Bone Mineral Density (BMD) 96 Weeks after Antiretroviral Therapy (ART) Initiation: A Randomized Trial Comparing Efavirenz (EFV)-Based Therapy to a Lopinavir/ritonavir (LPV/r)-Containing Regimen with Simplification to LPV/r Monotherapy

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Abstract

Background: Reductions in bone mineral density (BMD) have been described in HIV-infected patients initiating ART. It is unclear whether this is due to an effect of ART or changes in immunologic function and/or viral activity. We compared changes in BMD from baseline (BL) to 96 weeks (wks) in subjects randomized to either a LPV/r simplification strategy or EFV+ ZDV/3TC. We also sought to identify factors associated with a >5% reduction in BMD.

Methods: 155 ART-naïve HIV-1+ subjects were randomized (1:2) to receive EFV + ZDV/3TC (n=51) or LPV/r + ZDV/3TC induction (n=104) for 24–48 wks followed by LPV/r monotherapy (simplification). Subjects were followed for up to 96 wks with DEXA scans every 24 wks. Associations between BL total BMD and other BL factors were assessed by linear regression. Associations with a 5% decrease in total BMD through 96 wks were assessed by logistic regression. Factors tested included demographics, weight, HIV-1 RNA, CD4 cell count, smoking/alcohol history, body composition variables, HOMA-IR, TNF-alpha soluble receptors 1 and 2 (sTNFR).

Results: 74 LPV/r- and 32 EFV-treated subjects had DEXA scans available through 96 wks. BL characteristics including mean ± SD total BMD were similar between groups: 1.18±0.10 grams/cm^2 (LPV/r) and 1.19±0.12 grams/cm2 (EFV). In a multivariable analysis, higher BL BMD was independently associated with higher weight, black race, and higher BL HIV-1 RNA (p<0.003 for each), but was not associated with age, smoking status, use of alcohol, CD4 cell count or sTNFR. After 96 wks, mean percent change from baseline in total BMD was –2.5% (LPV/r) and –2.3% (EFV) (p<0.01 for within-group changes in either arm; p=0.86 for difference between groups). No alteration in the rate of BMD change was observed upon simplification to LPV/r monotherapy. Subjects with lower BL CD4 cell count, non-black race, and higher BL fasting glucose demonstrated a higher risk for >5% decrease in total BMD. Change in total BMD through 96 wks was not correlated with BL BMD, other parameters of glucose metabolism or changes in body composition.

Conclusions: Similar decreases in total BMD over 96 wks occurred in ART-naïve subjects receiving either EFV or LPV/r-based regimens, which was not altered by simplification to LPV/r monotherapy. These data suggest that the loss of BMD with ART initiation occurs independently of the ART regimen used. Non-black subjects and those with lower nadir CD4 cell count may be at increased risk of more pronounced BMD loss.

Background

In cross-sectional studies, the prevalence of osteoporosis in HIV-infected individuals was found to be more than 3-fold higher than non-HIV-infected individuals.[1] In addition, antiretroviral-treated subjects appeared to have an increased risk of decreased bone mineral density (BMD) and osteoporosis compared to antiretroviral-naïve subjects. While these data may suggest that both HIV and antiretroviral treatment impact BMD, longitudinal studies are required to understand the relative contributions of HIV infection and its treatment to decreased BMD observed in HIV-infected patients.

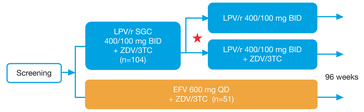
Longitudinal studies of HIV-infected subjects initiating antiretroviral therapy may be particularly informative in determining whether antiretroviral therapy is associated with reductions in BMD and whether some regimens have a greater impact than others.

Study 613 is a 96-week prospective study in previously antiretroviral-naïve subjects who were randomized to initiate either a protease inhibitor (PI) LPV/r-based regimen or an NNRTI efavirenz-based regimen. Those randomized to LPV/r and who met protocol specified criteria were later simplified to LPV/r monotherapy. Thus, this study allows us to evaluate BMD prospectively in a PI versus an NNRTI-based regimen and evaluate whether removal of the NRTI backbone impacts BMD. In addition, we also sought to identify factors associated with a potentially clinically significant BMD reduction [i.e. >5% (~0.6 SD)].

Methods

155 antiretroviral-naïve HIV-positive subjects were randomized to LPV/r+ZDV/3TC induction (n=104) for 24–48 weeks followed by LPV/r monotherapy if 3 consecutive HIV-RNA values <50 copies/mL were achieved, or to EFV+ZDV/3TC (n=51) for the entire study period. Overall study duration was 96 weeks (Figure 1).

Figure 1. Study M03-613 Design



Inclusion criteria
- Antiretroviral-naïve
- HIV-1 RNA >1000 copies/mL
- Any CD4 count
- No evidence of resistance to study drugs

★ Deintensification starting at Week 24 if 3 consecutive monthly HIV-1 RNA levels <50 copies/mL

92/104 subjects randomized to LPV/r + ZDV/3TC achieved 3 consecutive HIV-1 RNA levels <50 copies/mL, and then simplified to LPV/r monotherapy, and were followed for a median of 68 weeks on monotherapy. The majority of subjects simplified to LPV/r monotherapy at Week 24.

Subjects were followed for up to 96 weeks with DEXA scans every 24 weeks. Associations between baseline total BMD and other baseline factors were assessed by linear regression.

Associations with a 5% decrease in total BMD through 96 weeks were assessed by logistic regression. Factors tested included demographics, weight, standard chemistry lab parameters (e.g., alkaline phosphatase), HIV-1 RNA, CD4 cell count, smoking/alcohol history (user/ex-user vs. non-user and drinker/ex-drinker vs. non-drinker), body composition variables (e.g., trunk fat, limb fat), HOMA-IR, TNF-alpha soluble receptors 1 and 2 (sTNFR I and II), and glucose and insulin area under the curve (AUC) during a 2-hour oral glucose tolerance test (OGTT).

Results

Baseline Characteristics

- Demographics and baseline characteristics were generally comparable between treatment groups (Table 1).
- 74 LPV/r- and 32 EFV-treated subjects had DEXA scans available through 96 weeks.
- Mean total BMD at baseline was 1.17±0.10 g/cm^2 (LPV/r) and 1.19±0.12 g/cm^2 (EFV) (p=ns).

Table 1. Demographics and Baseline Characteristics

	LPV/r (n=74)	EFV (n=32)
Gender – Male	58 (78%)	25 (78%)
Age* (years) – Mean (range)	41 (20–73)	34 (20–50)
Race/ethnicity		
White	49 (66%)	21 (66%)
Black	19 (26%)	10 (31%)
Hispanic	4 (5%)	4 (13%)
Other	6 (8%)	1 (3%)
Baseline disease characteristics (mean ± SD)		
HIV-1 RNA (log_{10} copies/mL)	4.97 ± 0.62	4.80 ± 0.62
CD4+ T-cell count (cells/mm^3)	214 ± 146	273 ± 175
Body habitus measurements (mean ± SD)		
Weight (kg)	74.8 ± 14.9	76.7 ± 15.0
Total BMD (g/cm^2)	1.17 ± 0.09	1.19 ± 0.12
Limb fat (kg)	8.2 ± 4.7	7.4 ± 4.7
Trunk fat (kg)	9.3 ± 6.2	8.3 ± 6.3
Glucose metabolism measures (mean ± SD)		
Baseline glucose (mg/dL)	86.1 ± 10.4	83.3 ± 8.7
Baseline HOMA-IR	2.25 ± 3.8	2.37 ± 2.37
Baseline 2-hour OGTT values		
Glucose AUC over 2 hours (mg/dL*minutes)	3372 ± 2952	3792 ± 2568
Insulin AUC over 2 hours (mcIU/mL*minutes)	4440 ± 3768	5076 ± 3048
Other measures		
Tobacco use		
Current user	25 (34%)	16 (50%)
Ex-user	18 (24%)	2 (6%)
Never used	31 (42%)	14 (44%)
Alcohol use		
Current drinker	48 (65%)	20 (63%)
Ex-drinker	10 (14%)	5 (16%)
Non-drinker	16 (22%)	7 (22%)
Steroid use during study	15 (20%)	5 (16%)
Soluble TNF – R1 (pg/mL)	1236 ± 418	1241 ± 367
Soluble TNF – R2 (pg/mL)	3724 ± 1376	3488 ± 1174
Serum creatinine (mg/dL)	0.85 ± 0.18	0.86 ± 0.18

* p<0.05 between groups.

Associations with Baseline BMD

- In a multivariable analysis, lower baseline total BMD was statistically significantly associated with lower weight, non-black race and lower baseline HIV-1 RNA levels (Table 2).
- The relationship between weight and total BMD is shown by race in Figure 2.

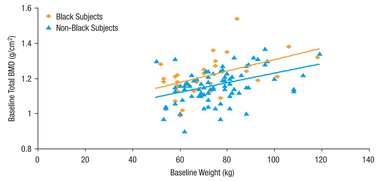
Table 2. Relationship Between Baseline BMD and Other Baseline Characteristics

	p-value	
Variable	Univariable Analysis	Multivariable Analysis
Gender	ns	
Age	ns	
Black race	0.02	<0.001
HIV-1 RNA	0.01	0.004
CD4+ T-cell count	ns	
Weight	<0.001	<0.001
Limb fat	ns	
Trunk fat	ns	
Baseline glucose	ns	
Baseline HOMA-IR	ns	
Glucose AUC over 2 hours (mg/dL*minutes)	ns	
Insulin AUC over 2 hours (mcIU/mL*minutes)	ns	
Tobacco use	ns	
Alcohol use	ns	
Steroid use	ns	
Soluble TNF – R1	0.04	—
Soluble TNF – R2 (per 100 pg/mL)	0.04	—
Serum creatinine	<0.001	—

ns = not significant

- Although higher baseline HIV-1 viral load was associated with black race, the positive association between baseline HIV-1 viral load and baseline BMD remained statistically significant after adjustment for race.
- Higher baseline HIV-1 viral load correlated with higher soluble TNF R1 and R2.

Figure 2. Baseline BMD is Positively Correlated with Black Race and Baseline Weight



Changes from Baseline in BMD

- After 96 weeks, similar mean decreases from baseline in BMD were observed by both treatment groups: –2.5% in the LPV/r group and –2.3% in the EFV group (p=0.86 for the difference between groups, Figure 3). Within treatment group, changes from baseline in BMD were statistically significant (p<0.01 for each group).
- No alteration in the rate of BMD change was observed when subjects in the LPV/r group simplified to LPV/r monotherapy (Figure 3).
- 16 subjects (15%) demonstrated a >5% decrease in BMD over 96 weeks.
- Subjects with lower baseline CD4 cell count, higher baseline fasting glucose and of non-black race demonstrated a higher risk for >5% decrease in BMD (Table 3, Figure 3). Changes in BMD were not correlated to baseline BMD, other parameters of glucose metabolism or changes in body composition.
- Figure 4 illustrates that within each CD4 cell count strata assessed, a higher proportion of non-black subjects had a >5% decrease in BMD.

Figure 3. Similar Changes from Baseline in Total BMD by Treatment Group

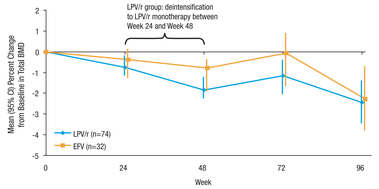
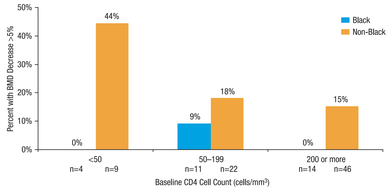


Table 3. Relationship Between Baseline Characteristics and the Risk of a 5% or Larger Decrease in BMD Over 96 Weeks (All Subjects)

	Odds Ratio (95% CI); p-value	
Variable	Univariable Analysis	Multivariable Analysis
Gender	ns	
Treatment group	ns	
Baseline BMD	ns	
Age	ns	
Black race	0.15 (0.02, 1.17); 0.07	0.11 (0.01, 0.97); 0.05
HIV-1 RNA (per log_{10} copies/mL)	2.17 (0.89, 5.27); 0.09	—
CD4+ T-cell count (per 10 cells/mm^3)	0.96 (0.92, 1.00); 0.06	0.94 (0.89, 0.99); 0.02
Weight	ns	
Limb fat	ns	
Trunk fat	ns	
Baseline glucose (per 1 mg/dL)	1.07 (1.01, 1.13); 0.02	1.09 (1.02, 1.17); 0.01
Baseline HOMA-IR	ns	
Glucose AUC over 2 hours (mg/dL*minutes)	ns	
Insulin AUC over 2 hours (mcIU/mL*minutes)	ns	
Tobacco use	ns	
Alcohol use	ns	
Steroid use	ns	
Soluble TNF – R1	ns	
Soluble TNF – R2 (per 100 pg/mL)	1.03 (1.00, 1.07); 0.06	—
Serum creatinine	ns	

ns = not significant

Figure 4. Non-Black Subjects with Lower Baseline CD4 Count Were at Greater Risk of a >5% Decrease in BMD



Discussion

- Prior to antiretroviral therapy initiation, lower baseline total BMD in HIV-infected persons was associated with lower weight and non-black race.
- The association between higher BMD and higher levels of HIV-1 RNA was unexpected and may be attributable to unmeasured confounding factors.
- Higher baseline markers of inflammation were correlated with higher baseline HIV-1 viral load levels, but were not correlated with lower baseline BMD.
- Over 96 weeks of therapy, total BMD decreased by about 2.4% in both treatment groups, indicating that bone loss occurs upon initiation of antiretroviral therapy, regardless of whether PIs or NNRTIs are used.
- In vitro evidence has suggested that AZT increases osteoclastogenesis and promotes bone loss.[2] However, in our study, discontinuation of AZT (with continuation of LPV/r monotherapy), did not attenuate the rate of BMD decline.
- Factors associated with bone loss of potential clinical significance (>5%) include low baseline CD4 count and non-black race. While higher fasting glucose was associated with BMD loss, other parameters of glucose metabolism did not show a similar relationship to the change in BMD.

Conclusions

- Similar decreases in total BMD over 96 weeks occurred in ART-naïve subjects receiving either EFV or LPV/r-based regimens (~2.4%), which was not altered by simplification to LPV/r monotherapy. These data suggest that the loss of BMD with ART initiation occurs independently of the ART regimen used.
- Non-black subjects and those with lower nadir CD4 cell count may be at increased risk of more pronounced BMD loss.

References

1. Brown, T. T. and Qaqish, R. B. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: A meta-analytic review. *AIDS* 2006;20:2165–2174.
2. Pan G, Wu X, McKenna MA, Feng X, Nagy TR, McDonald JM. AZT enhances osteoclastogenesis and bone loss. *AIDS Res Hum Retroviruses* 2004:608–20.