Improvement in bone mineral density after switching from tenofovir to abacavir in HIV-1-infected patients with low bone mineral density: two-centre randomized pilot study (OsteoTDF study)

Eugènia Negredo1,2, Pere Domingo2,3, Núria Pérez-Álvarez1,2,4, Mar Gutiérrez2,3, Gracia Mateo2,3, Jordi Puig1,2, Roser Escrig1,2, Patricia Echeverría1,2, Anna Bonjoch1,2*, and Bonaventura Clotet1,2,5

1Lluita contra la Sida Foundation, Germans Trias i Pujol University Hospital, Badalona, Spain; 2Universitat Autònoma de Barcelona, Barcelona, Spain; 3Santa Creu i Sant Pau Hospital, Barcelona, Spain; 4Statistics and Operations Research Department, Universitat Politècnica de Catalunya, Barcelona, Spain; 5Irsicaixa Foundation, Germans Trias i Pujol University Hospital, Badalona, Spain

*Corresponding author. E-mail: abonjoch@flsida.org

Received 27 March 2014; returned 12 May 2014; revised 18 June 2014; accepted 11 July 2014

Background: Tenofovir has been associated with a decrease in bone mineral density (BMD). However, data on changes in BMD after discontinuing tenofovir are lacking.

Methods: We performed a two-centre randomized pilot study in virologically suppressed HIV-infected patients receiving tenofovir with osteopenia/osteoporosis (OsteoTDF study, ClinicalTrials.gov number NCT 01153217). Fifty-four patients were randomly assigned to switch from tenofovir to abacavir (n = 26) or to continue with tenofovir (n = 28). Changes in lumbar and total hip BMD were evaluated at Week 48 from baseline.

Results: Five patients discontinued the study (three from the tenofovir group and two from the abacavir group). No significant differences were detected between the groups at Week 48 (P = 0.229 for total hip and P = 0.312 for lumbar spine). However, hip BMD improved by 2.1% (95% CI: 0.6 to 4.7) (P = 0.043) in the abacavir group and 0.7% (95% CI: 0.9 to 2.4) (P = 0.372) in the tenofovir group. Lumbar spine BMD varied by –0.7% (95% CI: –3.8 to 3.3) (P ≤ 0.001) in the abacavir group and –1.2% (95% CI: –3.8 to 0.4) (P < 0.001) in the tenofovir group.

Conclusions: Switching from tenofovir to abacavir led to a slight improvement in femoral BMD although no differences were detected between groups. Larger studies are necessary before firm recommendations can be made on the discontinuation of tenofovir in patients with a low BMD.

Keywords: osteoporosis, DXA scan, virologically suppressed, HIV-infected patients

Introduction

Clinical evidence shows a strong correlation between loss of bone mineral density (BMD) and infection by HIV.1 Both virological and immunological factors contribute to decreased BMD in HIV-infected patients.1–3 Exposure to antiretroviral therapy also induces bone demineralization1,4–9 and risk of fracture.5,10 Data suggest a lower BMD among patients receiving PI.1,5,6,11 However, tenofovir is currently the antiretroviral drug most associated with BMD loss.5,6,11 Nonetheless, published data on bone recovery after discontinuation of tenofovir are lacking.

Since osteoporosis is an increasing problem in HIV-infected patients, new therapeutic strategies should be investigated to delay or recover bone loss. Based on the hypothesis that the decrease in BMD during the first months of therapy with tenofovir can be recovered after withdrawal of the drug, we decided to assess changes in bone mineralization in patients with a low BMD after switching tenofovir in their regimen.

Methods

Study design, subjects and randomization

We performed a two-centre randomized pilot study (OsteoTDF study, ClinicalTrials.gov number NCT 01153217) in HIV-infected patients with a low BMD. The study was approved by the Ethics Committee of our centre and by the local health authorities. All participants signed the written informed consent document.

The inclusion criteria were virological suppression during a tenofovir-containing regimen for more than 48 weeks and meeting the criteria for osteopenia/osteoporosis by DXA scan, according to the WHO classification. The exclusion criteria were HLA B*5701 positivity, hepatitis B virus (Australia antigen) positivity, secondary causes of osteoporosis/osteopenia other than...
hypovitaminosis D, therapy with bisphosphonates within the last 48 weeks, and suspected or documented abacavir-related resistance mutations.

A total of 54 patients were randomized to switch from tenofovir to abacavir (abacavir group, n = 26) or to continue with tenofovir (tenofovir group, n = 28) and were followed at Weeks 4, 12, 24, 36 and 48.

**Objective, endpoints and assessments**

To determine the reversibility of bone loss 48 weeks after the switch from tenofovir to abacavir, we compared the groups in terms of lumbar spine (L2–L4) and femoral BMD at Week 48 and evaluated the changes from baseline in each group at Week 48.

DXA scans were performed using a Lunar Prodigy device (GE Healthcare, Belgium) for patients from one of the participating centres and a Hologic device (Discovery Wi, S/N 85173) for patients from the other centre. Only one reader per centre, blind in terms of the study treatment, evaluated all the scans. In order to compare the measurements made with each machine, determinations were corrected to a standardized BMD using specific equations, described elsewhere, for both the lumbar spine and hip and for the Lunar and Hologic devices.14

The percentages of patients who experienced virological failure (HIV RNA viral load >50 copies confirmed within 1 month) and grade 3–4 toxicity were compared between the groups.

**Statistical analyses**

Quantitative variables are expressed as mean (SD) or median and IQR. Statistical significance was calculated using the t-test or Mann–Whitney test for non-paired variables and a paired t-test or Wilcoxon test for repeated measurements. The summary statistics and the test were selected according to the distribution of the variables.

The qualitative variables were described using percentages and compared using the χ² test, with the continuity correction for the χ² or Fisher exact test when a subgroup included five or fewer subjects.

The changes in BMD scores were assessed by calculating the percentage change from baseline to the end of the study (Week 48). Statistical significance was set at <0.05 (two-tailed). The statistical analyses were performed using SPSS 15.0 software for Windows (SPSS Inc., Chicago, IL, USA).

**Results**

The epidemiological and clinical data are summarized in Table 1. In the tenofovir group, two patients discontinued the drug early because of renal damage (both at Week 36) and a third was lost to follow-up (Week 4). In the abacavir group, two patients interrupted treatment, one because of potentially abacavir-related

Table 1. Baseline epidemiological, HIV-related and biochemical characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Abacavir group (n = 26)</th>
<th>Tenofovir group (n = 28)</th>
<th>P value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.5 (6.9)</td>
<td>49.1 (8.3)</td>
<td>0.736</td>
</tr>
<tr>
<td>Male (%)</td>
<td>88.5</td>
<td>78.6</td>
<td>0.470</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 (2.9)</td>
<td>22.1 (2.9)</td>
<td>0.350</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>95.3</td>
<td>96</td>
<td>0.874</td>
</tr>
<tr>
<td>HIV-related data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV coinfection (%)</td>
<td>19.2</td>
<td>32.1</td>
<td>0.358</td>
</tr>
<tr>
<td>route of HIV transmission (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>57.7</td>
<td>39.3</td>
<td>0.095</td>
</tr>
<tr>
<td>intravenous drug use</td>
<td>11.5</td>
<td>28.6</td>
<td>0.315</td>
</tr>
<tr>
<td>heterosexual relations</td>
<td>11.5</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td>cumulative exposure (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>5.0 (3.6)</td>
<td>6.1 (5.3)</td>
<td>0.315</td>
</tr>
<tr>
<td>NNRTI</td>
<td>3.8 (3.9)</td>
<td>5.2 (4.0)</td>
<td>0.110</td>
</tr>
<tr>
<td>tenofovir</td>
<td>5.1 (4.7)</td>
<td>5.0 (4.0)</td>
<td>0.882</td>
</tr>
<tr>
<td>baseline antiretroviral therapy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>38.5</td>
<td>46.4</td>
<td>0.593</td>
</tr>
<tr>
<td>NNRTI</td>
<td>57.7</td>
<td>53.6</td>
<td>0.791</td>
</tr>
<tr>
<td>raltegravir</td>
<td>3.8</td>
<td>0</td>
<td>0.481</td>
</tr>
<tr>
<td>nadir CD4 cell count (cells/mm³)</td>
<td>229 (153)</td>
<td>232 (143)</td>
<td>0.950</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)</td>
<td>590 (184)</td>
<td>582 (242)</td>
<td>0.892</td>
</tr>
<tr>
<td>Biochemical parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 Hydroxyvitamin D (ng/mL)</td>
<td>22.8 (10.9)</td>
<td>20.2 (10.4)</td>
<td>0.382</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>41.5 (23.2)</td>
<td>49.2 (15.9)</td>
<td>0.320</td>
</tr>
<tr>
<td>TSH (µIU/mL)</td>
<td>1.9 (1.1)</td>
<td>1.9 (0.7)</td>
<td>0.761</td>
</tr>
</tbody>
</table>

All data are expressed as mean (SD) unless otherwise specified.

HCV, hepatitis C virus; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.
mild diarrhoea and a second because of anxiety episodes not related to the treatment (both at Week 4). No patient experienced virological rebound or grade 3–4 antiretroviral-related toxicity.

No statistically significant differences in BMD were recorded between the groups at Week 48 (P=0.229 for femoral BMD and P=0.312 for lumbar spine BMD) (Figure 1). However, the percentage changes in BMD from baseline at Week 48 in the abacavir group were 2.1% (95% CI –0.6 to 4.7) for femoral BMD (P=0.043) and –0.7% (95% CI –3.8 to 3.3) for lumbar spine BMD (P<0.001), while in the tenofovir group the percentage changes were 0.7% (95% CI –0.9 to 2.4) for femoral BMD (P=0.372) and –1.2% (95% CI –3.8 to 0.4) for lumbar spine BMD (P<0.001).

No significant changes were observed in levels of vitamin D, calcium, phosphate, parathyroid hormone, triglycerides, liver enzymes and gamma glutamyl transpeptidase.

In the abacavir group, LDL cholesterol concentrations increased significantly at Week 48 with respect to baseline values (0.3 mmol/L; P=0.027) and alkaline phosphatase decreased (15.0 U/L; P=0.005). In the tenofovir group, creatinine increased significantly (6.7 µmol/L; P=0.003) (Table S1, available as Supplementary data at JAC Online).

**Discussion**

According to the results of a meta-analytical review, 67% of HIV-infected patients had a reduced BMD and 15% of these had osteoporosis (OR of 6.4 and 3.7, respectively, compared with non-HIV-infected controls). Even higher percentages have been reported by our group and others. These data should point us toward strategies to delay or recover bone loss.

The above mentioned meta-analysis also revealed that subjects on treatment had a 2.5-fold increased probability of a reduced BMD. Tenofovir is the antiretroviral drug most associated with accelerated BMD loss. Nonetheless, no recommendations on the management of tenofovir-treated patients with osteopenia/osteoporosis have been made to date. The only available data to the present showed a 2%–3% improvement in lumbar and femoral BMD after tenofovir was switched to raltegravir in a one-arm, 48 week study (TROP study). In our study, no differences were found between the groups at Week 48. The small sample size and the fact that lifestyle modifications were also recommended to the tenofovir group could explain this. However, the switch from tenofovir to abacavir led to an improvement in femoral BMD (2.1%) similar to that observed in the TROP study, together with a decrease in alkaline phosphatase level; since liver enzymes did not vary in this group, changes in alkaline phosphatase could be related to bone variations. Lumbar spine BMD, however, diminished slightly in this group (–0.7%) and even more patients who continued with tenofovir (–1.2%). Although the femoral recovery was only partial, considering that the percentage of bone loss described when tenofovir was started was slightly greater (from –2% to –4%), it could be interesting to consider this, especially in those patients with severe osteoporosis.

Our findings support data suggesting that causes other than tenofovir could explain the loss of BMD in these patients, such as the virus itself, systemic inflammation, immune reconstitution or the use of PIs. However, since this is a pilot study, we were unable to draw comparisons between patients receiving PIs (~40%) or not receiving them.

The significant improvement in only femoral BMD in our patients was unexpected because it is well known that lumbar bone is more susceptible to changes than femoral bone. Studies with animal models suggest that tenofovir inhibits the mineralization of cortical bones, resulting in an osteomalacia-like condition. In this case, the interruption of tenofovir in our patients could reverse the defect in femur mineralization (cortical bone).

In addition to the small sample size and the short follow-up, the use of two different devices to evaluate our patients could limit our conclusions. However, to mitigate this potential caveat, all data from DXA scans were corrected to a standardized BMD using validated equations to properly compare the measurements.

In conclusion, further studies are necessary before we can make firm recommendations on the discontinuation of tenofovir in patients with a low BMD, although our data suggest that the switch from tenofovir to abacavir led to a certain recovery of femoral BMD.

**Funding**

This work was supported by funding from ViiV Healthcare. ViiV Healthcare was given the opportunity to review a preliminary version of this work.
manuscript for factual accuracy; the authors are solely responsible for the final content and interpretation.

Transparency declarations
E. N. has received personal fees from Merck, Abbvie, Janssen-Cilag, Boehringer Ingelheim, Roche, Gilead Sciences and ViIV Healthcare. P. D. has received unrestricted grants from Boehringer Ingelheim, Janssen-Cilag, Pfizer, Gilead Sciences and Abbvie, consulting fees and honoraria from Boehringer Ingelheim, Janssen-Cilag, Pfizer, Gilead Sciences, Abbvie, BMS, MSD, ViIV Healthcare, Theratechnologies and Ferrer International, and has acted as a consultant for Boehringer Ingelheim, Janssen-Cilag, Pfizer, Gilead Sciences, Abbvie, BMS, MSD, ViIV Healthcare, Theratechnologies and Ferrer International. J. P. has received personal fees from Abbott, Roche and GlaxoSmithKline. A. B. has acted as a consultant for Merck, Abbott, Janssen-Cilag, Boehringer Ingelheim, Roche and GlaxoSmithKline. All other authors: none to declare.

Supplementary data
Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References