Short Communication: Impact of Fat Changes on the Effect of Protease Inhibitors on Lumbar Spine Bone Mineral Density Changes with Antiretroviral Therapy Initiation

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Abstract

People living with HIV (PLWH) who are on protease inhibitor (PI)-containing regimens have been shown to have increases in visceral adipose tissue (VAT) and a greater decrease in spine bone mineral density (BMD) than those receiving non-PI regimens when initiating treatment. This increase in VAT has been hypothesized to falsely lower spine BMD measured via dual-energy X-ray absorptiometry, suggesting that the PI-associated BMD loss is an artefact rather than real. To test this, data collected from two completed 96-week clinical trials, AIDS Clinical Trial Group studies A5224s and A5260s, of antiretroviral therapy-naïve PLWH initiating treatment with PI and non-PI-containing regimens were analyzed comparing VAT accumulation and spine BMD loss. Results showed no significant decrease in spine BMD in persons in the highest quartile (Q4) of VAT gain versus the rest of the study population (Q1–3) in either the PI and non-PI arms, suggesting that PI-associated BMD loss is not likely to be an artefact of overlying VAT.

Keywords: bone mineral density, protease inhibitor, visceral adipose tissue, human immunodeficiency virus

Background

OSTEOPOROSIS AND FRAGILITY fractures are more common in people living with HIV (PLWH) compared to people without HIV.^{1,2} While the pathogenesis is multifactorial, specific antiretroviral therapies may contribute. Several randomized studies have shown that bone loss with antiretroviral therapy (ART), particularly at the lumbar spine, is greater with protease inhibitor (PI)-containing regimens compared to non-PI regimens.^{3–5}

It has been suggested that this observed PI-related effect on spine bone mineral density (BMD) may be due, in part, to concomitant increases in visceral adipose tissue (VAT) with ART initiation.⁶ This expansion of VAT has been hypothesized to falsely lower BMD at the adjacent spine, when BMD is measured by dual-energy X-ray absorptiometry (DXA). Indeed, in an *ex vivo* study, Yu *et al.* demonstrated that fat

layering of the trunk was associated with increased error, decreased reproducibility, and reduced DXA spine BMD values.⁷

To determine whether PI-related changes in spine BMD with ART initiation are confounded by VAT accumulation, we analyzed data from two completed 96-week clinical trials of ART-naïve PLWH who reported a greater decrease in spine BMD among those who were randomized to PI versus non-PI regimens and that also had measurements of VAT using computed tomography (CT).^{4,5} We hypothesized that, if the observed differences in spine BMD changes attributable to PIs were an artefact of the overlying VAT, then those with the greatest baseline-adjusted 96-week VAT levels would have the largest changes in spine BMD. Also, if overlying VAT falsely exaggerated decreases in BMD with ART initiation, those in the non-PI arms with the greatest amount of VAT at 96 weeks should have the greater apparent decreases in BMD compared to those with lesser amounts of VAT.

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Materials and Methods

The two study populations analyzed were from the AIDS Clinical Trial Group (ACTG) studies A5224s⁴ and A5260s.⁵ A5224s randomized participants to atazanavir/ritonavir (ATV/r) or efavirenz (EFV) with either abacavir (ABC)/lamivudine (3TC) or tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) and A5260s randomized participants to TDF/FTC plus ATV/r, darunavir (DRV/r), or raltegravir (RAL). VAT was measured by single-slice abdominal CT and lumbar spine BMD was measured by DXA at baseline and week 96. All scans were centrally read in blinded manner as previously described.^{8,9}

Analyses were conducted separately for each study using linear regression models with an interaction term between ART (PI vs. non-PI) and baseline-adjusted 96-week VAT strata [comparing those in the highest quartile (>Q3) to those in the other quartiles (≤Q3)] and were also adjusted for stratification factors (A5224s: screening HIV-1 RNA; A5260s: screening HIV-1 RNA and 10-year Framingham Risk Score.).

Results

Baseline characteristics of both studies are shown in Supplementary Table S1. In A5224s, mean VAT percent changes were 29.5% and 23.7% for the PI regimens

ATV/r+TDF/FTC ($n=65$) and ATV/r+ABC/3TC ($n=65$), respectively.⁸ The mean VAT percentage changes for the non-PI regimens, EFV+TDF/FTC ($n=69$) and EFV+ABC/3TC ($n=70$), were 14.8% and 9.9%, respectively, resulting in a VAT percent change difference in PI groups versus non-PI groups of 14.2% (95% CI -2.2%, 30.6%).⁸ The spine BMD percent change was -4.4%, -2.0%, -2.5%, and -0.8% for ATV/r+TDF/FTC, ATV/r+ABC/3TC, EFV+TDF/FTC, and EFV+ABC/3TC, respectively, resulting in a PI effect on spine BMD percent change of -1.5% (2.8%, -0.1%).⁴

Percent changes in spine BMD in the highest quartile VAT stratum were -4.14% ($n=23$, -6.14%, -2.14%), and -2.06% ($n=22$, -4.1%, 0.02%) in PI and non-PI groups, respectively, whereas quartiles 1-3 showed spine percentage BMD changes of -2.33% ($n=63$, -3.53%, -1.13%) and -1.49% ($n=82$, -2.53%, -0.45%) for PI and non-PI groups (Fig. 1). The PI treatment effect (PI-EFV) on BMD was -2.08% (-4.96%, 0.79%) in VAT Q4 and -0.84% (-2.44%, 0.76%) in VAT Q1-3.

In A5260s, mean VAT percent changes were 21.9%, 26.5%, and 29% for the groups ATV/r, RAL, and DRV/r, respectively, with no statistically significant difference in VAT percent change in the combined PI arms (pooled ATV/r and DRV/r groups) versus RAL arm.⁹ The PI effect on VAT was -2.7% (97.5% CI -19.2%, 13.9%).⁹ Spine BMD mean percent changes were -4.0% (ATV/r), -1.8% (RAL), and

FIG. 1. Percentage change in lumbar spine bone mineral density over 96 weeks by visceral adipose tissue strata (baseline adjusted): highest quartile versus Q1-Q3: (a) PI versus EFV in ACTG A5224s, (b) PI treatment effect (PI-EFV) in ACTG A5224s, (c) PI versus RAL in ACTG A5260s, (d) PI treatment effect (PI-RAL) in ACTG A5260s. ACTG, AIDS Clinical Trial Group; EFV, efavirenz; PI, protease inhibitor; RAL, raltegravir.

−3.6% (DRV/r), resulting in a pooled PI effect (PI-RAL) on spine BMD change of −1.96% (−3.1%, −0.82%).⁵

Percent changes in spine BMD by VAT strata were −4.31% ($n=45$, −5.41%, −3.21%) and −1.40% ($n=26$, −2.91%, 0.11%) in the highest quartile for PI and non-PI groups, respectively, whereas percent change in quartiles 1–3 were −3.02% ($n=150$, −3.65%, −2.39%) and −1.25% ($n=68$, −2.19%, −0.31%) for PI and non-PI groups, respectively (Fig. 1). The PI treatment effect on BMD (mean difference and 95% CI) was −2.90% (−4.82, −0.99) in VAT Q4 and −1.77% (−2.90, −0.63) in VAT Q1–3. Similar results were observed in both studies when examining change in VAT over 96 weeks or VAT levels at week 96 with respect to BMD loss (data not shown).

Discussion

In this analysis of two randomized clinical trials, which examined the effect of PI-containing regimens on bone loss, we were not able to detect a significant difference in PI-related bone loss in those in the highest quartile of baseline-adjusted VAT compared to quartiles 1–3 in either study. In addition, among those randomized to the non-PI arms, BMD losses were similar in those with the most VAT compared to those in the lower three quartiles. Our results suggest that the differential effect of PIs on BMD loss is likely to be real rather than an artefact of the concomitant VAT changes.

A specific effect of PIs on bone is corroborated by the SPIRAL-LIP study in which PLWH on suppressive ART remaining on PIs had greater bone loss at the femoral neck compared to those who switched to RAL.¹⁰ Additional evidence comes from preclinical studies, which have demonstrated impairment of osteoblast differentiation related to PIs.¹¹ Since concomitant pharmacologic boosting with ritonavir increases tenofovir concentrations by ~30%,¹² it has been suggested that that apparent effect of PIs on bone is due to an enhanced TDF effect on bone, rather than a specific PI effect.¹³ However, in ACTG A5224s, the PI effect on spine BMD (ATV/r vs. EFV) was also seen in those who received ABC/3TC, providing evidence against this hypothesis.⁴

Our study was limited by small sample sizes of the randomized studies, particularly when examining VAT strata. We also considered PIs as a class rather than focusing on individual PI medications in the analysis; however, in A5260s, spine BMD loss was similar in those randomized to ATV/r and DRV/r. Finally, BMD was measured by DXA, rather than quantitative computed tomography (QCT), which measures volumetric (i.e., three dimensional) BMD rather than areal (i.e., two dimensional) BMD, which is less susceptible to the effects of adjacent fat. The strengths of our study include the randomized treatment allocation and availability of longitudinal measures of VAT and BMD. In summary, our data suggest a VAT-independent effect of PIs on spine BMD and support the recommendation that in PLWH at higher risk of fracture receiving PIs, use of non-PI ART may help to preserve bone health.¹³

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Na-

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Supplementary Material

Supplementary Table S1

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