possibly improving its PK exposure through ritonavir–
fluconazole co-boosting. The prolonged half-life of fluconazole
(31–34 h), allowing once daily administration, would add only a
reasonable extra pill burden to the patients while providing a
more potent antiretroviral action.

Transparency declarations

None to declare.

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Non-nucleoside-reverse-transcriptase-inhibitor-
based HAART and osteoporosis in HIV-infected subjects

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Sirs,

A significant improvement of survival of people infected with
HIV has been observed since the introduction of HAART in
clinical practice.1 Several toxicities have arisen such as li-po-
dystrophy, insulin resistance, diabetes, dyslipidaemia and
also abnormalities of bone metabolism such as osteopenia/
osteoporosis and osteonecrosis.2–4 HIV infection, a prolonged
use of protease inhibitors (PIs), lactic acidosis, lipodystrophy,
immune reconstitution, nutritional and hormonal factors and
prior AIDS-related wasting are all factors that can contribute
to these abnormalities.5,6

No data are at the moment available on the frequency and on
the predictive factors of osteopenia/osteoporosis in HIV-infected subjects receiving a non-nucleoside-reverse-transcriptase-
inhibitor (NNRTI)-based HAART.

This observational prospective study involved 89 consecutive
HIV-infected subjects aged between 30 and 50 years; patients with
pathological or toxic conditions potentially affecting bone me-
tabolism such as hypogonadism, hyper- or hypothyroidism and
hypocortisolism, bed rest period >1 month, drug/alcohol abuse,
neoplasia, chronic diarrhoea or absorption dysfunction, body
mass index (BMI) < or >20% normal ranges (19.1–25.8 for
women and 20.7–26.4 for men), chronically treated with
corticosteroids, levothyroxine, lithium or oestrogens, and
women in menopause or amenorrhoea were excluded. We included
in the study both naive and HAART-treated subjects. Patients
receiving antiretroviral treatment were naive for PIs and were
receiving a stable, first-line, NNRTI-based HAART for at least
2 years with HIV-RNA < 50 copies/mL in the previous 6 months.

All subjects underwent dual energy X-ray absorptiometry
(DEXA) scans (Hologic, QDR 4500 Delphi system, Bedford,
MA, USA) in antero-posterior lumbar spine (L1-L4) and left
hip sites to evaluate mean bone mineral density (BMD), total
mean T-score and Z-score. DEXAs were performed at the same
radiological centre by a single radiologist, and WHO criteria were
considered for the diagnosis of osteopenia/osteoporosis. Written
informed consent was obtained from all participants, and the
study was conducted in adherence with local drug regulations,
guidelines on ‘Good Clinical Practice’ and the principles of the
Declaration of Helsinki.

Comparisons between categorical groups were performed by
χ2 and Wilcoxon tests. Potential predictive factors of osteopenia/
osteoporosis were evaluated by a multivariate regression logistic
analysis. Variables included in the model were gender, age, risk
factors for HIV infection, CDC stage, hepatitis C virus (HCV)
eros status, BMI, lipodystrophy, CD4 cell count at DEXA, months
since first HIV-positive test and use of NNRTI-containing
HAART. A similar analysis was repeated including only
NNRTI-treated subjects to evaluate the role of NNRTI-based
HAART duration in the occurrence of osteopenia/osteoporosis.

Table 1 summarizes demographic and clinical characteristics
of the subjects included in the study: 47 were naive and 42 were
NNRTI-treated. As expected, naive patients had a lower duration
of HIV infection and a lower CD4 cell count than NNRTI-treated
patients. Median duration of HAART was 41 months.
(IQR: 32–49); efavirenz was used by 27 subjects and nevirapine by 15; the most prescribed nucleoside backbone was zidovudine plus lamivudine (n = 36).

A total of 46 (51.7%) subjects, 23 in each group, had abnormal findings at DEXA: 35 (39.3%) had osteopenia and 11 (12.4%) had osteoporosis. Among naive subjects, 18 had osteopenia and 5 had osteoporosis; among NNRTI-treated subjects 17 had osteopenia and 6 had osteoporosis (P = not significant).

In the multivariate analyses on the whole cohort predictors of osteopenia/osteoporosis were older age (OR: 1.18, 95% CI: 1.05–1.33, P < 0.01 for each additional year) and low BMI (OR: 0.68, 95% CI: 0.54–0.85, P < 0.01 for each additional year). The use of NNRTI-containing HAART was not associated with osteopenia/osteoporosis (OR: 1.30, 95% CI: 0.64–3.36, P = 0.26). When considering only NNRTI-treated subjects, older age (OR: 1.93, 95% CI: 1.10–3.36, P = 0.02 for each additional year) and low BMI (OR: 0.43, 95% CI: 0.19–0.95, P = 0.03 for each additional unit) were confirmed to be predictive of osteopenia/osteoporosis; in this subgroup also a more prolonged exposure to NNRTI seemed predictive (OR: 2.48, 95% CI: 0.96–6.42, P = 0.06 for each additional year).

The presence of osteopenia/osteoporosis is a frequent finding in HIV-infected individuals, and its pathogenesis remains unex-
plained. The role of both HIV infection itself and HAART has been considered. In one of the first reports, Tebas et al. found that PI-containing regimens were associated with a higher risk of osteopenia/osteoporosis; in a more recent study, the rate of osteopenia and osteoporosis was comparable between naive and HAART-treated patients, and in both these populations BMD was lower than in healthy controls. However, in the present study the groups were not well balanced for age and BMI, both factors potentially related to bone abnormalities. In a previous report on an unselected population, we found that both higher HIV-RNA and HAART duration were predictors of osteopenia/osteoporosis. In this study, antiretroviral treatments were heterogeneous, and the role of specific drug classes was not evaluated.

To our knowledge, this is the first report evaluating the presence of osteopenia/osteoporosis in NNRTI-treated subjects. Traditional risk factors for osteopenia/osteoporosis, such as low BMI and older age, were also predictive in the HIV population; NNRTI-treated subjects did not seem at higher risk than naive subjects. However, when restricting the analysis to NNRTI-treated individuals, those with a more prolonged exposure to NNRTI seemed at higher risk of osteopenia/osteoporosis. This finding needs to be confirmed in studies with a longer follow-up.

To date, the presence of osteopenia/osteoporosis in HIV-infected subjects is of particular concern. Overall, our data suggest that this condition is not higher in NNRTI-treated than in naive subjects; however, when considering only NNRTI-treated subjects, a more prolonged NNRTI exposure seems to correlate with osteopenia/osteoporosis.

### Correspondence

**Table 1.** Demographic and clinical characteristics of the cohort according to treatment

<table>
<thead>
<tr>
<th>Clinical and demographic characteristics</th>
<th>NNRTI-treated (n = 42)</th>
<th>Naive (n = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>27 (64.3%)</td>
<td>29 (61.7%)</td>
<td>0.80*</td>
</tr>
<tr>
<td>Age (years) (median, IQR)</td>
<td>37 (35–39)</td>
<td>39 (34–43)</td>
<td>0.10*</td>
</tr>
<tr>
<td>Risk factor for HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>homosexual</td>
<td>14 (33.3%)</td>
<td>15 (31.9%)</td>
<td>0.88*</td>
</tr>
<tr>
<td>heterosexual</td>
<td>21 (50.0%)</td>
<td>22 (26.8%)</td>
<td>0.76*</td>
</tr>
<tr>
<td>IVDU/exIVDU</td>
<td>7 (16.7%)</td>
<td>10 (80.9%)</td>
<td>0.58*</td>
</tr>
<tr>
<td>HCV-antibody-positive</td>
<td>7 (16.7%)</td>
<td>10 (11.2%)</td>
<td>0.58*</td>
</tr>
<tr>
<td>CD4 (cells/mm³) (median, IQR)</td>
<td>492 (398–653)</td>
<td>398 (263–568)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>months since first HIV-positive test (median, IQR)</td>
<td>83 (49–117)</td>
<td>41 (11–93)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>BMI (median, IQR)</td>
<td>22.1 (19.8–24.6)</td>
<td>22.7 (20.6–24.8)</td>
<td>0.13*</td>
</tr>
<tr>
<td>CDC stage C</td>
<td>4 (9.5%)</td>
<td>2 (4.3%)</td>
<td>0.32*</td>
</tr>
</tbody>
</table>

### Transparency declarations

None to declare.

### References