ACTHIV 2016: A State-of-the-Science Conference for Frontline Health Professionals
HIV and Bone Disease: Through Thick and Thin!
Disclosures

- I serve in an adjudication panel in a VZV vaccine study (Glaxo)
- I consult for Merck
- My research is supported indirectly (through Penn) by all the manufacturers of HIV drugs
- I do not give non CME talks
Objectives

- To describe the epidemiology, and pathogenesis of osteoporosis in HIV-infected persons
- To review recent advances in our understanding of HIV infection and bone disease
- To identify which HIV-infected patients should be screened for osteoporosis.
- To recognize the secondary causes of bone loss that should be evaluated.
- To describe the optimal treatment strategy for the prevention and treatment of bone disease in HIV-infected persons.
Outline

- What do we know?
- What have we learn in the last couple of years?
- What can we do about bone disease and HIV?
What do we know?
#1. Both osteopenia and osteoporosis are very common in the HIV+ population

Osteoporosis

(a) Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Amiel (2004)</td>
<td>5.03 (1.47, 17.27)</td>
</tr>
<tr>
<td>Brown (2004)</td>
<td>4.26 (0.22, 82.84)</td>
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<tr>
<td>Bruera (2003)</td>
<td>4.51 (0.26, 79.27)</td>
</tr>
<tr>
<td>Dolan (2004)</td>
<td>2.11 (0.54, 8.28)</td>
</tr>
<tr>
<td>Huang (2002)</td>
<td>3.52 (0.15, 81.92)</td>
</tr>
<tr>
<td>Knobel (2001)</td>
<td>5.13 (1.80, 14.60)</td>
</tr>
<tr>
<td>Loiseau-Peres (2002)</td>
<td>4.28 (0.46, 39.81)</td>
</tr>
<tr>
<td>Madeddu (2004)</td>
<td>29.84 (1.80, 494.92)</td>
</tr>
<tr>
<td>Tebas (2000)</td>
<td>3.40 (0.19, 61.67)</td>
</tr>
<tr>
<td>Teichman (2003)</td>
<td>17.41 (0.97, 313.73)</td>
</tr>
<tr>
<td>Yin (2005)</td>
<td>2.37 (1.09, 5.16)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>3.68 (2.31, 5.84)</td>
</tr>
</tbody>
</table>
#2. HIV by itself is associated with osteopenia and osteoporosis

<table>
<thead>
<tr>
<th></th>
<th>N=269 *</th>
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</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>38 (31,44)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>85%</td>
</tr>
<tr>
<td>White non-Hispanic Race (%)</td>
<td>47%</td>
</tr>
<tr>
<td>HIV RNA $\log_{10}$ c/mL, median (IQR)</td>
<td>4.62 (4.24,4.90)</td>
</tr>
<tr>
<td>HIV RNA $\geq$ 100,000 c/mL (%)</td>
<td>41%</td>
</tr>
<tr>
<td>CD4 cells/mm$^3$, median (IQR)</td>
<td>233 (106,334)</td>
</tr>
<tr>
<td>CD4 &lt; 200 cells/mm$^3$ (%)</td>
<td>43%</td>
</tr>
<tr>
<td>Lumbar spine T score $\leq$-1 (%)</td>
<td>35%</td>
</tr>
<tr>
<td>BMI, Median (IQR)</td>
<td>24.9 (21.8, 28.2)</td>
</tr>
<tr>
<td>Limb fat kg, Median (IQR)</td>
<td>7.4 (4.7,10.1)</td>
</tr>
</tbody>
</table>

Baseline prevalence of osteopenia/osteoporosis 35%
When we start antiretroviral therapy patients lose bone. Independently of the regimen. Some drugs more than others.

#4. Some people lose more bone than others

- Patients with lower CD4s lose more bone
Predictors of initial bone loss

- Patients with higher viral loads and with more improvement in CD4s lose more bone
#5. Starting antiretrovirals induces a state of rapid bone turnover

![Graphs showing changes in bone turnover markers over time for different antiretroviral regimens.](image-url)

**CTx**
- Dolutegravir + abacavir/lamivudine
- Efavirenz/emtricitabine/tenofovir disoproxil fumarate

- **Change from baseline in CTx, %**
  - Baseline: 33, 30, 29, 25
  - Week 48: 68, 56, 39
  - Week 96: 56, 39
  - Week 144: 39

- **P value:** ≤0.001, ≤0.001, 0.002
- **DTG + ABC/3TC, n:** 356, 330, 304
- **EFV/FTC/TDF, n:** 330, 297, 255

**OC**
- Dolutegravir + abacavir/lamivudine
- Efavirenz/emtricitabine/tenofovir disoproxil fumarate

- **Change from baseline in OC, %**
  - Baseline: 22, 21, 23
  - Week 48: 48, 33
  - Week 96: 33, 32
  - Week 144: 32

- **P value:** ≤0.001, ≤0.001, 0.017
- **DTG + ABC/3TC, n:** 358, 336, 301
- **EFV/FTC/TDF, n:** 328, 299, 253

**BSAP**
- Dolutegravir + abacavir/lamivudine
- Efavirenz/emtricitabine/tenofovir disoproxil fumarate

- **Change from baseline in BSAP, %**
  - Baseline: 15, 32, 23
  - Week 48: 60, 76
  - Week 96: 76, 50
  - Week 144: 50

- **P value:** ≤0.001, ≤0.001, ≤0.001
- **DTG + ABC/3TC, n:** 361, 335, 304
- **EFV/FTC/TDF, n:** 327, 299, 252

**P1NP**
- Dolutegravir + abacavir/lamivudine
- Efavirenz/emtricitabine/tenofovir disoproxil fumarate

- **Change from baseline in P1NP, %**
  - Baseline: 66, 64
  - Week 48: 64, 45
  - Week 96: 64, 45
  - Week 144: 45

- **P value:** ≤0.001, ≤0.001, ≤0.001
- **DTG + ABC/3TC, n:** 361, 336, 306
- **EFV/FTC/TDF, n:** 332, 301, 256
#6. This problem is clinically relevant. Patients with HIV have more fractures than non HIV patients.
#7. The rate of fractures has increased in the HAART era

The VA cohort study

Pre-HAART Era:
1.61 Events/1000 PY

HAART Era:
4.09 Events/1000 PY

#8. Tenofovir and boosted PIs are associated with an increased the risk of fracture

**Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents**

Roger Bedimo\textsuperscript{a,b}, Naim M. Maalouf\textsuperscript{b}, Song Zhang\textsuperscript{b}, Henning Drechsler\textsuperscript{a,b} and Pablo Tebas\textsuperscript{c}

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MV Model 1: Controlling for CKD, age, race, tobacco use, diabetes and BMI;
MV Model 2: Controlling for Model 1 variables + concomitant exposure to other ARVs.

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Bedimo et al. AIDS 2012
What have we learned lately?
#1. The pathogenic mechanism is probably immune reconstitution (plus bone toxicity of tenofovir)

Ofotokum et al. Nature Communications 2015

What they did:
- transplant T cells into immunocompromised mice to mimic ART-induced T-cell expansion

What they saw:
- Bone loss associated with the reconstitution
#2. It can be partially prevented with vitamin D and Ca++

#3. It can be prevented with a single dose of zoledronic acid.
Should we do any of those?

Not yet*

* My opinion
#4. Tenofovir does something to your bones independently of HIV (and looks reversible)
TAF is more bone friendly than TDF (naive)

GS-0104-0111: Change in BMD

BMD decline > 5 %
- E/C/F/TAF: 10% spine; 7% hip
- E/C/F/TDF: 22% spine; 19% hip

Fractures
- E/C/F/TAF: 7 (0.8%)
- E/C/F/TDF: 12 (1.4%)
TAF is more bone friendly than TDF (switch)

Gallant et al. Lancet HIV 2016
How clinically important is that 1%

Lets say that you are 54 and your BMD is 1 g/cm² (normal)
Your risk of a major fracture in 10 years is 4.7%

Lets make your bones 2% better, your BMD is 1.02 g/cm² (normal)
Your risk of a major fracture in 10 years is 4.6%

Not much for most people
Should we start/switch everybody to TAF?

* Not yet*

* My opinion
Using cost-effectiveness methods, we find that current conditions warrant an annual premium of up to $1000 over the average wholesale price (AWP) of TDF.

Once generic coformulations of tenofovir/lamivudine become accessible, however, the appropriate premium for TAF will likely merit a downward adjustment.
What do you do with your patient?
Approach to bone problems in HIV patients

Initial approach

HIV infected individual

Assess risk factors
- Age
- Sex
- Weight/Height
- Hx. of Fractures
- Secondary causes

Lifestyle advice
- Smoking cessation
- Vitamin D and Calcium intake
- Weight bearing exercise
- Sun exposure

Indications for DXA

< 50 years ♂
PREmenopausal ♀
AND NO hx. of fracture?
WAIT

≥ 50 years ♂
POSTmenopausal ♀
AND/OR hx. of fracture?
Measure BMD by DXA

Work-up
What next?

**Work-up**

- **WAIT**
- **Measure BMD by DXA**
  - T-Score ≤ -2.5 OR fragility fracture
  - T-Score > -2.5 and ≤ -1 NO fragility fracture
  - T-Score > -1 NO fragility fracture

**Calculate FRAX score**

- 10 year fracture risk (USA) ≥ 20% major osteoporotic AND/OR ≥ 3% hip

**Secondary cause**

**Treatment**

- YES
  - Treat secondary cause
  - Consider Bisphosphonate or other treatment
  - Life style advice Continue ART
- NO
  - Life style advice Continue ART

**Follow up**

- Monitor DXA in 1-2 years
- Monitor DXA in 2-5 years
## Secondary causes of low BMD

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Lab Test</th>
</tr>
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<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>25-hydroxyvitamin D</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>iPTH, Ca, PO₄</td>
</tr>
<tr>
<td>Renal phosphate wasting in pts on TDF</td>
<td>Fractional excretion of phosphate</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>TSH</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Morning free testosterone, menstrual history, FSH</td>
</tr>
<tr>
<td>Idiopathic hypercalciuria</td>
<td>24-hr urinary calcium</td>
</tr>
</tbody>
</table>

National Osteoporosis Foundation.
Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

**Country:** Spain

**Name/ID:**

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth
   - Age: 50
   - Date of birth: Y: , M: , D: 

2. Sex
   - Male
   - Female

3. Weight (kg)
   - 50

4. Height (cm)
   - 162

5. Previous fracture
   - No

6. Parent fractured hip
   - No

7. Current smoking
   - No

8. Glucocorticoids
   - No

9. Rheumatoid arthritis
   - No

10. Secondary osteoporosis
    - Yes

11. Alcohol 3 or more units per day
    - Yes

12. Femoral neck BMD (g/cm²)
    - T-Score: -1.7

**BMI 19.1**

The ten year probability of fracture (%) with BMD

- Major osteoporotic: 1.7
- Hip fracture: 0.5

**Weight Conversion**

- Pounds → kg
  - Convert

**Height Conversion**

- Inches → cm
  - Convert

00042414

Individuals with fracture risk assessed since 1st June 2014
US NOF Guidelines 2008: Who to Treat*

- Those with hip or vertebral fractures
- Those with BMD T-scores \(\leq -2.5\) at the femoral neck, total hip, or spine by DXA
- Those with T-score b/t -1 and -2.5 (osteopenia) at above sites AND 10-year hip fracture probability \(\geq 3\%\) or 10-year all major osteoporosis-related fracture \(\geq 20\%\) based on FRAX model

*applies to post-menopausal women and men \(\geq 50\) years

Very few people with HIV*

* Not an opinion, a fact
#6. Alendronate appears to be the best treatment for osteoporosis in patients with HIV

Results: Change in lumbar BMD

Do not think bisphosphonates are innocuous

The FDA panel wants stronger warning for bone loss drugs
Wall Street Journal September 21, 2011