Bone Density Changes after Antiretroviral Initiation with Protease Inhibitors or Raltegravir

Todd T. Brown[1],Carlee Moser[2], Judith S. Currier[3] Heather Ribaudo[2], Jennifer Rothenberg[4], Michael P. Dubé[5], Robert Murphy[6], James H. Stein[7], Grace A. McComsey[8],

[1]Johns Hopkins University, [2]Harvard School of Public Health, [3]David Geffen School of Medicine at University of California - Los Angeles, [4]Social & Scientific Systems, Inc, [5]Keck School of Medicine at the University of Southern California, [6]Northwestern University, [7]University of Wisconsin School of Medicine and Public Health, [8]Case School of Medicine

Poster 779LB

For more information contact Todd Brown: tbrown27@jhmi.edu

Background

- Osteoporosis is common in HIV-infected populations and leads to a higher than expected risk of fracture.
- The initiation of antiretroviral therapy (ART) leads to a 2-6% loss of bone mineral density (BMD) over 48-96 weeks depending in part on the specific medications used.
- Among the nucleoside/nucleotide analogues, tenofovir disoproxil fumarate (TDF) has been consistently associated with a ~ 1-2% loss in BMD in the 48-96 weeks after ART-initiation.
- The independent BMD effects of the 3rd drug are less certain:
  - Protease inhibitors (PIs) have been implicated in BMD loss with ART initiation, but many studies have examined PIs as a class, rather than as individual medications, or have examined total body BMD, rather than the more clinically relevant hip or spine.
  - The BMD effects of PIs have been mostly compared to efavirenz and have generally shown differential effects at the lumbar spine, but not the hip (McComsey, 2010; Duvivier, 2009).
  - Integrase inhibitors (IIs) may have neutral effects on BMD based on switch studies and comparisons with TDF.
  - Only one study has compared the BMD effects of IIs vs PIs and found that elvitegravir/cobicistat was associated with smaller decreases in BMD over 96 weeks vs atazanavir/ritonavir (ATV/r) (Hip: -3.2% v -4.2%, p=0.07; Spine: -2.0% v -3.5%, p=0.05) (Rockstroh, 2013).

Objectives

- To determine whether BMD changes over 96 weeks after ART initiation differ in HIV-infected persons starting ATV/r, Darunavir-Ritonavir (DRV/r), or Raltegravir (RAL)
- To determine whether BMD changes with ART initiation are related to baseline HIV-related variables and biomarkers related to inflammation, monocyte activation and body composition

Methods

Study Participants and Design

- Limited site Cardiovascular/Bone Substudy of a large randomized clinical trial comparing TDF/emtricitabine (FTC) plus ATV/r, DRV/r, or RAL (ACTG A5257; Abstract 85)
- The primary endpoint of the substudy was subclinical cardiovascular disease (CVD). Therefore, subjects with known CVD or diabetes mellitus, or use of lipid-lowering medications were excluded.

Baseline Laboratory Assessment:

- Serum Inflammatory Markers: hsCRP ,IL-6
- Immune Activation Markers: soluble(s) CD14, sCD163,IL-2 receptor
- Adipose-derived Hormones: adiponectin, leptin
- Bone-related Cytokines: Osteoprotegerin (OPG) and Receptor activator of NFκB ligand (RANKL)

Outcomes Measures

- Percentage BMD change at the total hip, lumbar spine, and total body by DXA from baseline to week 96

Data Analysis

- All treatment group comparisons used mulivariable linear regression models with reverse Helmert contrasts. That is, we first compared the mean of the outcome for the ATV/r group to the mean of the outcome for the DRV/r group, and then compared the mean of the pooled PI/r group to the mean of the outcome for the RAL group.
- In the event of a significant difference between the ATV/r and DRV/r groups, all pairwise comparisons between the treatment groups were performed.
- To account for multiple group comparisons, all treatment comparisons were assessed with a type I error rate of 2.5% and 97.5% confidence intervals. All other statistical inferences were assessed with a 5% type I error rate.
- Analyses were adjusted for stratification factors (Framingham Risk Score and Baseline HIV-RNA)
- Primary analyses were intent-to-treat with secondary on-treatment analyses.
- Multivariable linear regression was used to determine the associations between baseline biomarkers and percentage BMD change

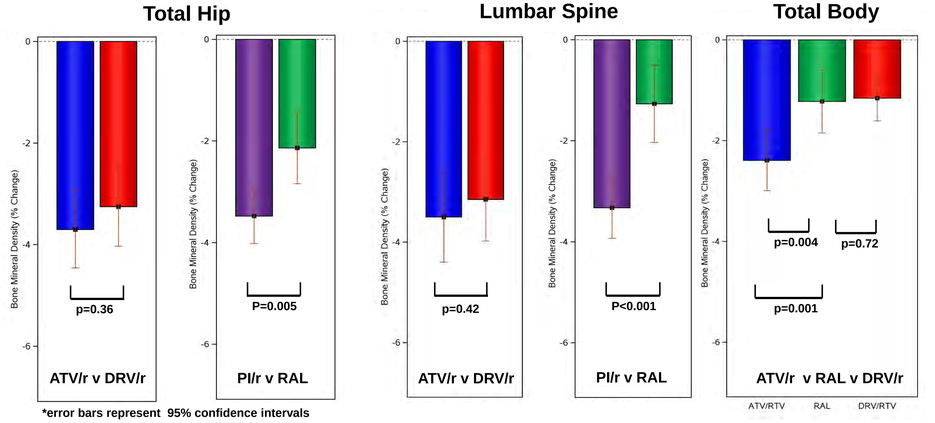
Results

Subject Characteristics at Baseline (N=328)

	ATV/r (n=109)	RAL (n=106)	DRV/r (n=113)
Age (y)	37 (31,45)	36 (27,44)	35 (27,46)
Sex	91% M, 9% F	89% M,11% F	89% M,11% F
Race/ethnicity†	49% W, 31% B, 18% H	41% W, 32% B, 19% H	44% W, 33% B, 22% H
Weight (kg)	80 (69,88)	77 (66,89)	77(67,83)
Body Mass Index (kg/m^2)	26 (23, 29)	24 (22,28)	24 (22, 27)
Concomitant Medications affecting Bone*	22%	22%	20%
Current Smoking	40%	37%	36%
CD4+ cell count (/mm^3)	350 (211, 461)	343 (207,461)	355(207, 461)
HIV-1 RNA (log_{10}c/mL)	4.62 (4.05, 5.10)	4.52 (4.13, 5.08)	4.52 (3.95, 4.95)
hsCRP (log_{10} mg/L)	0.16 (-0.15, 0.50)	0.13 (-0.16, 0.45)	0.07 (-0.18, 0.47)
IL-6 (log_{10} pg/mL)	0.26 (0.08, 0.43)	0.19 (0.03, 0.48)	0.25 (0.08, 0.44)
sIL-2R (log_{10} pg/ml)	3.27 (3.17, 3.38)	3.26 (3.06, 3.37)	3.22 (3.06, 3.35)
sCD14 (log_{10} ng/ml)	0.26 (0.08, 0.43)	0.19 (0.03, 0.48)	0.25 (0.08, 0.44)
sCD163 (log_{10} ng/ml)	3.06 (2.91, 3.20)	3.09 (2.92, 3.20)	3.01 (2.87, 3.19)
Adiponectin (log_{10} ng/ml)	3.84 (3.69, 4.02)	3.90 (3.74, 4.09)	3.91 (3.75, 4.08)
Leptin (log_{10} pg/ml)	3.68 (3.32, 3.95)	3.58 (3.20, 3.91)	3.51 (2.81, 3.87)
OPG (log_{10} pmol/L)	0.59 (0.50, 0.69)	0.60 (0.52, 0.67)	0.65 (0.56, 0.72)
RANK L (log_{10} pg/ml)	1.55 (1.23, 1.77)	1.43 (1.05, 1.73)	1.39 (1.05, 1.69)

Values represent median (Q1,Q3) or percent; † W: white; B: black; H:hispanic; remaining represents other
*includes androgen, anticonvulsants, proton pump inhibitors, corticosteroids, estrogens, SSRIs

Mean Percentage Change in BMD over 96 Weeks by Treatment Regimen*



*error bars represent 95% confidence intervals

- All of the treatment arms showed a statistically significant loss of BMD over 96 weeks at all of the sites (p<0.001)
- At the hip and the spine, the mean percentage BMD changes over 96 weeks were not different in the PI arms
  - Hip: ATV/r -3.9% v DRV/r -3.4%, p=0.36; Spine: ATV/r -4.0% v DRV/r -3.6%, p=0.42
- At the hip and the spine, the loss of BMD was greater in the combined PI arms than the RAL arm
  - Hip -3.7% v -2.4%, p=0.005;Spine: -3.8% v -1.8%, p<0.001

- Total body BMD loss was greater with ATV/r than DRV/r (-2.9% v -1.6%, p=0.001) and greater with ATV/r than RAL (-2.9% v -1.7%, p=0.004)

Multivariable Associations between Baseline Biomarkers and Percentage Change in BMD over 96 Weeks*

	Hip BMD			Spine BMD			Total Body BMD		
	Estimate	(95% CI)	p-value	Estimate	(95% CI)	p-value	Estimate	(95% CI)	p-value
hsCRP	**-0.47**	**(-0.72, -0.21)**	**<0.001**	-0.04	(-0.33, 0.24)	0.78	-0.04	(-0.23, 0.15)	0.68
IL-6	**-0.78**	**(-1.23, -0.34)**	**<0.001**	-0.22	(-0.71, 0.27)	0.38	-0.26	(-0.59, 0.07)	0.12
sIL-2R	**-0.86**	**(-1.58, -0.14)**	**0.019**	-0.21	(-0.99, 0.56)	0.59	-0.14	(-0.67, 0.38)	0.60
sCD14	**-2.11**	**(-3.52, -0.70)**	**0.003**	-1.06	(-2.60, 0.48)	0.18	-0.33	(-1.35, 0.70)	0.53
sCD163	-0.23	(-0.88, 0.43)	0.49	-0.05	(-0.76, 0.65)	0.88	0.32	(-0.14, 0.78)	0.17
Adiponectin	-0.23	(-0.74, 0.29)	0.39	**0.62**	**(0.07, 1.18)**	**0.029**	0.16	(-0.22, 0.53)	0.41
Leptin	**0.41**	**(0.03, 0.79)**	**0.034**	0.26	(-0.15, 0.68)	0.21	0.19	(-0.09, 0.46)	0.18
OPG	-0.35	(-1.27, 0.57)	0.46	-0.13	(-1.13, 0.86)	0.80	-0.01	(-0.67, 0.66)	0.99
RANKL	0.2	(-0.04, 0.44)	0.10	0.08	(-0.18, 0.35)	0.52	0.09	(-0.09, 0.26)	0.33

*all models adjusted for age, race, sex, weight, baseline CD4 cell count, baseline HIV-RNA, FRS and treatment arm; parameter estimates represent the percentage change in BMD per 2-fold increase in biomarker

- Higher baseline markers of inflammation and immune activation were associated with BMD loss at the total hip, but not other sites
- Lower baseline leptin associated with BMD loss at the total hip, independent other covariates including weight
- Lower baseline adiponectin associated with BMD loss at the spine, independent other covariates including weight

Conclusions

- In ART-naïve, HIV-infected individuals initiating ART with TDF/FTC, 96 week BMD losses at the lumbar spine and total hip were not different with ATV/r and DRV/r treatment.
- However, at these sites, BMD losses were less pronounced with RAL compared to the PIs, suggesting that RAL may have a more neutral effect on bone compared to PIs.
- At the total body, BMD loss was greater with ATV/r than DRV/r which deserves further investigation.
- Baseline markers of inflammation and immune activation were associated with increased BMD loss at the hip, independent of CD4 cell count and HIV-RNA level

Acknowledgements

This research was supported by NIH grants HL095132, HL095126, AI 068636, AI068634, and AI56933 with additional support from Gilead Sciences, BMS, Merck, and Janssen