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The Protease Inhibitors and HIV Associated Bone Loss

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Abstract

\textbf{Purpose of review—}HIV infection is an established risk factor for osteoporosis and bone fracture. Combination antiretroviral therapy (cART) increases bone resorption leading to an additional 2–6\% bone mineral density (BMD) loss within the first 1–2 years of therapy. While tenofovir disoproxil fumarate is often blamed for antiretroviral drug-associated bone loss, evidence abounds to suggest that other agents, including the protease inhibitors (PI) have adverse bone effects. In the current review, we examine bone loss associated with PI use, describing the relative magnitude of bone loss reported for individual PIs. We also review the potential mechanisms associated with PI-induced bone loss.

\textbf{Recent findings—}As a class, PIs contribute to a greater degree of bone loss than other anchor drugs. HIV disease reversal and the associated immune reconstitution following cART initiation play an important role in PI-mediated bone loss in addition to plausible direct effects of PIs on bone cells.

\textbf{Summary—}PIs remain an important component of cART despite their adverse effects on bone. A better understanding of factors that drive HIV/cART-induced bone loss is needed to stem the rising rate of fracture in the HIV-infected population.

Keywords

Protease inhibitors; cART-induced bone loss; osteopenia; osteoporosis; fracture; HIV

Introduction

Combination antiretroviral therapy (cART) is now recommended for all HIV-infected patients regardless of CD4 T cell counts \cite{1**–3}, and those treated with cART can expect to attain a near-normal life expectancy \cite{4}. However, many will experience age-related comorbidities including musculoskeletal abnormalities, cardiovascular diseases, renal
impairment, and certain non-AIDS associated malignancies with greater frequency and at younger ages than their HIV-uninfected counterparts [5, 6*, 7*]. Indeed, HIV infection is now an established risk factor for osteopenia and osteoporosis [8] as defined by the World Health Organization criteria [femoral neck or lumbar spine T-score as measured by dual energy X-ray absorptiometry (DXA) between −1.0 and −2.5 (osteopenia) and less than or equal to −2.5 (osteoporosis)] [9]. cART further aggravates rather than alleviates HIV-associated bone loss by inducing an additional 2% to 6% loss in bone mineral density (BMD) within the first two years of therapy, a rate of bone loss comparable to that seen in post-menopausal osteoporosis, the archetype of fragility bone disease [7*, 9, 10]. The rate of BMD loss decreases after 1–2 years of cART [11–13], but whether bone resorption returns to baseline (already elevated in HIV-infected subjects) or to levels associated with uninfected subjects remains unclear. Importantly, the bone effects of cART appear to be universal across all regimens, although the magnitude of the effect may vary by regimen [12, 14, 15]. In one meta-analysis, the odds ratio (OR) of osteoporosis among HIV-infected individuals compared with HIV-uninfected controls was 3.7 [95% confidence interval (CI) 2.3 – 5.9]; cART use conferred an additional 2.5 fold increased odds of low BMD among HIV-infected patients [16].

Despite the relatively young age of the HIV/AIDS population, the high prevalence of fragility bone disease in this group is accompanied by an increasing rate of bone fractures [17]. In the landmark study of Triant et al. [17] involving 8,525 HIV-infected patients and 2,208,792 HIV-negative controls, an increase in fracture prevalence of up to 4 fold was observed in both sexes over a wide age range. Importantly, while fracture rates in HIV-negative men historically have been low until advanced age, fracture rates in HIV-infected men have risen dramatically even at young ages. For example, age-adjusted fracture rates were 2–4 fold higher in the HOPS cohort of 5,826 HIV-infected patients compared with HIV-uninfected adults in the U.S. general population [18]. In the Veterans Aging Cohort Study Virtual Cohort (VASC-VC) comprising 40,115 HIV-infected patients, fracture rates were 24% – 32% higher compared with HIV-negative controls, and in the Women’s Interagency HIV Study (WIHS) cohort, HIV-infected patients were found to have a greater incidence of fragility fractures than HIV-uninfected patients [19, 20*]. In addition, a recent Spanish study with 2,489 HIV-infected and 1,115,667 HIV-uninfected participants revealed a 5-fold higher hip fracture rate among participants with HIV infection [21], and a large Danish case-control study using nationwide health registry data found a 9-fold higher risk of fracture at the hip in HIV-infected patients compared with HIV-uninfected patients [22**]. Of note, data from two prospective cohorts of HIV-infected patients with a median age of 43 years in the U.S. demonstrated that osteoporosis is associated with a four times greater risk of fracture compared with normal BMD, thus linking osteoporosis with the rising fracture rates observed in the HIV/AIDS population [23*], which is in contrast to the general population in which BMD is not a predictor of fracture in younger patients [24]. Taken together, these data suggest that an understanding of the factors underlying HIV/cART-induced bone loss is needed to guide effective preventive and therapeutic strategies to stem the looming epidemic of bone fracture in the aging HIV/AIDS population. In the current review, we examine the role of the PIs in HIV/cART-induced bone loss, describing the

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magnitude of bone loss reported for individual PIs relative to other PIs and non-PI based cART. We also review the potential mechanisms associated with PI-induced bone loss.

The bone effects of the HIV protease inhibitors

While the effects of the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) on bone resorption and BMD are well established [25–28*, 29, 30*], the effects of the PIs on BMD are less clear. However, most studies suggest an association between PI use and BMD loss [15, 31**–35*]. The magnitude of this effect was examined in a meta-analysis of cross-sectional studies by Brown and Qaqish, who found an OR for osteoporosis of 1.57 (95% CI 1.05 – 2.34) in HIV-infected patients treated with PIs compared with those on non-PI containing cART regimens [16]. In a Japanese cohort study, each year of PI exposure was associated with an OR of 1.100 [95% CI 1.003 – 1.207] and 1.187 (95% CI 1.043 – 1.351) for low BMD in the spine and femoral neck, respectively, independent of TDF exposure [31**]. Furthermore, data from the Veterans Affairs’ Clinical Case Registry showed that the cumulative exposure to ritonavir-boosted lopinavir (LPV/r) [but not ritonavir-boosted atazanavir (ATV/r), ritonavir-boosted indinavir (IDV/r) or ritonavir (RTV) alone] was independently predictive of osteoporotic fracture [36].

Randomized clinical trials have also provided mixed evidence regarding the effects of PI use on BMD loss in treatment-naïve HIV-infected individuals (Table 1). The AIDS Clinical Trials Group (ACTG) substudy A5005s found no significant difference in total body mean percent BMD change between patients randomized to efavirenz (EFV) vs. ritonavir-boosted nelfinavir (NFV/r) [42]. Brown et al. likewise found no difference in the total body mean percent BMD change in patients receiving EFV vs. LPV/r [14]. However, these studies were limited by their reliance on BMD measurements from whole body DXA rather than measurements obtained at specific body sites.

In studies in which BMD loss at specific body sites was compared, significant differences were seen between PIs and other anchor drugs. In the ACTG substudy A5224s, there was greater mean percent BMD loss in the spine among patients receiving ATV/r vs. those receiving EFV, although no statistically significant difference was seen in BMD loss in the hip [26]. Duvivier et al. also reported a greater loss of BMD in the spine, but not the hip, in patients on a ritonavir-boosted PI (Pr/r) vs. those on a non-nucleoside reverse transcriptase inhibitor (NNRTI) in the Hippocampe-ANRS 121 study [40]. Finally, Rockstroh et al. found that patients receiving ritonavir-boosted darunavir (DRV/r) with NRTI backbone tenofovir-emtricitabine (TDF-FTC) had significantly greater loss of spine, but not hip, BMD than those receiving elvitegravir/cobicistat/emtricitabine/tenofovir (EVG/c/FTC/TDF) [37]. The mechanisms accounting for this difference in body site measurements are unclear, but may be attributable in part to the weaker correlation between site-specific DXA and whole body DXA, particularly at the hip [44]. In addition, it has been speculated that this effect may be due to the faster turnover of trabecular vertebral bone compared with the relatively slow turnover of cortical bone in the hip [26].

To date, only two randomized clinical trials have compared the BMD loss associated with two different PIs. In the ACTG substudy 5260s, no difference was observed in the mean percent BMD loss in both the spine and hip in patients receiving ATV/r vs. DRV/r; however,
patients in both PI arms had a greater percent BMD loss than patients in the integrase strand transfer inhibitor (INSTI) raltegravir (RAL) arm in both the spine and hip [38**]. Interestingly, while there was no difference in total body mean percent BMD loss in the DRV/r and RAL arms, patients in the ATV/r arm experienced more total body BMD loss than those in either of the other two arms [38**]. Investigators in the CASTLE substudy reported a greater loss of trunk mean percent BMD in patients on LPV/r compared with those on ATV/r. While no statistically significant difference was seen overall in total body mean percent change between groups, when stratified by sex, greater total body mean percent BMD loss was seen in men on LPV/r compared with men on ATV/r, while no significant difference was seen among women [41*]. Although the evidence regarding the effects of PIs on bone health in treatment experienced patients is less robust, the SPIRAL-LIP study found a 0.01 g/cm² increase in the femoral neck BMD of virologically suppressed patients switched from a PI/r-based regimen to a RAL-based regimen, with no statistically significant difference in the total body or total hip BMD [43].

While the above results argue that bone loss especially soon after cART initiation is attributable to PIs, results from other clinical trials suggest that maintaining a PI while removing the NRTI backbone also results in less loss of BMD both in viremic and virologically suppressed patients (Table 2). Treatment experienced patients failing first line therapy who were randomized to second line therapy with either LPV/r + RAL or LPV/r + 2NRTIs experienced less bone loss in the LPV/r + RAL arm; the greatest effect was seen after 48 weeks with subsequent stabilization by 96 weeks [47**, 49]. Treatment naive patients enrolled in the RADAR study who were randomized to RAL + DRV/r experienced a smaller increase in markers of bone turnover as well as an increase in total and subtotal BMD from baseline compared with the greater increase in bone turnover markers and a decrease in BMD experienced by patients treated with TDF-FTC + DRV/r [48*]. Virologically suppressed patients in the Monarch RCT substudy who were randomized to DRV/r monotherapy experienced an increase in spine and hip BMD compared with those who were maintained on a 2NRTI + DRV/r regimen [45*]. Similarly, results from the MIDAS study demonstrate an improvement in BMD in patients switched from TDF/FTC/EFV to DRV/r monotherapy [46*]. Similar results were seen in a nonrandomized study in which cART experienced, virologically suppressed patients on a PI/r based regimen containing TDF were switched from TDF to RAL [50].

These data suggest that a proportion of the bone loss observed with PI use may be attributed to concomitant TDF use. Indeed, RTV has been shown to increase plasma tenofovir (TFV) concentrations by 32 – 50% [51, 52*, 53], via inhibition of active TFV secretion by the proximal convoluted tubule [54, 55]. Similarly, cobicistat (COBI), a CYP 3A4 inhibitor that acts similarly to RTV to boost PI and EVG levels, has been shown to increase plasma TFV concentrations by 24 – 30%, possibly via the inhibition of gastrointestinal efflux transporter P-glycoprotein (P-gp), resulting in greater TDF absorption [55, 56]. However, as seen in the study by Rockstroh et al., PIs have an effect on bone loss beyond what can be explained by increased TFV levels by COBI [37].

Although these studies provide significant evidence that PIs contribute to bone loss, the choice of a cART regimen is complex, involving many biologic and psychosocial factors.
The benefits of cART far outweigh any risks of future bone disease, and PIs remain part of recommended first-line and salvage regimens [57, 58**]. For treatment naïve patients with known osteoporosis, we concur with the recommendation that the clinician and patient weigh the risks and benefits of initiating a PI-based regimen and continue to monitor the patient’s bone health [58**]. The data are less clear on whether patients with osteoporosis who are virologically suppressed for more than 12 – 24 months on a PI-based regimen would benefit from switching to an alternative regimen.

**Proposed mechanisms of PI-associated bone loss**

Despite the abundance of evidence from clinical studies for PI-associated bone loss, the underlying mechanism remains unclear. The maintenance of skeletal health and bone homeostasis are complex processes mediated by a balance between osteoblastic bone formation and osteoclastic bone resorption [8, 59]. Osteoblasts are derived from mesenchymal stem cells (MSCs), while osteoclasts are cells of monocyte-macrophage origin whose differentiation is regulated by the receptor activator of nuclear factor-kappa B ligand (RANKL) and its decoy receptor, osteoprotegerin (OPG) [60, 61]. Therefore, processes that increase osteoclastic bone resorption relative to osteoblastic bone formation will lead to BMD loss.

**Direct effects of PI on bone cells**

Previously, it was thought that the bone effects of the antiretroviral drugs were mediated by direct toxicity of the drugs on bone cells. However, establishing this phenomenon in vivo has been challenging since these drugs are used together in cART. While certain data suggest that antiretroviral drugs do have effects on osteoclasts and osteoblasts in vitro, and in animal models in vivo, results from these experiments generally have failed to recapitulate the in vivo bone effects observed in the clinical setting. For example, in in vitro experiments, the PI fosamprenavir (FPV) increases OPG expression and decreases RANKL production, while PIs RTV and saquinavir (SQV) were found to abrogate a physiologic block to RANKL [62, 63], effects that should result in an increase in BMD rather than the clinically observed loss of BMD. As another example, RTV, long considered a major protagonist of bone loss in humans, was shown in one study to inhibit osteoclast function and suppress osteoclastogenesis in vitro and in vivo by impairing RANKL-induced signaling [60], although RTV concentrations in that study were greater than normal pharmacologic concentrations [64]. Of note, the related PI indinavir (IDV) had no effect on osteoclastogenesis [60]. In contrast, other in vitro data have suggested a potential mechanism for PI-associated bone loss. NFV and IDV have been shown to alter osteoblast gene expression leading to a decrease in osteoblastic phenotype including a decrease in bone alkaline phosphatase activity and calcium deposition [65], while an increase in senescence of human MSCs when exposed to ATV and LPV leads to a decrease in differentiation to osteoblasts [59], which is consistent with clinical observations [26, 40]. Additional studies have demonstrated that RTV, at serum concentrations achieved with standard dosing for PI-boosting, increases the differentiation of peripheral blood mononuclear cells (PBMCs) into osteoclasts by upregulating growth factors and suppressing transcripts of antagonists in vitro [64, 66, 67]. A greater effect was observed in bone turnover markers (BTMs) and osteoclast...
differentiation from PBMCs in sera obtained from women on RTV-containing regimens compared with sera from HIV-infected women on other cART regimens as well as from HIV-uninfected women [66]. Taken together, these results demonstrate that PIs have the potential to reduce the RANKL/OPG ratio, inhibit osteoblastic activity, and enhance osteoclast formation. The clinical significance of these effects remains unclear, and further research is needed.

**HIV disease reversal and immune reconstitution**

Because cART-induced bone loss is universal across all antiretroviral drug classes, it has been speculated that this effect may be due to drug-induced HIV disease reversal and T-cell restoration. Recently, our group examined bone turnover in treatment naïve HIV-infected patients initiating cART. We observed a surge in bone resorption, starting as early as 2 weeks after cART initiation and lasting through 24 weeks [68**]. Because T-cell recovery with cART reaches a significant magnitude by 12 weeks [69], the time point at which we observed a peak in bone resorption, we speculated that there was a link between immune reconstitution and cART-induced bone loss [68**]. Using an animal model of immune reconstitution created by adoptive transfer of T-cells into T-cell knock-out mice, we demonstrated that immune reconstitution did indeed result in a profound loss in BMD via activation of T-cells and/or other immune cells leading to RANKL and/or tumor necrosis factor-alpha (TNF-α) production [70*].

**Altered vitamin D metabolism by protease inhibitors**

Vitamin D is important for bone metabolism and for maintaining serum calcium levels. Vitamin D insufficiency and deficiency result in in some cases in secondary hyperparathyroidism, which in turn stimulates osteoclastogenesis via production of RANKL [71]. Vitamin D deficiency may further lead to osteomalacia (poorly mineralized bone matrix). Both Vitamin D insufficiency and deficiency are highly prevalent in HIV-infected individuals [72*, 73]. They are generally worsened by cART regimens that contain TDF and EFV [73, 74], and Vitamin D and calcium supplementation have been shown to mitigate the bone loss seen with initiation of an EFV-based regimen [75**]. The effect of PIs on vitamin D levels is less clear. Conversion of 25-hydroxyvitamin D [25-(OH)D] to the active metabolite 1,25-dihydroxyvitamin D [1,25-(OH)2D] is impaired by PIs in vitro via suppression of 25- and 1α-hydroxylase in hepatocyte and monocyte cultures, although the clinical significance of this inhibition remains unclear [76]. Most observational studies have evaluated the association between PIs and 25-(OH)D levels rather than 1,25-(OH)2D levels, and suggest an increase in 25-(OH)D levels with initiation of PI therapy, which may be due to inhibition of the conversion of 25-(OH)D [77–79]. In a small clinical trial of vitamin D-deficient HIV-infected postmenopausal women on cART, supplementation with high-dose cholecalciferol was shown to increase both 25-(OH)D and 1,25-(OH)2D levels with concurrent decrease in parathyroid hormone (PTH) levels regardless of PI therapy, suggesting that PI-induced 25- and 1α-hydroxylase suppression can be overcome, although the kinetics have not been described [80]. Further study of the clinical effects of PIs on vitamin D metabolism is warranted.
Conclusions

The HIV PIs contribute to bone loss in the setting of HIV infection, which appears to be a class effect that is observed with all PIs that have been studied. HIV disease reversal and the associated immune reconstitution following cART initiation may play a central role in cART-mediated bone loss. Other potential mechanisms specific to PIs include the direct effect of PIs on the RANKL/OPG axis and on osteoblasts and osteoclasts, as well as the inhibitory effect of PIs on vitamin D metabolism. The PIs remain an important component of cART, and future research is warranted to investigate both the pathophysiology of PI-induced bone loss and prevention strategies in order to impact the long-term health of an aging HIV-infected population.

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Key points

- HIV infection and cART use are established risk factors for osteoporosis, and protease inhibitors as a class contribute to cART-induced bone loss.
- Protease inhibitors are associated with a greater degree of bone loss than NNRTIs and INSTIs.
- The mechanisms of PI-associated bone loss are not fully elucidated; however, the effects of immune reconstitution and T cell recovery after cART initiation likely play a central role.
Randomized clinical trials: PIs compared with other anchor drugs

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<td>Brown TT et al 2015 [38**]</td>
<td>TDF/FTC</td>
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<td>EFV −3.1%, ATV/r 3.4%, NS</td>
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<td>Total body BMD mean % change: ATV/r −2.65%, LPV/r −3.7% (p=0.077) **</td>
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<td>LPV/r</td>
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<td>96 weeks</td>
<td>Total body BMD mean % change: **−2.5% LPV/r, −2.3% EFV NS (p=0.86)</td>
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<td>NFV/r</td>
<td>EFV</td>
<td>96 weeks</td>
<td>Total body BMD median % change: *** −2.25% average, NS between groups</td>
</tr>
<tr>
<td>Huang et al. 2013 [27]</td>
<td>ZDV/3TC d4T/3TC TDF/3TC</td>
<td>LPV/r</td>
<td>EFV</td>
<td>96 weeks</td>
<td>Total body BMD mean % change: NRTI-sparing: −2.21% EFV/ZDV+3TC: −1.59% LPV/ZDV+3TC: −1.89% EFV/d4T+3TC: −1.66% LPV/d4T+3TC: −2.35% EFV/TDF+3TC: −2.31% LPV/TDF+3TC: −3.98%</td>
</tr>
<tr>
<td>Hansen et al. 2011 [12]</td>
<td>ZDV/3TC</td>
<td>LPV/r</td>
<td>EFV</td>
<td>144 weeks</td>
<td>Spine BMD mean % change: *** PI-sparing: −3.2% NRTI-sparing: −2.7% Hip BMD mean % change: PI-sparing: −5.0% NRTI-sparing: −4.5%</td>
</tr>
</tbody>
</table>

Treatment experienced

| Curran et al. 2012 AIDS SPIRAL-LIP substudy [43] | TDF ABC ZDV ddI d4T 3TC/FTC | PI/r ATV/r fAPV/r LPV/r SQV/r | RAL | 48 weeks | Total body BMD (g/cm²): RAL: +0.01, PI/r: 0 PI/r 0 vs. RAL +0.01 *** Spine BMD (g/cm²): PI/r +0.02, RAL: +0.0 *** Total hip BMD (g/cm²): PI/r: 0, RAL: +0.01 PI/r vs. RAL: +0.01 *** |

NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ATV, atazanavir; EVG, elvitegravir; c, cobicistat; BMD, bone mineral density; DRV, darunavir; RAL, raltegravir; ABC, abacavir; 3TC lamivudine; EFV, efavirenz; ZDV, zidovudine; ddI, didanosine; fAPV, fosamprenavir; SQV, saquinavir; IDV, indinavir; LPV, lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; d4T, stavudine; NS, non-significant

* Most fractures were traumatic. 3 non-traumatic fractures were seen in the ATV/r arm.

** Differences in mean % change of both trunk and total body BMD mean % change were statistically significant for men, and were not statistically significant for women

*** Differences are not statistically significant

NS between PI arms; statistically significant for each PI vs. RAL comparison

++ p=0.007 PI/r + NNRTI vs. NNRTI + NRTI; p= 0.001 PI/r + NRTI vs. NNRTI + NRTI
### Table 2

#### Virologically suppressed

<table>
<thead>
<tr>
<th>Author (1st)/year</th>
<th>Baseline regimen</th>
<th>Comparison</th>
<th>Study duration</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guaraldi et al. 2014 [45*]</td>
<td>TDF/FTC + DRV/r or ABC/3TC + DRV/r</td>
<td>DRV/r</td>
<td>48 weeks</td>
<td>Lumbar spine BMD (g/cm²): +0.01 DRV/r, 0.0 DRV/r + 2NRTI Femur BMD (g/cm²): +0.02 DRV/r, 0.0 DRV/r + 2NRTI Total body BMD (g/cm²): +0.01 DRV/r, +0.01 DRV/r + 2NRTI</td>
</tr>
<tr>
<td>Hamzah et al. 2015 [46*]</td>
<td>TDF/FTC/EFV</td>
<td>DRV/r</td>
<td>48 weeks</td>
<td>Hip BMD mean % change: TDF/FTC/EFV −0.002%, DRV/r +1.8% Femoral neck BMD mean % change: TDF/FTC/EFV −0.003%, DRV/r +2.9% Lumbar spine BMD mean % change: TDF/FTC/EFV +0.008%, DRV/r +2.6%</td>
</tr>
</tbody>
</table>

#### Viremic

<table>
<thead>
<tr>
<th>Author (1st)/year</th>
<th>Baseline regimen</th>
<th>Comparison</th>
<th>Study duration</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haskelberg et al. 2014 [47**]</td>
<td>2NRTI + LPV/r</td>
<td>LPV/r + RAL</td>
<td>96 weeks</td>
<td>Hip BMD mean % change: 2NRTI + LPV/r −4.1%, LPV/r + RAL −2.2% Lumbar spine BMD mean % change: 2NRTI + LPV/r −4.9%, LPV/r + RAL −3.5%</td>
</tr>
<tr>
<td>Bedmo et al. 2014 [48*]</td>
<td>TDF/FTC + DRV/r</td>
<td>DRV/r + RAL</td>
<td>48 weeks</td>
<td>Subtotal BMD change (g/cm²): TDF/FTC −7.0, RAL +9.2</td>
</tr>
</tbody>
</table>

TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; DRV, darunavir/r; ritonavir-boosted; ABC, abacavir; 3TC, lamivudine; EFV, efavirenz