Antiretrovirals, fractures and osteonecrosis in a large European HIV cohort


* no financial relationships with commercial entities to disclose.
Background

- Fractures and osteonecrosis of the femoral head have emerged as important manifestations of bone disease during treated HIV infection.

- HIV+ persons have 1.5-3.0-fold greater risk of fractures and 100-fold greater risk of osteonecrosis compared with the general population.

- Initiation of antiretroviral therapy, in particular regimens containing tenofovir DF (TDF), is associated with increased levels of markers of bone turnover and reduction in bone mineral density. The clinical consequences of this have not been determined.

- The effect of antiretroviral exposure on the risk of fractures and osteonecrosis remains poorly understood.

Grund AIDS 2009
Morse CID 2007
Triant JCEM 2008
McComsey CID 2011
Bedimo AIDS 2012
Prieto-Alhambra JAIDS 2014
Objectives

• To determine factors independently associated with incident fractures and osteonecrosis

• To study the association between exposure to antiretrovirals and subsequent risk of fractures and osteonecrosis
Methods

- Inclusion criteria: EuroSIDA participants >16 y with prospective follow up after 1 January 2004 and baseline data on CD4 and viral load

- Poisson regression with appropriate adjustments for multiple events per patient was used to identify clinical, laboratory and demographic factors associated with fractures and osteonecrosis

- Factors with marginal associations (p<0.1) in univariate analyses were included in multivariate models

- Each antiretroviral was included in the best-fitting multivariate model to assess the effect of its exposure on the subsequent risk of either bone outcome.

- Secondary analyses restricted to osteoporotic fractures (grouped as fractures of the spine, arm, wrist and hip)
Results: Inclusion of participants

EuroSIDA cohort
N = 20854

Prospective FU > 1/1/2004
N = 14917

With gender, aged > 16 at baseline
N = 14909

With baseline CD4 and viral load
N = 13015

Including sites > 100 PYFU and reported events
N = 11820
86118 PYFU

496 persons develop **619 new fractures** during FU
Incidence/1000PYFU: 7.2 (6.6-7.7)

73 persons develop **89 cases of osteonecrosis** during FU
Incidence/1000PYFU: 1.0 (0.8-1.3)

Excluded
N = 5937*

N = 21

N = 1881

N = 1195

Baseline: latest of 1 January 2004 and recruitment to EuroSIDA. Baseline CD4/VL defined as last measurement before baseline (and within 6 months) or if none before, first after baseline (and within 6 months).

*Includes persons enrolled into Cohort 10 with only baseline data
Fracture sites (N=619): broad categories

- Arm: 122
- Hand: 31
- Leg: 135
- Foot: 42
- Foot: 22
- Spine: 44
- Ribs: 20
- Head: 20
- Unknown fracture site: 202
Fracture sites (N=619): broad categories

Osteoporotic fractures: N=132
Results: Incidence of new fractures and osteonecrosis
Stratified by current CD4

<table>
<thead>
<tr>
<th>Current CD4</th>
<th>Any fracture (Incidence/1000 PYFU, 95% CI)</th>
<th>Osteonecrosis of the femoral head (Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=200</td>
<td>8.9</td>
<td>7</td>
</tr>
<tr>
<td>201-350</td>
<td>8.3</td>
<td>19</td>
</tr>
<tr>
<td>351-500</td>
<td>7.5</td>
<td>26</td>
</tr>
<tr>
<td>501-750</td>
<td>5.5</td>
<td>21</td>
</tr>
<tr>
<td>&gt;750</td>
<td>5.0</td>
<td>16</td>
</tr>
</tbody>
</table>

Events
- Any fracture: 52, 115, 148, 151, 95
- Osteonecrosis: 7, 19, 26, 21, 16
Results: Factors independently associated with fractures (N=619)

Age (per 10y older)
Other race vs white
BMI (per Kg/m²)
≤18 19-30 (REF) >30
IV drug use vs other risk
Current CD4/doubling
Nadir CD4/doubling
Baseline HIV RNA <500 (REF) 500-100k >100k
Hepatitis C pos
Current smoking
Prior osteonecrosis
Prior fracture
Prior AIDS (not cancer)
Recent non-AIDS cancer (last 12 months)
Recent cardiovascular disease (last 12 months)

aIRR: adjusted incidence rate ratio. Models adjusted for depicted covariates plus calendar year and region. Only covariates significant (p<0.1) in univariate analyses were included in multivariate models to avoid overfitting.
Results: Factors independently associated with osteonecrosis
(N=89)

Age (per 10y older)

Other race vs white

BMI (per Kg/m$^2$)

≤18

19-30 (REF)

>30

Baseline CD4/doubling

Current smoking

Prior osteonecrosis

Prior fracture

Prior AIDS (not cancer)

Prior AIDS cancer

Prior non-AIDS cancer

aIRR: adjusted incidence rate ratio. Models adjusted for depicted covariates plus calendar year and region. Only covariates significant (p<0.1) in univariate analyses were included in multivariate models to avoid overfitting.
Results: Characteristics at last visit for those with no bone event, or at last diagnosis of fracture or osteonecrosis

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>No bone event</th>
<th>Fractures</th>
<th>Osteonecrosis</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N(%)/ Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>11266 (95.2)</td>
<td>496 (4.2)</td>
<td>73 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>583 (5.3)</td>
<td>26 (5.6)</td>
<td>5 (7.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>eGFR b mL/min/1.73 m²</td>
<td>95 (80,106)</td>
<td>96 (79,106)</td>
<td>94 (75,106)</td>
<td>0.58</td>
</tr>
<tr>
<td>Vitamin D c ng/ml</td>
<td>37 (22,65)</td>
<td>35 (15,83)</td>
<td>31 (9,40)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

(a) CKD chronic kidney disease at any time before last visit or event date; defined as confirmed (>3 months apart) eGFR < 60 for those with first eGFR > 60, or 25% decline where baseline eGFR < 60. eGFRs were calculated using CKD-EPI formula.

(b) eGFR was available for 11536 (97.5%); 11003 (97.7%) for those with no events, 466 (94.1%) for those with any fracture and 67 (91.8%) for those with femoral necrosis (p<0.0001).

(c) Data available for 3291 (27.8%) overall, 3210 (28.5%) for those with no events, 71 (14.3%) for those with fractures and 10 (13.7%) of those with femoral necrosis (p<0.0001).

*global p-values for comparing across the three groups
Results

Crude incidence of new fractures

TDF use

<table>
<thead>
<tr>
<th>Exposure to TDF</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>192</td>
</tr>
<tr>
<td>Ever</td>
<td>369</td>
</tr>
<tr>
<td>Off</td>
<td>283</td>
</tr>
<tr>
<td>On</td>
<td>278</td>
</tr>
<tr>
<td>On 0</td>
<td>192</td>
</tr>
<tr>
<td>On 1</td>
<td>60</td>
</tr>
<tr>
<td>On 2</td>
<td>61</td>
</tr>
<tr>
<td>On 3</td>
<td>41</td>
</tr>
<tr>
<td>On 4</td>
<td>53</td>
</tr>
<tr>
<td>On 5</td>
<td>52</td>
</tr>
<tr>
<td>On &gt;5</td>
<td>102</td>
</tr>
</tbody>
</table>

Incidence/1000 PYFU (95% CI)

- 4.7 ± 2
- 8.1 ± 4
- 7.8 ± 6
- 8.1 ± 8
- 8.5 ± 10
- 9.1 ± 12
- 10.6 ± 14
- 7.5 ± 16
## Results: Effect of TDF exposure on fracture risk

<table>
<thead>
<tr>
<th>TDF exposure</th>
<th>Any Fractures</th>
<th></th>
<th>Osteoporotic fractures&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td></td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Multivariate&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ever vs never TDF</td>
<td>1.71 (1.42-2.06)</td>
<td>1.40 (1.15-1.70)</td>
<td>1.10 (0.76-1.58)</td>
</tr>
<tr>
<td>On vs off TDF</td>
<td>1.38 (1.16-1.64)</td>
<td>1.25 (1.15-1.70)</td>
<td>1.12 (0.79-1.60)</td>
</tr>
<tr>
<td>Cumulative TDF exposure/5 years</td>
<td>1.28 (1.13-1.50)</td>
<td>1.08 (0.94-1.25)</td>
<td>0.99 (0.69-1.43)</td>
</tr>
</tbody>
</table>

IRR: incidence rate ratio. **P < 0.05** for IRR (95% CI) written with bold letters

<sup>a</sup> Grouped as fractures of the spine, arm, wrist and hip

<sup>b</sup> Adjusted for demographics, HIV-specific variables and co-morbidities
Results

Relationship between antiretroviral drugs and osteonecrosis

Each ARV is included in a separate model and adjusted for all other variables listed*

Each ARV is mutually adjusted for the use of the other ARVs and adjusted for all other variables listed*

*adjusted for race, prior femoral necrosis at baseline, fracture*, age, nadir CD4 count, diagnosis of an AIDS defining malignancy*, non-malignant AIDS event* and non-AIDS defining malignancy*

+time-updated variables
Conclusions

• Host factors, HIV-specific variables and co-morbidities contribute to risk of fractures and osteonecrosis in people living with HIV.

• Current or past exposure to TDF, but no other antiretroviral, was independently associated with higher incidence of any fracture. Similar results were seen in those with osteoporotic fractures.

• Persons who had ever used didanosine, indinavir, saquinavir, lopinavir/r, or TDF had higher risk of osteonecrosis, but this association was no longer significant after mutual adjustment.
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