Alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in HIV

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Background: Decreased bone mineral density (BMD) is prevalent in HIV-infected patients. Bisphosphonates are currently the mainstay of treatment for postmenopausal and male osteoporosis in HIV-uninfected individuals; however, their efficacy and safety in HIV-infected patients remains unclear.

Methods: In this prospective, randomized, placebo-controlled multicenter trial, we studied the effectiveness of calcium and vitamin D supplementation with or without alendronate in improving BMD in HIV-infected subjects receiving stable antiretroviral therapy. Subjects with secondary causes of osteoporosis were excluded. The study was powered to detect differences of 3.5% between arms and to detect a moderate sex effect in percentage change in lumbar spine BMD. All dual-energy X-ray absorptiometry scans were analysed centrally, blinded by arm.

Results: The 82 subjects enrolled were 71% men, 77% white, with a baseline median age of 48 years, CD4 cell count of 469 cells/μl, and lumbar spine *t*-score of less than 2.1; 91% had HIV-RNA levels less than 400 copies/ml, and 99% were taking antiretroviral drugs. Compared with calcium/vitamin D alone, alendronate plus calcium/vitamin D resulted in significant improvements in BMD at the lumbar spine, total hip, and trochanter, but not at the femoral neck, compared with baseline. There were trends towards significant increases in BMD values in the calcium/vitamin D group at the lumbar spine, total hip, and femoral neck. There were no apparent sex differences in the responses to therapy. Alendronate was well tolerated, without significant adverse events.

Conclusion: Once-weekly alendronate is safe and effective in the treatment of decreased BMD in HIV-infected patients.

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Introduction

Decreased bone mineral density (BMD) is common in patients with HIV infection. In a recent meta-analysis of 12 cross-sectional studies, 67% of patients with HIV infection had osteopenia or osteoporosis [1]. This suggests that low BMD is one of the most frequent metabolic complications associated with HIV infection and its treatment. Although the long-term implications of decreased BMD in this population are still unclear, several case reports have described fragility fractures in otherwise healthy, young patients with HIV infection [2–5]. The pathogenesis of reduced BMD in patients with HIV is probably multifactorial [6–8]. The duration and severity of HIV infection, antiretroviral therapy (ART), and secondary factors such as menstrual status, smoking and hypogonadism may impact the bone health of HIV-infected individuals. Calcium, vitamin D and several antiresoptive agents including alendronate have been shown to improve bone density and reduce fractures in HIV-uninfected osteoporotic populations [9–13]. Limited information is available on the safety and efficacy of these agents in HIV-infected individuals [14–16].

Alendronate, a potent bisphosphonate that inhibits osteoclast-mediated bone resorption, is approved for the treatment of postmenopausal and male osteoporosis in HIV-uninfected patients [9–11]. Its convenient once-weekly dosing and its good safety record in HIV-uninfected individuals with very few potential drug interactions makes alendronate particularly attractive for use in the HIV-positive population. The purpose of this trial was to evaluate the safety and effectiveness of alendronate when combined with calcium/vitamin D supplementation compared with calcium/vitamin D alone in the treatment of HIV-associated osteopenia and osteoporosis.

Methods

Study design

This was a prospective, randomized, placebo-controlled multicenter trial, to evaluate the safety and effectiveness of calcium/vitamin D supplementation with or without once-weekly alendronate (70 mg) in improving BMD in HIV-infected individuals.

Study subjects

The eligibility criteria for enrollment included: documented HIV infection; age 25 years and over; BMD at the lumbar spine that was at least 1.5 SD below the mean in normal young individuals of the same sex (t-score ≤ -1.5); plasma HIV-1-RNA level of 5000 copies/ml or less and a CD4 cell count of 100 cells/μl or greater. All subjects were required to be receiving stable ART for at least 12 weeks, with no plan to alter ART, exercise habits, or diet significantly for the duration of the study. We excluded individuals with secondary causes of osteoporosis, including untreated hypogonadism, hyperthyroidism, vitamin D deficiency (defined as a serum 25-hydroxyvitamin D level < 15 ng/ml), hyperparathyroidism (defined as a parathyroid hormone level > 80 pg/ml), renal disease (defined as creatinine clearance < 50 ml/min), chronic use of systemic corticosteroid therapy, recent use of anabolic steroids, history of cancer requiring systemic chemotherapy, or Paget's disease. Individuals on stable testosterone or estrogen therapy, such as hormone replacement or oral contraceptives, were permitted to enter the study provided they had received testosterone or estrogen therapy for at least 24 weeks at stable doses and had no plan to alter such therapy while on study. We also excluded subjects with a history of treatment for osteoporosis, recent bone fracture, history of severe esophageal reflux, esophagitis or any condition predisposing to esophageal inflammation, hepatitis C virus infection, or severe alcohol-related liver disease. In addition, because of ethical concerns, we excluded pregnant women and subjects with fragility fracture in their adult years or evidence of spinal fracture by a lateral spine X-ray performed before study entry.

The study was approved by the institutional review boards at each of the participating sites, and all subjects gave written informed consent.

Treatment

Subjects were randomly assigned in a double-blinded manner in a 1 : 1 ratio to receive 70 mg alendronate or matching placebo weekly. Randomization was stratified by CD4 cell count at screening (100–200 cells/μl or > 200 cells/μl). All subjects received calcium and vitamin D in co-formulated tablets (as calcium carbonate 500 mg/vitamin D 200 IU tablet twice a day). Strict instructions were given to study participants to take the study drug (alendronate/placebo) under fasting conditions in the morning and to remain fully upright for at least 30 min after taking study drugs.

Study evaluations

At baseline, a complete history including ART was obtained. Subjects completed standardized questionnaires on physical activity, dietary habits, current smoking and alcohol use, and, for women, gynecological history. Each subject underwent a complete physical examination, with measurement of height and weight. Laboratory analyses were performed including hematology, renal and hepatic function, pregnancy test, total testosterone (in men only), thyroid-stimulating hormone, prolactin (in women with amenorrhea only), 25-hydroxyvitamin D, and parathyroid hormone. A lateral radiograph of the thoracic and lumbar spine, and BMD measurements of the lumbar spine and left hip were obtained at baseline. Follow-up visits were scheduled at weeks 2, 12, 24, 36, and 48. At each follow-up visit, subjects were questioned about symptoms and changes in medications, and specimens

were obtained for hematology, renal and hepatic function, and calcium and phosphorus levels. BMD was measured at baseline, and at 24 and 48 weeks. At the week-48 visit, the subjects filled out questionnaires on physical activity, current smoking and alcohol use, and a gynecological questionnaire (for women only). Dietary questionnaires were completed at weeks 24 and 48 to determine changes in calcium intake during the study.

Measurements of bone mineral density

The BMD of the lumbar spine and hip was measured by dual-energy X-ray absorptiometry (DEXA) in the anteroposterior view (using hologic or lunar scanners). For the hip, we measured BMD at three different locations: total hip, femoral neck, and greater trochanter. Lumbar spine BMD was measured from L1 to L4. To determine the subjects' eligibility on the basis of their *t*-score (standard deviations from the mean value in young normal individuals) at the lumbar spine, we used manufacturers' sex and ethnicity-specific reference populations. Technicians scanned the same hip of each subject and used the same machine on the same individual throughout the study. DEXA procedures were standardized at the participating sites, then read centrally (Tufts University) by personnel blinded to treatment assignment.

Measurement of bone resorption marker

The bone resorption marker (CTx) was measured on serum collected from participants in the fasting state at baseline and at weeks 24 and 48. Serum samples were stored at -70°C for batched testing at the end of the study. Serum CTx (β-CrossLaps; Roche Diagnostic Systems, Inc., Branchburg, New Jersey, USA) was determined by sandwich electrochemiluminescence immunoassay at Quest Diagnostics laboratories. The within-assay coefficient of variation for serum CTx was 0.5–2.2% and the between-assay coefficient of variation was 2.9–4.2%.

Statistical methods

The primary endpoint was the treatment difference in percentage change in lumbar spine BMD in men. Assuming a 4% standard deviation of the changes from baseline to week 48 within an arm [14], a sample size of 22 men/arm had 80% power (two-sided $\alpha = 0.05$) to detect a 3.5% absolute difference in the mean change between arms. To protect against the possibility of a 10% drop-out rate and an additional 10% with unevaluable DEXA scans, a minimum of 27 men per arm were needed. To test for moderate treatment–sex interactions, a minimum of 10 women per arm were also included, for a grand total of 80 subjects. We did not adjust the α level for multiple testing in the secondary objectives.

The primary analysis was conducted using a two-sample *t*-test to assess whether the percentage change in lumbar spine BMD in men from baseline to week 48 was significantly different between the treatment arms. The planned stratified analysis could not be performed because there were too few subjects in the lower CD4 cell count stratum. Simple linear regression was used to look for predictors of clinical response. The response variable was the percentage change from baseline to week 48 in lumbar spine BMD. The baseline covariates considered were sex, race (white versus non-white; black versus non-lack), age (years), HIV-RNA viral load (>400 versus 400 copies/ml), screening CD4 cell count (cells/μl), antiretroviral use (years of antiretroviral use; years of protease inhibitor use; non-nucleoside reverse transcriptase inhibitor (NNRTI) use; protease inhibitor use; tenofovir use), body mass index (BMI; kg/m^2), weight (kg), smoking status (current versus never/past; never versus current/past), alcohol consumption (none versus infrequent versus one to four drinks versus five to 30), physical activity (<5 versus 5–12 versus 13–20 versus >20 h), and calcium intake (mg/day). The results of the univariate analyses were used to guide the multivariate analysis. The baseline covariates found to be associated (P value ≤ 0.10) with lumbar spine BMD were placed in multivariate linear regression models. The multivariate models were fit such that treatment was in the model even if it was not statistically significant. Similar methods were used in the analysis of the percentage change from baseline to week 48 in total hip, trochanter, and femoral neck BMD.

In addition, one-sample *t*-tests were used to assess the changes from baseline within a treatment arm. Associations between categorical variables were evaluated using the Fisher's exact test. Pearson's correlations were calculated. The analysis was based on the intention-to-treat principle and conducted using SAS version 9.1 (SAS Institute, Cary, North Carolina, USA); all statistical tests were two-sided.

As there was no evidence of treatment–sex interactions at any of the sites, we present the results based on all subjects before discussing sex differences.

Results

Characteristics of subjects

From October 2003 to March 2005, 82 subjects were enrolled from 22 AIDS Clinical Trials units. Baseline characteristics are shown in Table 1. The subjects were 71% male and 77% white, with 99% receiving ART, 96% having CD4 cell counts greater than 200 cells/μl, and 91% having HIV-RNA viral loads of 400 copies/ml or less. There were no significant differences between the treatment arms in baseline characteristics. Twenty-nine (35%) were current smokers and 14 (17%) reported a weekly average alcohol consumption of more than four alcoholic drinks. Among the 24 women in the study, 13 (54%) were postmenopausal. The median screening lumbar spine *t*-score was -2.1: -1.95 in the placebo arm and -2.15 in the alendronate arm ($P = 0.05$). Seventeen subjects (21%) had osteoporosis

Table 1. Baseline demographics, HIV characteristics, and bone-related risk factors of all study participants.

Characteristic	Total $N=82$	Alendronate $N=42$ n (%)	Placebo $N=40$ n (%)	P value
Age (years; median, range)	48 (30–68)	48 (33–63)	46 (30–68)	0.88[a]
Male sex	58 (71%)	30 (71%)	28 (70%)	1.00[a]
				0.22[a]
White, non-Hispanic	63 (77%)	29 (69%)	34 (85%)	
Black, non-Hispanic	14 (17%)	8 (19%)	6 (15%)	
Hispanic (any race)	7 (9%)	1 (2%)	6 (15%)	
Asian/Pacific Islander	4 (4%)	4 (10%)	0	
More than one race	1 (1%)	1 (2%)	0	
BMI (kg/m^2; median, range)	24 (19.1–38.6)	23.8 (20.1–38.6)	24.2 (19.1–35.1)	0.43[b]
Smoking status				0.76[c]
Past	21 (26%)	12 (29%)	9 (23%)	
Current	29 (35%)	15 (36%)	14 (35%)	
Never	32 (39%)	15 (36%)	17 (43%)	
Number of alcoholic drinks/week				0.15[c]
None	29 (35%)	12 (29%)	17 (43%)	
Infrequent (<2/month)	10 (12%)	7 (17%)	3 (8%)	
1–4	29 (35%)	18 (43%)	11 (28%)	
5–30	14 (17%)	5 (12%)	9 (23%)	
Median hours of physical activity in past 2 weeks	16	16	16	0.75[c]
<13	33 (40%)	17 (41%)	16 (40%)	
>20	31 (38%)	15 (36%)	16 (40%)	
Antiretroviral drug classes				0.14[a]
None	1 (1%)	0	1 (3%)	
NRTI	81 (99%)	42 (100%)	39 (98%)	
NNRTI	27 (33%)	19 (21%)	18 (45%)	
PI	54 (66%)	29 (69%)	25 (63%)	
Entry inhibitor (enfuvirtide)	2 (2%)	2 (5%)	0	
Tenofovir use	31 (38%)	16 (38%)	15 (38%)	1.00[a]
Screening CD4 cell count (cells/μl; median, range)	469 (105–1387)	482 (105–1387)	463 (189–1237)	0.78[b]
HIV-1 RNA (copies/ml; median)	<50	<50	<50	0.71[a]
<400	75 (91%)	38 (90%)	37 (93%)	
Calcium level (mg/dl; median,range)	9.20 (8.4–10.4)	9.20 (8.5–10.4)	9.20 (8.4–10.2)	0.39[b]
Screening DEXA lumbar t-score (median, range)	−2.1 (−3.3, −1.5)	−2.15 (−3.3, −1.5)	−1.95 (−3.0, −1.5)	0.05[b]
Lumbar spine BMD (g/cm^2; median, range)	0.90 (0.71, 1.09)	0.88 (0.72, 1.09)	0.92 (0.71, 1.08)	0.14[b]
Serum CTx (pg/ml, median, range)	413 (78–1174)	406 (151–1169)	420 (78–1174)	0.49[b]
Menopausal status	$n=24$	$n=12$	$n=12$	1.00[a]
Postmenopausal	13 (54%)	7 (58%)	6 (50%)	

BMD, Bone mineral density; BMI, body mass index; CTx, C-terminal telopeptide of type I collagen; DEXA, dual-energy X-ray absorptiometry; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
[a]Exact test.
[b]Wilcoxon test.
[c]Chi-square test.

(lumbar spine t-scores <-2.5): 10 (24%) in the alendronate arm and eight (18%) in the placebo arm ($P=0.59$).

Subject disposition

Both baseline and week 48 DEXA scans were available in 76 subjects (93%): 39 on the alendronate arm and 37 on the placebo arm. Of the six subjects excluded from the analysis, four prematurely discontinued the study, one missed the week 48 DEXA visit, and one had an unevaluable week 48 DEXA.

During the trial, there were no significant changes in smoking or alcohol intake, dietary calcium intake, BMI or physical activity. Seventeen subjects (21%) reported changes to their ART at some point during follow-up; six on placebo and 11 on alendronate. Three subjects (two on alendronate) discontinued tenofovir and three subjects started tenofovir (one on alendronate) after study entry.

Changes in bone mineral density in all participants

Lumbar spine BMD increased a mean 3.38% by week 48 in the alendronate arm ($P<0.001$ compared with baseline; Fig. 1). In the placebo arm, lumbar spine BMD increased a mean 1.10% from baseline ($P=0.08$). The difference in the mean percentage change in lumbar spine BMD between treatments was 2.29% [95% confidence interval (CI) 0.21%, 4.36%; $P=0.03$].

In the alendronate arm, BMD of the total hip, trochanter, and femoral neck increased a mean 3.95, 4.52, and 2.21%, respectively, from baseline ($P<0.001$, $P<0.001$, and $P=0.008$, respectively). In the placebo group, total hip and femoral neck BMD increased a mean 1.31 and 1.24%, respectively ($P=0.03$ and $P=0.07$, respectively); there was no significant change from baseline in trochanter BMD ($P=0.37$). The differences in the mean percentage change between treatments were statistically significant

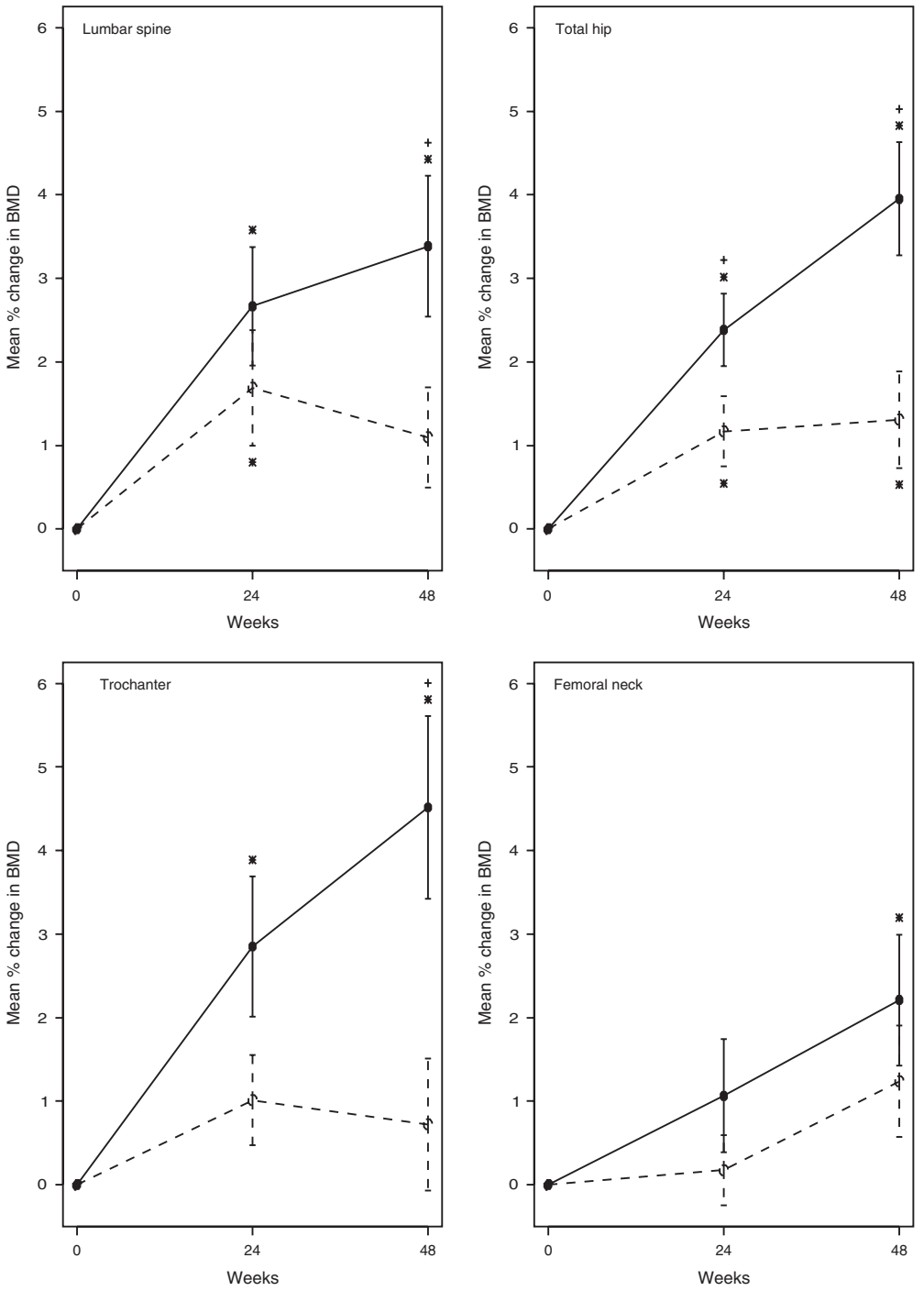

Fig. 1. Mean percentage changes from baseline in the bone mineral density of the lumbar spine, total hip, trochanter, and femoral neck. ——— Alendronate plus calcium/vitamin D; – – – calcium/vitamin D only. *Significant within arm; $^{+}$significant between arms.

for total hip and trochanter BMD. The mean differences were 2.64% (95% CI 0.86%, 4.43%; $P = 0.004$) for total hip BMD and 3.80% (95% CI 1.08%, 6.51%; $P = 0.007$) for trochanter BMD. The treatment difference for femoral neck BMD was not significant ($P = 0.35$).

Based on subjects with baseline and week-48 lumbar spine BMD data available, 23 out of 76 (30%) had osteoporosis (t-score < -2.5) at baseline: 9/37 (24%) in the placebo arm and 14/39 (36%) in the alendronate arm (between arms $P = 0.33$). At week 48, 19 out of 76 (25%) had osteoporosis (t-score < -2.5): eight out of 37 (22%) in the placebo arm and 11 out of 39 (28%) in the alendronate arm ($P = 0.60$). Within the alendronate arm, six subjects with osteoporosis at entry were not osteoporotic at week 48, whereas three subjects who

were not osteoporotic at entry progressed to osteoporosis by week 48. There was no significant difference in the rate of osteoporosis at both timepoints ($P = 0.32$).

During the trial, traumatic fractures were reported by two subjects: one in the alendronate arm (clavicular fracture; week 5) and one in the placebo arm (fifth metacarpal fracture; week 29).

Changes in bone mineral density by sex

There was no evidence of treatment–sex interactions when we considered the percentage change from baseline to week 48 in BMD assessed at the lumbar spine, total hip, trochanter, or femoral neck ($P = 0.41$, $P = 0.82$, $P = 0.19$, and $P = 0.48$, respectively). In addition, menopausal status at baseline did not affect the percentage change in BMD at any of the four sites ($P > 0.2$).

Predictors of bone mineral density and response to treatment

In an analysis of baseline data, BMI, weight, black race, and higher dietary calcium intake were positively associated with higher baseline lumbar spine BMD ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P = 0.01$, respectively). In contrast, tenofovir use at baseline and older age were associated with lower lumbar spine BMD ($P = 0.05$ for both). For total hip and femoral neck, similar associations to those found with baseline lumbar spine BMD were seen, with black race, weight, and BMI associated with higher BMD at those sites (all $P \leq 0.03$). In addition, older subjects had significantly lower baseline femoral neck BMD ($P = 0.009$), whereas there was a trend towards lower baseline total hip BMD ($P = 0.10$). Heavier subjects had higher baseline trochanter BMD ($P = 0.003$).

Table 2. Regression analyses.

	N	Parameter estimate	95% CI	*P* value
Baseline lumbar spine BMD				
Baseline BMI (per kg/m^2)	81	0.007	(0.0039, 0.0109)	< 0.001
Baseline weight (per 10 kg)	81	0.024	(0.01381, 0.0335)	< 0.001
Black race (vs non-black)	82	0.072	(0.0350, 0.1092)	< 0.001
Baseline dietary calcium (per 1000 mg/day)	82	0.028	(0.0069, 0.0488)	0.01
Baseline age (per 10 years)	82	−0.017	(−0.0337, 0.0001)	0.05
Tenofovir use at baseline	82	−0.030	(−0.0602, −0.0003)	0.01
Baseline total hip BMD				
Baseline BMI (per kg/m^2)	81	0.009	(0.0035, 0.0140)	0.001
Baseline weight (per 10 kg)	81	0.032	(0.0173, 0.0465)	< 0.001
Black race (vs non-black)	82	0.064	(0.0077, 0.1212)	0.03
Baseline age (per 10 years)	82	−0.021	(−0.0454, 0.0039)	0.10
Baseline femoral neck BMD				
Baseline BMI (per kg/m^2)	81	0.013	(0.0071, 0.0180)	< 0.001
Baseline weight (per 10 kg)	81	0.043	(0.0281, 0.0580)	< 0.001
Black race (vs non-black)	82	0.105	(0.0461, 0.1648)	0.001
Baseline age (per 10 years)	82	−0.036	(−0.0618, −0.0093)	0.009
Baseline trochanter BMD				
Baseline weight (per 10 kg)	81	0.019	(0.0065, 0.0316)	0.003
Multivariate percentage change in lumbar spine BMD				
Alendronate use	76	2.457	(0.4902, 4.4232)	0.02
Black race	76	−3.941	(−6.4769, −1.4058)	0.003
Multivariate percentage change in total hip BMD				
Alendronate use	76	2.613	(0.9220, 4.3050)	0.003
Male sex	76	−2.830	(−4.6705, −0.9897)	0.003
Multivariate percentage change in femoral neck BMD				
Alendronate use	76	1.010	(−0.9721, 2.9919)	0.31
Baseline weight (per 10 kg)	76	−0.834	(−1.5891, −0.0799)	0.03
Current smoking at baseline	76	2.326	(0.2896, 4.3616)	0.03
Multivariate percentage change in trochanter BMD				
Alendronate use	76	3.343	(0.7793, 5.9058)	0.01
DEXA *t*-score (≤ -2 vs > -2)	76	2.680	(0.0725, 5.2873)	0.04
Male sex	76	−4.022	(−6.771, −1.2662)	0.005
Baseline CTx				
Baseline weight (per 10 kg)	81	−39.69	(−77.07, −2.30)	0.04
Baseline age (per 10 years)	81	−64.85	(−121.37, −8.32)	0.03
Baseline NNRTI use	81	−126.30	(−229.38, −23.28)	0.02
Baseline PI use	81	102.88	(−0.51, 206.27)	0.05
Baseline tenofovir use	81	146.20	(47.56, 244.53)	0.004
Multivariate change in CTx				
Alendronate use	68	−0.421	(−0.5529, −0.2886)	< 0.001
Baseline NNRTI use	68	0.141	(0.0001, 0.2863)	0.05
Current smoking at baseline	68	0.144	(0.0106, 0.2767)	0.04

BMD, Bone mineral density; BMI, body mass index; CI, confidence interval; CTx, C-terminal telopeptide of type I collagen; DEXA, dual-energy X-ray absorptiometry; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Multivariate linear regression models explored the relationships between baseline variables of interest and percentage change in BMD (Table 2). After accounting for treatment increases ($P \leq 0.03$), smaller increases were predicted by black race in the lumbar spine ($P = 0.003$), by male sex in total hip ($P = 0.003$), and by higher *t*-score ($P = 0.04$) and male sex ($P = 0.005$) in the trochanter. Greater weight ($P = 0.03$) and smoking ($P = 0.03$) predicted smaller increases in femoral neck after accounting for treatment ($P = 0.3$).

Adverse events

The reporting of on-study adverse events and laboratory toxicities grade 2 (moderate) or higher were required (Table 3). The median time-to-first safety/tolerability event was 24.5 weeks; there were no significant differences between the treatment arms (log rank $P = 0.53$). There were significantly more grade 3 or more signs/symptoms in the placebo arm (15% versus 0% on alendronate; $P = 0.01$), but no difference between treatment arms in grade 3+ laboratory toxicities (15% on placebo versus 17% on alendronate; $P > 0.9$). Upper gastrointestinal adverse events, a concern with oral bisphosphonates, occurred in only one subject on alendronate and two subjects on placebo. The one subject with dysphagia on alendronate presented with several concomitant symptoms (all grade 2): dysphagia, swelling and pain in the tongue, and pain and burning in the mouth. The patient was diagnosed with stomatitis; the study drugs were held for 3 days then resumed without recurrence of the symptoms.

Table 3. Incidence of adverse events.

Adverse event (grade ≥ 2)	Alendronate group ($n = 42$)	Placebo group ($n = 40$)
Any	29 (69%)	23 (58%)
Serious (grade ≥ 3)	8 (19%)	14 (35%)
Cardiovascular system	1 (2%)	4 (10%)
Chemistries abnormalities	6 (14%)	7 (18%)
Endocrinology system	3 (7%)	2 (5%)
Gastrointestinal system	2 (5%)	4 (10%)
Upper gastrointestinal tract		
Abdominal pain	0 (0%)	1 (3%)
Dysphagia	1 (2%)	0 (0%)
Retrosternal pain	0 (0%)	1 (3%)
General body	6 (14%)	7 (18%)
Hematological system	1 (2%)	1 (3%)
Hepatic system	15 (36%)	12 (30%)
Metabolic	5 (12%)	4 (10%)
Neurological system	2 (5%)	4 (10%)
Pancreatic	3 (7%)	3 (8%)
Renal	1 (2%)	1 (3%)
Respiratory system	2 (5%)	3 (8%)
Skin	1 (2%)	2 (5%)
Urogenital system	0 (0%)	2 (5%)

Changes and predictors of the bone resorption marker

At baseline, lower CTx levels were associated with older age, higher weight and NNRTI use ($P = 0.03$, $P = 0.04$, and $P = 0.02$, respectively). Higher baseline CTx levels were associated with protease inhibitor and tenofovir use ($P = 0.05$ and $P = 0.004$, respectively). CTx decreased a median 77% by week 48 in the alendronate arm ($P < 0.001$ for the comparison with baseline; Fig. 2). In the placebo arm, CTx decreased a median 22% ($P = 0.07$). The

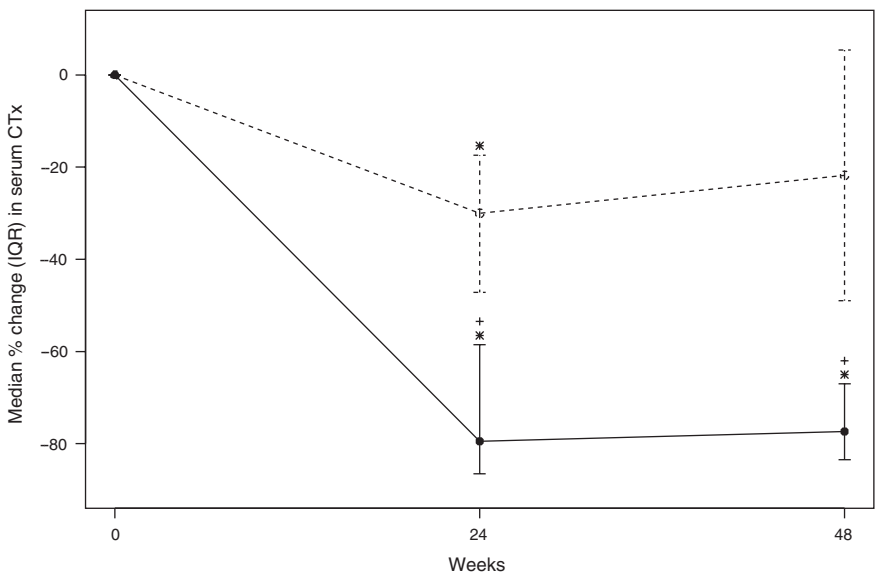

Fig. 2. Median percentage changes from baseline in the serum resorption marker C-terminal telopeptide of type I collagen. CTx, C-terminal telopeptide of type I collagen; IQR, interquartile range. ——— Alendronate plus calcium/vitamin D; – – – calcium/vitamin D only. *Significant within arm; $^{+}$significant between arms.

difference in the median percentage change in CTx between treatments was −62% [interquartile range (IQR) −79%, −22%; $P < 0.001$]. In the multivariate analysis, smaller increases in CTx were associated with alendronate use ($P < 0.001$), whereas larger increases in CTx were associated with current smoking ($P = 0.04$) and NNRTI use ($P = 0.05$). There were no correlations between the percentage change in CTx and percentage changes in BMD at any of the bone sites examined (all $P > 0.4$). Changes in CTx from baseline to week 24 predicted changes in CTx by week 48 ($r = 0.56$ and $r = 0.40$, $P < 0.001$ and $P < 0.02$ in the alendronate and placebo arms, respectively).

Discussion

The ACTG A5163 is the largest trial to date evaluating the use of alendronate in HIV-infected individuals. In this randomized, placebo-controlled trial of HIV-infected men and women with decreased BMD, the administration of weekly alendronate for one year was safe and effective in increasing lumbar spine and hip BMD when compared with calcium/vitamin D supplementation alone. This effect was independent of the baseline *t*-score and sex of the subject.

Adequate calcium and vitamin D are essential to maintain BMD and to prevent fractures in the aging population. Although subjects with profound vitamin D deficiency were excluded from this study, the administration of calcium/vitamin D with placebo led to a trend towards an improvement in BMD at the lumbar spine, total hip, and femoral neck. This modest increase is similar to that seen in the calcium/vitamin D only arms of other osteoporosis trials [10,17]. In the HIV population, calcium/vitamin D supplementation should be considered to maintain BMD, especially in high-risk individuals.

The magnitude of the improvements in BMD seen with alendronate therapy in HIV-infected men and women was similar to that observed in postmenopausal women and older men treated with this agent [10,11,13,18,19]. Although our study clearly demonstrates that alendronate is effective in increasing BMD in HIV-infected individuals with *t*-scores of −1.5 or less, it was not designed to address fracture prevention. Most HIV-infected patients enrolled in this study were relatively young and physically active, with a low risk of fragility fractures in the immediate future. The impact of age-associated bone loss and fractures, however, need to be considered in our aging HIV population. We are not suggesting that treatment with alendronate is necessarily indicated in all HIV-infected individuals with low BMD, but alendronate maybe a treatment option in high-risk HIV-infected individuals such as those with fragility fractures or at risk of severe bone loss.

In the HIV-uninfected population, bisphosphonates lead to changes in bone turnover markers that occur sooner than changes in BMD [20–22]. In postmenopausal women, changes in bone markers, including CTx, during alendronate therapy are related to the subsequent risk of fracture with a far greater effect on fracture reduction than treatment-induced changes in BMD [23]. Therefore, bone markers are considered useful in monitoring the response to treatment [24]. Our study was too short to make any observations related to the effect of alendronate on fracture reduction. We found CTx levels significantly decreased by 77% on alendronate, however, which is consistent with the results of bisphosphonates in HIV-uninfected subjects in whom bone resorption marker levels were reduced by 30–70% after as early as 3–6 months of therapy [20–22]. In our study, the changes in CTx did not correlate with changes in BMD at any of the bone sites examined, which is consistent with the lack of or weak correlation found between bone markers and BMD in HIV-uninfected individuals [20–22].

To date, there have been no similarly powered studies to guide in the selection of HIV-infected individuals for whom bisphosphonate treatment is indicated. Until treatment guidelines for osteopenia/osteoporosis are established for HIV-infected individuals, each patient should be individually assessed and the decision as to whether to treat with bisphosphonates should be cautiously made in consultation with a bone disease expert.

Our study had some limitations. The trial lasted only 48 weeks and thus could not assess the long-term safety of alendronate. Also, the long-term efficacy and tolerability of alendronate in this population should be investigated. Another possible limitation is that, despite an intention to remain on stable ART, 21% of subjects required a change of one or more antiretroviral drugs during the study. These changes, however, are unlikely to have confounded the results because earlier studies showed no changes in BMD after the discontinuation of protease inhibitors [25,26] or after switching within the class of nucleoside reverse transcriptase inhibitors (NRTI) [27]. The only exception to the lack of effect on bone density of treatment switches is related to tenofovir, an NRTI shown to lead to more bone loss when compared with other NRTI [28,29]. One study showed that switching stavudine to tenofovir led to significant worsening in BMD [30]. This, however, had little impact on our findings, because the results were unchanged when we excluded from the analyses the six subjects who added or discontinued tenofovir during the study period.

In summary, in HIV-infected men and women with decreased BMD, alendronate increased lumbar spine and hip BMD beyond that achieved with calcium/vitamin D alone, and was well tolerated without gastrointestinal or major adverse events.

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