Bone Density Changes after Antiretroviral Initiation with Protease Inhibitors or Raltegravir

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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 with TDF.
  • Protease inhibitors (PIs) have been implicated in 2-6% loss of bone mineral density (BMD) over 48-96 weeks after ART-initiation.
  • 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 its vs PIs and found that elvitegravir/cobicistat was associated with smaller decreases in BMD over 96 weeks vs atazanavir/ritonavir (ATV/ritinavir) (Hc-3.2% v 4.2% p=0.07, 2.0% - 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/ritinavir, 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

Study Participants and Design

• Limited Sample Cohort: Cardiovascular/Bone Substudy of a large randomized clinical trial comparing TDF/Emtricitabine (FTC) plus ATIV/ritinavir, 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 Analyses:
  • Serum Immunatory 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 RANKL

Outcomes Measures

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

Data Analysis

• All treatment group comparisons used multivariable linear regression models. Multimarker contrasts. That is, we first compared the mean of the outcome of the entire treatment group to the mean of the outcome for the drop-out 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 ATIV/ritravir group, all pairwise comparisons between the treatment groups were performed.
• To control for multiple 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 Associations between Baseline Biomarkers and Percentage Change in BMD over 96 Weeks

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<th>Biomarker</th>
<th>Hip BMD</th>
<th>Spine BMD</th>
<th>Total BMD</th>
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<td>vs RAL</td>
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<td>ATV/r vs DRV/r</td>
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| Values represent median (Q1,Q3) or percent; † W: white; B: black; H: hispanic; remaining represents other racial/ethnic categories
| Parameter estimates represent the percentage change in BMD per 2-fold increase in biomarker

Conclusions

• In ART-naive, HIV-infected individuals initiating ART with TDF/FTC, 96 week BMD losses at the lumbar spine and total hip were not different with ATIV or 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 the other ARTs.
• At the total body, BMD loss was greater with ATIV 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.

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