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Effects of Intravenous Zoledronate on Bone Turnover and Bone Density Persist for at Least Five Years in HIV-Infected Men

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Context: In HIV-infected men, the antiresorptive effects of zoledronate persist for at least 2 yr after the second annual dose.

Objective: Our objective was to determine the duration of action of zoledronate in men.

Design and Setting: This was 4-yr extension of a 2-yr, double-blind, randomized, placebo-controlled trial at an academic research center.

Participants: Participants included 43 HIV-infected men with bone mineral density (BMD) T score below −0.5, 35 of whom entered the extension study.

Intervention: Intervention was annual administration of 4 mg iv zoledronate or placebo at baseline and 1 yr and no intervention subsequently.

Main Outcome Measures: We evaluated changes in the bone turnover markers, serum osteocalcin and serum C-telopeptide (CTx), and changes in BMD at the lumbar spine, total hip, and total body.

Results: There was no time × treatment interaction between 1 and 5 yr after the second zoledronate dose for osteocalcin or CTx ($P > 0.4$) or any BMD site ($P > 0.7$). Between 1 and 5 yr after the second dose, on average, osteocalcin was 41% lower (95% confidence interval = 19–62%; $P < 0.001$), CTx 52% lower (33–71%; $P < 0.001$), lumbar spine BMD 3.7% greater (0.3–7.0%; $P = 0.03$), total hip BMD 2.3% greater (0.3–4.3%; $P = 0.02$), and total body BMD 2.5% greater (0.8–4.1%; $P = 0.004$) in the zoledronate group than the placebo group. Five years after the second dose, the between-groups differences were 38% (13–62%) for osteocalcin, 49% (20–77%) for CTx, 3.5% (0.7–6.7%) for lumbar spine BMD, 3.4% (1.4–5.4%) for total hip BMD, and 1.6% (0.2–3.1%) for total body BMD.

Conclusion: The effects of two annual 4-mg doses of zoledronate in men persist for at least 5 yr after the second dose. Larger trials assessing the antifracture efficacy of less frequent dosing of zoledronate are justified. **(*J Clin Endocrinol Metab* 97: 0000–0000, 2012)**

Zoledronate is a potent bisphosphonate that, when administered annually by iv infusion, increases bone mineral density (BMD) in men and women with osteoporosis (1, 2); prevents vertebral, nonvertebral, and hip fractures in women with osteoporosis (2); and prevents fractures and reduces mortality in people with a previous hip fracture (3). The optimal frequency of zoledronate dosing is yet to be determined. Previously, we reported that two

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Abbreviations: BMD, Bone mineral density; CI, confidence interval; CTx, β-C-terminal telopeptide of type I collagen; DXA, dual-energy x-ray absorptiometer; HAART, highly active antiretroviral therapy; NTx, N-telopeptide of type 1 collagen; 25OHD, 25-hydroxyvitamin D.

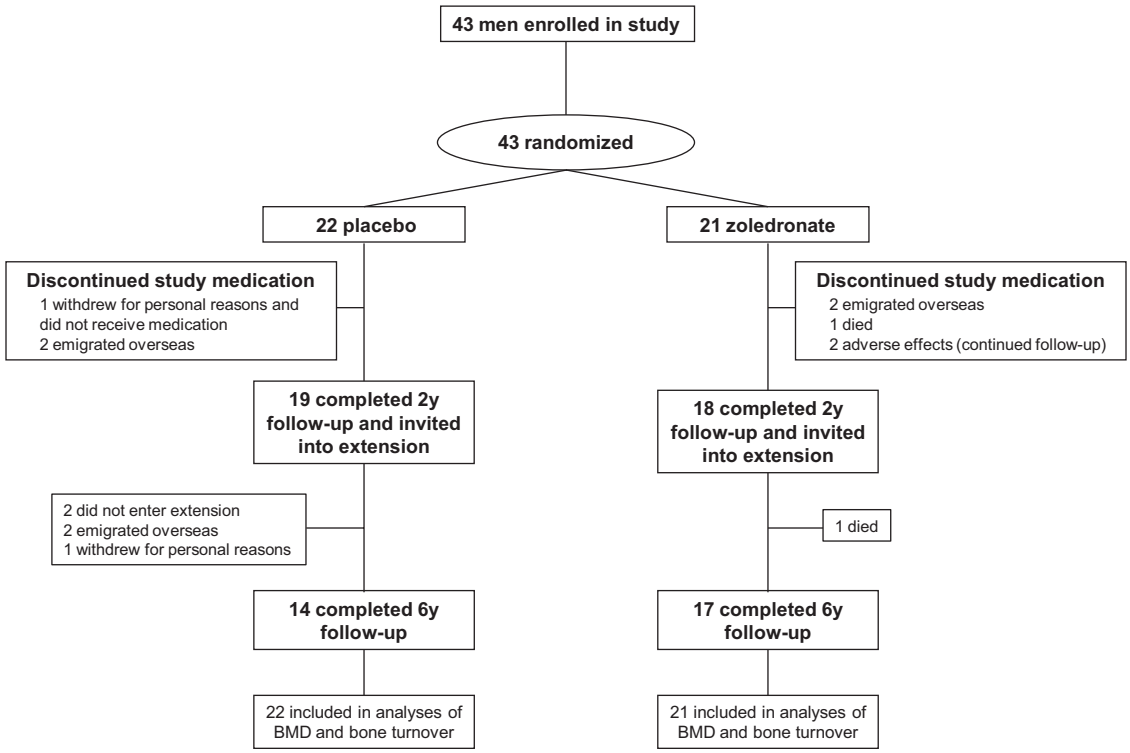

FIG. 1. Flow of participants.

annual 4-mg doses of zoledronate in HIV-infected men led to increases in BMD and decreases in markers of bone formation and resorption that persisted for 2 yr after the second dose of zoledronate (4, 5). After a single 5-mg dose of zoledronate in postmenopausal women with osteopenia, there were increases in BMD and decreases in markers of bone formation and resorption that persisted for at least 3 yr (6–8). In a *post hoc* analysis of the phase 3 trial of zoledronate, women receiving one dose of zoledronate had a 32% reduction in all clinical fractures after 3 yr compared with women receiving one dose of placebo (9). These findings suggest that the effects of zoledronate persist well beyond 12 months and that it could be administered less frequently than annually.

Here we report the findings from an extension of our 2-yr, randomized, placebo-controlled trial of annual 4 mg iv zoledronate in HIV-infected men (4). We studied participants for an additional 4 yr after completion of the trial, without administration of additional antiresorptive medication. Thus, we investigated the persistence of effects of zoledronate on markers of bone turnover and BMD in men for 5 yr after the second of two doses of zoledronate.

Subjects and Methods

Participants

The randomized placebo-controlled trial protocol has been previously published in full (4). Briefly, 43 HIV-infected men treated with highly active antiretroviral therapy (HAART) for at least 3 months and with a BMD T score below −0.5 at the lumbar spine or total hip were enrolled. HAART was defined as an HIV treatment regimen containing at least three antiretroviral agents. 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 were ineligible to participate. All participants who completed 2 yr of follow-up (n = 37) were invited to take part in an unblinded, open-ended extension study, and 35 agreed to continue follow-up (Fig. 1). Both the original study and the extension study received ethical approval from the Northern X regional ethics committee, and the trial was registered with the Australian New Zealand Clinical Trials Registry as ACTRN012605000208606. All participants gave written, informed consent.

Protocol

Participants were randomly allocated to receive an annual administration of either 4 mg zoledronate, given as a 15-min iv infusion in 100 ml 0.9% NaCl, or matching placebo for 2 yr, and all participants received a supplement of 400 mg/d calcium and 50,000 IU/month vitamin D (cholecalciferol). The 4-mg dose of zoledronate was used because the 5-mg preparation was not available at study inception. In the extension study, no additional study medication or calcium and vitamin D supplements were administered. No participants took agents that might affect BMD during the study.

Measurements

BMD was measured every 6 months at the lumbar spine, proximal femur, and total body using a Lunar Expert or a GE Prodigy dual-energy x-ray absorptiometer (DXA) (GE Lunar, Madison WI). A change in densitometer occurred during the

study. All scans for the first 3 yr of the study were carried out using the Expert DXA and thereafter progressively were carried out using the Prodigy DXA. For this study, data from each scan performed using the Expert DXA were converted to predicted Prodigy DXA values for use in the final analyses. Interconversion of BMD data was carried out as previously described (10). Briefly, 64 people not involved in this study had BMD measurements of the lumbar spine, total body, and total hip on both machines on the same day. Models allowing interconversion of data were developed from half of this sample and validated in the remaining half. The equations generated were as follows: for lumbar spine BMD, Prodigy = 0.895 × Expert + 0.1151; for total hip, Prodigy = 0.965 × Expert + 0.0307; and for total body, Prodigy = 1.035 × Expert − 0.0195.

At baseline, at 3 months, and at the end of each year, fasting blood and second-voided morning urine samples were collected. Serum osteocalcin and serum β-C-terminal telopeptide of type I collagen (CTx) were measured using the Roche Elecsys 2010 platform (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, HIV parameters (CD4 count and viral load), and bone turnover were performed (4). Measurements of bone turnover were repeated at 3 months and each year and HIV parameters at 2 and 6 yr. Because of an equipment malfunction, all stored serum baseline samples were lost, and assays of osteocalcin and CTx were unable to be performed on baseline samples.

Statistics

Differences between groups for continuous variables were assessed using Student's *t* test and for categorical variables using the χ^2 test. Urine NTx measurements were log transformed before analysis because they were not normally distributed and were normally distributed after transformation. BMD data were analyzed using raw data, although results are presented as percent change from baseline adjusted for baseline between-groups differences for ease of interpretation. All analyses were carried out on an intention-to-treat basis. A mixed-models approach to repeated measures was used to examine the time course of response in the treatment and control arms for bone turnover markers and BMD measurements and main effects reported. In sensitivity analyses, missing values were imputed for the BMD and bone turnover endpoints, first by carrying forward the most recent value and second by performing a Markov chain Monte Carlo simulation to create 10 imputed datasets, performing a mixed-models ANOVA on each and aggregating the results. All tests were two tailed, and statistical significance was set at $P < 0.05$. All statistical analyses were carried out using the SAS software package version 9.1 (SAS Institute, Cary, NC).

Results

The flow of participants through the study is shown in Fig. 1. The baseline and HIV-related clinical characteristics of the two groups were similar (Table 1). There were no significant differences in baseline characteristics between participants who completed the study and those who did not. There were no significant HIV-related clinical events in any of the participants during the study. At baseline, two men in the placebo group and one in the zoledronate group had a CD4 count below 200 cells/μl, whereas none of the men had a CD4 count below 200 cells/μl at 6 yr. The proportion of participants in each group having an undetectable viral load remained similar throughout (Table 1). Medication regimens were similar between the groups, and at 6 yr, four of 14 men in the placebo group were taking tenofovir compared with seven of 17 in the zoledronate group. None of the participants had any potential adverse affects from zoledronate during the extension study.

TABLE 1. Baseline characteristics of the treatment groups

	Placebo n = 22	Zoledronate n = 21
Characteristic		
Age (yr)	48.8 (9.0)	49.5 (9.0)
Weight (kg)	75 (12)	73 (10)
Current smoker (%)	27	24
Dietary calcium (mg/d)	854 (600)	963 (699)
L1–L4 BMD (g/cm^2)	1.11 (0.16)	1.15 (0.11)
Total femur BMD (g/cm^2)	0.94 (0.11)	0.94 (0.07)
Total body BMD (g/cm^2)	1.13 (0.09)	1.12 (0.07)
25OHD (ng/ml)	23 (11)	28 (10)
25OHD <20 ng/ml (%)	36	19
HIV-related characteristic		
Time since diagnosis (yr)	7.8 (5.5)	8.3 (5.6)
AIDS defining illness[a] (%)	27	38
Lipodystrophy[b] (%)	50	71
CD4 count[c] (cells/μl)		
Baseline	521 (250)	559 (235)
2 yr	520 (252)	509 (208)
6 yr	704 (250)	600 (180)
Undetectable viral load[d] (%)		
Baseline	86	76
2 yr	86	70
6 yr	93	76
Duration of HAART (months)	44 (24)	52 (22)

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

[a] AIDS was defined as a patient suffering a severe opportunistic infection or malignancy.

[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] Viral load was undetectable below 50 copies/ml at the baseline and 2-yr assessments and below 20 copies/ml at the 6-yr assessment.

The effect of zoledronate on bone turnover markers is shown in Fig. 2. Serum osteocalcin and CTx were measured from 2 yr (12 months after the second infusion of study medication) to 6 yr. There was no evidence of a time × treatment interaction between 2 and 6 yr for either bone turnover marker ($P > 0.4$). Between 2 and 6 yr, on average, serum osteocalcin was 41% lower [95% confidence interval (CI) 19–62%; $P < 0.001$] and serum CTx 52% lower (95% CI = 33–71%; $P < 0.001$) in the zoledronate group than the placebo group. At 6 yr, serum

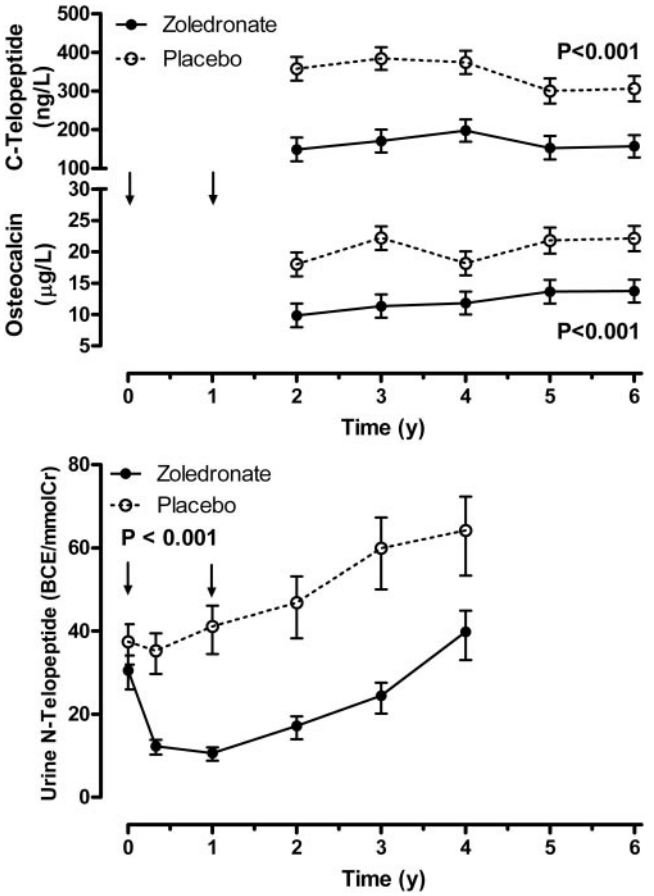

FIG. 2. The effect of two annual doses of 4 mg zoledronate or placebo (indicated by *arrows*) on serum CTx, serum osteocalcin, and urine NTx. Data are mean (SE). *P* values are for the main effects of treatment for CTx and osteocalcin and the time × treatment interaction for NTx. The units of urine NTx/creatinine are nanomolar bone collagen equivalents (BCE) per millimole urine creatinine (Cr).

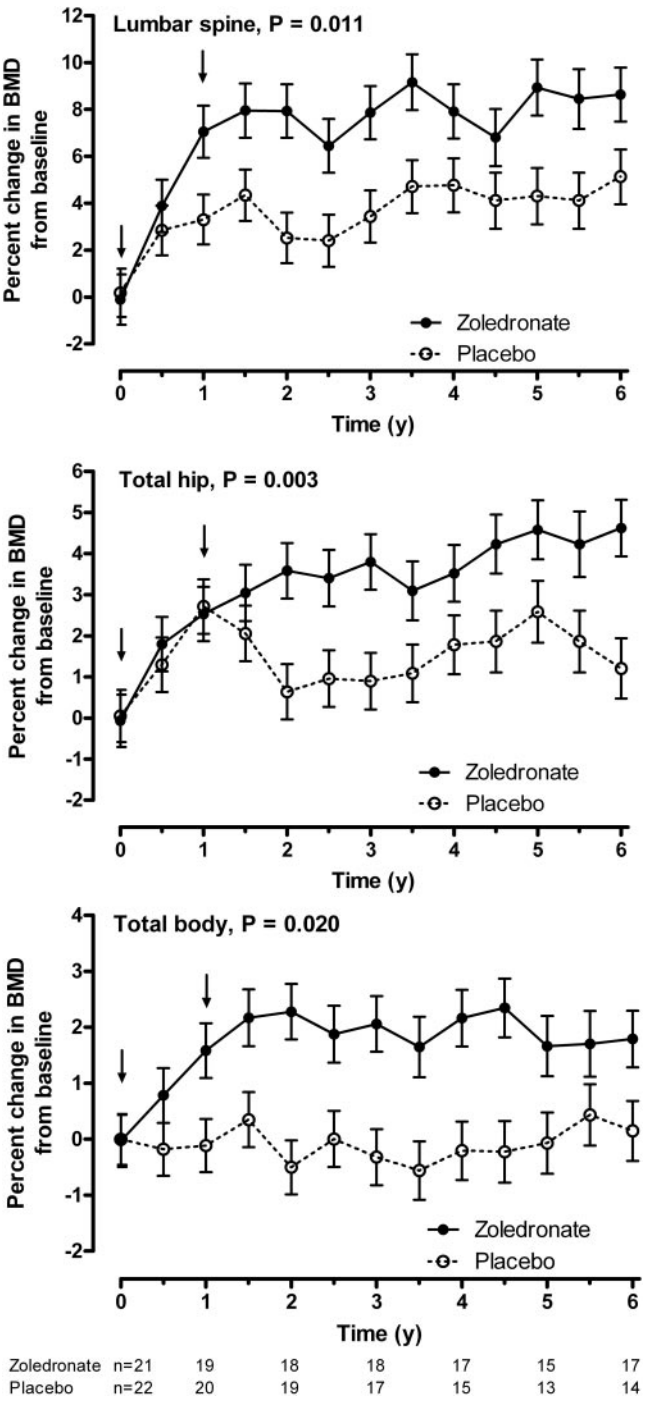

FIG. 3. The effect of two annual doses of 4 mg zoledronate or placebo (indicated by *arrows*) on BMD at the lumbar spine, total hip, and total body. Data are mean (SE) percentage change from baseline. *P* values are for the time × treatment interaction.

osteocalcin remained 38% lower (95% CI = 13–62%) and serum CTx 49% lower (95% CI = 20–77%) in the zoledronate group than the placebo group. Urine NTx was measured from baseline to 4 yr. After the first infusion of zoledronate, urine NTX decreased by 63% at 3 months. Thereafter, the absolute differences between the groups remained similar, although there was a steady upward drift in both treatment groups.

The effect of zoledronate on BMD is shown in Fig. 3. At all three sites, the difference in the changes in BMD between the treatment groups over the 6 yr was statistically significant ($P < 0.02$), and there was no evidence of a time × treatment interaction between 2 yr (12 months after the second infusion of study medication) and 6 yr ($P > 0.7$). Between 2 and 6 yr, on average, BMD was greater at the lumbar spine by 3.7% (95% CI = 0.3–7.0%; $P = 0.03$), at the total hip by 2.3% (95% CI = 0.3–4.3%; $P = 0.02$), and at the total body by 2.5% (95% CI = 0.8–4.1%; $P = 0.004$). At 6 yr, the between-groups difference in BMD at the lumbar spine was 3.5% (95% CI = 0.7–6.7%), at the total hip 3.4% (95% CI = 1.4–5.4%), and at the total body 1.6% (95% CI = 0.2–3.1%).

We assessed the impact of baseline vitamin D status on our findings. There were no significant differences between the groups in mean 25-hydroxyvitamin D (25OHD) level or the proportion of individuals with 25OHD below 20 ng/ml (Table 1). There were no significant vitamin D status × time interactions for BMD at any site in the placebo group for yr

TABLE 2. Sensitivity analyses assessing the impact of missing data

	Difference (95% CI)			
	Intention-to-treat unimputed	Last observation carried forward	Markov chain Monte Carlo simulation	Completers analysis
L14 BMD (%)	3.7 (0.3–7.0)	3.9 (0.7–7.0)	3.9 (−0.2–8.0)	3.2 (0.4–6.7)
Total hip BMD (%)	2.3 (0.3–4.3)	2.1 (0.3–3.9)	2.8 (0.1–5.5)	2.6 (0.3–4.9)
Total body BMD (%)	2.5 (0.8–4.1)	2.6 (1.0–4.2)	2.7 (0.8–4.6)	1.9 (0.5–3.4)
Osteocalcin (%)	41 (19–62)	39 (20–59)	47 (23–70)	38 (18–58)
CTx (%)	52 (33–71)	51 (32–71)	35 (8–63)	55 (32–76)

Data are the average differences between the zoledronate group and the placebo group (expressed as a percentage) from 2–6 yr obtained using the four different analyses.

0–2, 0–6, or 2–6 in the placebo group ($P > 0.1$). Likewise, in the entire cohort, baseline 25OHD did not independently predict changes in BMD at any site for any of these three time periods ($P > 0.3$).

Finally, we carried out sensitivity analyses to assess the effect of missing data. We imputed missing data first by carrying forward the most recent result and second by performing a Markov chain Monte Carlo simulation. The results of all these analyses were similar to those in which there was no imputation for missing data (Table 2). We then repeated all the analyses, restricting the analyses to participants who completed the 6-yr study. Again, the results did not change substantially from the intention-to-treat unimputed analyses (Table 2).

Two participants, both in the placebo group, sustained fractures during the study (one spine and one humerus fracture).

Discussion

In this study, the effects of two annual doses of 4 mg iv zoledronate on bone turnover and BMD in men lasted at least 5 yr after the second dose. Markers of bone formation and resorption showed sustained and stable suppression, and BMD remained stable between 1 and 5 yr after the second dose of zoledronate. The results are consistent with another clinical trial from our group that showed sustained, stable suppression of bone turnover and increased BMD 5 yr after a single dose of 5 mg zoledronate in postmenopausal women (submitted for publication). Taken together, the results extend findings from previous studies from our group and others that have also reported duration of effects of zoledronate in various population groups lasting at least 2–3 yr (5–8, 11). These results are also consistent with the extension of the original phase 3 Horizon study. Results from that study show that after 3 yr after three annual doses of zoledronate, femoral neck BMD decreased slightly and bone turnover increased slightly in older postmenopausal women (12). Our findings complement and extend the findings of the Horizon extension by reporting the effects of a different dose and duration of treatment, in a different population group, in a placebo-controlled study design, with a substantially longer duration of follow-up after discontinuation of zoledronate.

A key question is whether the effects of zoledronate observed on the surrogate endpoints of bone turnover and BMD will translate into reductions in the clinical endpoint of fractures. That question will be answered definitively only by a carefully designed prospective clinical trial. However, there are several lines of evidence that suggest that fracture prevention is likely. The changes in bone turnover and BMD 5 yr after the second dose of 4 mg zoledronate in this study are similar to those observed in men with osteoporosis after 2 yr of annual 5 mg zoledronate (1), weekly 70 mg alendronate (1), or 10 mg daily alendronate (13). In the latter study, daily alendronate reduced the incidence of morphometric vertebral fractures by 90% (13). In postmenopausal women, the changes in bone turnover and BMD 5 yr after a single dose of 5 mg zoledronate (submitted for publication) are similar to those observed in studies of 3–4 yr treatment with risedronate (14), alendronate (15), and annual administration of iv zoledronate (2, 3) that reported prevention of osteoporotic fractures with these agents. Finally, in a 3-yr trial of annual 5 mg zoledronate, women who received only one dose of zoledronate had a 32% reduction in all clinical fractures compared with women who received only one dose of placebo (9). These data provide a strong rationale for investigating alternative treatment regimens of zoledronate, including both lower doses and less frequent dosing intervals. If effective, such regimens might offer substantial cost savings and reduce concern regarding long-term safety.

Some important clinical issues arise from the prolonged effects of zoledronate. First, for men with HIV and high fracture risk, the current data suggest that infrequent dosing with zoledronate may be an effective therapy, with the benefit of not adding to daily oral medication regimens. Second, there should be less concern about poor compli-

ance than with some other osteoporosis agents. For example, after discontinuation of denosumab or odanacatib, there is a rapid increase in bone turnover and a rapid reduction in BMD to baseline levels (16, 17). Similarly, discontinuation of estrogen and teriparatide leads to a rapid decrease in BMD (18–20).

The current study has some limitations. It is a small study, although the narrow confidence intervals around the changes in bone turnover and BMD suggest that the findings are robust. Although there were no statistically significant baseline differences between the groups, the study did not have power to detect small differences in these variables. Twenty-eight percent of individuals enrolled in the study did not complete the 6-yr follow-up, although the majority of those lost to follow-up emigrated overseas so are likely to be missing at random rather than for reasons related to their treatment allocation. There was no evidence from the sensitivity analyses that the missing data affected the study findings, although this might be limited by the small study size. The study cohort was HIV-infected men treated with HAART whose HIV infection was well controlled, so the conclusions may not be generalizable to other groups, although the results were similar to results from studies of men with osteoporosis (1, 13). The congruent findings from a 5-yr trial of a single dose of zoledronate in postmenopausal women suggest that the current results are broadly applicable (manuscript submitted). Nevertheless, both studies have included only individuals with mildly low BMD, and the results may not apply to individuals with lower BMD and higher risk of fracture.

In summary, the effects of two annual 4-mg doses of zoledronate on bone turnover and BMD in men persist for at least 5 yr after the second dose. Additional randomized trials are justified to explore the antifracture efficacy of dosing schedules of zoledronate given less frequently than is currently recommended.

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