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Prevalence of and Risk Factors for Osteoporosis and Fracture among a Male HIV-Infected Population in the UK

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Summary

Rates of osteoporosis and fracture may be increased in HIV but there are few UK data. Our aim was to examine the prevalence of and risk factors for osteoporosis and fractures among a homogeneous cohort of well-characterized HIV-infected men. In total, 168 men were recruited: median age 45 years, 37 cART naïve, 46 with < 3 years cART exposure and 85 cART exposed longer-term (median >10 years). All participants provided information on bone health and underwent DEXA scanning. Osteopenia was found in 58% of subjects and osteoporosis in 12%. 14% reported fractures since HIV diagnosis. Numbers of fractures since HIV diagnosis were significantly increased amongst those with osteoporosis (OR 3.5, 95% CI 1.2–10.4, $p=0.018$). Duration of infection greater than 13 years was significantly associated with osteoporosis. Duration of cART was associated in univariate and not multivariate analyses. Strategies to prevent osteoporosis and fractures in HIV will require attention to viral and lifestyle factors and not just cART.

Keywords

Osteoporosis; fractures; HIV; male; lifestyle

Introduction

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and predisposition to fracture¹. Osteoporotic fractures increase in frequency with age, occur after low-trauma (typically a fall from standing height or less) and affect sites of predominantly trabecular bone, particularly the vertebrae, distal radius and hip, although fractures at other sites e.g. pelvis are also caused by osteoporosis². Osteoporotic fractures are devastating: for example, rates of mortality are 36% for men and 21% for women in the year after hip fracture and 50% of survivors lose the ability to live independently³. Costing

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an estimated £1.7 billion⁴ in the UK, osteoporosis is a condition for which prevention rather than cure is desirable.

In the era of near-normal life expectancy achieved with combined antiretroviral therapy (cART), osteoporosis is increasingly recognised as an important non-AIDS morbidity⁵. In a meta-analysis of available case-control studies, a 3.7-fold increased risk of osteoporosis and a 6.4-fold increased risk of osteopenia was estimated among HIV cases as compared with non-infected controls and protease inhibitors (PIs) were implicated as an important risk factor⁶. Data on prevalence of low BMD in the UK HIV-infected population are sparse. To date, 2 studies have shown a prevalence rate of low bone mineral density (BMD) of 56-71%^{7,8}. A criticism of published studies is that the classification criteria for low BMD varies, with some investigators applying WHO T-scores to all subjects, including those aged <50 years (amongst whom WHO T-scores are not validated) and thus result in an overestimate of the prevalence of low BMD^{9,10}.

Although there are data to suggest that HIV-infected adults have increased rates of osteoporosis compared with controls yet the question remains as to whether this translates into an increased fracture risk⁵, not least because the majority of fragility fractures occur later in life. There are some data suggesting increased rates of fracture among HIV-infected cohorts^{11–16} but few published studies of fracture in HIV have also included assessment of BMD. In one such study, similar rates of fracture were found among cases as among controls despite a higher prevalence of low BMD among cases¹⁶. In the cohort studies of HIV and fracture without BMD, some found that an excess of traditional osteoporosis risk factors explained the increase in fracture incidence¹³ but others found that HIV-associated factors such as stage of infection, low CD4 counts and co-infection with hepatitis C were associated with increased fracture risk^{14,15}.

Male osteoporosis has been under-researched. In the UK, the lifetime risk of a fragility fracture for a man aged 50 years is estimated at 20.7%, a risk similar to that of myocardial infarction and exceeding that of lung and prostate cancer combined¹⁷. Amongst men, 30-60% of osteoporosis is associated with a secondary cause (glucocorticoids, excess alcohol consumption and hypogonadism)^{17,18}. Hypogonadism is a recognized complication of long-term HIV infection and it may be that appropriate identification and treatment of this condition could prevent osteoporosis^{19–21}.

To expand the UK HIV-infected male low BMD prevalence data and examine the risk factors for low BMD, we carried out a cross-sectional study to investigate the prevalence of osteoporosis and fracture among a stable homogeneous UK cohort using age appropriate T and Z scores. We investigated the associations between BMD, fracture and traditional and HIV-associated risk factors.

Methods

A cross-sectional sample of attendees at a UK Teaching Hospital HIV outpatient clinic was recruited May-August 2008. Subjects were eligible if they were male with prevalent HIV infection. Exclusion criteria: <18 years of age; unable to give written, informed consent;

current participation in any other research and DEXA within the last 12 months. Patients were purposively sampled to represent a proportion who were combination antiretroviral (cART) naïve; a group recently exposed for the first time to cART (< 3years) and those exposed to longer term cART (> 3 years).

Each subject answered a validated questionnaire including information on traditional risk factors for low BMD (smoking, alcohol and illicit drug use, exercise, family history, comorbidities, use of glucocorticoids and other drugs with bone effects) and fractures. Height and weight was measured and venous blood taken for measurement of free testosterone. Low testosterone was defined as a free serum testosterone < 89 nmol/l (Electsys 2010, ROCHE, and Indianapolis, USA). Subjects gave permission for extraction of demographic and HIV parameters, cART regimen and Hepatitis B and C status from the department database. All subjects attended for DEXA scanning of the lumbar spine, total hip and femoral neck (HOLOGIC QDR 4500C, Hologic, Inc., Waltham, Massachusetts, USA). For subjects aged ≥ 50 years, WHO T-scores were generated according to subject height, weight and race¹. For subjects aged < 50 years, age-adjusted Z-scores were calculated. Using the appropriate age-defined cut-off of T<-1.0 or Z <-1.0, we estimated the prevalence of osteopenia amongst participants and using the cut-offs of T<-2.5 or Z <-2.5, we estimated the prevalence of osteoporosis.

The study was approved by the Northern and Yorkshire Research Ethics Committee, UK (Ref: 08/H0903/13). All participants provided written, informed consent.

Data were analysed in SPSS® version 19 for Macintosh. Univariate associations of osteoporosis were determined using Chi squared and Odds ratios for categorical data and linear regression for interval data. Independent risk factors for osteoporosis were assessed using multivariate logistic regression with a backward LR method. Co linearity amongst independent variables was excluded using Person correlation co-efficient. Differences within groups were analysed using paired T tests and ANOVA, differences between groups were analysed using independent T tests and ANOVA.

Results

Subjects

In total, 168 HIV-infected men were recruited amongst whom 37 were cART naïve; 46 had been exposed to cART recently (<3 years) and 85 had received longer-term cART (median 521 weeks). The median age of participants was 45 (IQR 38-51, range 20-85) years, 97% were Caucasian and 96% were men who have sex with men (MSM). Subjects in the naïve group were significantly younger and less likely to have a diagnosis of hypogonadism than subjects treated with cART but there were no other significant differences between groups (Table 1). At study entry 4% of participants had a CD4 count < 200 cells/mm³, 70% had an undetectable viral load (< 40 copies) and 18% had CDC class C disease²⁰. The median duration of cART was 157 weeks (IQR 4-544). 27% were taking protease inhibitor (PI) based regimes and 45% non-nucleoside reverse transcriptase (NNRTI) based regimes. 47% of patients were taking a nucleoside reverse transcriptase inhibitor (NRTI) backbone that included tenofovir (TDF).

Site-specific prevalence of osteopenia and osteoporosis

The prevalence of osteopenia occurring in at least one of the three sites was 58% and the majority of those affected had osteopenia at the lumbar spine with/without involvement of the hip. Nobody in any of the three cART groups was found to have osteoporosis of the total hip or femoral neck but spinal osteoporosis was found in 12% (Table 2). No significant differences in the prevalence of osteopenia or osteoporosis were found between cART groups.

Risk factors for osteoporosis

Traditional—Results of the univariate and multivariable logistic regression (adjusted for age and time since diagnosis) analyses of risk factors for osteoporosis are summarised in Table 3. There was a non-significant trend for BMI < 18 kg/m² (OR 7.63, 95% CI 0.46-127.1) and Hepatitis B co-infection (OR 2.3, 95% CI 0.9-6.0, *p*=0.076) to be associated with osteoporosis in univariate analyses. Neither hypogonadism, nor absolute serum testosterone were significantly associated with osteoporosis. Current alcohol use within recommended limits significantly attenuated the risk of osteoporosis in univariate (OR 0.24 (95% CI 0.08-0.74) *p*=0.008) and multivariate analyses (OR 0.26, 95% CI 0.08-0.91), *p*=0.034). Excess alcohol intake >21 units per week and >35 units/week was not significantly associated with osteoporosis but the risk ratios tended to increase with consumption. Intravenous drug abuse tended to increase the risk of osteoporosis (OR 3.8, 95% CI 0.33-43.8, *p*=0.25). Regular exercise tended to attenuate the risk of osteoporosis (OR 0.57, 95% CI 0.31-1.06, *p*=0.076).

HIV factors—Time since diagnosis of HIV infection/year increase (OR 1.39, 95% CI 1.02-1.91, *p*=0.039) was statistically significantly associated with osteoporosis in univariate analysis. The strength of this association increased with time since diagnosis, first attaining statistical significance after 8 years of disease (*p*=0.05) with the strongest association beyond 13 years of HIV infection (OR 4.03, *p*=0.003). Furthermore, when compared with time since HIV diagnosis <13 years, duration of disease ≥13 years retained statistical significance in the multivariable analyses (OR 3.54, 95% CI 1.2-10.2). Duration of exposure to cART (any class) was not associated with osteoporosis. Of the 45 patients who were current PI users, 71% were osteopenic versus 54% of non-PI users (*p*=0.042) and 20% were osteoporotic versus 9% of non-PI users (*p*=0.05). In patients currently taking NNRTIs, 44% were osteopenic versus 69% of non-NNRTI users (*p*=0.001) and 10% were osteoporotic versus 13% of non-NNRTI users (*p*=0.484). Of patients who were current TDF users 60% were osteopenic versus 57% of non-TDF users (*p*=0.694) and 13% were osteoporotic versus 11% of non-TDF users (*p*=0.608). In the univariate analyses, current PI use tended towards a statistically significant increase in the risk of osteoporosis (OR 2.55, 95% CI 0.98-6.63, *p*=0.05) but this association became non-significant in the multivariate analyses.

Fracture since HIV diagnosis

23 (14%) subjects reported at least one fracture since HIV diagnosis. 1 patient reported a distal forearm fracture and 1 patient reported a fractured neck of femur but there were no reported vertebral fractures. Three of the fracture subjects were cART naïve; three were in

the group exposed short-term (<3 years) and 17 were in the longer term cART group. Median age of patients reporting fracture was 46 years (IQR 41-49), 9 (39%) reported current tobacco use, 7 (30%) reported an alcohol intake > 21 units/week, 8 (35%) reported no regular exercise and 2 (9%) had a history of hypogonadism. 1 (4%) subject reported IV drug use and 1 (4%) had a calculated BMI < 18 kg/m². Amongst fracture subjects, the median CD4 count was 570 cells/mm³ (IQR 415-666) with no counts under 200 cells/mm³; 19 (83%) had an undetectable viral load; 5 (22%) had CDC class C disease; and the median duration of cART was 340 weeks (IQR 84-522). Further analyses were undertaken to explore risk factors for fracture since HIV diagnosis (data not shown). Fracture was significantly associated with a diagnosis of osteoporosis (OR 3.50, 95% CI 1.18-10.43, p=0.018) in multivariate analysis adjusted for age and time since diagnosis. No other parameters (age, smoking, hypogonadism, duration of HIV, CD4 count or viral load) were significantly associated with fracture in univariate analyses. Excess alcohol intake (>35 units/week) was reported by 30% of those with fractures compared to 21% of those without fractures (NSIG). A comparison of cART class among fracture subjects showed that 46% of those with fractures since diagnosis were on PI-based regimes at the time of the study and 36% were on NNRTI-based regimes (NSIG). 77% of patients who reported a fracture were taking an NRTI backbone that included TDF.

Discussion

We report the results of the first UK study evaluating BMD, risk factors for osteoporosis (traditional and HIV-associated) and risk of fracture since HIV diagnosis. We have shown a prevalence of osteoporosis and osteopenia of 12% and 58% respectively and a 3.5-fold increased risk of any fracture with osteoporosis on DEXA. We have shown that both traditional and HIV-factors were associated with the risk of osteoporosis. Modest alcohol consumption, for example, significantly attenuated the risk of osteoporosis and there was a trend for low body mass index and intravenous drug use to be significant risk factors. The HIV factor which was most strongly associated with osteoporosis was duration since diagnosis with a relationship which increased with time and most significant after 13 years. Compared with duration, cART use had less effect on the risk of osteoporosis although current PI use was associated with osteoporosis in univariate analyses but this relationship became non-significant when duration since diagnosis was added to the multivariable model.

A number of studies have evaluated the prevalence of low BMD in HIV-infected cases as compared with controls^{6,7,16} but many of these studies have been criticised due to variable, if any, attention to confounding factors⁹ and their heterogeneity for example, including men with women, assessing different ethnicities using the same DEXA criteria and including subjects who acquired HIV through different transmission routes. The current study benefits from its homogeneity of gender and HIV transmission route and its rigorous attention to those factors recognised important in male secondary osteoporosis. A strength of the current study is that transparent pre-defined criteria have been applied to the assessment of both osteoporosis and osteopenia. We have also applied transparent pre-defined cut-offs to the Z scores as rigid as those applied to the T scores in the WHO definition (i.e. <-1.0=osteopenia and <-2.5=osteoporosis)¹⁰. In doing so, these estimates of the prevalence of low bone mass may be relative under-estimates but at least are not inappropriately over-estimated. It is

interesting that even with our strict case definitions, we found prevalence rates similar to those reported in other HIV-infected cohorts^{6,7}.

Study participants reported a total of 22 fractures since diagnosis of HIV (14% of total). In the general population, fracture rates demonstrate a bimodal distribution with the first peak of fractures occurring under the age of 20 years (usually high-trauma) and a second peak of fractures associated with low-trauma occurring over the age of 60 years among women and 70 years among men²². Among men, distal forearm fractures and hip fractures are rare below 70 years. It is noteworthy that the median age of our study subjects was 45 years (IQR 38-51). Therefore, after fractures sustained in childhood and adolescence, we would expect low rates of fractures amongst a cohort of healthy men. One weakness of the study was that fracture occurrence was obtained from self-reported responses to a questionnaire.

Unfortunately, many of the fractures had not occurred locally so that fractures could not be independently verified radiographically. Despite this, it is important that we have found a strong and statistically significant relationship between osteoporosis on DEXA scan and self-reported fracture since HIV diagnosis especially given that the study questionnaires were completed before the DEXA scan so that systematic recall bias was unlikely. The evidence that HIV causes increased fragility fractures is growing: Triant and colleagues found increased hospitalization for fractures amongst HIV-infected patients as compared with non-infected patients in two large hospitals in one geographic location¹¹. However, in this enormous observational study, BMD could not be assessed. In fact, to date, studies of bone in HIV have usually explored either fractures or bone mineral density but not both^{6,11-15}. Where both have been evaluated, findings have been contradictory. For example, Arnsten and colleagues could only find a statistically significant relationship between BMD and fracture when HIV-infected cases were combined with 'at risk' HIV-uninfected controls¹⁶. In their study of HIV-infected women, Prior et al showed higher rates of self-reported fracture among cases than controls but with similar BMD at hip and lumbar spine¹⁵. Although more research is required, our results suggest a strong association between fractures after diagnosis of HIV and osteoporosis on DEXA, a finding of potentially major importance to this field.

We demonstrated a significant protective effect of alcohol taken within recommended daily limits for a diagnosis of osteoporosis on DEXA. However, a greater proportion of those with fractures reported consuming > 35 units/week (30% vs. 21%, NSIG) compared to those without. Excessive alcohol use is a major risk factor for osteoporosis in most studies²³⁻²⁵ and is one of the three major causes of secondary osteoporosis among men^{17,18}. Previously, two studies in HIV patients have shown a statistically significantly increased risk of fracture among excess alcohol drinkers^{14,26}. There is evidence that at high levels alcohol is directly toxic to osteoblast function, but a considerable proportion of the increased risk of fracture is explained by increased falls risk. To our knowledge, a protective effect of alcohol at low levels on BMD has not been previously shown among HIV-infected patients, but among other populations, especially women, regular intake of small quantities of alcohol has shown benefit for bone health^{23,24}.

The role of cART in osteoporosis causation remains controversial^{9,27}. Although PI use was implicated in the first meta-analysis of case-control studies⁶, subsequent re-analysis

suggested that the adverse effects may be mediated through body mass index²⁹. The results of the current study, with rigorous adjustment for confounding factors, again suggest a lesser role for cART than that found in the early studies. Comparison of those naïve to cART with those taking cART <3 years and long-term cART users suggested no significant differences between groups. PI use was associated with osteoporosis in univariate but not multivariable analyses and duration since infection appeared a more important factor. It must be borne in mind however that this study was cross-sectional and the methods only applied 'current use' of drug classes. Many of the subjects treated with long-term cART will have been exposed to different drugs in different combinations over variable time periods. Clearly what is required to identify true effects of cART are longer-term prospective studies with fracture as the outcome.

It is surprising that bone mineral density was not significantly associated with BMI <18 kg/m² in this study. Low BMI is usually an important determinant of risk of osteoporosis and we would have expected to see a significant relationship. However, this study was powered for the principal outcome measure and as such we calculated that we had only a 44% power to demonstrate a statistically significant relationship of low BMI with BMD.

Hypogonadism is a well-recognized risk factor for osteoporosis among men^{17,18}. Previous work from this centre³⁰ demonstrated that mean lumbar spine BMD was significantly lower in hypogonadal versus eugonadal patients ($p=0.05$). However, the findings of this study did not replicate this. There are several possible explanations for this. Firstly, there is increasing agreement amongst endocrinologists that measurement of serum testosterone as performed in most laboratories is relatively inaccurate³¹. Plasma concentrations of testosterone vary depending upon age, other disease, time of day and other circulating steroid levels. Moreover only 1-3% of testosterone is not bound to plasma proteins so that it is unclear if free testosterone is the most clinically useful measure. Therefore, our lack of association may have arisen as a result of the assay used in this study. Our study found an unexpectedly relatively low proportion of subjects (1%) who were hypogonadal on baseline free testosterone assay. Certainly, a larger number of subjects ($n=10$, 12%) had a pre-existing diagnosis of hypogonadism and were being treated with supplementation and therefore the recent measurement of testosterone may have reflected adequate treatment. Recently however, other studies have failed to show an association between hypogonadism and low BMD in HIV infected populations³². Observing 1325 HIV infected men, Rochira and colleagues found low testosterone in 16%. It was mainly associated with low or normal serum luteinising hormone and the main predictor was visceral adipose tissue (lipodystrophy) and body mass index. It is currently therefore unclear what proportion of HIV infected patients are truly hypogonadal and further work is needed to understand the vital relationships between body mass, body fat distribution and HIV associated low bone mass.

In conclusion, this study has shown a high prevalence of low BMD amongst an HIV-infected male cohort and a 3.5-fold increased risk of self-reported fracture amongst those with osteoporosis on DEXA. The principal risk factor for osteoporosis was time since diagnosis

of HIV infection >13 years and neither cART use *per se* nor any particular cART class were strongly implicated.

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Table 1
Demographic factors, gonadal state and prevalence of low BMD stratified into cART exposure

	cART naïve (n=37)	cART <3 years (n=46)	cART >3 years (n=85)	Total (n=168)	P value
Demographic					
Age/years (median (IQR))	41 (32-46)	45 (36-52)	47 (41-54)	45 (38-51)	0.010
Caucasian (%)	35 (95)	44 (96)	84 (99)	163 (97)	0.366
MSM (%)	35 (95)	43 (93)	84 (99)	162 (96)	0.230
BMI/kg/m ² (mean (95% CI))	25 (24.3-26.5)	25 (23.6-25.9)	25 (24.2-26.1)	25 (24.5-25.7)	0.746
BMI <18 (%)	0 (0)	0 (0)	2 (2)	2 (1)	0.372
Current smoker (%)	16 (44)	20 (43)	40 (47)	76 (45)	0.886
Alcohol >21units/week	7 (19)	16 (35)	29 (34)	52 (31)	0.206
IDU (%)	0 (0)	0 (0)	3 (4)	3 (2)	0.225
History of hypogonadism (%)	0 (0)	0 (0)	10 (12)	10 (6)	0.005*
No regular exercise (%)	5 (14)	20 (43)	34 (40)	59 (35)	0.154
Family history of OPS (%)	9 (24)	9 (20)	13 (15)	31 (18)	0.452
Exposure to drugs related to bone metabolism					
-Testosterone (%)	0 (-)	0 (-)	7 (8)	7 (4)	0.084
-Bisphosphonates (%)	0 (-)	1 (2)	0 (-)	1 (0.3)	0.457
-Oral Glucocorticoids (%)	1 (3)	6 (13)	8 (9)	15 (9)	0.254
-Chemotherapy (%)	1 (3)	4 (9)	5 (6)	10 (6)	0.681
HIV parameters					
Time since diagnosis/months (median (IQR))	24 (9-52)	39 (21-63)	136 (100-222)	74 (34-149)	<0.001*
CDC stage A (%)	36 (97)	30 (65)	33 (39)	99 (59)	0.003*
B (%)	1 (3)	4 (9)	34 (40)	39 (23)	<0.001*
C (%)	0 (0)	12 (26)	18 (21)	30 (18)	0.005*
VL undetectable (<40 copies/mL (%))	1 (3)	36 (78)	81 (95)	118 (70)	<0.001*
CD4 count/cells/mm ³ (median (IQR))	585 (415-742)	481 (298-570)	619 (455-767)	565 (415-735)	<0.001*
CD4 <200 cells/mm ³ (%)	0 (0)	1 (2)	5 (6)	6 (4)	0.007*
cART exposure/weeks (median (IQR))	0 (0)	54 (18-114)	521 (310-599)	157 (4-522)	<0.001*
Current PI use (%)	0 (0)	14 (30)	31 (36)	45 (27)	<0.001*
Current NNRTI use (%)	0 (0)	30 (65)	41 (48)	71 (42)	<0.001*
Current TDF use (%)	0 (0)	28 (61)	47 (55)	75 (45)	<0.001*
Free testosterone/pmol/L (mean (95%CI))	394 (331-457)	303 (261-346)	280 (259-301)	312 (290-333)	<0.001*
Hypogonadism (free testosterone <90pmol/l (%))	1 (3)	0 (0)	1 (1)	2 (1)	0.529

Note: cART= combined anti-retroviral therapy; BMI= body mass index; IDU= intravenous drug user; VL= viral load; PI= protease inhibitor; NNRTI= non-nucleoside reverse transcriptase inhibitor; TDF= tenofovir; BMD= bone mineral density

Table 2
Bone mineral density at lumbar spine, total hip and femoral neck compared by cART exposure and stratified by age-appropriate T scores and Z scores

	cART naïve (n=37)	cART <3 years (n=46)	cART >3 years (n=85)	Total (n=168)	P value
BMD/g/cm² (mean (95% CI))					
Total hip	0.96 (0.92-1.00)	0.96 (0.93-1.00)	0.93 (0.91-0.96)	0.95 (0.93-0.96)	0.241
Femoral neck	0.83 (0.81-0.85)	0.83 (0.81-0.85)	0.80 (0.79-0.81)	0.81 (0.80-0.82)	0.156
Lumbar spine	0.96 (0.92-1.00)	0.97 (0.94-1.01)	0.95 (0.92-0.98)	0.96 (0.94-0.98)	0.580
Prevalence of osteopenia and osteoporosis stratified by age – Age < 50 years (defined by Z-scores)					
	(n=32)	(n=32)	(n=59)	(n=123)	
Total hip osteoporosis	0 (-)	0 (-)	0 (-)	0 (-)	
Total hip osteopenia	6 (19%)	8 (25%)	11 (19%)	25 (20%)	0.747
Femoral neck osteoporosis	0 (-)	0 (-)	0 (-)	0 (-)	
Femoral neck osteopenia	7 (22%)	11 (34%)	13 (22%)	31 (25%)	0.381
Lumbar spine osteoporosis	0 (-)	4 (13%)	7 (12%)	11 (9%)	
Lumbar spine osteopenia	20 (63%)	10 (31%)	26 (44%)	56 (46%)	0.07
Prevalence of osteopenia and osteoporosis stratified by age – Age ≥ 50 years (defined by T-scores)					
	(n=5)	(n=14)	(n=26)	(n=45)	
Total hip osteoporosis	0 (-)	0 (-)	0 (-)	0 (-)	
Total hip osteopenia	2 (40%)	2 (14%)	13 (50%)	17 (38%)	0.184
Femoral neck osteoporosis	0 (-)	0 (-)	0 (-)	0 (-)	
Femoral neck osteopenia	3 (60%)	5 (36%)	17 (65%)	25 (55%)	0.193
Lumbar spine osteoporosis	2 (40%)	1 (7)	6 (23%)	9 (20%)	
Lumbar spine osteopenia	2 (40%)	6 (43%)	8 (31%)	16 (36%)	0.482
Prevalence of osteoporosis and osteopenia at any site stratified by age – Age < 50 years (defined by Z-scores)					
	(n=32)	(n=32)	(n=59)	(n=123)	
Osteoporosis	0 (-)	4 (13%)	7 (12%)	11 (9%)	0.189
Osteopenia	20 (63%)	15 (47%)	33 (56%)	68 (55%)	0.128
Prevalence of osteoporosis and osteopenia at any site stratified by age – Age ≥ 50 years (defined by T-scores)					
	(n=5)	(n=14)	(n=26)	(n=45)	
Osteoporosis	2 (40%)	1 (7%)	6 (23%)	9 (25%)	0.240
Osteopenia	4 (80%)	8 (57%)	18 (69%)	30 (67%)	0.592
Prevalence of osteoporosis or osteopenia at any one site for all subjects (defined by age-appropriate Z scores or T Scores)					
	(n=37)	(n=46)	(n=85)	(n=168)	
Osteoporosis	2 (5%)	5 (11%)	13 (2%)	20 (12%)	0.291
Osteopenia	24 (65%)	23 (50%)	51 (60%)	98 (58%)	0.357

Table 3

Factors associated with osteoporosis at the TH or LS on logistic regression

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Demographics						
Age (per year)	1.03	0.99-1.08	0.158	1.04	0.99-1.09	0.104
Caucasian	0.59	0.06-5.55	0.642			
Clinical						
Time since diagnosis (per year)	1.08	1.02-1.14	0.013	0.92	0.79-1.08	0.322
HIV infection >14 years	4.24	1.64-10.92	0.002	6.12	2.12-17.69	0.001
Previous AIDS dx	1.58	0.57-4.40	0.378			
CD4 count (cells/mm ³)						
<100	1.01	1.00-1.03	0.581			
<200	1.04	1.01-1.08	0.333			
per 100 cells increase	1.02	0.85-1.23	0.812			
Log increase HIV RNA	0.72	0.51-1.02	0.061	0.83	0.59-1.17	0.289
BMI (per 1 kg/m ²)	0.99	0.88-1.11	0.857			
BMI <18	6.81	0.41-113.01	0.123	5.71	0.27-119.30	0.262
Current smoker	0.64	0.25-1.62	0.341			
per 1 pack year increase	1.02	1.00-1.04	0.073	0.99	0.97-1.02	0.638
Current alcohol use	0.28	0.10-0.84	0.017	0.22	0.07-0.77	0.018
Alcohol >21 units	0.79	0.28-2.26	0.665			
Alcohol >35 units	1.36	0.47-3.93	0.569			
per 1 unit/week increase	1.00	0.98-1.02	0.795			
Free testosterone (10pmol/L increase)	0.98	0.94-1.02	0.229			
History of hypogonadism	1.07	1.03-1.12	0.204			
IVDU	14.30	1.24-164.99	0.006	4.08	0.26-63.93	0.316
Hepatitis C co-infection	1.05	1.01-1.09	0.294			
Hepatitis B co-infection	1.82	0.74-4.49	0.189			
Regular exercise per hour/week	1.06	0.75-1.47	0.757			
cART therapy						
cART exposure (per year)	1.11	1.02-1.21	0.012	0.94	0.76-1.16	0.550
	2.90	1.12-7.55	0.024	1.49	0.06-1.95	0.225
cART >4 years						
Current PI use	2.12	0.84-5.36	0.109	1.10	0.31-3.91	0.889
Current NNRTI use	0.94	0.38-2.33	0.890			
Current TDF use	1.58	0.64-3.89	0.316			

Note: TH= total hip; LS= lumbar spine; BMI= body mass index; IVDU= intravenous drug user; cART= combined anti-retroviral therapy; PI= protease inhibitor; NNRTI= non-nucleoside reverse transcriptase inhibitor; TDF= tenofovir