Supplemental Material:

Study Coordination and Oversight:

The BLIR Steering Committee designed the protocol and Manual of Operations (MOO) and CRFs, regularly reviewed the progress of the trial for patient accrual and retention, quality control, safety and efficacy based on blinded monthly reports regenerated by the DCC. Major scientific decisions regarding the core data and inclusion/exclusion criteria were determined by the Steering Committee. The Steering Committee held monthly meetings. All decisions made by the Steering Committee required a majority of the members.

The BLIR Data Coordinating Center (DCC) was located at the Emory University Rollins School of Public Health, Department of Biostatistics and Bioinformatics. The DCC was responsible for data management and quality control, case report form (CRF) generation, randomization procedures, SAE and AE monitoring and statistical analysis for the trial.

Data Management:

The database management system was a distributed database, designed and implemented using ColdFusion + JavaScript programming languages and a Microsoft SQL server 2008 database engine for data storage. A secure web application layer was built for data entry and for tracking data changes and user activity. The electronic data entry screens were designed to be similar to the paper case report forms (CRFs). Data entry screens incorporated range and validity checks to help assure data quality. Database reports were generated monthly to summarize the timeliness and completeness of expected study CRFs.

CTx Multivariable Repeated-Measures Analyses:

All the covariates listed in Supplemental Table 1 were included in a multivariable repeated-measures model. After adjusting for each covariate, mean CTx after 12, 24 and 48 weeks of follow-up was significantly lower in the ZOL group than in the PL group. The mean difference at 48 weeks of follow-up was 0.151 ng/ml lower in the ZOL group than in the PL group (a 62% reduction in bone resorption for ZOL relative to PL). Furthermore the mean CTx was statistically higher for men compared to women after adjusting for the other covariates in the model ($p = 0.03$).

CTx Subgroup Analyses:

Post-hoc subgroup analyses were done to assess possible heterogeneity of treatment effects on CTx across levels of six baseline covariates. Each of the six repeated measures analyses included five predictors (treatment group, time on study, the interaction between treatment group and time on study, the interaction between treatment group and the baseline covariate and the interaction between the treatment group and the baseline covariate and time on study). A statistical test of the interaction between treatment group and each covariate indicated treatment effects were not statistically different between treatment group and race ($p = 0.64$), age at randomization ($p = 0.27$), baseline CD4 T cell count ($p = 0.12$), baseline HV viral load ($p = 0.45$), and baseline osteopenia ($p = 0.10$) on CTx. However treatment effects on CTx were different for men compared to women ($p = 0.007$, test for interaction between treatment group and gender). Generally bone loss was higher in men compared to women in the PL group and the protection against bone loss appeared higher in men than in women in the ZOL group.

Supplemental Tables:

Supplemental Table 1. Multivariable repeated-measures analysis of CTx (ng/mL) adjusted for baseline characteristics

	Adjusted Mean (95% CI)	Mean difference (95% CI)	P
Treatment			<0.001
ZOL	0.103 (0.077, 0.130)	-	
PL	0.263 (0.207, 0.318)	-	
Clinic visit			0.01
Baseline	0.158 (0.122, 0.194)	-	
12 weeks	0.180 (0.136, 0.225)	-	
24 weeks	0.214 (0.172, 0.256)	-	
48 weeks	0.179 (0.139, 0.219)	-	
Treatment by visit			<0.001
Baseline			
ZOL	0.140 (0.105, 0.174)	-0.036 (-0.096, 0.023)	0.23
PL	0.176 (0.120, 0.233)		
12 weeks			
ZOL	0.068 (0.037, 0.099)	-0.225 (-0.308, -0.142)	<0.001
PL	0.293 (0.213, 0.373)		
24 weeks			
ZOL	0.102 (0.069, 0.135)	-0.224 (-0.298, -0.150)	<0.001
PL	0.326 (0.254, 0.397)		
48 weeks			
ZOL	0.103 (0.067, 0.138)	-0.153 (-0.219, -0.087)	<0.001
PL	0.256 (0.192, 0.320)		
Sex			
Female	0.160 (0.108, 0.211)	-0.046 (-0.093, 0.000)	0.05

Male	0.206 (0.179, 0.233)		
Race			
White	0.190 (0.149, 0.230)	0.014 (-0.016, 0.043)	0.38
Black	0.176 (0.144, 0.209)		
Age			
<40	0.197 (0.157, 0.236)	0.028 (-0.004, 0.060)	0.09
40+	0.169 (0.134, 0.204)		
Baseline CD4 count[a]			
<97	0.195 (0.156, 0.235)	0.025 (-0.007, 0.058)	0.14
97+	0.170 (0.135, 0.205)		
Baseline viral load			
<100,000	0.183 (0.146, 0.221)	0.001 (-0.025, 0.026)	0.96
+100,000	0.183 (0.148, 0.217)		
Baseline osteopenia			
No	0.196 (0.161, 0.230)	0.026 (-0.005, 0.056)	0.10
Yes	0.170 (0.131, 0.209)		

[a]*Dichotomized at the median value of baseline CD4 count.*

Supplemental Table 2. Self-reported 20 most common adverse events by treatment arm

AE Symptom	ART + PL (n=29)	ART + ZOL (n=34)	P
Weight Loss	4 (13.8%)	10 (29.4%)	0.14
Fatigue	6 (20.7%)	7 (20.6%)	0.99
Diarrhea	4 (13.8%)	9 (26.5%)	0.22
Insomnia	3 (10.3%)	8 (23.5%)	0.20
Rash (*head, shoulder, feet*)	3 (10.3%)	8 (23.5%)	0.17
Headache	6 (20.7%)	4 (11.8%)	0.49[a]
Flatulence	5 (17.2%)	4 (11.8%)	0.72[a]
Cough	4 (13.8%)	5 (14.7%)	1.00[a]
Chills	4 (13.8%)	4 (11.8%)	1.00[a]
Nausea	5 (17.2%)	3 (8.8%)	0.45[a]
Myalgia	2 (6.9%)	6 (17.6%)	0.27[a]
Flu-like symptoms	4 (13.8%)	3 (8.8%)	0.69[a]
Nasal/sinus drainage	4 (13.8%)	3 (8.8%)	0.69[a]
Decreased Libido	3 (10.3%)	4 (11.8%)	1.00[a]
Depression	2 (6.9%)	5 (14.7%)	0.44[a]
Shortness of breath	3 (10.3%)	3 (8.8%)	1.00[a]
Fever	3 (10.3%)	2 (5.9%)	0.65[a]
Arthalgia	2 (6.9%)	3 (8.8%)	1.00[a]
Night sweats	1 (3.4%)	3 (8.8%)	0.62[a]
Dyspepsia	4 (13.8%)	0 (0%)	0.04[a]

[a]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 groups with a chi-square or Fisher's exact test.

Supplemental Table 3. Grade 3 or higher laboratory toxicities occurring at one or more visits, by treatment arm

Laboratory Test	Toxicity Level (Grade 3+)	ART + PL (n=29)	ART + ZOL (n=34)	P
Calcium HIGH (mg/dL)	>12.5	0 (0%)	0 (0%)	
Calcium LOW (mg/dL)[a]	<7.5	0 (0%)	1 (3.0%)	1.00[b]
Sodium HIGH (mEq/L)	>155	0 (0%)	0 (0%)	
Sodium LOW (mEq/L	<125	0 (0%)	0 (0%)	
Creatinine (mg/dL)	>2.16	0 (0%)	0 (0%)	
AST/SGOT (U/L)	>210	0 (0%)	0 (0%)	
ALT/SGPT (U/L)	>315	0 (0%)	0 (0%)	
Alkaline Phosphatase (U/L)[a]	>630	0 (0%)	1 (3.0%)	1.00[b]
Albumin (g/dL)	<2.0	0 (0%)	0 (0%)	
Glucose (mg/dL)[a]	>250	1 (3.4%)	1 (3.0%)	1.00[b]
Total Bilirubin (mg/dL)	>4	7 (24.1%)[c]	8 (23.5%)[d]	0.95
Platelet Count ($x10^3$ µL)[a]	<50	1 (3.4%)	0 (0%)	1.00[b]
WBC ($x10^3$ µL)[a]	<1.5	0 (0%)	1 (3.0%)	1.00[b]
ANC (per µL)	<750	4 (13.8%)[e]	5 (14.7%)	1.00[b]

Laboratory tests graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (available on the DAIDS RCC Web site: *http://rcc.tech-res.com/tox_tables.htm*).

[a]*No subject had grade III toxicity level for 2 or more consecutive visits.*

[b]*Fisher's exact test result.*

[c]*There were 2 subjects in the placebo group with elevated total bilirubin on 2 or more consecutive visits.*

[d]*There were 2 subjects in the treatment group with elevated total bilirubin on 2 or more consecutive visits.*

[e]*There was 1 subject in the placebo group with decreased platelet count on 2 or more consecutive visits.*

Supplemental Figure Legends

Supplemental Figure 1. Longitudinal change in hip and femoral neck BMD outcomes by treatment arm.

S1A. Model-based mean longitudinal changes in BMD at the hip (g/cm^2) by treatment arm and weeks on study.

S1B. Model-based mean for hip BMD percentage change from baseline by treatment arm and weeks on study.

S1C. Model-based mean longitudinal changes in BMD at the femoral neck (g/cm^2) by treatment arm and weeks on study.

S1D. Model-based mean for femoral neck BMD percentage change from baseline by treatment arm and weeks on study.

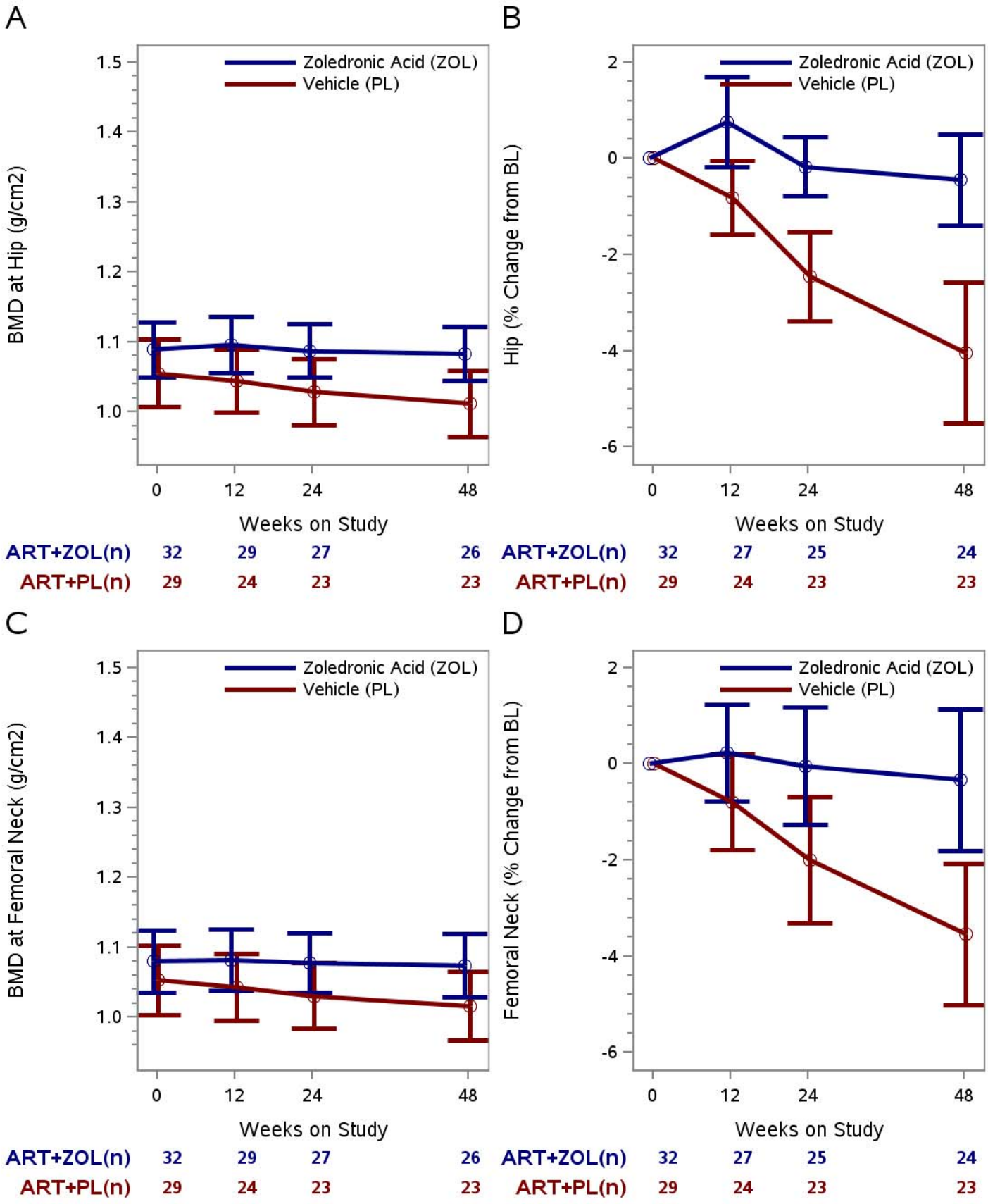
For each of the 4 panels, the vertical bars are the 95% confidence intervals and the numbers below time points signify the number of subjects in each treatment group at each time interval.

Supplemental Figure 2. Time to initial viral load suppression and immunologic response.

S2A. Cumulative initial virological suppression by treatment arm ($p = 0.24$, log-rank test). The numbers below weeks on study signify the number of patients with virus who remained under follow-up (number of patients at risk) by treatment group.

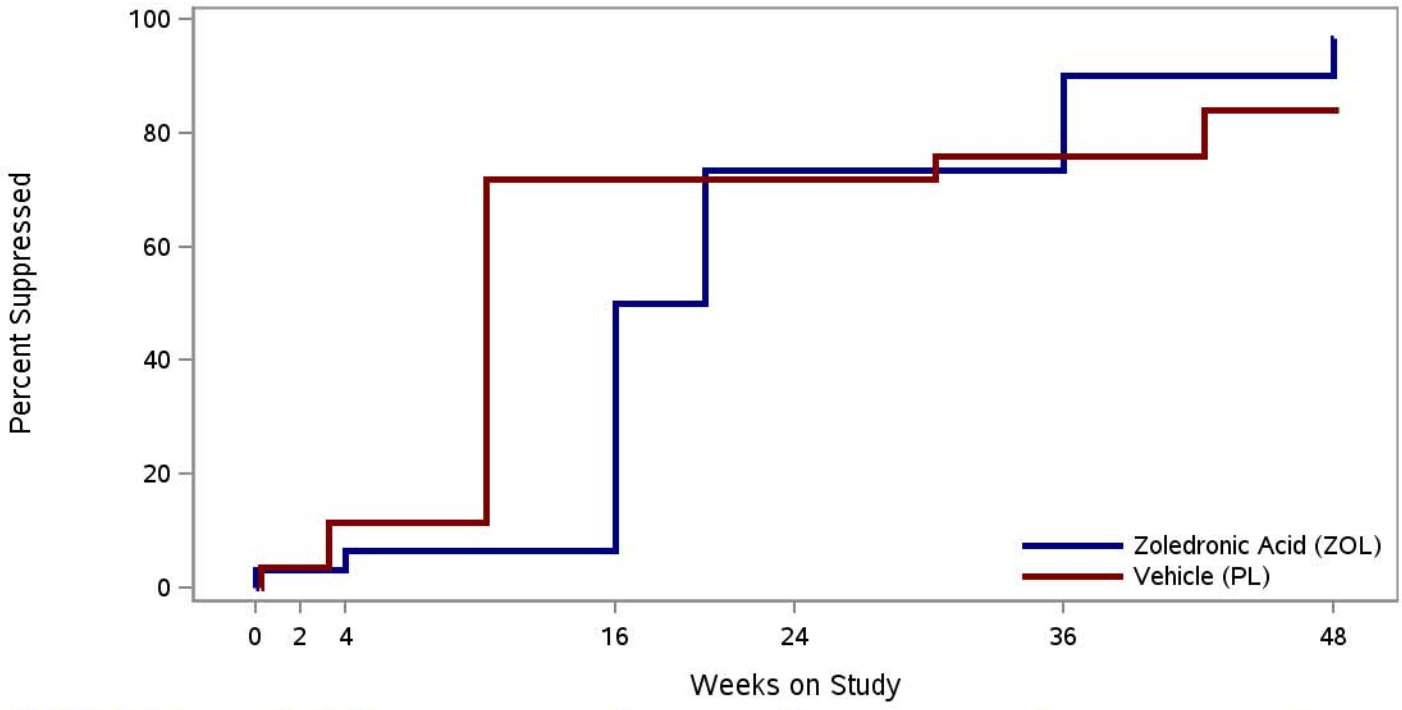
S2B. Model-based mean longitudinal changes in CD4 T cell count (µL) by treatment arm and weeks on study. The vertical bars are the 95% confidence intervals and the numbers below time points signify the number of subjects in each treatment group at each time interval.

Supplemental Figure 1



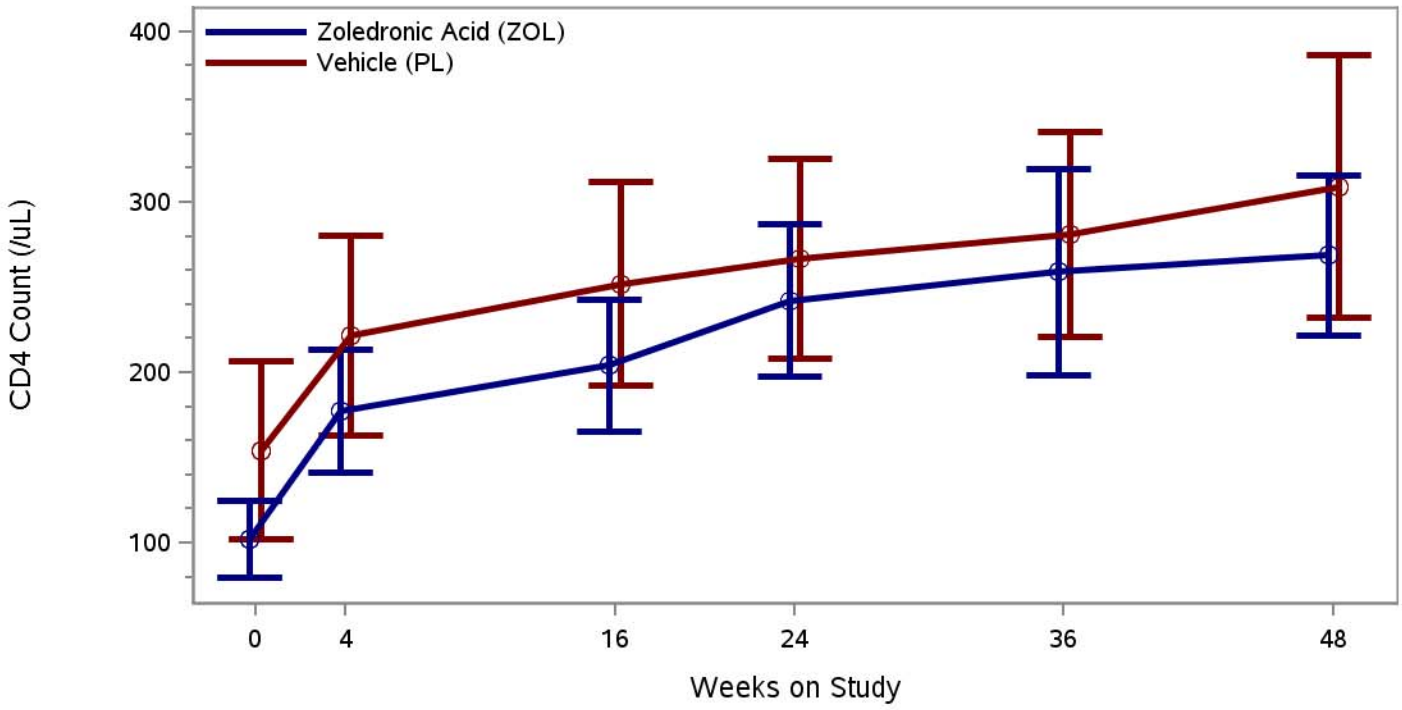
Supplemental Figure 2

A



ART+ZOL(n)	30	29	28	27	14	7	2
ART+PL(n)	27	25	24	7	7	6	5

B



ART+ZOL(n)	34	31	30	31	27	27
ART+PL(n)	29	26	25	24	24	24