

## Correspondence

### Determinants of bone diseases in tenofovir-treated HIV patients

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Bedimo and Co-workers have recently reported the results of a prospective, cross-sectional study aimed at investigating the mechanisms of increased bone loss in male subjects with HIV and HCV mono-infections or HIV/HCV co-infections [1]. They found that HIV and HCV were significantly and independently associated with lower bone mineral density (BMD). The statistical models adjusted for tenofovir (TDF) use greatly attenuated the association of HIV with decreased BMD, suggesting that the effect of HIV on BMD was mainly driven by TDF. Furthermore, the Authors documented that, at variance with HCV, HIV infection was associated also with altered bone turnover, as documented by increased telopeptide X (CTX) and osteocalcin (OC) serum concentrations. Here we intend to extend these findings by assessing the potential contribution of TDF overexposure on bone diseases, in consideration of the recently reported associations between high TDF plasma concentrations and the development of kidney impairment [2,3].

In this retrospective analysis we included all HIV-infected patients from our local database treated with TDF for at least six months and with at least one assessment of TDF plasma trough concentrations. Bone diseases were assessed through evaluation of BMD by dual-energy x-ray absorptiometry (DXA) (osteopenia and osteoporosis were diagnosed as a spine or hip T-score between -1 and -2.5 or  $\leq -2.5$ , respectively) and/or by markers of bone formation and resorption such as OC (reference values: 11-46 ng/mL) and CTX (reference values: <580, <704 and <1000 pg/mL for all patients <50 years, males >50 years and females >50 years, respectively). 198 out of the 478 patients from our database fulfilling the inclusion criteria performed at least one DXA evaluation. They were at a mean of  $2080 \pm 1209$  days of therapy with TDF and were mainly given a

protease inhibitor (54%) or a non-nucleoside reverse transcriptase inhibitor (34%) as the third drug of the antiretroviral therapy. Overall, 150 out of the 198 patients (76%) had DXA alterations (92 and 90 patients with osteopenia and osteoporosis, respectively). As shown in Table 1, these patients had lower body mass index, were older and were treated longer with TDF as compared to patients with normal DXA, whereas no differences on TDF trough concentrations were found ( $157\pm 139$  vs.  $142\pm 136$  ng/mL,  $p=0.51$ ). The same trends were confirmed also when repeating the analysis by considering only patients with osteoporosis. Data on markers of bone turnover were available for 133 out of the 478 patients. Significantly higher TDF concentrations were found in patients with altered vs. normal OC levels (TDF concentrations:  $288\pm 173$  vs.  $153\pm 115$  ng/mL,  $p<0.01$ ). Conversely, no association between TDF concentrations and CTX level were documented (TDF concentrations:  $147\pm 103$  vs.  $165\pm 128$  ng/mL,  $p=0.74$  in patients with altered vs. normal CTX values).

In agreement with previous findings, we firstly documented that a large proportion of HIV-infected patients on long-term antiretroviral therapy developed bone metabolism alterations; these events were significantly associated with patients' age and lower body mass index [4,5]. We also extended the findings by Bedimo et al [1] by recognizing that bone disease was significantly associated with the duration of TDF therapy but not with TDF plasma trough concentrations. The latter finding seems to argue against a potential contribution of TDF overexposure on the development of bone diseases, at variance with findings in HIV-infected patients experiencing TDF-related kidney complications [2,3]. This may be eventually related to the fact that, at variance with kidney diseases – in which a direct mechanism linked to the selective accumulation of TDF within renal

tubular cells has been identified [6-8] – TDF is only one of the risk factors for bone loss, and its effect may be eventually diluted by the presence of other clinical covariates (such as, patients' sex, age, diet, body mass index, etc) known to play a key pathogenetic role in bone diseases [4,5]. This hypothesis has been indirectly confirmed by the findings that patients with altered OCT levels have significantly higher TDF plasma trough concentrations compared with patients with physiologic OC levels, whereas no association was found with CTX levels. Taken together, these results suggest an essential involvement of TDF only in the process of bone formation. Indeed, assuming that OC is a marker which a) is secreted solely by osteoblasts, b) is pro-osteoblastic and c) whose alterations induce pathologic alterations in BMD [9], it can be reasonably speculated that the detrimental effects of TDF on bone metabolism might be driven mainly by OC-mediated loss of osteoblast function. Accordingly, our results provide for the first time *in vivo* indirect evidence that the effect of TDF on osteoblast activity is concentration-dependent, as previously documented *in vitro* in osteoblast cultures [10].

In conclusion, in this hypothesis-generating study we have provided preliminary evidence that exposure of patients to high plasma TDF concentrations might induce early pathologic alterations in bone turnover, eventually favoring the development of osteopenia/osteoporosis through impaired bone formation in high-risk HIV-infected patients.

**Disclosure statement**

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All Authors have read and approved the text.

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Table 1. Patients characteristics clustered according to the development or not of bone diseases

<b>Parameters</b>	<b>No bone diseases (n=48)</b>	<b>Osteopenia or osteoporosis (n=150)</b>	<b>P-value</b>
TDF therapy, days	1683 ± 1417	2209 ± 1109	<0.01
TDF concentrations, ng/mL	142 ± 136	157 ± 139	0.51
Female gender, %	47.9%	43.3%	0.33
Age, years	46 ± 10	51 ± 8	<0.01
Concomitant ARV drugs, %	50% PI 33% NNRTI 17% other	55% PI 35% NNRTI 10% other	0.74
Body mass index, Kg/m <sup>2</sup>	23.8 ± 4.6	22.2 ± 3.9	<0.05
S.creatinine before TDF, mg/dL	0.80 ± 0.19	0.78 ± 0.19	0.65
S. creatinine last f.u., mg/dL	1.0 ± 0.3	0.9 ± 0.3	0.16
CD4, cells/mL	585 ± 252	654 ± 286	0.15
HBV or HCV coinfection, %	38%	43%	0.51

TDF: tenofovir; ARV: antiretroviral; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; f.u.: follow-up; HBV: hepatitis B virus; HCV: hepatitis C virus