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ORIGINAL RESEARCH

Long-Term Stable Bone Mineral Density in HIV-Infected Men Without Risk Factors for Osteoporosis Treated with Antiretroviral Therapy

Mark J. Bolland[1,4] · Anne M. Horne[1] · Simon E. Briggs[2] · Mark G. Thomas[2,3] · Ian R. Reid[1] · Greg D. Gamble[1] · Andrew Grey[1]

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Abstract

Introduction Most prospective studies of bone mineral density (BMD) in HIV-infected cohorts taking antiretroviral therapy (ART) have been of short duration, typically < 3 years. Such studies have reported short-term stable or increasing BMD. We assessed whether this BMD stability persists for > 10 years in middle-aged and older men established on ART.

Methods A 12-year, prospective, longitudinal study in 44 HIV-infected men treated with ART who had measurements of BMD at the lumbar spine, proximal femur and total body at baseline, 2, 6 and 12 years.

Results At baseline, the mean age of participants was 49 years, the mean duration of HIV infection was 8 years, and the mean duration of ART was 50 months. After 12 years, BMD increased by 6.9% (95% CI 3.4 to 10.3) at the lumbar spine, and remained stable (range of BMD change: − 0.6% to 0.0%) at the total hip, femoral neck and total body. Only two individuals had a decrease of > 10% in BMD at any site during follow-up and both decreases in BMD were explained by co-morbid illnesses.

Conclusions BMD remained stable over 12 years in middle-aged and older HIV-infected men treated with ART. Monitoring BMD in men established on ART who do not have risk factors for BMD loss is not necessary.

Keywords HIV · Bone density · Osteopenia · Osteoporosis · Body weight

Introduction

International experts recommend measuring bone mineral density (BMD) in all older men with HIV, with regular follow-up measurements every 18 months to 5 years [1–3]. Numerous longitudinal studies of BMD in HIV-infected individuals have been published but most have been of short duration (< 3 years) [4]. Studies of individuals initiating antiretroviral therapy (ART) show short-term accelerated BMD loss averaging 2–3% over 1–2 years followed by a longer period of BMD stability or increase, whereas cohorts already established on ART at study inception have stable or increasing BMD over similar time periods [5]. Although the short-term effects of HIV and ART on BMD are now well described, there are few reports available of medium to long-term effects.

Investigating the long-term effects on BMD of HIV infection is important because of the large number of people living with the disease, and because of the health service resource implications of recommendations to regularly measure BMD in this population. Previously, we reported that BMD was stable in HIV-infected men treated with ART followed for up to 6 years, and that changes in BMD over time were similar to those in uninfected healthy controls [6]. To determine whether this BMD stability persists over > 10 years, we have extended follow-up of this cohort out to 12 years.

✉ Mark J. Bolland
m.bolland@auckland.ac.nz

1 Department of Medicine, University of Auckland, Auckland, New Zealand

2 Department of Infectious Diseases, Auckland City Hospital, Auckland, New Zealand

3 Department of Molecular Medicine and Pathology, University of Auckland, Auckland, New Zealand

4 Bone and Joint Research Group, Department of Medicine, University of Auckland, Private Bag 92 019, Auckland 1142, New Zealand

Methods

Subjects

The methods of the study have been described in detail previously [6–8]. Briefly, we invited all HIV-infected men from infectious disease clinics at our institution to participate in a study of bisphosphonate therapy. The inclusion criterion was treatment with combination ART for at least 3 months and exclusion criteria were significant renal, hepatic or thyroid dysfunction, concurrent major systemic illness including malignancy, metabolic bone disease, or current use of a bisphosphonate or systemic glucocorticoids. Figure 1 shows the flow of participants. 71 eligible men had a screening measurement of BMD; 43 men with BMD T score < -0.5 entered the intervention study, and were followed for up to 12 years; 28 men with BMD T score > -0.5 were invited to have a repeat BMD measurement after 2, 6 and 12 years. Here we report the results of the 44 participants who were either in the placebo group of the intervention study ($n = 19$) or the longitudinal study ($n = 25$), and had at least one follow-up BMD measurement. Participants in the intervention study received calcium 400 mg daily and vitamin D 50,000 IU monthly for 2 years according to the study protocol, but otherwise no participant received bone-active medication during follow-up.

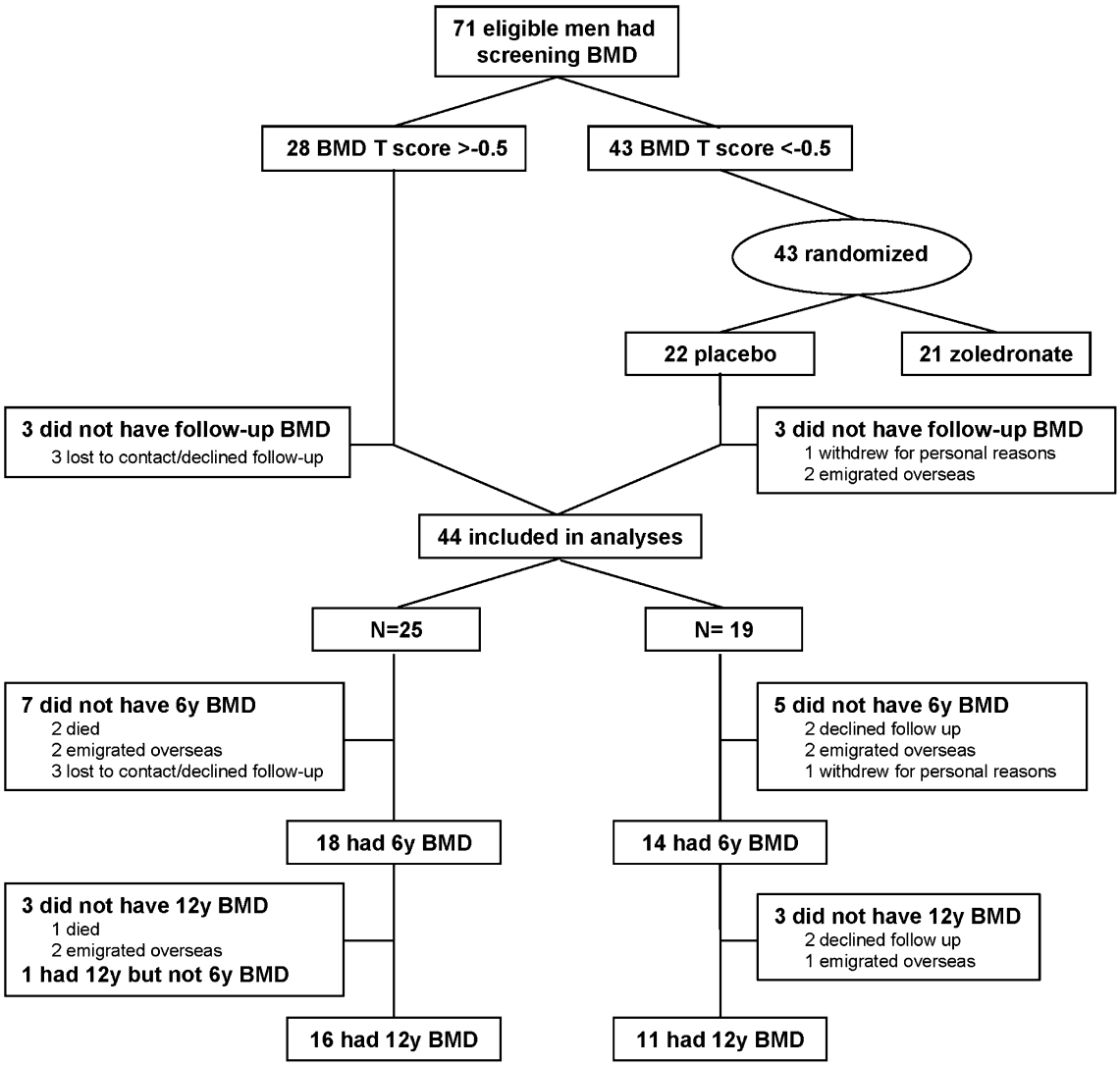

Fig. 1 Flow of participants

Measurements

BMD of the lumbar spine, proximal femur and total body were measured at baseline and 2 years using a Lunar Expert dual-energy X-ray absorptiometer (DXA) (GE Lunar, Madison, WI) and at 6 and 12 years using a GE Prodigy DXA (GE Lunar, Madison WI). Data from each scan from the Expert DXA were converted to predicted Prodigy DXA results, using equations derived from BMD measurements on both machines on the same day for 64 people, as previously described [9].

Statistics

Continuous variables were compared between participants with complete and incomplete follow-up and between those with BMD *T* score < -0.5 and ≥ -0.5 at baseline using Student's *t* test, and categorical variables using Fisher's exact test. BMD data were analysed using raw data, but for ease of interpretation, results are presented as percentage change from baseline adjusted for baseline between-group differences, where appropriate. A mixed models approach to repeated measures was used to examine the time course of changes in BMD and main effects reported for the comparison of changes in BMD by baseline BMD status. $P < 0.05$ was considered statistically significant and all tests were two-tailed. All statistical analyses were obtained using the SAS software package (SAS Institute, Cary, NC version 9.4).

Results

Figure 1 shows the flow of study participants, and relevant clinical and HIV-related characteristics are shown in Table 1. Seven men emigrated and 3 died during follow-up, and 27 of the remaining 34 men (79%) had a follow-up BMD measurement at 12 years (Fig. 1). About 80% of participants had an undetectable viral load at each time point. Three participants had CD4 counts < 200 cells/μL at baseline (two with undetectable viral load), but none had a CD4 count < 200 cells/μL at 6 or 12 years. Table 1 shows that participants who had a measurement of BMD at 12 years tended to be older than those who did not, but otherwise clinical and HIV-related characteristics of these groups were similar. The mean duration of follow-up was 12.4 years in the 27 men completing the study, and 9.0 years in the entire cohort.

At baseline, 43 participants were prescribed a three-drug ART regimen and one a four-drug regimen. At their final follow-up visit, 34 participants (75%) were prescribed a three-drug regimen and 10 (25%) more than three drugs. These proportions were similar in the 27 participants who completed the study. At the 12-year visit, 13 different regimens were prescribed, with the most common being emtricitabine, tenofovir disoproxil fumarate and efavirenz ($n = 10$). Tenofovir disoproxil fumarate use increased throughout the study (Table 1), and by the final visit 67% were taking a regimen that included tenofovir disoproxil fumarate.

Figure 2 and Table 2 show the percentage change in BMD at the lumbar spine, total hip, femoral neck and total body after 12 years in the HIV-infected men and controls. BMD increased by 6.9% (95% CI 3.4 to 10.3) at the lumbar spine, but remained stable (range of BMD change: −0.6% to 0.0%) at the other sites. When we restricted the analyses to the 27 men who had a BMD scan at 12 years, the results were very similar to the results for the entire cohort (data not shown). Two participants had a decrease of > 10% since baseline at the lumbar spine or total hip during follow-up. One had medication-induced vitamin D deficiency causing osteomalacia recognised 23 months after study entry, with an increase in BMD following treatment with cholecalciferol [10]. The second had a 20% decrease in total hip BMD between 2 and 6 years associated with end-stage chronic obstructive pulmonary disease, substantial weight loss (7.7 kg) and at least 6 courses of short-term high-dose prednisone per year. BMD remained within the normal range for age, but he died before subsequent scans were obtained.

Figure 3 shows that there was no difference in the change in BMD over time at any site between HIV-infected men with BMD *T* score < -0.5 at baseline who entered the intervention study, and those with BMD *T* score > -0.5 who did not (all $P > 0.14$).

Discussion

In this prospective 12-year study, HIV-infected men treated with ART had stable BMD, with no evidence of accelerated BMD loss. This BMD stability occurred although the cohort had established risk factors for osteoporosis at baseline, including lower body weight and higher smoking rates than healthy controls [6], and other possible risk factors for accelerated BMD loss such as tenofovir disoproxil fumarate exposure.

Previously, we reported that there was no evidence of greater loss of BMD over 6 years in this cohort compared to healthy controls, and, in fact, there were increases in lumbar spine BMD of about 5% relative to controls [6]. The current results extend these findings to 12 years. Although the non-HIV-infected control group was not assessed at the 12-year point and their data are not included in this paper, Figs. 2 and 3 show that BMD remained stable between 6 and 12 years. Body weight increased by about 5% on average over the 12 years. Changes in body weight affect BMD, and a body weight increase of this amount might be expected to increase total hip BMD by about 1–1.5% over this time frame [11]. The study did not have sufficient power to detect

Table 1 Selected characteristics at baseline and during follow-up

Characteristic	Entire cohort $n=44$	With BMD at 12 years $n=27$	No BMD at 12 years $n=17$	*P*
Age (years)	48.7 (9.1)	50.9 (9.2)	45.2 (8.1)	0.05
Weight (kg)				
Baseline ($n=44$)	76.4 (11.4)	77.9 (10.8)	74.0 (12.2)	0.27
12 years ($n=27$)	80.7 (13.6)	80.7 (13.6)	N/A	
BMI (kg/m^2)				
Baseline ($n=44$)	24.7 (3.5)	25.5 (3.5)	23.5 (3.3)	0.07
12 years ($n=27$)	26.4 (3.4)	26.4 (3.4)	N/A	
Smoke baseline (%)	37	33	47	0.53
L1-4 BMD (g/cm^2)	1.23 (0.17)	1.27 (0.19)	1.21 (0.19)	0.31
T score L1-4	0.2 (1.6)	0.4 (1.6)	−0.1 (1.6)	
Z score L1-4	0.4 (1.6)	0.6 (1.6)	0.0 (1.6)	
Total hip BMD (g/cm^2)	1.05 (0.14)	1.09 (0.14)	1.02 (0.15)	0.10
T score total hip	−0.2 (1.1)	0.0 (1.1)	−0.6 (1.2)	
Z score total hip	0.2 (1.1)	0.4 (1.1)	−0.2 (1.2)	
Femoral neck BMD (g/cm^2)	1.01 (0.15)	1.03 (0.12)	0.97 (0.18)	0.19
T score femoral neck	−0.5 (1.1)	−0.3 (1.0)	−0.7 (1.4)	
Z score femoral neck	0.1 (1.1)	0.3 (0.9)	−0.3 (1.3)	
Total body BMD (g/cm^2)	1.22 (0.10)	1.22 (0.08)	1.18 (0.11)	0.18
25-hydroxyvitamin D (nmol/L)	66.9 (27.5)	68.0 (24.8)	65.2 (32.1)	0.75
Hepatitis C co-infection (*n*)	1	1	0	
HIV-related characteristic				
Time since diagnosis (years)	7.8 (4.8)	8.0 (4.6)	7.6 (5.3)	0.84
AIDS defining illness[a] (%)	27	26	29	>0.9
Lipodystrophy[b](%)	41	41	41	>0.9
Mode of infection (%)				
Men who had sex with men	81	85	75	
Heterosexual	17	15	19	
Blood transfusion	2	0	6	
Injected drug use	0	0	0	
CD4 count[c] (cells/μL)				
Baseline ($n=44$)	521 (231)	554 (235)	469 (220)	0.23
2 years ($n=41$)	488 (245)	542 (249)	402 (221)	0.07
6 years ($n=33$)	655 (246)	658 (262)	647 (193)	0.92
12 years ($n=27$)	642 (223)	642 (223)	N/A	
Undetectable viral load[d] (%)				
Baseline ($n=44$)	80	85	71	0.27
2 years ($n=41$)	83	96	62	0.01
6 years ($n=32$)	82	77	100	0.30
12 years ($n=27$)	78	78	N/A	
Duration of ART[e] (months)	50 (24)	52 (23)	47 (26)	0.47
Tenofovir disoproxil fumarate use (%)				
Baseline ($n=44$)	0	0	0	N/A
6 years ($n=32$)	27	29	24	0.74
12 years ($n=27$)	67	67	N/A	

Data are mean (standard deviation) or percentage

N/A not applicable

[a]AIDS was defined using the Centers for Disease Control Indicator Conditions in Case Definition of AIDS (Adults)—1997

[b]Lipodystrophy was defined as evidence of peripheral fat loss or central fat accumulation on clinical examination

[c]Reference range: 500–1650 cells/μL

[d]HIV viral load was defined as undetectable when <50 copies/mL at baseline and 2 years, and when <20 copies/mL at the 6- and 12-year assessments

[e]ART was defined as an HIV treatment regimen containing at least three antiretroviral agents

Table 2 Bone mineral density data at 12 years

Site	*T* score	Percentage change from baseline
Lumbar spine (L1-4)	1.0 (2.0)	6.9 (8.7)
Total hip	−0.2 (1.0)	−0.6 (5.1)
Femoral neck	−0.5 (1.1)	−0.3 (6.6)
Total body	0.2 (1.1)	0.0 (3.5)

Data are mean (SD)

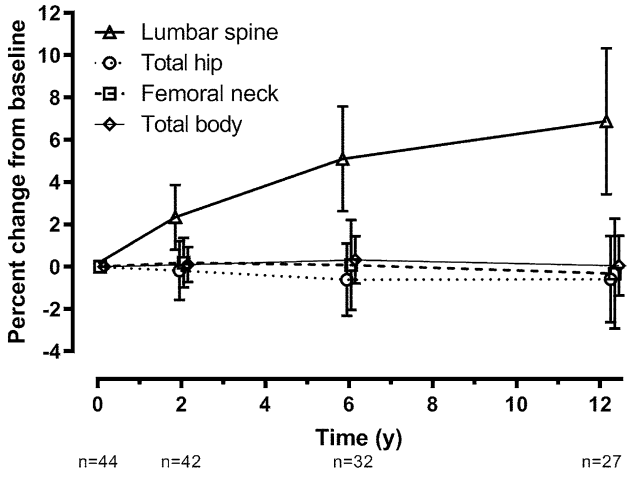

Fig. 2 Change in bone mineral density (BMD) from baseline at the lumbar spine, total hip, femoral neck and total body. BMD is mean (95% CI) percent of initial values

increases of this size, but an effect of this magnitude lies within the 95% confidence intervals of the observed effect size for the entire cohort.

There are few other published studies that have examined the long-term changes in BMD in HIV-infected individuals. Cassetti reported an open-label extension study of 86 individuals randomised to tenofovir disoproxil fumarate, lamivudine and efavirenz who completed a 144-week double-blind randomised controlled trial of initiation of two different ART regimens [12]. The overall duration of follow-up was 5.5 years. BMD decreased by about 3% over the first year at both the spine and hip, but subsequently it remained stable over the next 4.5 years. Madeddu reported follow-up of 51 ART-treated patients who did not receive bone-active medication and were followed for 4–5 years [13]. BMD at the spine and hip remained stable over time. Giacomet reported BMD increases in 26 HIV-infected youths treated with ART over 10 years that were similar to increases seen in uninfected controls [14]. Grant reported BMD data on 97 ART-treated patients followed for a median of 7.6 years compared to uninfected controls [15]. Between 48 weeks and 7.6 years, there was little change in BMD at the spine, but hip BMD decreased by about 1%. The control group BMD in that study was only measured at baseline and at 6.9 years, but extrapolating these data to the time points in the HIV group suggests little difference in changes in BMD between the HIV group and controls after 48 weeks.

Data from HIV clinics have also been reported, which contrast to the results reporting BMD stability. Negredo reported that 6% of individuals in an HIV clinic transitioned from normal BMD or osteopenia to osteoporosis over a median follow-up of 5 years [16]. Erlandson reported results from a HIV clinic in which 2598 individuals had at least 2 BMD scans over a median duration of 4.7 years [17]. Although the exact magnitude of BMD change was not reported, the figures in the paper suggest BMD loss of 5–10% in men and women at the lumbar spine and femoral neck over 5 years. The reasons for the difference in these results with those of controlled prospective studies are not certain. We are not aware of other studies of cohorts with HIV with prolonged follow-up for BMD.

The results from the current study are consistent with a previous systematic review of longitudinal studies of BMD in HIV-infected patients that reported stable BMD compared to baseline at 1, 2 and > 2.5 years in patients established on ART, and no clinically relevant differences in changes in BMD over time compared to uninfected controls [5]. In contrast, meta-analysis of studies of ART initiation shows short-term loss of BMD averaging 2–3% at one year, with stable or increasing BMD thereafter [5]. A number of prospective longitudinal studies have been reported since this systematic review was published, but the studies tend to be short duration < 3 years, and have had similar results to those included in the review [4].

Our study has strengths and limitations. Although small, it is a prospective 12-year study with substantially longer follow-up than other published studies to date. All participants were middle-aged men taking ART who generally had well-controlled HIV infection throughout follow-up. The results may not apply to other age groups, to women, or where HIV infection is poorly controlled or the baseline characteristics differ from those of this cohort. Lastly, participants lost to follow-up may have had different results from those who continued in follow-up, although the analyses of the entire cohort and those who completed 12 years of follow-up were similar.

In summary, these results suggest that accelerated bone loss is not an issue for the majority of middle-aged men with HIV infection taking ART. Taken together with the literature summarised above, our results have implications for clinical care of men with well-controlled HIV infection, and for use of health care resources. They demonstrate that monitoring of BMD in such men is unnecessary, and that additional testing need only be undertaken

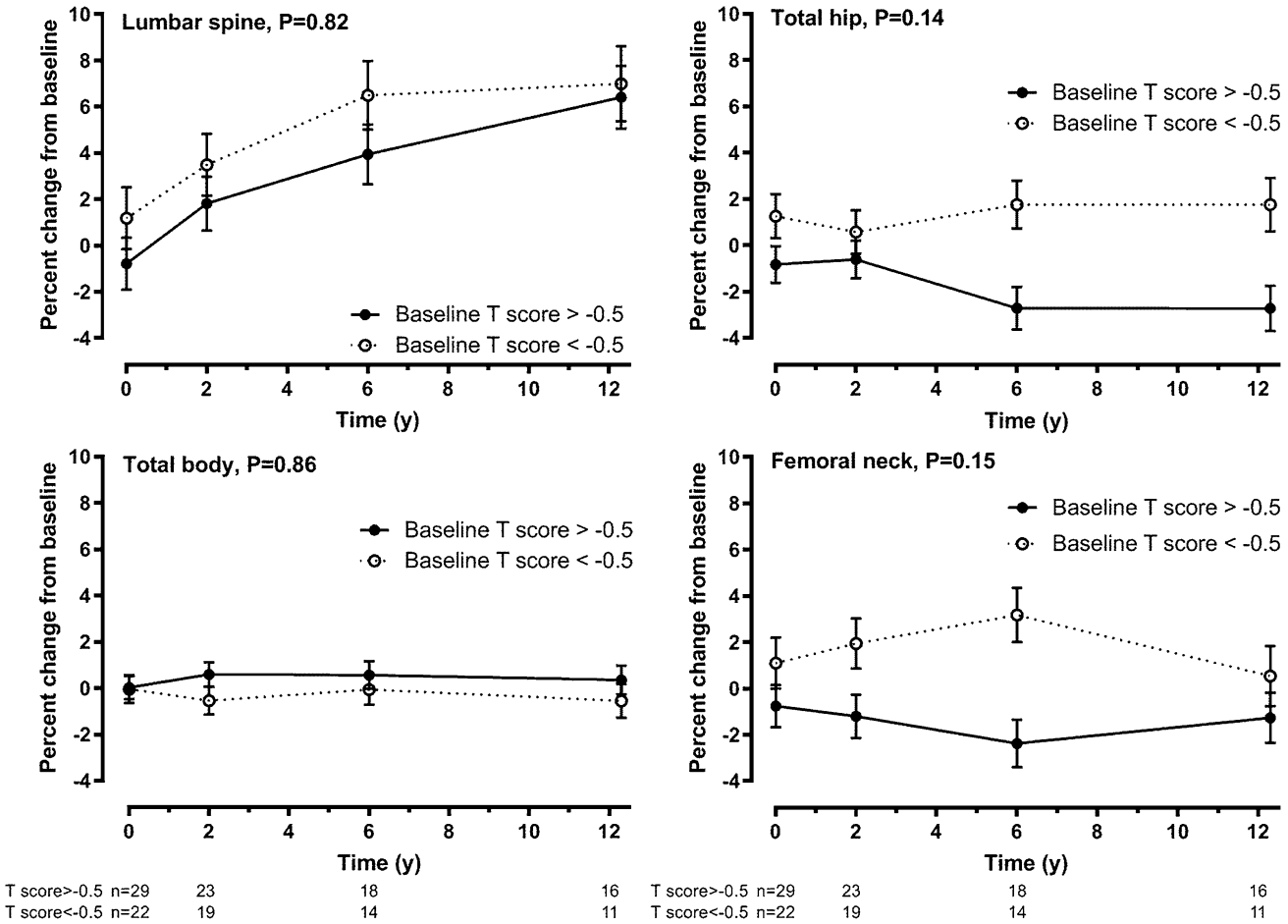

Fig. 3 Change in bone mineral density (BMD) at the lumbar spine, total hip, femoral neck and total body by baseline BMD. Data are mean (SE) percentage change from baseline adjusted for baseline differences in BMD between groups. *P* values are for the time*treatment interaction

in the event of coincident development of established risk factors for bone loss, such as weight loss or prolonged high-dose glucocorticoid use. Thus, measurement of BMD in HIV-infected men can generally follow recommendations for the general population, with particular focus on modifiable risk factors for low BMD or fractures, such as alcohol use, cigarette smoking and low body weight [4]. Younger adults adequately treated with stable, effective ART without risk factors for fracture do not need specific investigations, monitoring or advice. If bone densitometry is readily available, measuring BMD in men > 65–70 years is often recommended, and it could be considered at an earlier age in men with significant risk factors for fracture [4]. Another approach is to estimate fracture risk using an online calculators (e.g. www.shef.ac.uk/FRAX, www.qfracture.org, www.garvan.org.au/bone-fracture-risk/) substituting body mass index as a surrogate for BMD. Individuals with low risk can be reassured; those with high risk offered treatment; and those with intermediate risk referred for BMD measurement [4]. Ensuring adequate nutritional status and effective antiretroviral treatment remain the most important factors in maintaining skeletal health in HIV-infected populations.

Author Contributions MB, AH, SB, MT, IR, GG and AG designed the study. MB drafted the manuscript and is the guarantor. MB and AH ran the study. MB and GG did the statistical analyses. All authors revised the paper critically for intellectual content and approved the final version. All authors agree to be accountable for the work and to ensure that any questions relating to the accuracy and integrity of the paper are investigated and properly resolved.

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Compliance with Ethical Standards

Conflict of interest Mark Bolland, Anne Horne, Simon Briggs, Mark Thomas, Ian Reid, Greg Gamble and Andrew Grey declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent The study received ethical approval from the Northern X Regional ethics committee, and all participants provided written, informed consent.

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