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HIV/AIDS

A Single-dose Zoledronic Acid Infusion Prevents Antiretroviral Therapy–induced Bone Loss in Treatment-naive HIV-infected Patients: A Phase IIb Trial

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Background. Human immunodeficiency virus (HIV) infection and antiretroviral therapy (ART) are associated with bone loss leading to increased fracture rate among HIV-infected individuals. ART-induced bone loss is most intense within the first 48 weeks of therapy, providing a window for prophylaxis with long-acting antiresorptives.

Methods. In a phase 2, double-blind, placebo-controlled trial, we randomized 63 nonosteoporotic, ART-naive adults with HIV initiating ART with atazanavir/ritonavir + tenofovir/emtricitabine to a single zoledronic acid (ZOL) infusion (5 mg) vs placebo to determine the efficacy of ZOL in mitigating ART-induced bone loss. Plasma bone turnover markers and bone mineral density (BMD) were performed at weeks 0, 12, 24, and 48 weeks. Primary outcome was change in C-terminal telopeptide of collagen at 24 weeks. Repeated-measures analyses using mixed linear models were used to estimate and compare study endpoints.

Results. The ZOL arm had a 65% reduction in bone resorption relative to the placebo arm at 24 weeks (0.117 ng/mL vs 0.338 ng/mL; $P < .001$). This effect of ZOL occurred as early as 12 weeks (73% reduction; $P < .001$) and persisted through week 48 (57% reduction; $P < .001$). The ZOL arm had an 8% higher lumbar spine BMD at 12 weeks relative to the placebo arm ($P = .003$), and remained 11% higher at 24 and 48 weeks. Similar trends were observed in the hip and femoral neck.

Conclusions. A single dose of ZOL administered at ART initiation prevented ART-induced bone loss through the first 48 weeks of ART, the period when ART-induced bone loss is most pronounced. Validation of these results in larger multicenter randomized clinical trials is warranted.

Clinical Trials Registration. NCT01228318.

Keywords. antiretroviral therapy–induced bone loss; zoledronic acid; human immunodeficiency virus.

Increasing longevity of the human immunodeficiency virus (HIV) population has renewed interest in the long-term complications of HIV infection [1]. Among the metabolic complications of chronic HIV infection is skeletal deterioration [2]. Osteopenia prevalence in HIV-infected cohorts ranges from 22% to 71%, with rates of osteoporosis varying from 3% to 33% [3]. An intriguing aspect of this phenomenon is that antiretroviral therapy (ART) exacerbates rather than ameliorates bone loss [4]. The skeletal effects of ART, although varied in magnitude, appear to be universal to all ART types including tenofovir alafenamide (TAF)–containing and tenofovir disoproxil fumarate (TDF)–sparing regimens [5–10]. Losses of up to 6% in bone mineral density (BMD) were observed with earlier regimens within 1–2 years of ART initiation [2]. With TAF, an average loss in BMD of 0.66% at the hip and 1.30% at the lumbar spine was observed after 48 weeks in ART-naive, HIV-infected patients. Of note, although reductions in BMD cannot be quantitatively correlated to fracture incidence, a 2- to 9-fold higher fracture prevalence is reported with HIV infection relative to the general population [11, 12]. There is also a growing concern that the bone loss induced by ART on a background of a preexisting virally induced weakened skeleton will synergize with the natural age-related bone loss to cause an epidemic of fragility fracture [13].

To better understand the mechanism underlying this phenomenon, we previously examined bone turnover in HIV-infected patients initiating ART, and observed a surge in bone resorption, starting as early as 2 weeks and lasting through 24 weeks [14]. Because T-cell recovery with ART reaches a significant magnitude by 12 weeks [15], the time point at which we observed a peak in bone resorption, we speculated that there was a link between immune reconstitution and ART-induced bone loss. Using an animal model of immune reconstitution created by syngeneic adoptive transfer of T cells into T-cell

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knockout mice, we observed that immune reconstitution resulted in a profound loss in BMD [16]. Importantly, in this animal model, bone loss was prevented by zoledronic acid (ZOL), a potent, long-acting antiresorptive, administered before T-cell transfer [16].

In the current report, we tested the efficacy of ZOL in preventing ART-induced bone loss in treatment-naive HIV-infected patients initiating ART. We hypothesized that the preponderance of bone loss in this setting would occur during early period of therapy when T-cell recovery is most pronounced, providing an exploitable window for preemptive intervention to mitigate ART-induced bone resorption and preserve natural bone in this population.

METHODS

Trial Design

This phase IIb clinical trial was conducted at the Grady Infectious Diseases Program Clinic in Atlanta, Georgia, between January 2010 and January 2015. All subjects provided written informed consent, and the study was approved by the Institutional Review Board of Emory University. Investigational new drug approval was obtained from the US Food and Drug Administration for off-label use of ZOL. The study was registered at ClinicalTrials.gov (identifier NCT01228318).

Objectives

The primary objective was to evaluate whether ZOL ameliorates ART-induced bone resorption in the study population. Secondary objectives included ZOL's impact on BMD outcomes at key fracture-prone anatomical sites, and safety and clinical measures.

Participants

Viremic (HIV type 1 [HIV-1] RNA > 1000 copies/mL), treatment-naive, HIV-infected patients aged 30–50 years who were planning ART initiation, had no history of bone or active immunological disease other than HIV infection, and were in generally good health, were eligible for the study if they had serum vitamin D3 level ≥12 ng/mL and serum calcium level ≥8 mg/dL within 60 days before enrollment. Sexually active women of reproductive age were required to agree to use at least one reliable method of contraception during the study. Patients who had osteoporosis (t score < −2.5), prior or current use of antiresorptives, recent (within 6 months) or planned invasive dental procedures, active peptic ulcer disease or recent history of gastrointestinal bleed, serious systemic illness, or were pregnant or breastfeeding were excluded.

Randomization

Treatment assignments were stratified according to screening HIV-1 RNA (<100 000 or ≥100 000 copies/mL), age (30–39 or 40–49 years), and sex, and were generated using a pseudo-random-number generator with permuted blocks for each of the 8 levels of stratification. The unblinded study pharmacist maintained 8 color-coded sets of sealed, sequenced, opaque envelopes containing the treatment assignment. Each envelope uniquely identified each stratum and the sequence number. All other individuals involved in the study were blinded to the randomization, with the exception of the data coordinating center biostatisticians.

Interventions

At entry, participants initiated ART per standard of care with standard doses of atazanavir/ritonavir + TDF/emtricitabine (FTC) [17]. ART change was allowed after study entry in the case of drug intolerance or virologic failure. On the same day of ART initiation, participants also received a single intravenous infusion of ZOL (5 mg per 100 mL ready-to-infuse solution), if assigned to the ZOL arm, or a single infusion of placebo (220 mg mannitol and 24 mg sodium citrate per 100 mL ready-to-infuse solution), if assigned to the placebo arm.

Follow-up

Study outcomes were assessed at baseline and at study weeks 12, 24, 36, and 48. The study was unblinded when the last enrolled participant completed the 24-week visit. Clinical and safety laboratory tests were performed at week 2, week 12, and every 3 months thereafter.

Outcome Measures

Blood samples for biomarkers of bone turnover were processed within 60 minutes of collection, and plasma was separated by centrifugation and frozen at −80°C until analysis. Commercial enzyme-linked immunosorbent assays from Immunodiagnostic Systems, (Scottsdale, Arizona) were used according to the manufacturer's instructions [18, 19] to quantify plasma C-terminal telopeptide of collagen (CTx) and osteocalcin, sensitive and specific markers of bone resorption and bone formation, respectively. BMD was assessed using a Lunar prodigy scanner (GE Lunar, Madison, Wisconsin) dual-energy X-ray absorptiometry (DXA) machine and Encore Software, version 2010 13.31, at Emory University Hospital. Osteopenia was defined as t scores between −1.0 and −2.5, and osteoporosis as t scores < −2.5 per World Health Organization criteria [20]. Clinical and safety laboratory tests were performed at a Clinical Laboratory Improvement Amendments–adherent laboratory. Safety reports were generated by the data coordinating center every year and reviewed by an independent medical safety monitor.

Sample Size and Power Considerations

Pilot data from a study of treatment-naive HIV-infected patients on therapy for 24 weeks with lopinavir/ritonavir + TDF/FTC [14] form the basis for estimating sample size. Assuming an increase on average of 1.2 μg/L for CTx in the active placebo arm and on average no change in the ZOL arm and an estimated standard deviation in each group of 1.4 μg/L, a sample size of 30 patients per treatment arm achieves 90% power to detect a treatment difference of 1.2 μg/L in CTx between active placebo

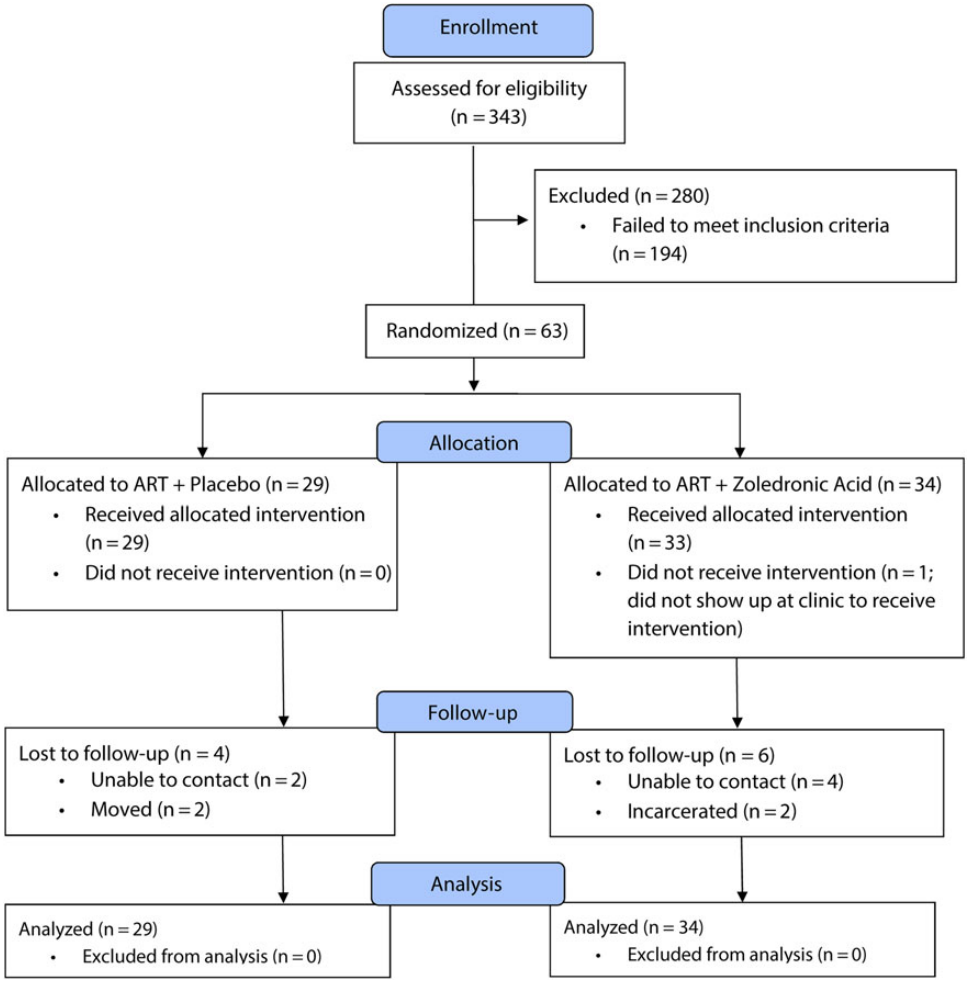

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. The progress through the phases (enrollment, intervention allocation, follow-up, and data analysis) of a double-blind, randomized controlled trial in nonosteoporotic, viremic, antiretroviral therapy (ART)–naive, human immunodeficiency virus-infected adults comparing a single zoledronic acid (5 mg) infusion at the time of ART initiation with active placebo infusion is shown.

and ZOL at 24 weeks if the true difference between treatments is 1.2 μg/L (2-sided, 2-sample equal-variance t test and $\alpha = .05$).

Statistical Analysis

The primary analyses of the data were performed on an intention-to-treat basis, and data from all randomized participants were included in the final analysis. Time to viral suppression was analyzed using Kaplan–Meier curves and compared between treatment arms using log-rank tests. Repeated-measures analyses of CTx, osteocalcin, and BMD (lumbar spine, mean of right and left measurements for hip and femoral neck) were performed with a means model using SAS version 9 (Proc Mixed, mixed linear models) providing separate estimates of the means by time on study (baseline and weeks 12 [range, 6–16], 24 [20–28], and 48 [44–52]) and treatment arm. Clinical visits for CD4 T-cell count included baseline and 4, 16, 24, 36, and 48 weeks. The same model was used to analyze percentage change from baseline for CTx, osteocalcin, and BMD. Each model included 3 predictors (treatment arm, time on study, and the statistical interaction between treatment arm and time on study). A compound-symmetric variance-covariance form in repeated measurements was assumed for each outcome, and robust estimates of the standard errors of parameters were used to perform statistical tests and construct 95% confidence intervals (CIs) [21]. The model-based means are unbiased with unbalanced and missing data, so long as the missing data are noninformative (missing at random), and t tests were used to compare the differences between the model-based treatment means (least-squares means) at each time point and to compare differences over time within each treatment arm. Specific statistical tests were done within the framework of the mixed-effects linear model. All statistical tests were 2-sided and unadjusted for multiple comparisons. A value of $P < .05$ indicated statistical significance. The study was designed as a fixed-sample size study and no formal interim analyses were performed for safety and efficacy. Statistical stopping

Table 1. Baseline Demographic and Clinical Characteristics by Treatment

Characteristic	ART + PL (n = 29)	ART + ZOL (n = 34)
Age, y, mean (SD)	39.4 (6.9)	39.7 (6.6)
Sex, No. (%)		
Male	23 (79.3)	27 (79.4)
Female	6 (20.7)	7 (20.6)
Race		
White	3 (10.3)	7 (20.6)
Black	26 (89.7)	27 (79.4)
History of smoking		
Yes	26 (89.7)	24 (70.6)
No	3 (10.3)	10 (29.4)
Current smoking		
Yes	23 (79.3)	19 (55.9)
No	6 (20.7)	15 (44.1)
Cigarettes smoked per day (in patients with history of smoking)	7.6 (4.5)	7.5 (6.0)
Years of cigarette smoking (in patients with history of smoking)	13.4 (8.1)	13.9 (9.6)
Alcohol use in past 30 d		
Daily	1 (3.4)	2 (5.9)
5–6 times/wk	0 (0)	1 (2.9)
3–4 times/wk	1 (3.4)	4 (11.8)
1–2 times/wk	8 (27.6)	3 (8.8)
2–3 times/mo	2 (6.9)	2 (5.9)
Once/mo	3 (10.3)	8 (23.5)
Never	14 (48.3)	14 (41.2)
Baseline osteopenia in any area[a]		
Yes	10 (34.5)	7 (21.9)
No	19 (65.6)	25 (78.1)
Baseline lumbar spine BMD, g/cm^3	1.23 (0.14)	1.29 (0.14)
Baseline lumbar spine BMD *t* score	0.16 (1.16)	0.67 (1.22)
History of bone fracture		
Yes	5 (17.2)	10 (29.4)
No	24 (82.8)	24 (70.6)
HIV-1 RNA, $\log_{10}$ copies/mL (SD)	4.81 (0.96)	5.26 (0.44)
CD4$^+$ count, cells/uL (SD)	155 (145)	102 (69)
Serum calcium, mg/dL (SD)	9.3 (0.4)	9.1 (0.4)
Serum vitamin D, ng/mL (SD)	27.8 (10.0)	28.1 (11.7)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; BMD, bone mineral density; HIV, human immunodeficiency virus; PL, active placebo; SD, standard deviation; ZOL, zoledronic acid.

[a] Osteoporotic patients not enrolled in the study. Baseline dual-energy X-ray absorptiometry measurements for 2 patients were performed with a different machine and were not included in the analyses.

boundaries were not established as an aide to early stopping of the study. Monthly data reports were generated to summarize the timeliness and completeness of expected study case report forms. Monthly data quality checks and data queries were generated when creating analytic data sets used to generate monthly safety reports and monthly summary statistics. Each of 36 solicited adverse events was counted only once per patient as the most severe level reported across the 4 study visits during the 48-week follow-up period and compared between treatment arms with a χ^2 or Fisher exact test. Statistical analyses were limited to the 20 most commonly reported adverse effects (AEs) after excluding those symptoms reported as mild.

RESULTS

Demographic and Clinical Characteristics

A total of 343 patients were assessed for eligibility (Figure 1), and 63 were randomized to receive either ZOL (n = 34) or active placebo (n = 29). Demographic and clinical characteristics were comparable between the 2 study arms (Table 1).

ZOL Blunted ART-Induced Bone Resorption

CTx in the treatment arms changed in significantly different ways (ie, different temporal patterns over time) during the 48 weeks of follow-up ($P < .001$, test for interaction between time on study and treatment arm). Mean CTx was similar in both treatment arms at randomization (0.154 ng/mL vs 0.190 ng/mL for ZOL vs placebo, respectively; $P = .22$) but became significantly lower in the ZOL arm at 12 weeks (0.083 ng/mL vs 0.305 ng/mL; $P < .001$), 24 weeks (0.117 ng/mL vs 0.338 ng/mL; $P < .001$), and 48 weeks (0.116 ng/mL vs 0.269 ng/mL; $P < .001$; Figure 2*A*). Treatment with ZOL led to a 73% reduction in bone resorption relative to placebo at 12 weeks (CTx mean difference = −0.222 ng/mL [95% CI, −.306 to −.139]), with a 65% and 57% relative reduction at 24 weeks (mean difference, −0.221 ng/mL [95% CI, −.300 to −.145]) and 48 weeks (mean difference, −0.153 ng/mL [95% CI, −.221 to −.085]). The CTx mean percentage increase from baseline to 12, 24, and 48 weeks was 145%, 244%, and 140%, respectively, in the placebo arm. The CTx mean percentage decrease from baseline to 12, 24, and 48 weeks was 39%, 13%, and 18%, respectively, in the ZOL arm (Figure 2*B*; Table 2).

Bone Formation Was Not Affected by ZOL

Osteocalcin levels in the treatment arms were consistently different ($P < .001$), with the placebo arm having significantly higher serum osteocalcin levels than ZOL arm at each time point except baseline. Mean difference in osteocalcin between the arms pooled over the 48-week follow-up period was −4.8 ng/mL (95% CI, −7.4 to −2.2 ng/mL; Figure 2*C*). Mean difference at 12 weeks, 24 weeks, and 48 weeks was −4.2 ng/mL (95% CI, −7.6 to −.8 ng/mL), −5.3 ng/mL (95% CI, −8.4 to −2.3 ng/mL), and −8.1 ng/mL (95% CI, −12.9 to −3.3 ng/mL), respectively. The osteocalcin mean percentage increases from baseline to 12 and 48 weeks were 61% (95% CI, 27% to 95%) and 137% (95% CI, 58% to 216%), respectively, in the placebo arm (Figure 2*D*). Osteocalcin did not change from baseline to 48 weeks in the ZOL arm ($P = .22$).

ZOL Prevented ART-Induced BMD Loss

Lumbar spine BMD in the treatment arms changed in significantly different ways (ie, different temporal patterns over time) during the 48 weeks of follow-up ($P < .001$, test for interaction between time on study and treatment arm). Mean lumbar spine

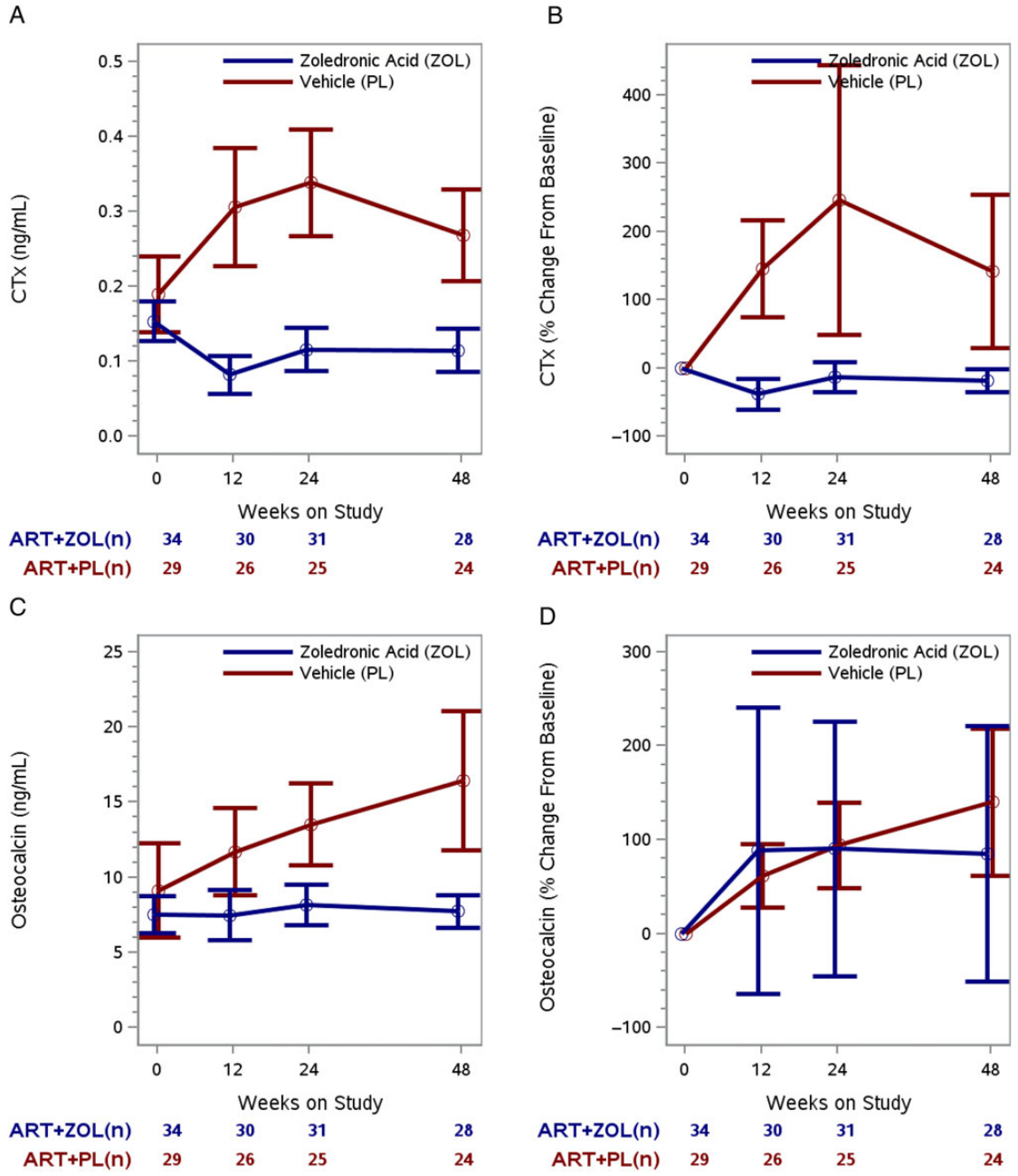

Figure 2. Longitudinal change in bone resorption outcomes by treatment arm. *A*, Model-based mean longitudinal changes in C-terminal telopeptide of collagen (CTx) by treatment arm and weeks on study. *B*, Model-based mean CTx percentage change from baseline by treatment arm and weeks on study. *C*, Model-based mean longitudinal changes in osteocalcin by treatment arm and weeks on study. *D*, Model-based mean osteocalcin percentage change from baseline by treatment arm and weeks on study. For each of the 4 panels, the vertical bars are the 95% confidence intervals and the numbers below the time points signify the number of subjects in each treatment group at each time interval. Abbreviations: ART, antiretroviral therapy; PL, active placebo; ZOL, zoledronic acid.

was similar in both treatment arms at randomization ($P = .08$) but became significantly higher in the ZOL arm at 12 weeks (1.304 g/cm^2 vs 1.203 g/cm^2; $P = .003$), 24 weeks (1.307 g/cm^2 vs 1.179 g/cm^2; $P < .001$), and 48 weeks (1.303 g/cm^2 vs 1.175 g/cm^2; $P < .001$; Figure 3*A*). ZOL led to an 8% increase in lumbar spine BMD at 12 weeks relative to placebo (mean difference, 0.101 g/cm^2 [95% CI, .034 to .167 g/cm^2]), with an 11% increase at 24 weeks (mean difference, 0.128 g/cm^2 [95% CI, .059 to .197 g/cm^2]). The mean difference at 48 weeks remained 0.128 g/cm^2 (11% increase relative to placebo). BMD at the lumbar spine did not change from baseline to 48 weeks in the ZOL arm (mean percentage change, +0.9% [95% CI, −.47% to 2.19%]; $P = .20$), but decreased −4.4% (95% CI, −6.21% to −2.63%; $P < .001$) in the placebo arm (Figure 3*B*). Similar trends

Table 2. Baseline-Adjusted Means at 48 Weeks of Follow-up for Bone Resorption and Bone Mineral Density Outcomes by Treatment Arm

Variables	Treatment	No.	Adjusted Mean (95% CI)[a]	Mean Difference (95% CI)	*P* Value
CTx, ng/mL	ART + ZOL	28	0.126 (.021–.231)	−0.215 (−.374 to .056)	.0118
	ART + PL	24	0.341 (.222–.460)		
Osteocalcin, ng/mL	ART + ZOL	28	8.752 (3.077–14.426)	−8.739 (−17.634 to .155)	.0536
	ART + PL	24	17.491 (11.003–23.978)		
Lumbar spine, g/cm^2	ART + ZOL	26	1.268 (1.247–1.289)	0.072 (.042 to .102)	<.0001
	ART + PL	23	1.196 (1.175–1.217)		
Lumbar spine *t* score	ART + ZOL	26	0.471 (.298–.644)	0.589 (.337 to .840)	<.0001
	ART + PL	23	−0.118 (−.295 to .059)		
Lumbar spine *z* score	ART + ZOL	26	−0.284 (−.481 to −.088)	0.449 (.165 to .733)	.0027
	ART + PL	23	−0.734 (−.934 to −.533)		
Hip, g/cm^2	ART + ZOL	26	1.066 (1.052–1.079)	0.040 (.021 to .060)	.0001
	ART + PL	23	1.025 (1.011–1.039)		
Hip *t* score	ART + ZOL	26	−0.027 (−.151 to .097)	0.311 (.133 to .489)	.0010
	ART + PL	23	−0.337 (−.465 to −.210)		
Hip *z* score	ART + ZOL	26	−0.840 (−.965 to −.716)	0.268 (.090 to .445)	.0041
	ART + PL	23	−1.108 (−1.235 to −.981)		
Femoral neck, g/cm^2	ART + ZOL	26	1.061 (1.044–1.077)	0.036 (.013 to .060)	.0035
	ART + PL	23	1.024 (1.008–1.041)		
Femoral neck *t* score	ART + ZOL	26	0.106 (−.034 to 0.245)	0.318 (.119 to .517)	.0025
	ART + PL	23	−0.212 (−.354 to −.070)		
Femoral neck *z* score	ART + ZOL	26	−0.641 (−.783 to −.499)	0.216 (.014 to .419)	.0371
	ART + PL	23	−0.857 (−1.002 to −.712)		

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; CTx, C-terminal telopeptide of collagen; PL, active placebo; ZOL, zoledronic acid.

[a] Adjusted mean defined as the predicted response value obtained by fitting the regression equation for each treatment arm at the mean baseline value for the 2 treatment arms, and estimated using analysis of covariance at 48 weeks for each outcome.

were observed for BMD in the hip and femoral neck (Supplementary Figure 1).

ZOL Treatment Did Not Impact the Rate of Virologic Suppression or Immunologic Response

Supplementary Figure 2*A* summarizes the cumulative initial virologic suppression by treatment arm ($P = .24$, log-rank test). By 48 weeks, initial virologic suppression was 97% in the ZOL arm and 84% in the placebo arm. CD4 T-cell counts in the 2 treatment arms increased over time ($P < .001$). Neither the pattern of change ($P = .63$) nor the difference between treatment arms was significant ($P = .25$; Supplementary Figure 2*B*). The week 48 mean (±SEM) CD4 T-cell count was 270 ± 24 cells/μL and 311 ± 40 cells/μL for the ZOL and placebo arms, respectively ($P = .38$).

Serious Adverse Effects, Adverse Effects, and Laboratory Toxicities

No serious adverse effects (SAEs) was reported to be possibly or definitively related to ZOL treatment. SAEs were similar between the ZOL and the placebo arms. Three patients in each arm were hospitalized during the 48 weeks of follow-up. Supplementary Table 2 summarizes patient-reported AEs by treatment arm. There were no statistically significant differences in the rates of moderate or severe diarrhea, weight loss, rash, insomnia, and myalgia between the ZOL and placebo arm. Moderate or severe dyspepsia was more frequent in the placebo arm ($P = .04$). There were no statistically significant differences between the 2 treatment arms for the other 14 self-reported AEs. Supplementary Table 3 summarizes laboratory toxicities. There were no statistically significant differences between treatment arms for the incidence of any grade 3 or higher laboratory toxicities during 48 weeks of follow-up.

DISCUSSION

ART initiation led to an early surge in bone resorption in patients randomized to the placebo arm. A compensatory increase in bone formation was noted that may have tempered the extent of bone loss in some patients. Nevertheless, the net effect of these changes in biomarkers of bone turnover was an expected significant loss of BMD in the placebo arm. Importantly, however, we demonstrated that ART-induced bone loss can be successfully prevented with an antiresorptive. Specifically, the heightened bone resorption following ART initiation was completely blunted by ZOL, resulting in durable BMD preservation at fracture-prone sites that lasted through 48 weeks. These findings corroborate our earlier animal studies in which ZOL prophylaxis completely ablated immune reconstitution–induced bone loss following T-cell adoptive transfer in immunocompromised T-cell knockout mice [16].

These findings are relevant for several reasons. First, the magnitude of bone loss observed with almost all ART regimens during the relatively short study period approaches, if not exceeds,

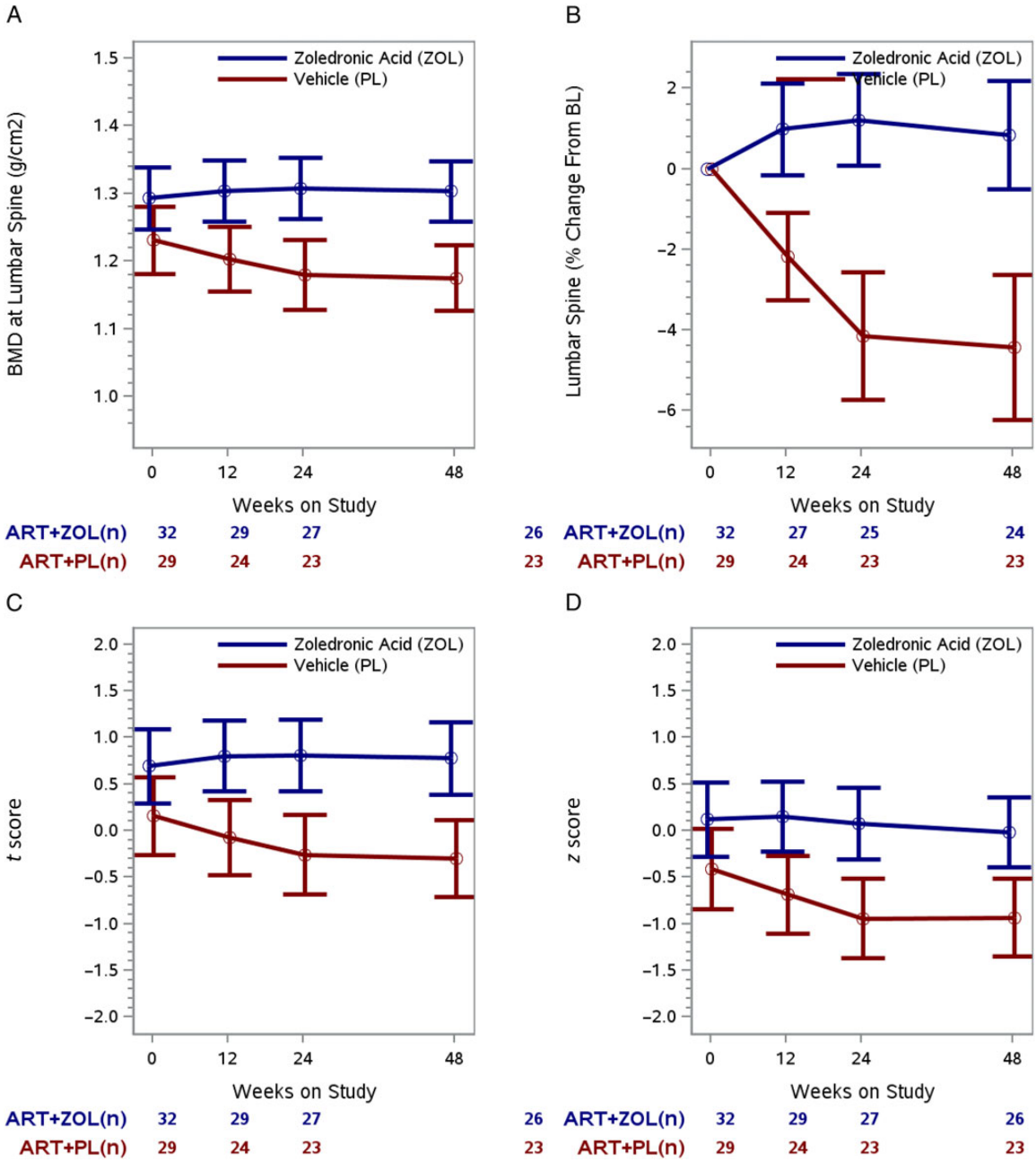

Figure 3. Longitudinal change in lumbar spine bone mineral density (BMD) outcomes by treatment arm. *A*, Model-based mean longitudinal changes in BMD at the lumbar spine by treatment arm and weeks on study. *B*, Model-based mean BMD at the lumbar spine percentage change from baseline (BL) by treatment arm and weeks on study. *C*, Model-based mean longitudinal changes in lumbar spine *t* scores by treatment arm and weeks on study. *D*, Model-based mean longitudinal changes in lumbar spine *z* scores by treatment arm and weeks on study. For each of the 4 panels, the vertical bars are the 95% confidence intervals and the numbers below the time points signify the number of subjects in each treatment group at each time interval. Abbreviations: ART, antiretroviral therapy; PL, active placebo; ZOL, zoledronic acid.

that seen in the first years of the archetypal fragility bone disease of postmenopausal osteoporosis [22]. Second, this significant bone loss is occurring in a population with compromised skeletal reserve, likely contributing to the increased fracture rates observed in the aging HIV population. Finally, homeostasis between bone formation and resorption is very short lived. Shortly after peak BMD is achieved in early adulthood (20–30 years of age), resorption begins to outpace formation, leading to a steady decline in BMD with age. Once lost after early adulthood, bone is seldom recovered without pharmacological intervention. Thus, preserving natural modeled/remodeled bone, as was done in this study, is essential for optimal skeletal health over the long term.

The above-enumerated considerations underscore the significance of current efforts to preemptively preserve naturally

accreted bone in the HIV population. The overall 60% lower bone resorption in the ZOL arm relative to the placebo arm and the corresponding 11% relative higher BMD at the lumbar spine observed with ZOL at 48 weeks are the largest reported effect sizes for any prophylactic intervention directed at ameliorating ART-induced bone loss. At 48 weeks, supplementation with vitamin D and calcium carbonate in treatment-naive, HIV-infected patients in a recent study resulted in a relative treatment difference in total hip BMD of 1.86% [23], while in the A5303 study, the use of a TDF-sparing ART regimen was associated with relative treatment differences in total hip and lumbar spine BMD of 0.89% and 1.47%, respectively [9].

Although modern-era ART regimens induce less bone loss, they are, however, not completely innocuous to the skeleton [5–10]. As an example, in the report by Sax et al [10], 16% and 27% of patients treated with TAF-containing regimens sustained >3% loss in BMD at the hip and lumbar spine, respectively, within 48 weeks of ART therapy. These findings suggest that there are subsets of HIV-infected patients for whom bone loss prophylaxis will be beneficial following ART initiation, regardless of the regimen.

Furthermore, ZOL had no suppressive effect on bone formation and resulted in negligible overall change in BMD in our study. This relative lack of effect on formation with a single dose of ZOL is important, as remodeled bone that occurs with the prolonged use of bisphosphonates is paradoxically susceptible to microcracks [24, 25]. ZOL at a single dose was safe and well tolerated, and resulted in comparable rate of virologic suppression and similar magnitude of CD4 T-cell reconstitution.

Our study was a proof-of-concept phase IIb study with a small sample size, conducted at a single site, and thus is subject to several limitations. The study population was relatively homogenous, reflecting the demography of our clinic population with a predominance of African American men, thereby limiting the generalizability of our findings. Furthermore, the 48-week study duration could not evaluate the impact of our intervention on long-term bone outcomes.

These limitations notwithstanding, a single infusion of ZOL at the time of ART initiation mitigated ART-induced bone resorption and prevented bone loss in nonosteoporotic, HIV-infected patients. These effects were observed as early as 12 weeks, and persisted through 48 weeks, the period when ART-induced bone loss is most intense. These data define an optimal window for a preemptive intervention to forestall ART-induced bone loss and provide robust information needed to guide the design and implementation of larger confirmatory phase 3, multicenter randomized clinical trials.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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