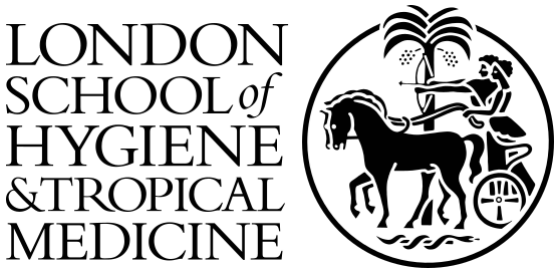

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DUAL-ENERGY X-RAY ABSORPTIOMETRY AND CALCULATED FRAX RISK SCORES MAY UNDERESTIMATE OSTEOPOROTIC FRACTURE RISK IN VITAMIN D–DEFICIENT VETERANS WITH HIV INFECTION

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Abstract

Objective—We evaluated the utility of the World Health Organization Fracture Risk Assessment Tool (FRAX) in assessing fracture risk in patients with human immunodeficiency virus (HIV) and vitamin D deficiency.

Methods—This was a retrospective study of HIV-infected patients with co-existing vitamin D deficiency at the Atlanta Veterans Affairs Medical Center. Bone mineral density (BMD) was assessed by dual-energy X-ray absorptiometry (DEXA), and the 10-year fracture risk was calculated by the WHO FRAX algorithm. Two independent radiologists reviewed lateral chest radiographs for the presence of subclinical vertebral fractures.

Results—We identified 232 patients with HIV and vitamin D deficiency. Overall, 15.5% of patients met diagnostic criteria for osteoporosis on DEXA, and 58% had low BMD (T-score between −1 and −2.5). The median risk of any major osteoporotic and hip fracture by FRAX score was 1.45 and 0.10%, respectively. Subclinical vertebral fractures were detected in 46.6% of patients. Compared to those without fractures, those with fractures had similar prevalence of osteoporosis (15.3% versus 15.7%; P>.999), low BMD (53.2% versus 59.3%; P = .419), and similar FRAX hip scores (0.10% versus 0.10%; P = .412). While the FRAX major score was lower in the nonfracture group versus fracture group (1.30% versus 1.60%; P = .025), this was not clinically significant.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

Conclusion—We found a high prevalence of subclinical vertebral fractures among vitamin D–deficient HIV patients; however, DEXA and FRAX failed to predict those with fractures. Our results suggest that traditional screening tools for fragility fractures may not be applicable to this high-risk patient population.

Keywords

HIV; Vitamin D; osteoporosis; FRAX; fractures; veterans

INTRODUCTION

It has been well established that individuals infected with the human immunodeficiency virus (HIV) are more prone to decreased bone mineral density (BMD) and osteoporosis (1–4). Furthermore, a growing amount of data have demonstrated a high prevalence of vitamin D deficiency among HIV-infected individuals (5–10), which has also been associated with increased risk of developing decreased BMD (11,12). The pathophysiologic mechanisms of bone disease in HIV infection are complex and not fully understood. In addition to traditional risk factors, individuals with HIV are at increased risk for decreased BMD due to concomitant risk factors such as malnutrition, vitamin D deficiency, hypogonadism, antiretroviral therapies, chronic inflammation, and HIV infection itself (5,13–17).

Currently, the optimal screening for bone disease in HIV disease remains controversial, and it is unclear whether the World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX) algorithm applies to this patient population. The WHO FRAX algorithm, used to calculate the 10-year probability of a hip fracture or major osteoporotic fracture, has not been fully validated in HIV-infected individuals. Similarly, fracture risk assessment by T-scores on dual-energy X-ray absorptiometry (DEXA) alone may be inadequate to reliably screen for patients with HIV who are at a higher risk for fracture than their HIV-negative counterparts. As seen in other causes of secondary osteoporosis, measurements of BMD alone may be inadequate to predict fracture risk in HIV-infected individuals (18,19).

These data raise the question of whether traditional screening tools are sufficient to identify those at risk for bone disease in this high-risk population of patients with concomitant HIV and vitamin D deficiency, which has important clinical implications from both a preventive and treatment perspective. Thus, the aim of our study was to investigate the utility of the FRAX risk assessment tool and WHO criteria for osteoporosis based on T-scores in the vitamin D–deficient HIV population. The prevalence of subclinical vertebral fractures in this patient population was also investigated.

METHODS

Study Design and Participants

We performed a retrospective study of 232 patients with HIV and co-existing vitamin D deficiency as part of a substudy investigating the prevalence of vitamin D deficiency in the HIV patient population at the Atlanta Veterans Affairs (VA) Medical Center (20). Data were obtained from the HIV Atlanta VA cohort, a clinical database collecting longitudinal data

from electronic medical records on all HIV-infected patients seen at the Atlanta VA Medical Center since 1982. All patients with HIV and a 25-hydroxyvitamin D (25[OH]D) level <20 ng/mL collected during routine medical care between 2007 and 2010 were identified. Routine care included obtaining a DEXA scan on patients with vitamin D deficiency. DEXA testing was not done routinely for subjects without vitamin D deficiency. Patients were then included in our study only if they had BMD assessment by DEXA, calculated FRAX scores, and lateral chest radiographs during the study period. The chest radiographs had been obtained during routine clinical care for a variety of indications. Individuals who had received bisphosphonate therapy prior to or during the study period were excluded. Patient characteristics (age, sex, and race), body composition (height, weight, and body mass index [BMI]), medical comorbidities (diabetes mellitus, hypertension, tobacco use, alcohol use, and hepatitis B and/or C co-infection), type of antiretroviral therapy, and other potential risk factors for low BMD were obtained from electronic medical records. Standard, routine laboratory assays were used to measure baseline biomarkers of bone metabolism, including calcium, parathyroid hormone (PTH), alkaline phosphatase, and phosphorous, as well as HIV-related parameters (CD4 lymphocyte count and HIV RNA viral load). The liquid chromatography/tandem mass spectrometry method was used for measuring 25(OH)D levels (Quest Laboratories). Vitamin D deficiency was defined as a 25(OH)D level <20 ng/mL. The glomerular filtration rate was estimated by the Cockcroft-Gault equation. The study was approved by the Emory University Institutional Review Board and the VA Research and Development Committee.

Assessment of BMD and Fractures

BMD was assessed by DEXA (Hologic, Inc.). Criteria established by the WHO were used to diagnose those with osteoporosis (hip or spine T score ≤ −2.5) or low bone density (hip or spine T score > −2.5 and < −1.0). Patients classified as having osteoporosis or low bone density were compared with those patients with normal BMD (hip and spine T score > −1.0). The 10-year probabilities of hip fracture and of a major osteoporotic fracture were calculated using the WHO FRAX algorithm, which integrates several clinical risk factors (age, sex, weight, height, previous fracture history, parent hip fracture, smoking history, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and alcohol consumption ≥3 units/day) with BMD (T score) at the femoral neck. FRAX prediction values were calculated based on a patient's risk at the time of the DEXA examination. The presence of subclinical vertebral fractures was assessed by lateral chest radiographs, which were interpreted by two independent radiologists who were blinded to each other's read. Using the Genant et al (21) semiquantitative method, thoracic and lumbar vertebrae were graded on visual inspection of lateral spinal images as grade 0 (normal), grade 1 fracture (mildly deformed; 20 to 25% reduction in height), grade 2 fracture (moderately deformed; 26 to 40% reduction in height), and grade 3 (severely deformed; approximately 40% or greater reduction in height). There was 90% agreement between the two readers, and disagreements were resolved by consensus.

Statistical Analysis

Results for continuous variables with a nonnormal distribution are summarized as median values with interquartile intervals or as proportions for categorical variables. The Mann-

Whitney *U* test was used to compare the difference in nonnormally distributed variables. The chi-square test was used for comparison of categorical variables. Multivariate logistic regression models, with the presence of subclinical vertebral fracture as a binary dependent variable, were used to adjust for potential confounding factors. Variables examined included age, sex, race, BMI, type of antiretroviral therapy, CD4 T-cell count, HIV RNA viral load, hypertension, hepatitis B co-infection, hepatitis C co-infection, alcohol use, tobacco use, osteoporosis or osteopenia status, FRAX scores, renal function, serum 25(OH)D calcium and phosphorus concentrations, and plasma PTH concentrations. Analyses were performed with SPSS software (version 21.0, SPSS, Inc, Chicago, IL). Statistical significance was based on 2-tailed tests, and *P* values ≤.05 were considered significant.

RESULTS

Patient Characteristics

We identified 232 patients with HIV (median CD4 count, 494.5 cells/mm^3; interquartile range [IQR], 306.5 to 673.8) and vitamin D deficiency (median 25[OH]D, 13 ng/mL; IQR, 9.0 to 16.0). The majority of patients were male (97.8%), African American (90.1%), and with a median age of 49.1 years (IQR, 42.8 to 56.1). Most patients were receiving antiretroviral therapy (81.5%), and almost two-thirds had an undetectable HIV viral load (61%). The study patient characteristics are further shown in Table 1.

Baseline BMD and Prevalence of Subclinical Vertebral Fractures

Overall, 73.5% of our patients with HIV and co-existing vitamin D deficiency had low BMD. The prevalence of patients meeting diagnostic criteria for osteoporosis by DEXA was 15.5% (n = 36), and 58% (n = 130) had low bone density (T score between −2.5 and −1 at the hip or spine). Notably, there was a high prevalence of subclinical vertebral fractures detected on lateral chest radiographs (46.6%), and the majority of these fractures were grade 1 (90.7%).

Characteristics of Patients According to Presence or Absence of Subclinical Vertebral Fractures

When compared to the group of patients with subclinical vertebral fractures, those without fractures had similar prevalence of osteoporosis (15.3% versus 15.7%; *P*>.999) and low bone density (53.2% versus 59.3%; *P* = .419) by WHO criteria on DEXA (Fig. 1). Other than being slightly older (52.1 versus 48.2 years; *P* = .001), patients with subclinical vertebral fractures had no statistically significant differences in patient demographics, antiretroviral regimen, or medical comorbidities compared to those without fractures. Phosphorous was the only marker of bone metabolism that was statistically different between the two groups (3.1 versus 3.3 mg/dL; *P* = .006), but the difference was not clinically significant. Density at the hip was statistically higher in the nonfracture group versus fracture group (1.011 versus 0.965 g/cm^2; *P* = .023), but there was no difference in density at the spine between the two groups. Femoral neck T score was also statistically higher in the nonfracture group versus fracture group (−1.00 versus −1.40; *P* = .028), but there was no difference in T score at the spine. Characteristics of our study patients according to the presence or absence of subclinical vertebral fractures are shown in Table 2.

Ten-Year Estimate of Fracture Risk

The median risk of any major osteoporotic and hip fracture calculated by the WHO FRAX algorithm for the entire study population was 1.45% (IQR, 1.00 to 2.70) and 0.10% (IQR, 0.00 to 0.40), respectively, well below the recommended threshold to initiate pharmacologic therapy. Compared to those without fractures, those with subclinical vertebral fractures had similar FRAX hip (0.10% versus 0.10%; $P = .412$) scores. The FRAX risk score for any major osteoporotic fracture was statistically higher in the fracture group (1.60% versus 1.30%; $P = .025$) but was not clinically relevant, as both scores were well below the recommended threshold for pharmacologic treatment. Furthermore, when the FRAX scores were adjusted for the presence of vertebral fractures on lateral chest radiographs in our patients, there was no significant difference between the baseline FRAX and modified scores.

Risk Factors for Future Fracture Risk

After multivariable analysis, only older age and diabetes were associated with future risk of subclinical vertebral fractures. Other variables that were not predictive of vertebral fractures included sex, race, BMI, CD4 count, HIV viral load, type of antiretroviral therapy, hypertension, hepatitis B co-infection, hepatitis C co-infection, alcohol use, tobacco use, osteoporosis and osteopenia status, FRAX scores, renal function, serum 25(OH)D and calcium concentrations, and plasma PTH concentrations.

DISCUSSION

Our study found a high prevalence of subclinical vertebral fractures among HIV patients with vitamin D deficiency, but screening with DEXA and the WHO FRAX algorithm failed to distinguish between patients with and without subclinical vertebral fractures. Osteoporosis and decreased BMD (T score < −1.0) was found in 73.5% of our study patients, similar to prior data reported among HIV patients in the literature (3,22). However, subclinical vertebral fractures were detected in about half of our study participants (46.6%), which is almost twice as prevalent as had been reported in recent studies (23–25). Most notably, we found a similar prevalence of osteoporosis and decreased BMD between patients with and without subclinical vertebral fractures. Finally, there was no clinically significant difference in the calculated WHO FRAX score between patients with and without subclinical vertebral fractures, consistent with prior studies that suggest poor sensitivity of FRAX in HIV patients (26,27).

It is well established that individuals infected with HIV are at an increased risk for decreased BMD and osteoporosis. Brown et al (3) reported a 67% prevalence of low BMD and 15% prevalence of osteoporosis in a meta-analysis among HIV-infected individuals, a 3.7-fold increase compared to age-matched non–HIV infected persons. Mounting data have now also shown that fracture prevalence is significantly higher among the HIV patient population, with reported overall fracture rates 24 to 70% higher than the general population (1,28–31). In particular, HIV-infected patients have been shown to have high rates of vertebral fractures and may have more severe and multiple fractures compared to age-matched non–HIV infected controls (24,25). This is of clinical concern, as radiographic vertebral fractures are

associated with higher risk for hip and other future fractures (32), and age-related increases in fracture rates appear to be greater in HIV-infected individuals compared to controls, suggesting that fracture rates may further increase as the HIV-infected patient population ages (1).

The pathogenesis of HIV-associated bone loss is complex and likely multifactorial. In addition to traditional risk factors (advanced age, gender, low bone mass index, smoking, alcohol use, vitamin D deficiency), patients with HIV are at increased risk for decreased BMD and osteoporosis due to chronic malnutrition, weight loss, and hypogonadism. Furthermore, several studies have implicated HIV infection itself in increased risk for decreased BMD causing alterations in bone remodeling (33,34). In vitro, HIV viral proteins have been shown to increase levels of RANK ligand, promoting osteoclastogenesis (35), and also are associated with suppression of osteoblast activity and increased osteoblast apoptosis (33,35). In addition, chronic inflammation and T-cell activation resulting in increased production of pro-inflammatory cytokines may further promote osteoclast activation and high bone turnover in HIV disease (35,36). Finally, treatment with antiretroviral therapy has also been associated with increased bone loss, in particular protease inhibitors and tenofovir (16,37).

In agreement with other studies, we found that the WHO FRAX algorithm is a poor screening tool to assess fracture risk in the HIV patient population. The study of Calmy et al (27) was the first to demonstrate that FRAX has a poor sensitivity in HIV patients and fails to distinguish between HIV patients with normal BMD and those with decreased BMD. A subsequent study by Gazzola et al (26) found that when compared to DEXA screening, FRAX scores failed to identify a large number of HIV patients with decreased BMD, with a sensitivity of only 22%. Furthermore, when the authors added HIV as a secondary cause of osteoporosis to calculate a modified FRAX score, the sensitivity only increased to 37.5%, still grossly underestimating those at risk for bone disease (26).

Recently, Porcelli et al (23) found a high prevalence of radiologic vertebral fractures in HIV patients (27%), yet over half of these patients with fractures had normal or only mildly reduced BMD on DEXA assessment. Our study differs from that of Porcelli et al in that we found a significantly higher prevalence of subclinical vertebral fractures in our HIV patient population, likely due to co-existing vitamin D deficiency, which further increased fracture risk. Furthermore, subclinical vertebral fractures in our study were not associated with lower BMD on DEXA.

Current guidelines recommend DEXA screening in all HIV patients who are postmenopausal, have a fracture history, or are 50 years of age or older with an additional traditional risk factor for low BMD (38). Based on the results of our study, current screening guidelines may underdiagnose many of these high-risk individuals. Thus, we propose considering the use of lateral spine imaging to screen for subclinical vertebral fractures in HIV patients, especially given that this is a low-cost and widely available screening modality. The presence of a subclinical vertebral fracture may provide grounds for initiating pharmacologic therapy for osteoporosis in patients who would have not otherwise qualified

based on a normal or only slightly decreased BMD on DEXA and/or calculated FRAX scores below the current recommended threshold to treat.

Our study has several limitations. Our study patient population lacked heterogeneity (mostly African American males); thus, our findings may not be applicable to other ethnic groups and/or females. All patients were vitamin D deficient, which may have increased the risk for subclinical vertebral fractures compared to HIV individuals who are vitamin D sufficient. Furthermore, we did not have further detailed information regarding the vitamin D status of our patients and whether they had received vitamin D replacement therapy prior to or during the study period. It is also unknown whether treatment with vitamin D replacement or other pharmacologic therapy would have changed the study outcomes (prevalence of fracture and decreased BMD). Our study also lacked data regarding risk factors for fractures, such as glucocorticoid or testosterone use, testosterone levels, nutritional status, prior fracture history or trauma, or HIV defining illnesses. Notably, our patient population represents a relatively well-controlled cohort, with a median CD4 count of 494.5, most of whom are on treatment (81.5%) and with undetectable viral load (61%). We may have underestimated fracture risk by using lateral chest radiographs as the only imaging modality to detect subclinical vertebral fractures. The fracture rate may actually have been higher if dedicated lateral spine radiographs had been used. Finally, we do not have fracture data on HIV patients without vitamin D deficiency and cannot comment on the prevalence of vertebral fractures in this population. Notably, the FRAX score has not been validated in younger patients, who constituted the majority of our patient population. Whether this contributes to the lack of discrimination of FRAX with respect to fracture risk in our study is uncertain. However, HIV patients tend to be a younger population at risk for fractures in general, and this may further highlight the lack of applicability of FRAX in this population. Finally, the chest X-rays were performed at the clinical discretion of the treating physician. Whether the indication for these chest X-rays affect the baseline fracture risk for these patients is unknown.

CONCLUSION

In conclusion, our study demonstrated a high prevalence of subclinical vertebral fractures in HIV patients with co-existing vitamin D deficiency. Screening with DEXA and the WHO FRAX algorithm grossly underestimated fracture risk in this patient population and failed to discriminate between patients with and without subclinical vertebral fractures. Additional imaging and/or a lower threshold to initiate pharmacologic therapy may be warranted in this high-risk group.

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Abbreviations

25(OH)D 25-hydroxyvitamin D

BMD	bone mineral density
BMI	body mass index
DEXA	dual-energy X-ray absorptiometry
FRAX	Fracture Risk Assessment Tool
HIV	human immunodeficiency virus
IQR	interquartile range
PTH	parathyroid hormone
VA	Veterans Affairs
WHO	World Health Organization

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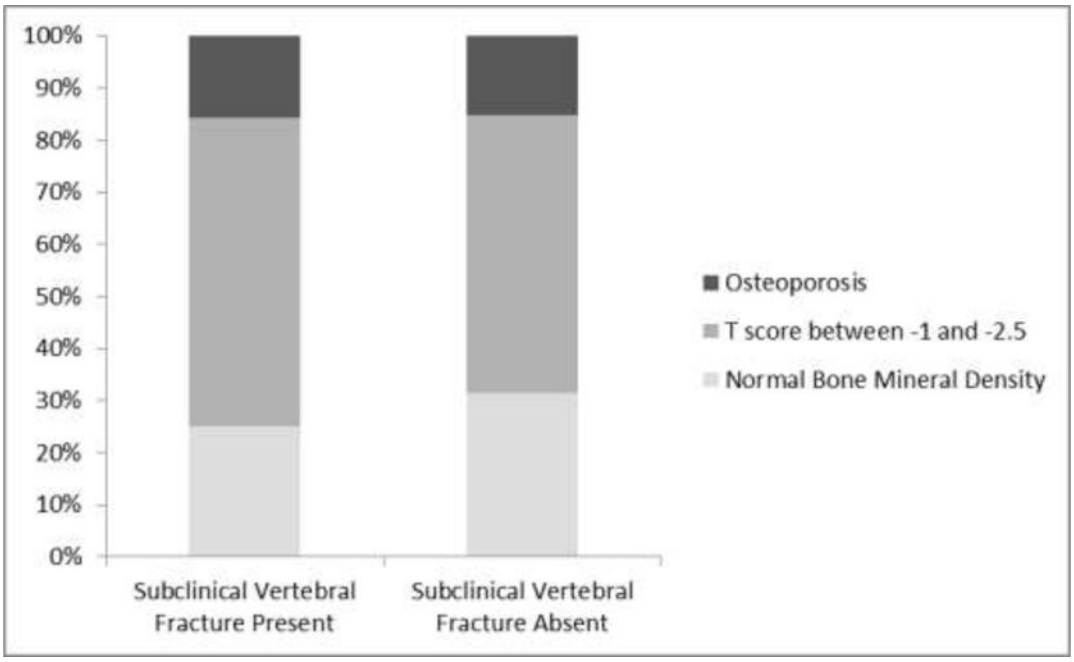

Fig. 1.

Bone mineral density in patients with HIV and vitamin D deficiency with and without subclinical vertebral fractures on lateral chest radiographs. Compared to the group of patients with subclinical vertebral fractures, those without fractures has similar prevalence of osteoporosis and low bone density by WHO criteria on DEXA.

Table 1

Baseline Characteristics of Study Patients and According to the Presence or Absence of Subclinical Vertebral Fracture on Lateral Chest Radiograph

Patient characteristics	Total population (N = 232)	Fracture present (n = 108)	Fracture absent (n = 124)	*P* value
Male (%)	227 (97.8)	108 (100.0)	119 (96.0)	.666
Age (years) (IQR)	49.1 (42.8–56.2)	52.1 (46.3–58.5)	48.2 (41.0–54.1)	.001
Body mass index (kg/m^2) (IQR)	25.9 (23.1–30.1)	26.2 (22.9–30.3)	25.8 (23.2–29.9)	.763
Medical Comorbidities				
Diabetes mellitus (%)	29 (12.5)	9 (8.3)	21 (16.1)	.078
Hypertension (%)	129 (55.6)	67 (62.0)	62 (50.0)	.085
Cardiovascular disease (%)	27 (11.6)	13 (12.0)	14 (11.3)	>.999
Current or prior tobacco abuse (%)	113 (48.7)	51 (47.2)	62 (50.0)	.695
Current or prior alcohol abuse (%)	45 (19.4)	22 (20.4)	23 (18.5)	.742
Chronic hepatitis B co-infection (%)	24 (10.3)	12 (11.1)	12 (9.7)	.610
Chronic hepatitis C co-infection (%)	33 (14.2)	16 (14.8)	17 (13.7)	.852
Antiretroviral Therapy				
PI-containing regimen (%)	78 (33.6)	31 (28.7)	47 (37.9)	.164
EFV-containing regimen (%)	88 (37.9)	44 (40.7)	44 (35.5)	.419
TDF-containing regimen (%)	133 (57.3)	62 (57.4)	71 (57.3)	>.999
Atripla (%)	70 (30.2)	35 (32.4)	35 (28.2)	.567
No therapy (%)	43 (18.5)	16 (14.8)	27 (21.8)	.181
Biological Data				
CD4 cell count (cells/mm^2) (IQR)	494.5 (306.5–673.8)	480.0 (300.3–657.3)	506.0 (327.0–710.0)	.416
Undetectable HIV RNA level (%)	141 (61.0)	69 (63.9)	72 (58.1)	.345
25-hydroxyvitamin D (ng/mL) (IQR)	13.0 (9.0–16.0)	14.0 (10.0–16.0)	13.0 (9.0–16.0)	.425
Calcium (mg/dL) (IQR)	9.3 (9.0–9.5)	9.2 (8.9–9.5)	9.3 (9.0–9.5)	.351
Phosphorous (mg/dL) (IQR)	3.2 (2.9–3.6)	3.1 (2.7–3.6)	3.3 (3.0–3.7)	.006
Parathyroid hormone (pg/mL) (IQR)	56.4 (39.1–80.6)	51.1 (36.4–78.9)	62.1 (41.7–83.1)	.093
Alkaline phosphatase (units/L) (IQR)	78.0 (60.3–94.0)	78.0 (65.0–96.3)	78.0 (60.0–94.0)	.604
eGFR (mL/min/1.73 mm^2) (IQR)	93.6 (80.5–111.6)	92.9 (77.4–110.0)	94.2 (81.7–113.0)	.326
Bone Mineral Density Data				
Osteopenia according to T score (%)	130 (58.0)	64 (59.3)	66 (53.2)	.419
Osteoporosis according to T score (%)	36 (15.5)	17 (15.7)	19 (15.3)	1
Spine T score (IQR)	−1.00 (−1.90 to −0.10)	−0.85 (−1.88 to −0.03)	−1.00 (−1.98 to −0.10)	.341
Femoral neck T score (IQR)	−1.10 (−1.80 to −0.40)	−1.40 (−1.90 to −0.60)	−1.00 (−1.60 to −0.40)	.028
Hip T score (IQR)	−0.90 (−1.50 to −0.40)	−1.05 (−1.63 to −0.45)	−0.80 (−1.40 to −0.30)	.116
Spine Z score (IQR)	−0.30 (−0.80–0.15)	−0.50 (−1.30–0.375)	−0.75 (−1.70–0.20)	.376
Hip Z score (IQR)	−0.30 (−0.80–0.15)	−0.40 (−1.0–0.03)	−0.30 (−0.80–0.20)	.562
Density at spine (g/cm^2) (IQR)	1.071 (0.974–1.180)	1.071 (0.973–1.180)	1.071 (0.976–1.174)	.911

Patient characteristics	Total population (N = 232)	Fracture present (n = 108)	Fracture absent (n = 124)	*P* value
Density at hip (g/cm^2) (IQR)	0.985 (0.891–1.088)	0.965 (0.862–1.080)	1.011 (0.923–1.092)	.023
FRAX score, 10-year risk of a major osteoporotic fracture (IQR)	1.45 (1.00–2.70)	1.60 (1.1–3.08)	1.30 (0.90–2.50)	.025
FRAX score, 10-year risk of a hip fracture (IQR)	0.10 (0.00–0.40)	0.10 (0.00–0.50)	0.10 (0.00–0.30)	.412

Abbreviations: EFV= efavirenz; eGFR= estimated glomerular filtration rate; FRAX = Fracture Risk Assessment Tool; HIV = human immunodeficiency virus; IQR = interquartile range; PI= protease inhibitor; TDF= tenofovir.