Evaluation and Management of Bone Fragility in HIV

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Conflicts of interest

• Lecture fees, advisory boards: Amgen, Gilead, Galenica, Genesis, Pfizer, ELPEN, Vianex, UniPharma, Leo, Rafarm, UCB, Takeda, ITF, Innovis Pharma, BENNETT

• Research grant: Amgen, Gilead, Galenica, ITF
In the United States, a 20-year-old HIV-positive patient can now expect to live into his/her early 70s.

1. Palella FJ et al. JAIDS 2006;43:27–34;
Average life expectancy of an HIV-positive patient is increasing and is now close to that of the uninfected population.

Estimated percentage of persons living with HIV/AIDS who are aged ≥50 years

Current situation

- Viral suppression
- Inflammation
- Patient
- Chronic disease
- HAART
- Comorbidities

Accumulating risks
Long-term impact of HIV and ARVs
Beyond undetectable
HIV infection and HAART: long-term effects on human health


Neurological impairments
Cancer
Bone disease
Liver disease
Kidney disease
CVD

Bone disease
Multi-factorial effect on bone strength

- Low vitamin D
- Age (>40 years)
- Nutritional factors
- Race
- Gender
- HAART
- Toxic habits
- Co-infections (e.g. Hep C)
- Low BMI
- Hypogonadism

Das S et al. Recent Pat Antiinfect Drug Discov 2014; Biver E. CTI 2022
Gut microbiome

Chronic HIV infection

Microbial dysbiosis

↓ Microbial diversity and functional capacity

↑ Permeability

Gut barrier

Depletion of T-cells

Innate immune activation

Proinflammatory cytokines

HAART

Osteoclastogenesis
Bone resorption
Bone microstructure - histomorphometry

- Alterations in volumetric BMD predominate in trabecular than cortical bone

- Untreated: low bone turnover (defective formation and mineralization)

- HAART: increased bone remodelling (still mineralization defect, increased osteoid)
Increased risk of bone loss and fractures

- 6.4-fold increased risk of low BMD and a 3.7-fold increased risk of osteoporosis\(^1\)
- Prevalence of osteoporotic fracture up to 60% higher \(^2\)
- Nearly x5 increased risk in hip fracture incidence independent of sex, age, smoking\(^3\)
- 58% believe that they are at low risk of fracture\(^4\)
- Younger patients still developing will be adversely impacted with BMD-lowering HIV treatments\(^5\)

n=1006, 83% ♂

Mean age: 43 years

36% osteopenia, 4% osteoporosis

85 fractures
Effect of HAART
HAART classes

- **Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)**
  - Examples: tenofovir, abacavir, emtricitabine, lamivudine, stavudine, zidovudine, etc

- **Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**
  - Examples: delavirdine, efavirenz, nevirapine, and rilpivirine

- **Protease inhibitors (PIs)**
  - Examples: atazanavir, darunavir, indinavir, ritonavir, lopinavir

- **Integrase Strand Transfer Inhibitors (INSTIs)**
  - Examples: raltegravir, dolutegravir, elvitegravir

- **Fusion inhibitors (FIs)**
  - Example: enfuvirtide

- **Chemokine Receptor Antagonists (CCR5 Antagonists)**
  - Example: maraviroc

The standard of care is a combination of two NRTIs (typically tenofovir-emtricitabine) plus one NNRTI or INSTI.
HAART is correlated with BMD loss of 2% - 6% during the first 1-2 years from onset

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts, N</th>
<th>Duration, Wks</th>
<th>ART</th>
<th>Change in BMD, %</th>
<th>Spine</th>
<th>Hip</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallant 2004</td>
<td>602</td>
<td>144</td>
<td>EFV + TDF/3TC, EFV + D4T/3TC</td>
<td>-2.2, -1.0</td>
<td>-2.8</td>
<td>-2.4</td>
<td>-</td>
</tr>
<tr>
<td>Brown 2009</td>
<td>106</td>
<td>96</td>
<td>LPV/RTV + ZDV/3TC, EFV + ZDV/3TC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-2.5, -2.3</td>
</tr>
<tr>
<td>Duvivier 2009</td>
<td>71</td>
<td>48</td>
<td>PI, Non-PI</td>
<td>-4.4 to -5.8, -1.5</td>
<td>-2.4 to -3.7</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>van Vonderen 2009</td>
<td>50</td>
<td>104</td>
<td>LPV/RTV + ZDV/3TC, LPV/RTV + NPV</td>
<td>-5.1, -2.6</td>
<td>-6.3</td>
<td>-2.3</td>
<td>-</td>
</tr>
<tr>
<td>Stellbrink 2010</td>
<td>385</td>
<td>48</td>
<td>EFV + TDF/FTC, EFV + ABC/3TC</td>
<td>-3.6, -1.9</td>
<td>-2.4</td>
<td>-1.6</td>
<td>-</td>
</tr>
<tr>
<td>McComsey 2011</td>
<td>269</td>
<td>96</td>
<td>TDF/FTC, ABC/3TC, ATV/RTV, EFV</td>
<td>-3.3, -1.3, -3.1, -1.7</td>
<td>-4.0, -2.6, -3.4, -3.1</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

ARVs can exacerbate low BMD issues

Initiation of therapy is associated with a 2–6% decrease in BMD over the first two years of treatment\(^2\)

Effect of HAART on BMD and bone metabolism

- Although muscle mass and cytokine (IL-6, TNF-α) levels improve, BMD continues to decrease after onset of 1st and 2nd line HAART

- Bone remodelling increases following treatment’s onset (especially with TDF)

- There is an initial increase in osteoclastic function followed much later by an increase in the function of osteoblasts (“catabolic” window) for the first 48 weeks – stabilization thereafter

Cotter AG, Mallon PWG, Curr Opin HIV Aids, 2014
Schematic presentation of bone remodelling following HAART initiation.
Tenofovir disoproxil fumarate (TDF)

- Hypophosphataemia due to dysfunction of the renal proximal tubule ➔ bone absorption to maintain phosphate levels

- High levels of Vit. D binding protein ➔ functional vit. D deficiency [with normal levels of 25(OH)D] ➔ secondary hyperparathyroidism

- Decrease of BMD during the first 24 weeks (1-3% more than other ART) and further aggravation until 96 weeks

- Switch from TDF-containing treatment to TDF-free one improves bone markers (decrease of bone remodeling) and decrease sclerostin, leading to increase of BMD

Switch From TDF to ABC or From TDF to RAL in Pts With Low BMD

Switch From TDF to ABC

Switch From TDF to RAL

TDF (tenofovir disoproxil fumarate) and TAF (pro-drug of tenofovir; tenofovir alafenamide)

Mechanism of action

Changes (%) in BMD LS and Hip at week 96

Less BMD loss with E/C/F/TAF which was maintained at 96 weeks, no further decrease after week 48

Wohl D. et al., JAIDS, 2016

-E/C/F/TAF=single tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
-Stribild= single tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
FRAX probably underestimates the fracture risk among HIV (+)

VACS Virtual Cohort Study
2003–2009

- Based on their FRAX score, 97% of HIV-positive men with an actual fracture would not have been flagged for treatment.

- Considering HIV infection as reason for ‘secondary’ osteoporosis improved the accuracy of FRAX prediction.

No difference were found between the cost effective 10-year major osteoporotic fracture probabilities of PLWH and uninfected population both within females [14.32 ± 2.28 (HIV +) Vs. 12.52 ± 1.61 (HIV -), p=0.32] and males [10.03 ± 1.40 (HIV +) Vs. 13.12 ± 3.02 (HIV -), p=0.17].

No differences were found between the cost effective 10-year hip fracture probabilities of HIV infected and uninfected male population [3.56 ± 1.01 (HIV +) Vs. 3.21 ± 0.76 (HIV -), p=0.23].

Higher cost-effective thresholds of females ≥ 70-years old [9.4 ± 1.94 (HIV +) Vs. 5.55 ± 1.18 (HIV -), p=0.01], while for the younger population no significant differences were found [1.7 ± 0.3 (HIV +) Vs. 1.5 ± 0.18 (HIV -), p=0.28].
No difference in FRAX based cost effective intervention thresholds among PLWH and uninfected population in Greece

- **Up to 75 years**
  - major osteoporotic Fx: 10%
  - Hip Fx: 2.5%

- **>75 years**
  - major osteoporotic Fx: 15%
  - Hip Fx: 5%

Makras et al. Osteoporos Intern 2015; Makras et al. JMNI 2017
## Alendronate

### Alendronate in people living with HIV: main published studies

<table>
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<tr>
<th>References</th>
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<th>Population</th>
<th>Vitamin D and calcium</th>
<th>Results</th>
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<tr>
<td>Guaraldi</td>
<td>Randomized to alendronate or not 52 weeks</td>
<td>N=41, receiving ARVT</td>
<td>Calcium/vitamin D supplements</td>
<td>No differences of BMD between groups. Decrease in serum type I collagen N-telopeptides in the alendronate group T-score &lt;−1</td>
</tr>
<tr>
<td>Mondy</td>
<td>Randomized to alendronate or not 48 weeks</td>
<td>N=31, receiving ARVT T-score &lt;−1</td>
<td>Calcium/vitamin D supplements</td>
<td>Alendronate increased lumbar spine BMD</td>
</tr>
<tr>
<td>Negredo</td>
<td>Randomized to alendronate or not 96 weeks</td>
<td>N=25, receiving ARVT T-score &lt;−2.5</td>
<td>Dietary calcium and vitamin D counseling</td>
<td>Alendronate improved lumbar spine BMD at week 48 Improvements in trochanter BMD were obtained at week 96</td>
</tr>
<tr>
<td>McComsey</td>
<td>Randomized placebo-controlled 48 weeks</td>
<td>N=82, receiving ARVT lumbar spine T-score &lt;−2.1</td>
<td>Calcium/vitamin D supplements</td>
<td>Alendronate improved BMD at the lumbar spine, total hip and trochanter, but not at the femoral neck</td>
</tr>
<tr>
<td>Rozenberg</td>
<td>Randomized placebo-controlled 96 weeks</td>
<td>N=44, receiving ARVT T-score &lt;−2.5 (75% in alendronate group and 71% in placebo group)</td>
<td>Calcium/vitamin D supplements</td>
<td>Alendronate improved BMD</td>
</tr>
</tbody>
</table>

ARVT, antiretroviral therapy.
## Zoledronate in HIV-infected patients: main published studies

<table>
<thead>
<tr>
<th>References</th>
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<th>Population</th>
<th>Vitamin D and calcium</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolland</td>
<td>Randomized placebo-controlled study</td>
<td>$N=43$, receiving ARVT</td>
<td>Calcium/vitamin D supplements</td>
<td>Zoledronate improved lumbar and spine BMD</td>
</tr>
<tr>
<td></td>
<td>Zoledronate 4 mg 96 weeks</td>
<td>T-score $&lt;-0.5$</td>
<td></td>
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</tr>
<tr>
<td>Bolland</td>
<td>Extension study (1 year) of those who completed the previous study</td>
<td>$N=33$, receiving ARVT</td>
<td>Calcium/vitamin D supplements</td>
<td>Results suggest antiresorptive effects of zoledronate during last 2 years</td>
</tr>
<tr>
<td></td>
<td>No intervention</td>
<td>T-score $&lt;-0.5$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolland</td>
<td>Extension study (4 years)</td>
<td>$N=35$, receiving ARVT</td>
<td>Calcium/vitamin D supplements</td>
<td>The effect in BMD and turnover markers of two annual 4-mg doses of zoledronate persist for at least 5 years after the second dose</td>
</tr>
<tr>
<td></td>
<td>No intervention</td>
<td>T-score $&lt;-0.5$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang</td>
<td>Randomize placebo-controlled study</td>
<td>$N=30$, receiving ARVT</td>
<td>Calcium/vitamin D supplements</td>
<td>T-scores significantly improved in zoledronate recipients as compared with minimal changes in those receiving placebo</td>
</tr>
<tr>
<td></td>
<td>Zoledronate 5 mg 48 weeks</td>
<td>T-score $&lt;-1$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negredo</td>
<td>Randomized (two zoledronate: one control) study</td>
<td>$N=31$, receiving ARVT</td>
<td>Dietary calcium and vitamin D counseling</td>
<td>Similar benefits for BMD of a single dose of zoledronate in 2 years and of two doses after 96 weeks</td>
</tr>
<tr>
<td></td>
<td>Zoledronate 5 mg 96 weeks</td>
<td>T-score $\leq-1$</td>
<td></td>
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</tbody>
</table>

ARVT, antiretroviral therapy.
Denosumab versus zoledronate for the treatment of low bone mineral density in male HIV-infected patients

Polyzois Makras a,*, Panagiotis Petrikkos b, Athanasios D. Anastasilakis c, Artemis Kolynou d, Angeliki Katsarou b, Olga Tsachouri d, Symeon Metallidis e, Maria P. Yavropoulou f
68 Subjects with HIV evaluated at the osteoporosis outpatient clinics

- 48 patients needing osteoporosis treatment
  - 12 patients excluded due to:
    - Previous osteoporosis treatment (10)
    - Steroid use (1)
    - Uncontrolled diabetes (1)
  - 36 patients fulfilled inclusion/exclusion criteria
    - 30 gave informed consent
      - 15 assigned to ZOL treatment
        - 5 removed informed consent
          - 10 received ZOL and completed the study
      - 15 assigned to Dmab treatment
        - 2 removed informed consent
          - 13 received Dmab and completed the study
  - 20 subjects with no need for osteoporosis treatment
    - 15 gave informed consent
      - 1 removed informed consent
    - 14 followed for one year
### BMD and FRAX score at baseline

<table>
<thead>
<tr>
<th></th>
<th>Dmab group (n=13)</th>
<th>ZOL group (n=10)</th>
<th>Control (n=14)</th>
<th>p-value #</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRAX Hip (%)</td>
<td>1.85±0.80&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.99±1.24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.38±0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FRAX MOF (%)</td>
<td>6.94±1.64&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.74±2.20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.20±0.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMD L1-L4</td>
<td>1.002±0.156&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.000±0.140&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.200±0.166</td>
<td>0.003</td>
</tr>
<tr>
<td>BMD FN</td>
<td>0.748±0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.763±0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.963±0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-score L1-L4</td>
<td>-1.79±1.28&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-1.86±1.17&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.29±1.45</td>
<td>0.006</td>
</tr>
<tr>
<td>T-score FN</td>
<td>-2.44±0.30&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-2.13±0.71&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.83±0.66</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

#: Comparison between 3 groups.

<sup>a</sup>: p<0.001 vs. Control; <sup>b</sup>: p<0.05 vs. Control; <sup>c</sup>: p<0.005 vs. Control
Conclusions

- HIV patients are living longer now, having an average life expectancy quite close to that of the general population, and presenting long term effects from all aspects of the disease.
- There is an increased risk of bone loss and fractures (10 years earlier than the general population).
- Untreated HIV bone disease is low turnover become a high turnover one after HAART initiation.
- HAART is possible to further induce bone loss during the first 1-2 years (especially tenofovir disoproxil fumarate, TDF) which stabilizes afterwards.
- Therapeutic options: bisphosphonates (alendronate, zolendronate), denosumab (?).
- When calculating FRAX score, HIV disease should be considered as a reason for secondary osteoporosis.
Thank you for your attention!
THANK YOU

On behalf of IOF, we thank you for your participation in this webinar
Our vision is a world without fragility fractures, in which healthy mobility is a reality for all.