BMD was examined at baseline and over time using Pearson correlation. Multivariable linear regression assessed relationship between baseline TBS and HIV status, adjusting for study site, menopause, smoking, and alcohol use.

Multivariable logistic regression evaluated associations between normal TBS category at baseline and HIV status. Marginal linear regression models that account for within-person correlation in repeated measurements were applied to assess the effect of HIV status on TBS of lumbar spine over three DXA scans, by adding (adjusting for) each of the following potential confounders into the model individually: demographic covariates including age at

index visit, race/ethnicity, study center and enrollment cohort; behavioral factors including cigarette use, alcohol use, opiate use and vitamin D, calcium or multivitamin use; body composition measures including trunk fat, leg fat, FFM, TBF, and PBF; and other factors such as menopause status at visit and HCV infection at enrollment. Multivariable models all adjusted for study site, menopause, smoking, and alcohol use. Interactions between years since index visit and HIV status, body components, age at index visit, and HIV-specific factors were assessed individually, and the significant interactions were included in the model. Subgroup analyses were performed among women with HIV to assess the association between TBS and ART use, type of ART, CD4 nadir, CD4 cell counts, and plasma HIV RNA levels. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Participant characteristics at index visit

Participant characteristics are shown in Table 1. A total of 437 women (319 HIV+, 118 HIV −) completed up to three DXA scans over 1144 person-visits. Median time between consecutive scans was 2.0 years (2.0 years between the 1st and 2nd scans and 3.5 years between the 2nd and 3rd scans). Women with HIV were older (median 43 vs. 37 yrs), more likely to be HCV-infected (32% vs. 14%) and post-menopausal (27% vs. 4%) compared to uninfected women. Among postmenopausal women, 98% did not report ever having an oophorectomy, and 73% did not report ever having a hysterectomy. Over half of all women were African-American. Among women with HIV, median CD4 count was 395 cells/mL, median HIV viral load was 575 copies/mL, and 60% were currently on ART. At baseline, TBS correlated with LS BMD among all women ($r=0.35$, $p<0.0001$), women with HIV ($r=0.32$, $p<0.001$), and uninfected women ($r=0.21$, $p=0.02$). Among women with at least 2 TBS measures, annual change in TBS correlated with annual change in LS BMD among HIV-infected women ($r=0.36$, $p<.0001$) and uninfected women ($r=0.26$, $p=0.018$), and annual percent TBS change correlated with annual percent LS BMD change among both HIV-infected ($r= 0.37$, $p<.0001$) and uninfected ($r= 0.27$, $p=0.013$) women.

Factors associated with normal baseline TBS in HIV-infected and uninfected women

In unadjusted analyses, women with HIV were 76% less likely to have normal TBS category compared with uninfected women (Table 2). Older age, postmenopausal status, current or former tobacco use, opiate use ever, and HCV infection were also associated with reduced likelihood of having normal TBS in unadjusted analyses. Normal LS BMD T-score, higher BMI, and greater trunk, leg or total fat mass were associated with greater odds of normal TBS in unadjusted analyses. In multivariate models, HIV status was associated with a 64% reduced odds of having normal TBS (aOR 0.36; 95%CI: 0.21–0.62; $p=0.0003$). Older age, black race, ever use of opiates, and greater trunk fat were associated with lower odds of normal TBS, whereas normal LS T-score and greater leg fat were associated with greater odds of normal TBS in adjusted analyses (Table 2.)

Association of HIV infection with baseline TBS

HIV infection was associated with lower TBS at baseline, compared with uninfected women (−0.111; 95%CI: −0.141,−0.082; p<0.001) (Table 3). After adjustment for HCV infection, the association of HIV infection with lower TBS was attenuated by 12% (−0.098; 95% CI: −0.127, −0.069; p<0.001), and slightly attenuated after additional adjustment for LS BMD (−0.080; 95%CI: −0.109, −0.051; p<0.001). The association of HIV infection with lower TBS was further attenuated by 24% after additionally adjusting for demographics and substance use (−0.056; 95% CI: −0.084, −0.028; p<0.001). There was little change in the association of HIV with lower TBS, after further adjusting for body composition measures (Table 3). Full models depicting the relationships between body composition measures and TBS are included in supplemental Table 1.

Relationship between HIV serostatus and TBS change over time

Figure 1 shows TBS change over time among women with and without HIV. Women with HIV had lower overall TBS compared with uninfected women over the follow-up period (−0.112; 95%CI:−0.142, −0.082; p<.0001). Neither mean absolute change in TBS per year (−0.012; 95%CI: −0.016, −0.008 for HIV+ vs. −0.011; 95%CI 0.015, −0.006 for HIV− women, p=0.65) nor percent change in TBS per year (−0.97%; 95%CI: −1.31%, 0.62% for HIV+ vs. −0.77%; 95%CI: −1.10%, −0.44% for HIV− women, p=0.52) differed by HIV status.

TBS change over time in HIV-infected and uninfected women

In multivariable analyses of TBS change, we found a significant time * lean mass interaction (−0.001; 95%CI: −0.001, −0.000; p=0.03), indicating that women with greater lean mass had slower decline in TBS over time. Figure 2 depicts the relationship between tertile of lean mass and change in TBS, showing that women with higher lean mass have slower decline in TBS compared with women with less lean mass, although the overall TBS change was small. Other factors associated with lower TBS at each time point in multivariable models, but not with more rapid TBS decline included: HIV (−0.051; 95%CI: −0.080, −0.021; p=0.001), older age (−0.031 per 10 years; 95% CI: −0.050, −0.012; p= 0.002), black race vs. white (−0.062; 95%CI: −0.105, −0.018; p=0.006), current smoking (−0.040; 95%CI: −0.073, −0.006; p=0.022), opiate use (−0.041; 95%CI: −0.069, −0.013; p=0.005), and greater trunk fat (−0.008; 95%CI: −0.011, −0.005; p<0.0001). Greater LS BMD (0.238; 95%CI: 0.164, 0.312; p<0.0001) and greater leg fat (0.014; 95%CI: 0.010, 0.018; p<0.0001) were associated with higher TBS overall, however neither was associated with gain in TBS. Exploratory analyses found that the key factor that strengthens the association between black race and lower TBS is leg fat; LS BMD, demographics, behavioral factors, and other body composition measures (BMI, total fat and lean mass) further strengthen this association, whereas HCV attenuates this association, and regional fat and HIV serostatus had little effect (data not shown).

In multivariable analyses limited to HIV-infected women, factors associated with lower TBS at each time point, but not with more rapid TBS decline included: older age (−0.054 per 10 years; 95% CI: −0.077, −0.030; p= 0.00002), current smoking (−0.051; 95%CI: −0.092,

−0.010; p=0.016), opiate use (−0.037; 95%CI: −0.072, −0.003; p=0.036), and ART use (−0.026; 95%CI: −0.050, −0.002; p=0.034) (Table 4).

DISCUSSION

Women with HIV were 64% less likely to have normal TBS, an indirect marker or assessment of bone microarchitecture, compared with women without HIV, despite adjusting for factors associated with altered bone metabolism. HIV was also associated with lower baseline TBS in unadjusted and adjusted analyses; and although the inclusion of chronic hepatitis C virus infection attenuated the relationship between HIV and TBS, HIV remained significantly associated with lower TBS. While HIV was associated with lower TBS over time, the annual change in TBS (amount and percent) did not differ by HIV serostatus. Ours is the first study to evaluate TBS in women with HIV. Previous published studies on TBS in populations with HIV are limited to a pilot case-control study of 54 HIV-infected persons,[26] a comparison of tenofovir/emtricitabine or abacavir/lamivudine effects on bone,[27] and a cross-sectional study of predominantly Caucasian men under age 50 years,[28] none of which included an HIV-uninfected comparison group. Ciullini et al found a 13.5% prevalence of asymptomatic vertebral fractures in a study of majority white middle-aged men with HIV, in whom an observed vertebral fracture risk reduction of 44% was found for each SD increase in TBS.[28] In a case-control study of 23 adults with HIV and fracture history and 23 without fracture, Tan et al found no difference in TBS or bone turnover markers between groups, although they did find lower BMD measured by DXA, greater bone structural abnormalities measured by high resolution peripheral quantitative tomography (HRpQCT), and decreased composite measures of bone strength on hip structural analyses (HAS) and HRpQCT among those with a reported history of fracture.[26]

We found that women with HIV had reduced LS BMD compared with uninfected women; however HIV remained independently associated with lower TBS despite accounting for LS BMD. While baseline TBS correlated with LS BMD, the magnitude of this correlation was modest, suggesting that TBS and BMD are complementary approaches that do not capture the same information, yet both contribute to assessment of bone strength. Moreover, our findings suggest that HIV infection is associated with degraded bone microstructure, as well as lower BMD, both of which may contribute to fracture risk. Although we are unable to assess the contribution of TBS on fracture rate among women with and without HIV in the current analyses, several published studies in older HIV-uninfected populations have suggested that TBS is a useful adjunct to both BMD and clinical risk factors for prediction of fracture, and that TBS provides additional information that is not captured by measurement of BMD in terms of fracture risk assessment.[17,29] Although TBS has not been well-studied in populations with HIV, several studies have demonstrated abnormal bone microarchitecture associated with HIV using HRpQCT, including alterations in trabecular number and cortical bone among premenopausal women with HIV,[30] and decreased tibial trabecular volumetric BMD, diminished cortical dimensions, and significant endocortical bone loss measured by pCT, in comparing HIV/HCV-coinfected women with controls without HIV or HCV infection.[31] In contrast, Yin et al found that among postmenopausal women, no differences were observed by HIV status for cortical and trabecular vBMD,

trabecular microarchitecture at the distal radius or trabecular parameters at the tibia, using HRpQCT.[32]

We found that women with older age, black race, opiate use history, and cigarette smoking were more likely to have abnormal TBS. Although older age, opiate use, and smoking are also known risk factors for osteoporosis and fracture, black race is not. Rather, among HIV-uninfected populations, the lifetime risk of osteoporotic fracture in black women is about half that of white women.[33–35] In the Study of Osteoporotic Fractures, at the same BMD level, the prevalence of vertebral fracture was lower among black women vs. white women[36] and fracture incidence was 30% to 40% lower among black compared with white women at every BMD tertile,[37] leading the authors to speculate that reduced fractures rates might be explained by skeletal factors such as bone microarchitecture or other nonskeletal factors including lifestyle and anthropometric factors. Similar to our findings, in the National Health and Nutrition Examination Survey (NHANES), non-Hispanic White women had higher mean TBS than either non-Hispanic Black or Mexican American women in all age groups, contrasting with LS BMD distribution in NHANES, where the highest LS BMD was in Black women, followed by White women, and lowest LS BMD in Mexican American women.[38]

Ours is the first study to evaluate TBS in relation to body composition among persons with HIV. We found that higher BMI, higher total fat mass, and higher leg fat were associated with higher TBS, whereas trunk fat was inversely associated with TBS. Our findings differ from those reported for men and women in the NHANES, in which TBS inversely correlated with BMI, weight, waist circumference, total fat mass, trunk fat mass, and lean fat mass; and in contrast LS BMD was positively associated with these body size and composition variables.[38] Several other studies of HIV-uninfected women have reported negative correlations between TBS and BMI, (range −0.13 to −0.19), and TBS and weight (range −0.16 to −0.17).[39–43] In the Osteoporotic Fractures in Men (MrOS) study of HIV-uninfected men ≥65 years of age, TBS was inversely related to BMI, trunk fat mass, and trunk lean mass.[44]

Moreover, we found a significant interaction between total lean body mass and time, which was inversely related to TBS, suggesting that women with less lean mass experienced a greater reduction of TBS, or degradation of bone microarchitecture over time. Ours is the first study to evaluate the contribution of lean and fat mass on TBS over time in HIV-infected persons. Our findings extend the literature on the relationship between fat, muscle and bone. In a large cohort of well-functioning HIV-uninfected older adults participating in the Health, Aging, and Body Composition (Health ABC) Study, lean mass was a significant and independent determinant of BMD, as was fat mass, and for limb BMD, muscle strength as well.[45] Many studies have shown that sarcopenia, defined as low appendicular lean mass plus slowness or weakness, has been associated with a number of adverse outcomes, including mortality, functional decline, falls, and a higher incidence of hospitalizations,[46] and when combined with low BMD in particular, increased risk of fracture.[47] Our data suggest that maintaining or increasing lean mass may be an important strategy to prevent fractures in aging HIV-infected women, in whom both BMD and TBS may be altered, leading to bone fragility.

Ours is the first study of trabecular bone score conducted among women with HIV, and the largest study conducted in a population with HIV to date. Our study has a number of strengths. First, we performed both cross-sectional and longitudinal assessments of TBS, along with LS BMD and body composition. Second, we measured total and regional fat and lean mass in women with a range of BMI, to assess their associations with TBS. Third, the WIHS cohort is representative of the HIV epidemic among US women and has a demographically similar comparison group of HIV-uninfected women with similar risk factors for bone disease.

Our study has several limitations as well. First, we did not measure amount of regional subcutaneous or visceral fat. Second, we are unable to assess the extent to which TBS predicts fracture, which would require larger number of subjects and longer follow up time, given the age of the cohort. Third, because the WIHS is comprised entirely of women, and several studies in HIV-uninfected populations have reported significant sex differences in relationships between TBS and BMI, our findings may not be generalizable to men with HIV.

In conclusion, in this cohort of women with and without HIV, HIV status was independently associated with abnormal bone microarchitecture, measured with TBS. Loss of lean mass was associated with reduction in TBS, suggesting that maintaining or increasing lean mass may be an important therapeutic target for improving bone strength and potentially reducing risk of falls and fractures among aging women with HIV. Future studies should evaluate the extent to which TBS improves fracture prediction beyond clinical risk factors and BMD in populations with HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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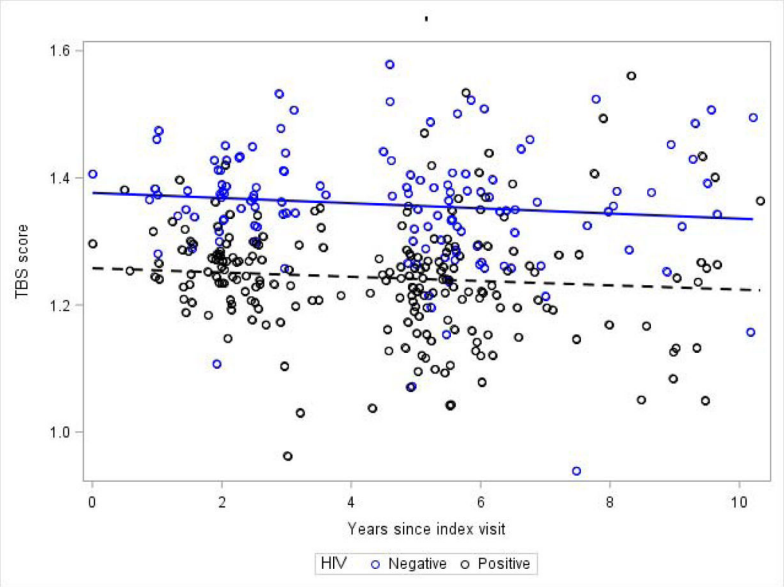

Figure 1.
Trabecular Bone Score Change Over Time in HIV-infected and Uninfected Women

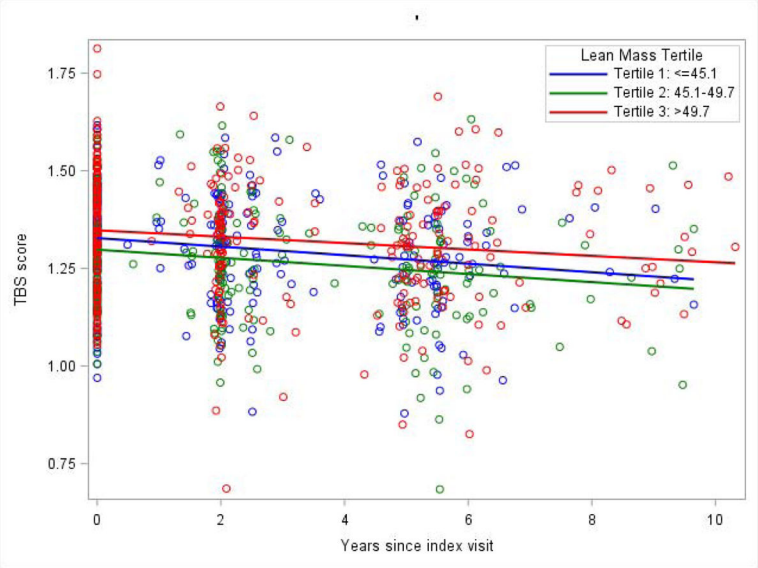

Figure 2.

Trabecular Bone Score Change Over Time by Lean Mass Tertile in HIV-infected and Uninfected Women

Table 1

Characteristics of HIV uninfected women and HIV infected women at index visit**

	HIV-uninfected (N=118)	HIV-infected (N=319)	P value
Age (yr), median (IQR)	37 (31, 44)	43 (38, 49)	<.0001
Race, n (%)			
African American	66 (56%)	186 (59%)	0.71
Hispanic	36 (31%)	80 (25%)	
Caucasian	13 (11%)	41 (13%)	
Other	3 (2.5%)	9 (3%)	
Study center, n (%)			0.11
Bronx/Manhattan	47 (40%)	130(41%)	
San Francisco	43 (36%)	119 (37%)	
Chicago	28 (24%)	70 (22%)	
Enrollment cohort, n (%)			<.0001
Original (1994–95)	44 (37%)	211 (66%)	
2nd enrollment (2001–02)	74 (63%)	108 (34%)	
Smoking status, n (%)			0.055
Never smoker	26 (21%)	57 (18%)	
Past smoker	16 (13%)	69 (22%)	
Current smoker	80 (66%)	189 (60%)	
Recent alcohol use, n (%)			0.01
None	42 (36%)	168 (53%)	
Light (< 3 drinks/wk)	59(50%)	123 (39%)	
Moderate (3–13 drinks/wk)	8 (7%)	13 (4%)	
Heavy (≥14 drinks/wk)	9 (8%)	15 (5%)	
Opiate use ever at index visit, n (%)	31 (28%)	92 (31%)	0.85
Calcium/Vitamin D/Multivitamin use, n (%)	4 (3%)	26 (9%)	0.11
Postmenopausal status at index visit, n (%)	4 (3.6%)	82 (27%)	<.0001
BMI (kg/m^2), median (IQR)	29.9 (25.2, 36.2)	27.5 (23.4, 31.5)	0.001
Body components, median (IQR)			
Trunk fat (kg)	15 (10, 22)	13 (9, 17)	0.001
Leg fat (kg)	12 (8.4, 16)	8.7 (5.6, 13)	<.0001
Fat free mass (kg)	48 (44, 52)	47 (43, 51)	0.11
Total body fat (kg)	29 (19, 43)	24 (16, 33)	0.003
Percent body fat (%)	39 (30, 46)	34 (26, 40)	0.003
Hepatitis C virus infection, n (%)	17 (14%)	103 (32%)	<.0001
Bone Turnover Marker levels, median (IQR)			
Osteocalcin (ng/mL)	6.0 (4.1, 8.4)	6.3 (4.3, 9.1)	0.56
C-Telopeptide (ng/mL)	0.1 (0, 0.2)	0.1 (0.1, 0.2)	0.37

	HIV-uninfected (N=118)	HIV-infected (N=319)	P value
Lumbar Spine (L1–L4) BMD, median (IQR)	1.3 (1.2, 1.4)	1.2 (1.1, 1.3)	<.0001
Trabecular Bone Score (TBS), median (IQR)	1.4 (1.3, 1.5)	1.3 (1.2, 1.4)	<.0001
TBS category, n (%)			<.0001
Normal (≥1.35)	79 (67%)	104 (33%)	
Intermediate (1.20–1.35)	28 (24%)	128 (40%)	
Degraded (≤1.20)	11 (9%)	87 (27%)	
AIDS diagnosis, n (%)	-	141 (44%)	
CD4 count (cells/ml), median (IQR)*	-	395 (262, 586)	
CD4 nadir (cells/ml), median (IQR)*	-	241 (120, 349)	
HIV RNA viral load, median (IQR)	-	575 (80, 6850)	
On ART, n (%)	-	192 (60%)	
On tenofovir, n (%)	-	72 (23%)	

P value is shown for Chi-squared test, two sample t-test (for age) or Wilcoxon rank-sum test (for other continuous variables that are not normally distributed). Index visit refers to the first visit when BMD was measured. Abbreviations: HIV: human immunodeficiency virus; BMI: body mass index; ART: antiretroviral therapy; PI: protease inhibitor; NNRTI: non-nucleoside analog reverse transcriptase inhibitor

Table 2

Odds of Having Normal (≥1.35) TBS Score in HIV-infected and Uninfected Women

	Crude Odds			Adjusted Odds		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
HIV seropositive	0.24	0.15–0.37	<0.0001	0.36	0.21–0.62	0.0003
Normal lumbar spine T-score	4.05	2.12–7.75	<0.0001	2.35	1.10–5.04	0.03
Age (per 10 years)	0.36	0.27–0.47	<0.0001	0.55	0.37–0.83	0.004
Race (REF: White)						
Black	0.84	0.46–1.53	0.57	0.48	0.21–1.08	0.004
Hispanic	1.22	0.63–2.33	0.56	0.85	0.35–2.08	0.72
Other	1.89	0.53–6.71	0.33	0.99	0.23–4.32	0.99
Post-menopausal status	0.17	0.09–0.33	<0.0001	0.6	0.25–1.44	0.25
WIHS Site (REF: Bronx)						
San Francisco	0.92	0.60–1.41	0.7	0.74	0.40–1.37	0.33
Chicago	0.77	0.46–1.28	0.31	0.58	0.29–1.15	0.12
Smoking status (REF: Never)						
Past	0.53	0.29–0.97	0.04	0.82	0.28–1.72	0.58
Current	0.43	0.26–0.71	0.0008	0.71	0.38–1.34	0.29
Ever opiate use	0.33	0.19–0.60	0.0002	0.33	0.13–0.75	0.008
HCV infection	0.32	0.20–0.51	<0.0001	0.83	0.44–1.57	0.56
Recent alcohol use (REF: none)						
Light (< 3 drinks/wk)	1.31	0.88–1.96	0.19	0.96	0.58–1.59	0.86
Moderate (3–13 drinks/wk)	0.61	0.23–1.64	0.33	0.31	0.09–1.12	0.06
Heavy (≥14 drinks/wk)	1.09	0.46–2.58	0.84	1.01	0.38–2.68	0.99
BMI (per 10%, kg/m^2) *	1.15	1.06–1.25	0.001	-	-	-
Trunk fat (kg)	1.03	1.00–1.06	0.04	0.89	0.84–0.96	0.003
Leg fat (kg)	1.09	1.05–1.14	<0.0001	1.22	1.12–1.33	<0.0001
Total lean mass (kg)	0.99	0.96–1.02	0.65	0.95	0.92–1.02	0.17
Total fat mass (kg) *	1.02	1.00–1.03	0.02	-	-	-

* BMI and total fat mass were not included in models that contained regional fat (trunk and leg fat) and lean mass. All covariates included in adjusted models are shown in Table 2 above.

Table 3

Association of HIV infection with Trabecular Bone Score in the WIHS Metabolic Study

	Parameter Estimate	95% CI	P value
Model 1: HIV only	−0.111	−0.141, −0.082	<.0001
Model 2: adjusted for HCV	−0.098	−0.127, −0.069	<.0001
Model 3: adjusted for HCV and LS BMD	−0.080	−0.109, −0.051	<.0001
Model 4: adjusted for HCV, LS BMD, demographics, and substance use	−0.061	−0.089, −0.033	<.0001
Model 5: adjusted for HCV, LS BMD, demographics, substance use, and BMI	−0.056	−0.084, −0.028	<.0001
*Model 6: adjusted for HCV, LS BMD, demographics, and substance use, total body fat, and total lean mass	−0.057	−0.086, −0.029	<.0001
*Model 7: adjusted for HCV, LS BMD, demographics, substance use, trunk fat, leg fat, and total lean mass	−0.049	−0.076, −0.022	<.0001

Demographics include age, race, menopause status, WIHS site; substance use includes smoking, alcohol use, and opioid use.

*Models do not include BMI

Table 4

Change in Trabecular Bone Score among HIV-infected Women in the WIHS Metabolic Study

	Parameter Estimate	95% CI	P value
LS BMD (g/cm^2)	0.207	0.120, 0.295	0.00001
Age (per 10 years)	−0.054	−0.077, −0.030	0.00002
Race (REF: White)			
Black	−0.042	−0.097, 0.012	0.13
Hispanic	−0.000	−0.059, 0.058	0.99
Other	−0.015	−0.126, 0.096	0.79
Post-menopausal status	−0.002	−0.039, 0.035	0.90
WIHS Site (REF: Bronx)			
San Francisco	−0.012	−0.047, 0.023	0.49
Chicago	−0.028	−0.073, 0.016	0.21
Smoking status (REF: Never)			
Past	−0.022	−0.068, 0.023	0.33
Current	−0.051	−0.092, −0.010	0.016
Ever opiate use	−0.037	−0.072, −0.003	0.036
HCV infection	−0.004	−0.037, 0.029	0.80
Recent alcohol use (REF: none)			
Light (< 3 drinks/wk)	−0.001	−0.026, 0.023	0.92
Moderate (3–13 drinks/wk)	−0.029	−0.082, 0.025	0.29
Heavy (≥14 drinks/wk)	0.004	−0.047, 0.055	0.89
ART use *	−0.026	−0.050, −0.002	0.034

*Antiretroviral therapy (ART) is time-dependent