Original article

Low bone mineral density and risk of incident fracture in HIV-infected adults

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Background: Prevalence rates of low bone mineral density (BMD) and bone fractures are higher among HIV-infected adults compared with the general United States (US) population, but the relationship between BMD and incident fractures in HIV-infected persons has not been well described.

Methods: Dual energy X-ray absorptiometry (DXA) results of the femoral neck of the hip and clinical data were obtained prospectively during 2004–2012 from participants in two HIV cohort studies. Low BMD was defined by a T-score in the interval >-2.5 to <-1.0 (osteopenia) or ≤-2.5 (osteoporosis). We analysed the association of low BMD with risk of subsequent incident fractures, adjusted for sociodemographics, other risk factors and covariables, using multivariable proportional hazards regression.

Results: Among 1,006 participants analysed (median age 43 years [IQR 36–49], 83% male, 67% non-Hispanic white, median CD4+ T-cell count 461 cells/mm^3 [IQR 311–658]), 36% (*n*=358) had osteopenia and 4% (*n*=37) osteoporosis; 67 had a prior fracture documented. During 4,068 person-years of observation after DXA scanning, 85 incident fractures occurred, predominantly rib/sternum (*n*=18), hand (*n*=14), foot (*n*=13) and wrist (*n*=11). In multivariable analyses, osteoporosis (adjusted hazard ratio [aHR] 4.02, 95% CI 2.02, 8.01) and current/prior tobacco use (aHR 1.59, 95% CI 1.02, 2.50) were associated with incident fracture.

Conclusions: In this large sample of HIV-infected adults in the US, low baseline BMD was significantly associated with elevated risk of incident fracture. There is potential value of DXA screening in this population.

Introduction

Recent research and clinical experience in developed countries have brought an increasing appreciation of risks of bone disease among persons living with HIV infection. Studies in the United States (US) have shown high prevalence of low bone mineral density (BMD) among persons living with HIV [1–3]. Low BMD has been studied in various populations of antiretroviral therapy (ART)-naive and ART-experienced HIV-infected persons [3–6] and has been attributed to metabolic changes associated with HIV infection and use of some antiretrovirals, such as combination ART (cART) containing tenofovir [4,6,7]. Additionally, systemic inflammation/chronic immune activation has been associated with development of osteopenia and osteoporosis among HIV-infected persons [8,9].

Elevated bone fracture rates have been reported in multiple HIV cohorts [4,7,10–12]. We previously reported an increased risk of incident fractures among HIV Outpatient Study (HOPS) participants compared with the general population [12]. In this study, an increased fracture risk was associated with increasing age, lower nadir CD4+ T-cell count (CD4), HCV infection, diabetes and substance use.

There is a paucity of data on the association between low BMD and incident fractures in HIV-infected persons [2]. In the current analysis, we characterize the relationship between low BMD and incident fracture risk in HIV-infected persons using data from two clinical HIV cohort studies in the US funded by the Centers for Disease Control and Prevention (CDC).

Methods

HIV cohorts in the US contributing study data

The HIV Outpatient Study (HOPS) is an ongoing prospective observational cohort study of HIV-infected adults that has accrued data longitudinally since 1993 and has been described previously [13]. Presently, the HOPS gathers data from nine clinics (university-based, public and private) located in six cities: Chicago, IL; Denver, CO; Stony Brook, NY; Philadelphia, PA; Tampa, FL and Washington, DC. This analysis includes data from only one HOPS clinic, Denver Infectious Disease Consultants (DIDC) which offered DXA scans routinely to all HOPS participants. The present analysis is based on the HOPS dataset updated as of 30 September 2012.

The Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study) was a prospective, observational cohort study that monitored the clinical course of HIV-infected individuals treated with cART from seven HIV-specialty clinics in four US cities: St Louis, MO; Providence, RI; Minneapolis, MN and Denver, CO [14]. A total of 700 HIV-infected patients were enrolled from March 2004 through June 2006; the study closed follow-up on 30 June 2012. Of the 700 Sun Study patients, 664 had at least one qualifying DXA scan. The study design, data collection and management methods have been described previously [14]. Participants were generally healthy HIV-infected adult patients receiving routine outpatient care and whose entire antiretroviral experience consisted only of exposure to cART. In addition to medical records abstraction, additional data were collected through periodic (every 6 months) physical examination, and baseline and annual non-invasive imaging including dual-energy X-ray absorptiometry (DXA). Data collection occurred at the clinic site and coincided with participants' schedule of routine care. DXA scans were conducted at a single site within each city.

For both cohorts, patient data, including demographic and social characteristics, symptoms, diagnoses, prescribed medications (including dose and duration) and laboratory values were abstracted from medical charts and entered by trained staff into a database. These data were reviewed for quality and analysed centrally at Cerner Corporation (Kansas City, MO, USA). Study protocols conform to the guidelines of the US Department of Health and Human Services (DHHS) for the protection of human participants in research, and were reviewed and approved annually by the CDC and each site's institutional review board.

Study population

For this analysis, we used data from one HOPS site (Denver Infectious Disease Consultants [HOPS-DIDC]), which routinely offered and performed DXA scans at the discretion of the clinician, and data from all of the SUN Study sites, which performed DXA at baseline and annually at years 1 through 4. We defined our study population as HOPS participants seen at HOPS-DIDC in 2008 or later and SUN Study participants observed in 2004 or later. The study observation period began with the date of first DXA (baseline date), and extended to last contact date or 30 September 2012 for HOPS-DIDC participants and last contact date or 30 June 2012 for SUN participants. The study population was restricted to persons who had at least one DXA scan during the observation period. The first DXA scan during the observation period was used for this analysis.

Measurements and definitions

Routinely collected DXA data in the SUN Study and HOPS-DIDC included values for BMD (g/cm^2), T-score and Z-score for lumbar vertebrae one through four, and left or right femoral neck. For this analysis, T-scores of the left femoral neck were analysed unless only data from the right femoral neck were available, in which case right-side femoral neck data were used. Femoral neck T-scores were used as recommended by the World Health Organization (WHO) [15]. Z-scores were also examined in a sensitivity analysis. We performed an additional sensitivity analysis using just the SUN Study participants and femoral neck T-scores, as well as a third sensitivity analysis using the mean of L1–L4 lumbar T-scores. For all DXAs, the machine types used were either Lunar (General Electric [GE]; Madison, WI, USA) or Hologic (Hologic; Bedford, MA, USA).

We used the WHO definitions for normal BMD (BMD ≥1 standard deviation [SD] of the young adult reference mean, that is, T-score ≥-1), osteopenia (BMD up to 1 SD below the young adult mean but no less than 2.5 SDs below the young adult mean, that is, a T-score in the interval >-2.5 to <-1.0) and osteoporosis (BMD of 2.5 SDs or more below the young adult mean, that is, T-score ≤-2.5) [16]. The reference standard used by WHO, from which the T-score was calculated, was based on data from white females aged 20–29 years in the National Health and Nutrition Examination Study (NHANES) [16]. We analysed Z-scores using the International Society of Clinical Densitometry definitions of low BMD for chronological age or

below the expected range for age (Z-score ≤-2.0) and bone mineral density within the expected age range (Z-score >-2.0) [17].

We investigated the association between low BMD, defined as osteopenia or osteoporosis, and any incident fracture. In this analysis, incident fracture was defined as the first fracture that occurred after the date of the participant's first DXA. Prior fracture was defined as a fracture that occurred before start of the study observation period (defined above) for incident fractures. Participants with a prior fracture were not excluded from the analyses of incident fracture rates, as fractures may occur repeatedly and at different anatomical sites. Major osteoporotic fractures included hip, spine, shoulder and forearm. We calculated person-years of observation from the date of the patient's first DXA through last contact date or 30 June 2012, corresponding to the duration of the SUN Study follow-up, or through 30 September 2012 for HOPS-DIDC patients. For baseline demographic and clinical characteristics, we used the values assessed closest to the baseline date. Insurance status was classified as private, public or none (that is, uninsured). HCV coinfection status was defined based on a diagnosis of HCV infection, evidence of HCV seropositivity or a report quantifying detectable plasma HCV RNA.

Statistical analyses

We used χ^2 tests for categorical variables and Wilcoxon or Kruskal–Wallis tests for continuous variables to compare characteristics of patients with normal BMD to those with osteoporosis or osteopenia. We used Cox proportional hazards regression models to investigate risk factors associated with incident fracture, and used Kaplan–Meier (KM) time-to-event analyses and log-rank tests to compare KM curves across BMD strata. CIs for fracture rates were completed using OpenEpi.com and the Byar approximation for the Poisson distribution. In all models, separate indicator variables for osteopenia and osteoporosis were included in each model for comparison of each of these BMD groups versus the reference category of normal BMD. Use of tenofovir disoproxil fumarate (TDF)-containing cART was treated as a time-dependent variable. During follow-up, persons contributed time to the 'unexposed' category until TDF use began, after which they contributed time to the 'exposed' category. The full multivariable model included all variables analysed in univariate models. We constructed the final multivariable model by retaining variables with $P<0.2$ in the full multivariable model, and then removing variables with the highest P-values first, retaining both indicators for BMD and only those other variables for which the significance level was <0.05. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

We studied 1,006 participants (HOPS-DIDC, n=342; SUN Study, n=664; baseline median age 43 [IQR 36–49] years, 83% male sex, 67% non-Hispanic white, median CD4$^+$ T-cell count 461 cells/mm^3 [IQR 311–658]) with at least one qualifying DXA scan (Table 1). Compared with SUN Study participants, HOPS-DIDC participants at baseline were significantly older, more likely to be male and white non-Hispanic/Latino, have had as their HIV transmission risk factor being a man who had sex with men (MSM), have been privately insured, have had a higher baseline and nadir CD4$^+$ T-cell count, and have taken a TDF-containing cART regimen (Table 1). A lower percentage of HOPS-DIDC participants were a current or prior tobacco smoker; consumed 14 or more alcoholic drinks per week; and had HCV coinfection (all $P\leq0.01$; Table 1).

Since our combined cohort was predominantly male and <50 years of age we analysed Z-scores in addition to T-scores [17]. Z-scores and T-scores were qualitatively the same in this population (data not shown) and so we elected to use T-scores in this analysis. Of the 1,006 participants, 61% had a normal baseline BMD, 36% had osteopenia and 4% had osteoporosis (Table 1). HOPS-DIDC and SUN Study participants did not differ significantly in terms of the distributions of normal bone density. In total, 67 participants (6.7%) had prior fractures. HOPS-DIDC and SUN Study participants also did not differ statistically in the percentage of prior fractures (7.6% versus 6.2%, respectively). Although SUN Study participants had significantly more incident fractures during follow-up than HOPS-DIDC participants: 5.6% for HOPS-DIDC participants versus 9.9% for SUN Study participants (P=0.025), the rates of fracture per 100 person-years were 2.71 and 1.96 for HOPS-DIDC and SUN Study, respectively (P=0.27).

Osteoporosis at baseline, in univariate analyses compared to normal BMD, was significantly ($P<0.05$) associated with older age, lower nadir CD4$^+$ T-cell count, HCV coinfection, lower body mass index and history of fracture. Black non-Hispanic/Latino race/ethnicity had the lowest percentage with osteoporosis, 18.9%, of the race/ethnicity groups compared (Table 2). Osteopenia at baseline, in univariate analysis, was significantly ($P<0.05$) associated with older age, male sex, white non-Hispanic/Latino race/ethnicity compared with all other race/ethnicities, MSM HIV risk compared with all other HIV risk categories, having ≥14 alcoholic drinks per week and lower body mass index. Notably, osteoporosis or osteopenia were not associated with current or prior tobacco smoking, type of cART used (boosted protease inhibitor, non-nucleoside reverse transcriptase inhibitor [NNRTI], other or none) or TDF use. The median ages of the participants in the three BMD classifications (that is, normal, osteopenia and

Table 1. Participant risk characteristics and selected outcome variables, by study data source, SUN Study and HOPS-DIDC (*n*=1,006)

	Overall (*n*=1,006)	SUN Study (*n*=664)	HOPS-DIDC (*n*=342)	*P*-value[a]
Baseline predictor variables				
Median age, years (IQR)[b]	43 (36–49)	41 (35–47)	46 (39–51)	<0.001
Sex,				<0.001
Male, *n* (%)	837 (83.2)	512 (77.1)	325 (95.0)	
Female, *n* (%)	169 (16.8)	152 (22.9)	17 (5.0)	
Race/ethnicity				<0.001
White, non-Hispanic/Latino, *n* (%)	674 (67.0)	393 (59.2)	281 (82.2)	
Black, non-Hispanic/Latino, *n* (%)	212 (21.1)	192 (28.9)	20 (5.8)	
Hispanic/Latino, *n* (%)	90 (8.9)	54 (8.1)	36 (10.5)	
Other/unknown, *n* (%)	30 (3.0)	25 (3.8)	5 (1.5)	
HIV risk				<0.001
IDU, *n* (%)	58 (5.8)	50 (7.5)	8 (2.3)	
MSM, *n* (%)	689 (68.5)	387 (58.3)	302 (88.3)	
Heterosexual, *n* (%)	197 (19.6)	174 (26.2)	23 (6.7)	
Other/unknown, *n* (%)	62 (6.2)	53 (8.0)	9 (2.6)	
First HOPS/SUN visit year				<0.001
<2008, *n* (%)	919 (91.4)	663 (99.8)	256 (74.9)	
2008–2009, *n* (%)	68 (6.8)	1 (0.2)	67 (19.6)	
≥2010, *n* (%)	19 (1.9)	0 (0.0)	19 (5.6)	
Insurance[b]				<0.001
Private, *n* (%)	565 (56.2)	280 (42.2)	285 (83.3)	
Public, *n* (%)	263 (26.1)	222 (33.4)	41 (12.0)	
Other/unknown payer, *n* (%)	178 (17.7)	162 (24.4)	16 (4.7)	
Median $CD4^+$ T-cell count/mm^3[b] (IQR)	461 (311-658)	446 (302-624)	500 (332-699)	0.003
Median nadir $CD4^+$ T-cell count/mm^3 (IQR)	188 (70-299)	178 (70-275)	221 (71-335)	0.01
Viral load <400 copies/ml[b], *n* (%)	758 (75.3)	490 (73.8)	268 (78.4)	0.13
Current/prior tobacco smoker, *n* (%)	545 (54.2)	393 (59.2)	152 (44.4)	<0.001
≥14 alcoholic drinks/week, *n* (%)	34 (3.4)	30 (4.5)	4 (1.2)	0.01
cART type[b]				0.001
Boosted PI, *n* (%)	295 (29.3)	188 (28.3)	107 (31.2)	
NNRTI, *n* (%)	401 (39.9)	286 (43.1)	115 (33.6)	
Other, *n* (%)	271 (26.9)	159 (23.9)	112 (32.7)	
None, *n* (%)	39 (3.9)	31 (4.7)	8 (2.3)	
TDF-containing cART[b], *n* (%)	513 (51.0)	298 (44.9)	215 (62.9)	<0.001
HCV coinfection[c], *n* (%)	123 (12.2)	102 (15.4)	21 (6.1)	<0.001
Median BMI, kg/m^2 (IQR)	24.9 (22.5–27.7)	25.4 (22.6–28.5)	24.3 (22.2–26.7)	<0.001
Bone density				0.93
Normal (femoral neck T-score ≥-1.0), *n* (%)	611 (60.7)	401 (60.4)	210 (61.4)	
Osteopenia (femoral neck T-score >-2.5 to <-1.0), *n* (%)	358 (35.6)	239 (36.0)	119 (34.8)	
Osteoporosis (femoral neck T-score ≤-2.5), *n* (%)	37 (3.7)	24 (3.6)	13 (3.8)	
Femoral neck Z-score >-2.0, *n* (%)	968 (96.2)	634 (95.5)	334 (97.7)	0.12
Femoral neck Z-score ≤-2.0, *n* (%)	38 (3.8)	30 (4.5)	8 (2.3)	
Prior fracture, *n* (%)	67 (6.7)	41 (6.2)	26 (7.6)	0.47
Outcome variables				
Incident fracture, *n* (%)	85 (8.4)	66 (9.9)	19 (5.6)	0.025
Median follow-up, years (IQR)	3.2 (1.7–6.5)	6.0 (3.1–7.0)	2.0 (1.3–2.7)	<0.001
Follow-up, total years	4,068	3,366	702	
Fracture rate per 100 person-years (95% CI)	2.09 (1.67, 2.58)	1.96 (1.52, 2.50)	2.71 (1.63, 4.23)	0.27

[a]Yates corrected χ^2 test for categorical variables, Wilcoxon rank-sum test for continuous variables. [b]At or closest to first DXA. [c]Determined by diagnosis or detection of viral RNA, DNA or genotype. BMI, body mass index; cART, combination antiretroviral therapy; HOPS-DIDC, HIV Outpatient Study-Denver Infectious Disease Consultants; IDU, intravenous drug use; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SUN, Study to Understand the Natural history of HIV infection; TDF, tenofovir disoproxil fumarate.

Table 2. Prevalence of factors associated with low bone mineral density (osteoporosis or osteopenia, determined by DXA femoral neck T-score), SUN Study and HOPS-DIDC (*n*=1,006)

	Osteoporosis (*n*=37)	Osteopenia (*n*=358)	Normal T-score (*n*=611)	Normal T-score row %	Osteoporosis versus Normal T-score *P*-value[a]	Osteopenia versus Normal T-score *P*-value[a]
Baseline predictor variables						
Median age, years (IQR)[b]	48 (42–53)	45 (39–51)	41 (34–47)		<0.001	<0.001
Sex					0.11	<0.001
Male, *n* (%)	34 (91.9)	317 (88.5)	486 (79.5)	58.1		
Female, *n* (%)	3 (8.1)	41 (11.5)	125 (20.5)	74.0		
Race/ethnicity					0.032	0.011
White, non-Hispanic/Latino, *n* (%)	21 (56.7)	263 (73.5)	390 (63.8)	57.9		
Black, non-Hispanic/Latino, *n* (%)	7 (18.9)	60 (16.7)	145 (23.7)	68.4		
Hispanic/Latino, *n* (%)	9 (24.3)	28 (7.8)	53 (8.7)	58.9		
Other/unknown, *n* (%)	0 (0.0)	7 (2.0)	23 (3.8)	76.7		
HIV risk					0.06	0.003
IDU, *n* (%)	4 (10.8)	21 (5.9)	33 (5.4)	56.9		
MSM, *n* (%)	25 (67.6)	261 (72.9)	403 (66.0)	58.5		
Heterosexual, *n* (%)	4 (10.8)	50 (14.0)	143 (23.4)	72.6		
Other/unknown, *n* (%)	4 (10.8)	26 (7.3)	32 (5.2)	51.6		
First HOPS/SUN visit year					0.18	0.015
<2008, *n* (%)	36 (97.3)	336 (93.9)	547 (89.5)	59.5		
2008–2009, *n* (%)	0 (0.0)	20 (5.6)	48 (7.9)	70.6		
≥2010, *n* (%)	1 (2.7)	2 (0.6)	16 (2.6)	84.2		
Insurance[b]					0.08	0.51
Private, *n* (%)	17 (45.9)	198 (55.3)	350 (57.3)	61.9		
Public, *n* (%)	16 (43.2)	89 (24.9)	158 (25.9)	60.1		
Other/unknown payer, *n* (%)	4 (10.8)	71 (19.8)	103 (16.9)	57.9		
Median CD4$^+$ T-cell count/mm^3[b] (IQR)	412 (255–607)	445 (294–653)	466 (323–662)		0.26	0.23
Median nadir CD4$^+$ T-cell count/mm^3 (IQR)	123 (20–251)	180 (58–288)	199 (85–305)		0.006	0.08
Viral load <400 copies/ml[b], *n* (%)	31 (83.8)	275 (76.8)	452 (74.0)	74.0	0.26	0.36
Current/prior tobacco smoker, *n* (%)	20 (54.1)	206 (57.5)	319 (52.2)	58.5	0.96	0.12
≥14 alcoholic drinks/week, *n* (%)	1 (2.7)	19 (5.3)	14 (2.3)	41.2	0.59	0.021
cART type[b]					0.34	0.96
Boosted PI, *n* (%)	10 (27.0)	107 (29.9)	178 (29.1)	60.3		
NNRTI, *n* (%)	17 (45.9)	144 (40.2)	240 (39.3)	59.9		
Other, *n* (%)	10 (27.0)	93 (26.0)	168 (27.5)	62.0		
None, *n* (%)	0 (0.0)	14 (3.9)	25 (4.1)	64.1		
TDF-containing cART[b], *n* (%)	22 (59.5)	181 (50.6)	310 (50.7)	60.4	0.39	1.00
HCV coinfection[c], *n* (%)	11 (29.7)	50 (14.0)	62 (10.2)	50.4	0.001	0.09
Median BMI, kg/m^2 (IQR)	21.6 (20.4–23.7)	23.7 (21.6–26.5)	25.9 (23.3–29.0)		<0.001	<0.001
Prior fracture, *n* (%)	8 (21.6)	24 (6.7)	35 (5.7)	52.2	0.002	0.64
Outcome variables						
Incident fracture, *n* (%)	10 (27.0)	32 (8.9)	43 (7.0)	50.6	<0.001	0.35
Median follow-up, years (IQR)	3.0 (1.7–6.0)	3.7 (2.1–6.6)	3.3 (1.7–6.5)		0.27	0.015
Follow-up, total years	131.2	1,521.2	2,415.4			
Fracture rate, per 100 person-years (95% CI)	7.62 (3.65, 14.0)	2.10 (1.44, 2.97)	1.78 (1.29, 2.40)		<0.001	0.61

[a]Likelihood ratio χ^2 or Fisher exact test for categorical variables, Kruskal–Wallis test for continuous variables, overall three group comparisons. [b]At or closest to first DXA. [c]Determined by diagnosis or detection of viral RNA, DNA or genotype. BMI, body mass index; cART, combination antiretroviral therapy; IDU, intravenous drug use; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

osteoporosis), were 41 years (IQR 34–47), 45 years (IQR 39–51) and 48 years (IQR 42–53), respectively (*P*<0.001).

Of the 85 participants with incident fractures (median age 44 years, IQR 38–51), 43 (50.6%) had normal baseline BMD, 32 (37.6%) had osteopenia and 10 (11.8%) had osteoporosis (Table 3). The most frequent anatomical sites of incident fractures were: rib/sternum (*n*=18), hand (*n*=14), foot (*n*=13) and wrist (*n*=11), with the remainder being another or unknown site (*n*=29). Baseline factors associated with incident fracture in univariate analyses included older age, current or prior tobacco smoking, HCV coinfection, and

Table 3. Baseline characteristics of participants with and without incident fracture, SUN Study and HOPS-DIDC (*n*=1,006)

Patient characteristics	Fracture (*n*=85)	No fracture (*n*=921)	*P*-value[a]
Median age, years (IQR)[b]	44 (38–51)	43 (36–49)	0.046
Sex			0.81
Male, *n* (%)	72 (84.7)	765 (83.1)	
Female, *n* (%)	13 (15.3)	156 (16.9)	
Race/ethnicity			0.94
White, non-Hispanic/Latino, *n* (%)	56 (65.9)	618 (67.1)	
Black, non-Hispanic/Latino, *n* (%)	18 (21.2)	194 (21.1)	
Hispanic/Latino, *n* (%)	9 (10.6)	81 (8.8)	
Other/unknown, *n* (%)	2 (2.4)	28 (3.0)	
HIV risk			0.053
IDU, *n* (%)	8 (9.4)	50 (5.4)	
MSM, *n* (%)	57 (67.1)	632 (68.6)	
Heterosexual, *n* (%)	19 (22.4)	178 (19.3)	
Other/unknown, *n* (%)	1 (1.2)	61 (6.6)	
First HOPS/SUN visit year			0.07
<2008, *n* (%)	82 (96.5)	837 (90.9)	
2008–2009, *n* (%)	3 (3.5)	65 (7.1)	
≥2010, *n* (%)	0 (0.0)	19 (2.1)	
Insurance[b]			0.036
Private, *n* (%)	45 (52.9)	520 (56.5)	
Public, *n* (%)	31 (36.5)	232 (25.2)	
Other/unknown payer, *n* (%)	9 (10.6)	169 (18.3)	
Median $CD4^+$ T-cell count/mm^3[b] (IQR)	418 (312–600)	464 (311–661)	0.31
Median nadir $CD4^+$ T-cell count/mm^3 (IQR)	181 (38–296)	191 (71–299)	0.59
Viral load <400 copies/ml[b], *n* (%)	61 (71.8)	697 (75.7)	0.50
Current/prior tobacco smoker, *n* (%)	56 (65.9)	489 (53.1)	0.032
≥14 alcoholic drinks/week, *n* (%)	3 (3.5)	31 (3.4)	0.76
cART type[b]			0.07
Boosted PI, *n* (%)	24 (28.2)	271 (29.4)	
NNRTI, *n* (%)	44 (51.8)	357 (38.8)	
Other, *n* (%)	15 (17.6)	256 (27.8)	
None, *n* (%)	2 (2.4)	37 (4.0)	
TDF-containing cART[b], *n* (%)	41 (48.2)	472 (51.2)	0.68
Boosted PI-containing cART[b], *n* (%)	25 (29.4)	279 (30.3)	0.96
HCV coinfection[c], *n* (%)	19 (22.4)	104 (11.3)	0.005
Median BMI, kg/m^2 (IQR)	25.0 (22.2–27.9)	24.9 (22.5–27.7)	0.71
Prior fracture, *n* (%)	9 (10.6)	58 (6.3)	0.20
Bone density			0.003
Femoral neck Z-score >-2.0, *n* (%)	76 (89.4)	892 (96.9)	
Femoral neck Z-score ≤-2.0, *n* (%)	9 (10.6)	29 (3.2)	
Bone density			0.002
Normal (femoral neck T-score ≥-1.0), *n* (%)	43 (50.6)	568 (61.7)	
Osteopenia (femoral neck T-score >-2.5 to <-1.0), *n* (%)	32 (37.6)	326 (35.4)	
Osteoporosis (femoral neck T-score ≤-2.5), *n* (%)	10 (11.8)	27 (2.9)	

[a]Yates corrected χ^2 test for class variables, Wilcoxon rank-sum test for continuous variables. [b]At or closest to first DXA. [c]Determined by diagnosis or detection of viral RNA, DNA or genotype. BMI, body mass index; cART, combination antiretroviral therapy; IDU, intravenous drug use; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

the presence of osteopenia or osteoporosis (all $P<0.05$; Table 3).

In unadjusted Cox regression models, baseline factors associated with incident fracture were older age (hazard ratio [HR] 1.34 per 10 years, 95% CI 1.06, 1.69), current or prior tobacco smoking (HR 1.63, 95% CI 1.04, 2.56), HCV coinfection (HR 1.90, 95% CI 1.14, 3.16), prior fracture (HR 2.31, 95% CI 1.23, 4.35) and presence of osteoporosis (HR 4.16, 95% CI 2.09, 8.28; Table 4). In multivariable analyses, current or prior tobacco smoking (adjusted hazard ratio [aHR] 1.59, 95% CI 1.02, 2.50) and osteoporosis (aHR 4.02,

Table 4. Factors associated with incident fracture, SUN Study and HOPS-DIDC (n=1,006 patients; 85 incident fractures)

Independent variables	Univariate HR (95% CI)	*P*-value	Full multivariable aHR (95% CI)	*P*-value	Final multivariable aHR (95% CI)	*P*-value
Age (per 10 years)	1.34 (1.06, 1.69)	0.014	1.23 (0.96, 1.59)	0.10		
Female sex	0.72 (0.40, 1.31)	0.28	0.77 (0.35, 1.69)	0.51		
MSM HIV risk (versus all other risk)	1.09 (0.69, 1.71)	0.72	1.22 (0.66, 2.25)	0.52		
Public insurance (versus private/other)	1.44 (0.92, 2.24)	0.11	1.21 (0.73, 2.02)	0.46		
CD4+ T-cell count (per 100 cells/mm^3)	0.97 (0.89, 1.05)	0.47	0.96 (0.87, 1.06)	0.38		
Nadir CD4+ T-cell count (per 100 cells/mm^3)	0.98 (0.85, 1.13)	0.76	1.07 (0.90, 1.27)	0.45		
Current/prior tobacco smoker	1.63 (1.04, 2.56)	0.032	1.46 (0.92, 2.33)	0.11	1.59 (1.02, 2.50)	0.042
TDF-containing cART[a]	0.97 (0.62, 1.53)	0.90	0.98 (0.61, 1.57)	0.92		
Boosted PI-containing cART[a]	0.99 (0.64, 1.52)	0.96	0.98 (0.62, 1.55)	0.92		
HCV coinfection[b]	1.90 (1.14, 3.16)	0.014	1.47 (0.82, 2.66)	0.20		
BMI, kg/m^2	1.01 (0.97, 1.06)	0.50	1.04 (1.00, 1.09)	0.07		
Prior fracture	2.31 (1.23, 4.35)	0.010	1.20 (0.59, 2.44)	0.61		
Osteopenia (femoral neck T-score >-2.5 to <-1.0; versus normal BMD)	1.19 (0.75, 1.88)	0.46	1.13 (0.70, 1.84)	0.61	1.17 (0.74, 1.84)	0.51
Osteoporosis (femoral neck T-score ≤-2.5; versus normal BMD)	4.16 (2.09, 8.28)	<0.001	3.61 (1.62, 8.02)	0.002	4.02 (2.02, 8.01)	<0.001

[a]Time-dependent variable, including use during follow-up. [b]Determined by diagnosis or detection of viral RNA, DNA or genotype. aHR, adjusted hazard ratio; BMD, bone mineral density; BMI, body mass index; cART, combination antiretroviral therapy; HR, hazard ratio; MSM, men who have sex with men; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

95% CI 2.02, 8.01), were associated with incident fracture, but HCV coinfection and current or nadir CD4+ T-cell count were not (Table 4). In a sensitivity analysis using femoral neck Z-scores, current or prior tobacco smoking (aHR 1.60, 95% CI 1.02, 2.51) and osteoporosis (aHR 3.06, 95% CI 1.53, 6.12) were associated with incident fracture, as was older age (aHR 1.31, 95% CI 1.04, 1.66). In a second sensitivity analysis using just the SUN Study participants and femoral neck T-scores, current or prior tobacco smoking (aHR 1.71, 95% CI 1.01, 2.90) and osteoporosis were associated with incident fracture (aHR 3.61, 95% CI 1.61, 8.13). In a third sensitivity analysis using the mean of L1–L4 lumbar T-scores, only osteoporosis was associated with incident fracture (aHR 3.28, 95% CI 1.84, 5.84).

Baseline femoral neck BMD T-scores were significantly lower among participants with incident fracture than those participants without incident fracture (P<0.001; Figure 1). The small sample size for major osteoporotic fractures (hip, spine, forearm or shoulder; n=22) in our analytic sample precluded analyses limited to this group. In KM time-to-event analysis, a higher proportion of participants with osteoporosis experienced incident fracture earlier in follow-up than those with normal BMD or osteopenia (log-rank P<0.001; Figure 2).

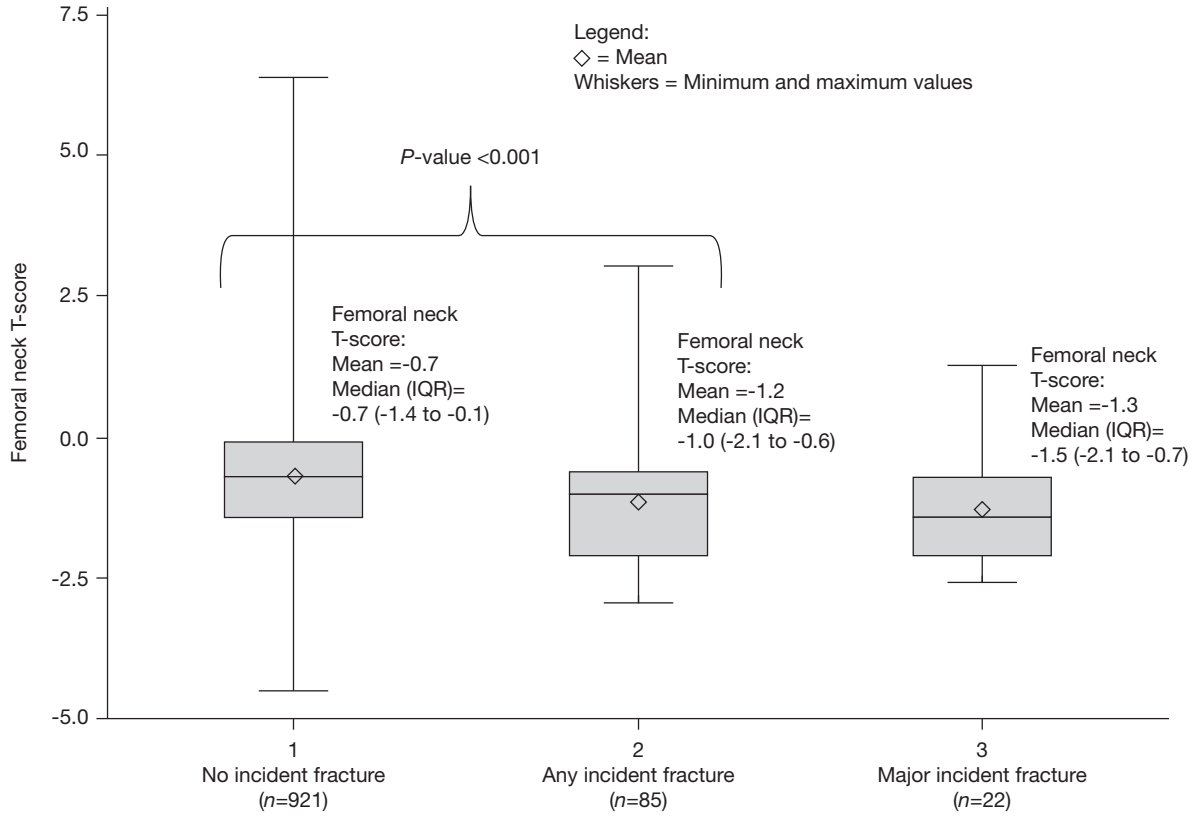
Discussion

In this combined cohort of over 1,000 HIV-infected persons of relatively young age, low BMD indicative of osteopenia and/or osteoporosis was found in close to 40% of individuals. In this cohort, factors associated with osteoporosis or osteopenia included older age, lower nadir CD4+ T-cell count, MSM HIV transmission risk [18,19] and history of fracture. Osteoporosis was, in turn, associated with increased fracture risk; in our study the HIV-infected participants with osteoporosis had fracture rates fourfold higher than those of HIV-infected participants with normal BMD. In addition to low BMD the other significant predictor of incident fracture was current or prior tobacco use.

The association of increasing age with decreasing T-score value and increasing risk of fracture has been documented in the general US population [20]. In a large health-care system study, a higher fracture prevalence in HIV-infected individuals compared with uninfected individuals was reported across gender and multiple age categories [11]. In our study, almost one in ten participants experienced an incident fracture. The median age of participants with low BMD was below the minimum age at which clinical guidelines recommend DXA screening for persons in the general population [21] as well as in the HIV-infected population [22,23]. These results are consistent with previously reported increased fracture rates among HIV-infected persons as compared with the general population [10]. The present analysis demonstrates that low BMD is associated with increased risk of incident fracture in HIV-infected persons, most of whom were ART treated.

Our analyses covered a period through 2012, and preceded most of the latest, diverse recommendations for DXA screening based on age and clinical factors, some of which specifically addressed HIV-infected persons. Systematic DXA screening was not mentioned in the 2015

Figure 1. Femoral neck T-score distribution by any or major incident fracture, SUN Study and HOPS-DIDC (*n*=1,006 participants; 85 incident fractures, 22 major incident fractures)



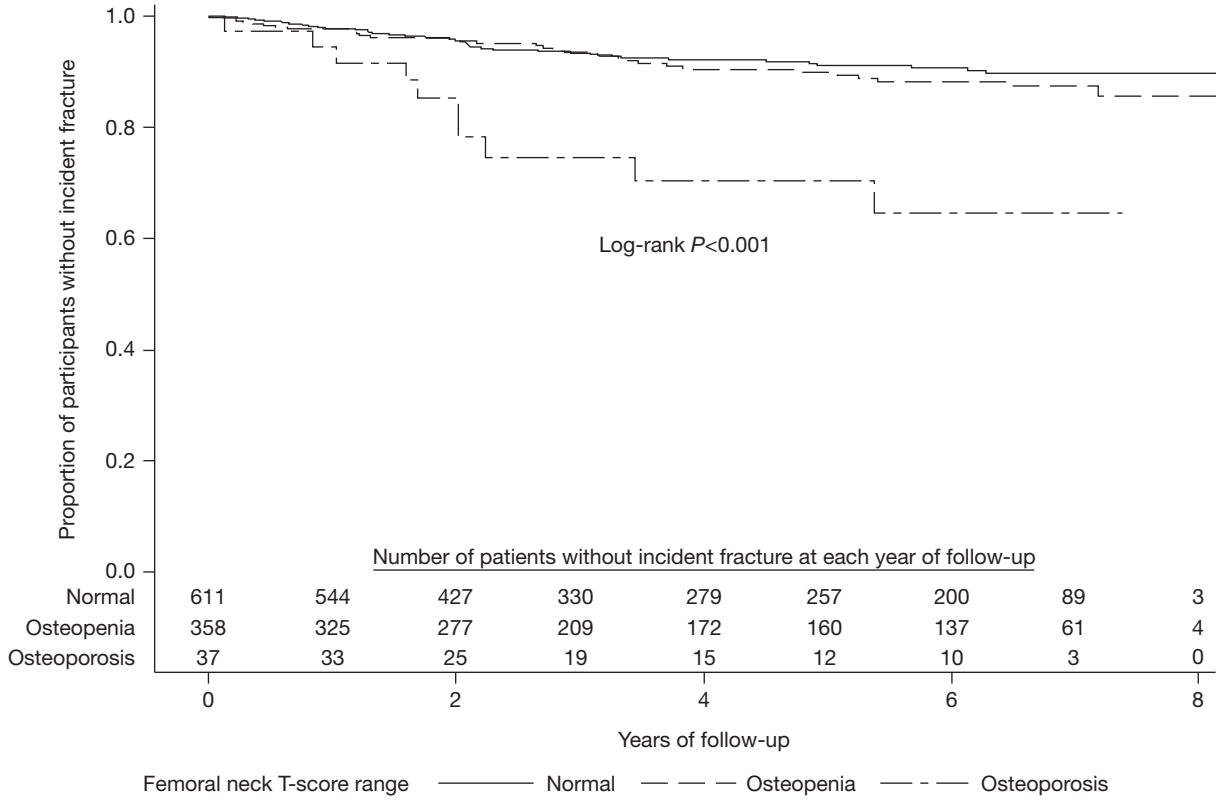
Femoral neck T-scores were compared between those with and without incident fracture, using the Wilcoxon rank-sum test. No statistical tests were performed comparing the subset of patients with major incident fracture to those with no incident fracture.

DHHS Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [24]. The US National Osteoporosis Foundation (NOF) does not specifically address DXA screening for HIV-infected individuals but recommends DXA screening for osteoporosis in all women aged ≥65 years and men aged ≥70 years, adults >50 years of age who have had a fracture, and adults with risk factors including rheumatoid arthritis or glucocorticoid use [21]. The Infectious Diseases Society of America (IDSA) and the European AIDS Clinical Society (EACS) recommend DXA in HIV-infected postmenopausal women and men age ≥50 years [23,25]. EACS recommends screening for other risk groups and prior to ART initiation [22]. Brown *et al.* [26] recommend DXA scans in men aged 40–49 years or premenopausal women aged ≥40 years with a FRAX® score of >10% for 10-year risk of major osteoporotic fracture; all post-menopausal women; all men ≥50 years of age, and adults with major fragility fracture risk factors regardless of age. In an analysis we undertook using the same study population, we found that FRAX® scores of ≥3% were associated with increased risk for incident fracture [27].

Our analysis is subject to several important limitations. Our findings of the overall prevalence of osteoporosis may be conservative, because we based our results on DXA scores at one anatomical site (femoral neck of the hip), and patients may have low BMD at other sites (for example, spine but not femoral neck). Fractures which occurred before entry into the HOPS-DIDC or SUN Study may be missing from medical records, leading to misclassification of fractures observed during follow-up as first incident fractures. Fractures may have also been underreported during observation if they were not reported to the study investigators or recorded in the medical record. HCV status was based on HCV seropositivity or detectable plasma HCV RNA but we were unable to determine if chronic HCV infection was present. Although HOPS-DIDC participants did not have per-protocol annual DXA scans, our results were similar when limited to SUN Study participants. Finally, our study population had relatively few female participants, thus our results principally reflect findings for antiretroviral-treated men.

In summary, our analysis revealed an association between low BMD and risk of incident fractures in

Figure 2. Kaplan–Meier graph of years to incident fracture by baseline T-score range of the femoral neck, SUN Study and HOPS-DIDC (*n*=1,006)



HIV-infected persons. A majority of participants in our study were aged <50 years, the minimum age recommended for bone densitometry screening in most current guidelines [21–23]. Our findings suggest the need to reconsider when to screen for low BMD in HIV-infected patients. Early detection of low BMD provides opportunity for earlier intervention to help prevent fractures in HIV-infected persons.

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Disclosure statement

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