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Annual Zoledronate Increases Bone Density in Highly Active Antiretroviral Therapy-Treated Human Immunodeficiency Virus-Infected Men: A Randomized Controlled Trial

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Context: Recent studies have reported low bone mineral density (BMD) in HIV-infected patients. Annual iv administration of 4 mg zoledronate has been shown to increase BMD and suppress bone turnover in postmenopausal women.

Objective: The objective of the study was to determine whether annual administration of 4 mg zoledronate will increase BMD in HIV-infected men receiving highly active antiretroviral therapy.

Design and Setting: A 2-yr randomized placebo-controlled trial was conducted in a clinical research center.

Participants: A total of 43 HIV-infected men were treated with highly active antiretroviral therapy for at least 3 months, with BMD T score less than −0.5.

Intervention: Participants received annual iv administration of 4 mg zoledronate or placebo. All participants took 400 mg/d calcium and 1.25 mg/month vitamin D.

Measurements: BMD at the lumbar spine, total hip and total body, and bone turnover markers were measured.

Results: At the lumbar spine, BMD increased by 8.9% over 2 yr in the zoledronate group compared with an increase of 2.6% in the control group ($P < 0.001$). At the total hip, BMD increased by 3.8% over 2 yr in the zoledronate group compared with a decrease of 0.8% in the control group ($P < 0.001$). At the total body, BMD increased by 2.3% over 2 yr compared with a decrease of 0.5% in the control group ($P < 0.001$). Urine N-telopeptide decreased by 60% at 3 months in the zoledronate group and thereafter remained stable.

Conclusions: Annual administration of zoledronate is a potent and effective therapy for the prevention or treatment of bone loss in HIV-infected men. The current data provide the first trial evidence of the BMD effects of annual zoledronate beyond 1 yr in any population, as well as being the first reported trial in men. **(*J Clin Endocrinol Metab* 92: 1283–1288, 2007)**

RECENTLY, MANY cross-sectional studies have reported low bone mineral density (BMD) or higher than expected rates of osteopenia and osteoporosis in people infected with HIV (1, 2), although not all studies have found such associations (3). The cause of the association between HIV infection and low BMD is not known but has been attributed to HIV infection itself, or to treatment with protease inhibitors or highly active antiretroviral therapy (HAART) (1, 2). Patients infected with HIV may also potentially be at risk for osteoporosis because of increased exposure to more traditional risk factors for osteoporosis, such as chronic illness, low body weight, and hypogonadism (4).

Bisphosphonates are widely used and highly effective agents for the treatment and prevention of osteoporosis (5). In patients infected with HIV, three small randomized, open-label studies of weekly oral 70 mg alendronate treatment for 48–96 wk have produced conflicting results. One study reported increases in BMD at the spine and hip but only significant between-group differences favoring alendronate at the trochanter (6). There was one study that showed between-group differences in BMD favoring alendronate at the spine, but not other sites (7), and one study reported no between-group differences in BMD at either the spine or hip (8).

Zoledronate is a potent third-generation bisphosphonate. Recently Reid *et al.* (9) reported that iv administration of a single dose of 4 mg zoledronate produced significant increases in BMD and suppression of bone turnover markers over the following 12 months in postmenopausal women with low BMD. The effects of annual administration of zoledronate in men, patients infected with HIV, or any population beyond 12 months of follow-up have not yet been reported. Therefore, we performed a 2-yr randomized, double-blind, placebo-controlled trial of annual administration of zoledronate to determine the effects on BMD and bone turnover markers in men infected with HIV who were taking HAART.

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Abbreviations: ALP, Alkaline phosphatase; BMD, bone mineral density; HAART, highly active antiretroviral therapy; NTx, N-telopeptide of type 1 collagen.

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Subjects and Methods

Participants

Between February 2003 and March 2004, all HIV-infected men who attended infectious disease clinics at our institution were approached by their primary physician to participate. Men were eligible to participate

if they had been treated with HAART for at least 3 months and had a BMD T score of less than −0.5 at the lumbar spine or total hip. HAART was defined as an HIV treatment regimen containing at least three antiretroviral agents. We excluded men with: significant renal, hepatic, or thyroid dysfunction; concurrent major systemic illness, including malignancy; metabolic bone disease; or current use of a bisphosphonate or systemic glucocorticoids. Approximately 220 men were approached, and 72 agreed to have a screening bone density scan. A total of 45 men had a BMD T score below −0.5 at the lumbar spine or total hip. One man was excluded because of liver cirrhosis, and one because of newly diagnosed primary hypogonadism. Thus, 43 men were enrolled in the 2-yr study.

Figure 1 shows the flow of participants through the trial. One man withdrew from the study for personal reasons after randomization but before administration of study medication, one died of unknown causes, and four emigrated during the study. Thus, 37 men completed 2 yr of follow-up. Two men (both received zoledronate) stopped iv study medication because of influenza-like illnesses after the first administration of study drug but remained in the study. However, after the intention to treat principle, all 43 men enrolled in the trial were included in the analyses. One man in the zoledronate group was taking testosterone supplementation at baseline but emigrated 2 months into the study and, so, was not included in any of the outcome data. Another man in the zoledronate group took testosterone supplementation for 5 months during the study. No subjects took GH, anabolic steroids, or other agents that might impact upon BMD during the study. The study received ethical approval from the Auckland Ethics Committee and was registered with the Australian Clinical Trials Registry (ACTRN012605000208606). All participants gave written informed consent.

Protocol

Participants were randomly allocated to receive an annual administration of either zoledronate 4 mg, given as a 15-min iv infusion in 100 ml 0.9% NaCl, or placebo for 2 yr. Randomization was performed in blocks of variable size, using computer-generated random numbers (Excel 2000; Microsoft Corp., Redmond, WA). Subject numbers were allocated and medication dispensed by staff that had no direct contact with the participants. All study staff and participants remained blinded to treatment allocation throughout. In addition, all participants received a supplement of 400 mg/d elemental calcium and 1.25 mg/month vitamin D (cholecalciferol). Participants were seen every 6 months during the study period.

Measurements

BMD and body composition were measured every 6 months at the lumbar spine, proximal femur, and total body using a Lunar Expert dual-energy x-ray absorptiometer (GE Lunar, Madison, WI). BMD T and Z scores were calculated using the manufacturer-supplied Lunar US/Northern Europe database for men. At baseline and 2 yr, vertebral morphometry was also performed. Daily calcium intake was assessed at baseline using a validated questionnaire (10). At baseline, and 3, 12, and 24 months, fasting blood and second-voided morning urine samples were collected. The following assays were used: serum 25-hydroxyvitamin D was measured by RIA (DiaSorin, Stillwater, MN); serum PTH and serum testosterone by electrochemiluminescence immunoassays (E170; Roche Diagnostics, Indianapolis, IN); and urine N-telopeptide of type 1 collagen (NTx) by ELISA (Ostex International Inc., Seattle, WA). At baseline, measurements of biochemistry, calcium metabolism, testosterone, HIV parameters (CD4 count, viral load), and bone turnover were performed. Measurements of bone turnover were repeated at 3, 12, and 24 months, and HIV parameters at 24 months.

Statistics

The primary endpoint was the difference between groups in the change in BMD at the spine over 2 yr. This study had a power of at least 80% to detect a between-group difference in percent change from baseline BMD of the lumbar spine of 4% ($\alpha = 0.05$). Differences between groups for continuous variables were assessed using Student's t test and for categorical groups using the χ^2 test. Pearson correlation analysis was used to test for significant linear correlations between variables. BMD data were analyzed as absolute changes from baseline values, although results are presented as percentage change from baseline for ease of interpretation. A mixed models approach to repeated measures (analysis of covariance) was used to examine the time course of response in treatment and control arms for BMD measurements, bone turnover markers, and measurements of body composition. Changes in variables between time points were furthered explored using the method of Tukey. Inspection of plots for urine NTx showed that data were not normally distributed. Therefore, these data were ranked, and the ranked values were analyzed using a nonparametric mixed models approach, although data are presented using medians and confidence intervals (binomial method: Confidence Interval Analysis, version 2.1.1) for ease of interpretation. All tests were two-tailed, and statistical significance was set at $P < 0.05$. All statistical analyses were performed using the SAS software package (version 9.1; SAS Institute, Cary, NC).

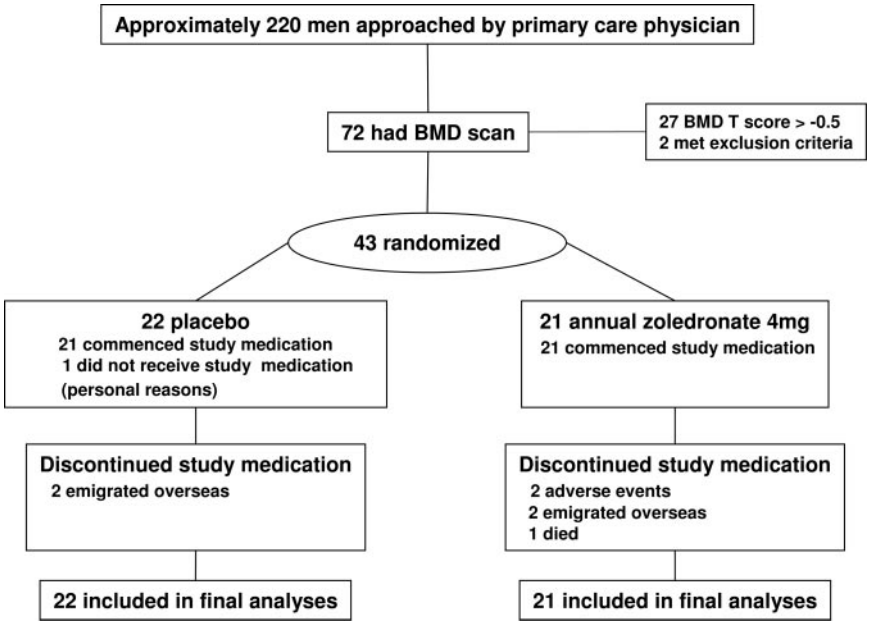

FIG. 1. Flow of subjects through the study.

Results

Table 1 shows the baseline characteristics of the study participants, and Table 2 shows the HIV-related clinical characteristics. There were no statistically significant differences between the groups in these parameters at baseline or in anthropometric and HIV-related clinical characteristics after 2 yr. The study participants had similar baseline HIV-related clinical characteristics to a nationwide New Zealand cohort of HIV-infected men (11). There were no significant HIV-related clinical events for any of the participants during the study. Of 43 participants, 34 were treated with HAART regimens that achieved consistent suppression of HIV replication (viral load < 1.7 log copies/ml). There were nine participants treated with regimens that were only partially or intermittently effective due either to infection with HIV resistant to antiretroviral medications or to inadequate treatment adherence. Of 34 participants with sustained suppression of HIV replication, 32 had CD4 counts greater than 200 cells/μl, whereas of nine subjects with intermittently effective treatment, two had at least 1 CD4 count less than 200 cells/μl. At baseline, eight subjects in the zoledronate group and eight subjects in the control group were treated with regimens that included a protease inhibitor. During the trial, six subjects had changes in their medication regimens: three subjects (one zoledronate group, two placebo) changed from one protease inhibitor-based regimen to another, and three subjects (one zoledronate group, two placebo) changed from a protease inhibitor-based regimen to one that did not include a protease inhibitor. No subjects were treated with tenofovir at any point during the trial.

TABLE 1. Baseline anthropometric, BMD, biochemical parameters, and other characteristics of the groups

Characteristic	Placebo (n = 22)	Zoledronate (n = 21)
Age (yr)	48.8 (9.0)	49.5 (9.0)
European descent (%)	82	81
Height (cm)	176 (8)	176 (4)
Weight (kg)	75 (12)	73 (10)
BMI (kg/m^2)	24.6 (3.4)	23.5 (3.1)
Percent fat	20.8 (5.6)	17.2 (6.7)
Fat mass (kg)	15 (5)	12 (7)
Lean mass (kg)	55 (9)	56 (7)
Previous smoker (%)	68	52
Current smoker (%)	27	24
Alcohol intake (standard drinks/d)	<1 (0–4)	<1 (0–4)
Dietary calcium (mg/d)	854 (600)	963 (699)
GGT (U/liter)	59 (54)	78 (57)
Serum adjusted calcium (mg/dl)[a]	8.9 (0.3)	9.1 (0.4)
PTH (pg/ml)[b]	47 (20)	36 (15)
25-hydroxyvitamin D (ng/dl)[c]	23 (11)	28 (10)
Testosterone (ng/dl)[d]	488 (171)	558 (311)
L1–L4 BMD (g/cm^2)	1.11 (0.16)	1.15 (0.11)
T score L1–L4	−0.9 (1.3)	−0.6 (0.9)
Z score L1–L4	−0.8 (1.3)	−0.4 (1.0)
Total femur BMD (g/cm^2)	0.94 (0.11)	0.94 (0.07)
T score total femur	−1.2 (0.9)	−1.2 (0.6)
Z score total femur	−0.8 (0.9)	−0.7 (0.6)
Total body BMD (g/cm^2)	1.13 (0.09)	1.12 (0.07)

Data are mean (SD) or percentage except for alcohol intake, which is median (range). There were no statistically significant differences between the groups. BMI, Body mass index; GGT, γ-glutamyl transferase.

To convert to SI units, multiply by: [a] 0.25, [b] 0.11, [c] 2.5, and [d] 0.035.

TABLE 2. HIV-related clinical characteristics of the groups

Characteristic	Placebo (n = 22)	Zoledronate (n = 21)
Time since diagnosis (yr)	7.8 (5.5)	8.3 (5.6)
AIDS-defining illness (%)	27	38
Lipodystrophy (%)[a]	50	71
First recorded body weight (kg)[b]	73 (13)	73 (13)
Body weight nadir (kg)[b]	70.6 (13.7)	69.5 (13.3)
CD4 count (cells/μl)		
Nadir[b,c]	130 (82)	131 (97)
Study entry[c]	521 (250)	559 (235)
After 2 yr[c]	520 (252)	509 (208)
Viral load (log copies/ml)		
Peak[b]	4.9 (0.5)	4.4 (0.9)
Study entry	1.8 (0.5)	2.1 (0.9)
After 2 yr	1.9 (0.8)	2.3 (1.1)
Duration of treatment (months)	55 (44)	67 (40)
Duration of HAART (months)	44 (24)	52 (22)

Data are mean (SD) or percentage. There were no statistically significant differences between the groups.

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

[b] Nadir/peak refers to lowest/highest value while under regular follow-up before study entry.

[c] Reference range: 500-1650 cells/μl.

The effect of zoledronate on BMD is shown in Fig. 2. At the lumbar spine, BMD increased by 8.9% over 2 yr in the zoledronate group compared with an increase of 2.6% in the control group ($P < 0.001$). At the total hip, BMD increased by 3.8% over 2 yr in the zoledronate group compared with a decrease of 0.8% in the control group ($P < 0.001$). At the total body, BMD increased by 2.3% over 2 yr compared with a decrease of 0.5% in the control group ($P < 0.001$). In the zoledronate group, the prevalence of osteopenia (T score < -1) at the lumbar spine or total hip declined from 52% at baseline to 28% at 2 yr, while remaining stable in the control group (55% at baseline, 53% at 2 yr). There were no statistically significant correlations between the changes in BMD at any site in the zoledronate group and laboratory or HIV-related parameters at baseline, or the change in HIV-related parameters over 2 yr, although the study had limited power to detect such associations.

The effect of zoledronate on bone turnover markers is shown in Fig. 3. In the zoledronate group, urine NTx levels decreased by 61% from baseline at 3 months ($P < 0.001$), and thereafter levels remained stable within the lowest tertile of the normal range for men and premenopausal women. Urine NTx levels in the placebo group were stable over the 2 yr ($P > 0.9$). The between-group differences in urine NTx over 2 yr were statistically significant ($P < 0.001$). In the zoledronate group, total serum alkaline phosphatase (ALP) decreased by 21% from baseline at 3 months ($P < 0.001$), and thereafter levels remained stable. ALP levels were stable in the placebo group over the 2 yr. Levels of urine NTx ($P = 0.66$) and ALP ($P = 0.97$) measured at 24 months did not decline from their respective levels measured at 12 months, despite a second dose of zoledronate, administered at 12 months.

Both groups tended to gain weight [mean change from baseline (95% confidence interval) 0.5 kg (−0.8–1.7), $P = 0.45$ for zoledronate group, and 1.3 kg (0.0–2.5), $P = 0.05$ for placebo group] and fat mass [mean change from baseline 0.5 kg (−0.8–1.8), $P = 0.46$ for zoledronate group, and 1.7 kg

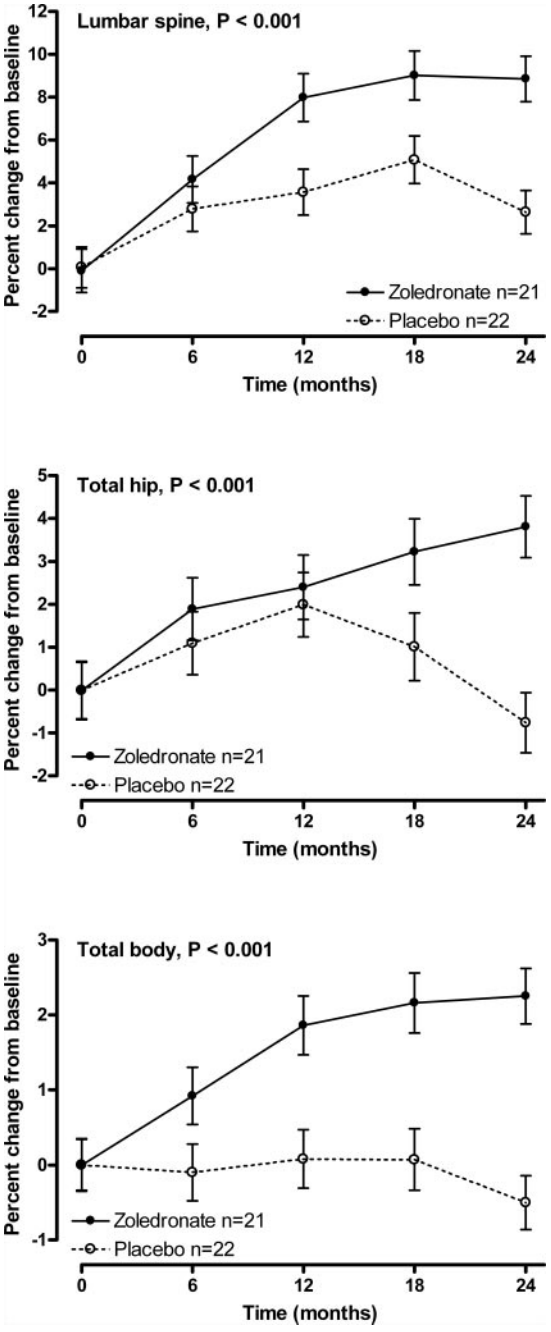

FIG. 2. The effects of 4 mg annual zoledronate or placebo on bone density at the lumbar spine, total hip, and total body in HIV-infected men. Bone densities are expressed as mean (SE) percent of initial values. *P* values are for the time-treatment interaction.

(0.4–3.0), $P = 0.01$ for the placebo group] during the study, whereas lean mass remained unchanged [mean change from baseline 0.0 kg (−0.9–0.9), $P = 0.99$ for zoledronate group, and 0.1 kg (−0.8–0.9), $P = 0.84$ for placebo group]. There were no significant between-group differences in the change from baseline for either weight or body composition ($P > 0.2$), and body weight and body composition at baseline and the change in body weight and body composition from baseline did not correlate with change in BMD at any site in either group ($P > 0.2$).

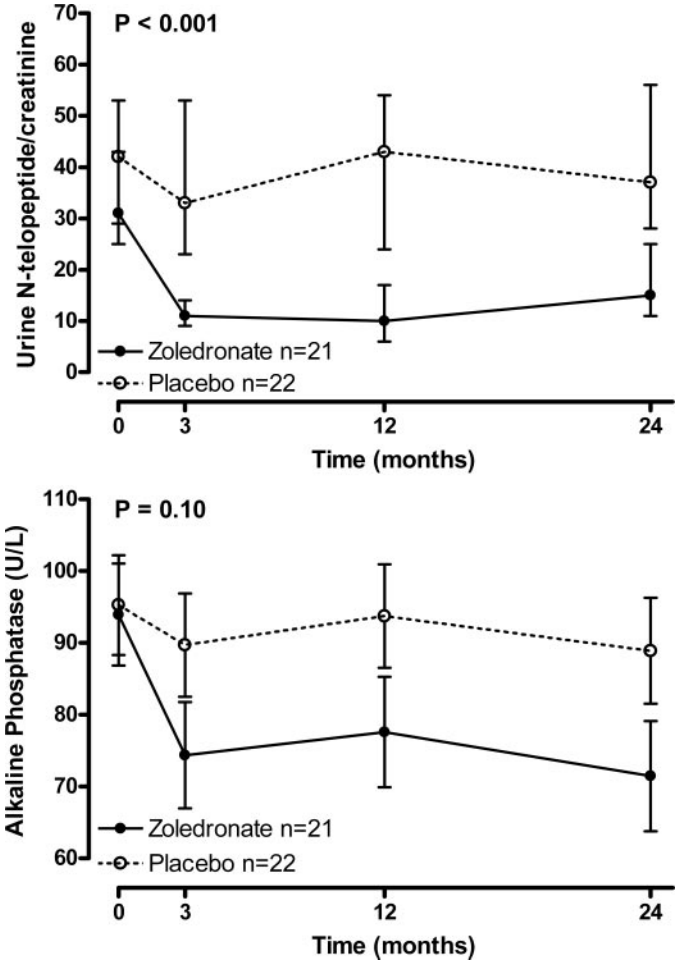

FIG. 3. The effects of 4 mg annual zoledronate or placebo on bone turnover markers in HIV-infected men. Data are median (98% confidence interval) for urine N-telopeptide and mean (SE) for ALP. *P* values are for the time-treatment interaction. The units of urine N-telopeptide/creatinine are nanomole bone collagen equivalents per millimole urine creatinine.

Zoledronate was generally well tolerated. Two men in the zoledronate group experienced acute-phase reactions that led them to discontinue study treatment after the first infusion, but no other treatment-related adverse effects were reported. One man who received placebo suffered a vertebral fracture at month 21 of the study. There were no other clinical fractures reported, and no other participants had fractures detected by vertebral morphometry at baseline or 2 yr.

Discussion

The current study provides evidence for the efficacy of zoledronate in the treatment of HIV-infected men who manifest significant bone loss. We found that zoledronate significantly increased BMD at the lumbar spine, hip, and total body in HIV-infected men treated with HAART, and that the between-group differences in BMD at all sites tended to increase throughout the study. Bone resorption decreased substantially by 3 months and remained stable thereafter. This is the first report of the effects on BMD of annual administration of the potent bisphosphonate, zoledronate, in

men, in HIV-infected subjects, or with drug administration beyond 12 months. These results are consistent with those of Reid *et al*. (9) who reported an increase in BMD at the lumbar spine of 5% and at the femoral neck of 2.5%, and a reduction in bone resorption markers of 50–60% in postmenopausal women at 12 months after a single administration of 4 mg of iv zoledronate. Thus, our findings extend the beneficial actions of zoledronate on BMD to men, and HIV-infected subjects, and suggest that there are ongoing benefits from annual administration of zoledronate for at least 24 months. The annual administration of this agent is an additional benefit in HIV-infected patients because many HAART regimens involve a complicated daily schedule of ingestion of several different medications, which is likely to impact adversely on compliance with other treatments.

There are few published studies on the use of bisphosphonates in men. Two studies have reported on the effect of daily 10 mg alendronate on men with primary osteoporosis (12, 13). Both studies reported significant increases in BMD from baseline over 2 yr of treatment with increases of 7.1–10.1% at the lumbar spine and 3.5–5.2% at the femoral neck. These increases in BMD were associated with a 7% reduction in vertebral fractures compared with placebo (12) and an 11% reduction compared with alfacalcidol (13). We observed similar changes in BMD to these two studies suggesting that annual administration of zoledronate may have similar efficacy to daily treatment with alendronate.

An important finding of the current study is that suppression of bone resorption remains stable and does not progressively decline during the second year of zoledronate therapy. Recently, concerns have been raised about potential over-suppression of bone turnover during long-term bisphosphonate therapy. Such over-suppression could increase susceptibility to fractures that fail to heal or heal poorly (14, 15). We found that annual administration of zoledronate led to a rapid 60% decrease in urine NTx levels after the first dose, but thereafter, median levels of urine NTx remained stable, within the lower part of the normal range, between 3 and 24 months. Epidemiological evidence suggests that suppression of bone resorption into this range is associated with optimal antifracture efficacy conferred by antiresorptive therapy (16).

There are three previous studies of bisphosphonate treatment in patients infected with HIV. All were randomized, open-label trials of alendronate 70 mg weekly, and produced conflicting results. Guaraldi *et al*. (8) reported a 52-wk trial of alendronate compared with placebo in 41 HIV-infected patients who had been taking HAART for at least 6 months and had a BMD T score below −1. All participants took calcium carbonate 1000 mg daily and vitamin D 500 IU daily. There were no statistically significant between-group differences in bone turnover markers or BMD at the spine or femoral neck. Mondy *et al*. (7) reported a 48-wk trial of alendronate compared with placebo in 31 HIV-infected patients treated with HAART for at least 6 months who had a lumbar spine T score below −1. All participants received 1000 mg calcium and 400 IU vitamin D daily. BMD at the spine increased by 5.2% in the alendronate group compared with 1.3% in the control group ($P < 0.05$), whereas there were no between-group differences at the femoral neck, trochanter, total hip, or total body. Bone turnover markers decreased in both groups, but the between-group difference was only statistically significant for bone-specific ALP. Negredo *et al*. (6) reported a 96-wk trial of alendronate with dietary counseling to ensure a daily calcium intake of more than 1200 mg compared with dietary counseling alone in 25 HIV-infected patients taking HAART with T score less than −2.5. There were increases in BMD at the spine and hip in the alendronate group, whereas BMD tended to decrease in the control group. The between-group differences in BMD were only statistically significant at the trochanter. The conflicting results between these studies may be due to the small size of the studies or the differences in study design and duration of follow-up. Our study provides rigorous evidence that bisphosphonate therapy improves BMD in HIV-infected subjects.

Although we have shown that annual administration of zoledronate causes significant increases in BMD in men infected with HIV, it remains uncertain what proportion of HIV-infected patients are likely to require treatment with bisphosphonates. The stability of BMD in the placebo group in this study is consistent with other recent studies that also report stable BMD in HIV-infected patients taking HAART (17–19). Therefore, in the absence of definitive evidence of increased skeletal morbidity in HIV-infected subjects, it seems reasonable to apply standard guidelines for the treatment of patients with osteoporosis to HIV-infected subjects (20, 21). The present study provides evidence for efficacy, tolerability, and convenience of annual zoledronate therapy for those HIV-infected patients who require treatment for osteoporosis.

Conclusions

The annual administration of 4 mg zoledronate is a potent and effective treatment for bone loss in men infected with HIV. It produces substantial increases in BMD and suppression of bone turnover that persist for at least 2 yr. The only previous report of annual zoledronate treatment showed benefits for postmenopausal women with low BMD over 12 months of follow-up. Our findings extend the potential benefits of annual treatment with zoledronate to include men, and low BMD in association with HIV infection, and show that benefits persist for at least 2 yr. Annual administration of zoledronate is a convenient and effective option for the treatment or prevention of bone loss for HIV-infected men with low BMD.

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