Osteoporosis in HIV+ adults

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Conflicts of interest

- None
Overview

- Review of bone metabolism
- Pathogenesis of osteoporosis in HIV+ adults
- Epidemiology of osteoporosis and fractures in HIV+ populations
- Clinical considerations:
  - Screening & Diagnosis
  - Treatment
  - Prevention
19th c. – English surgeon Sir Astley Cooper noted “the lightness and softness that (bones) acquire in the later stages of life”

1940 – Dr. Fuller Albright (USA) linked it to postmenopausal state

Current definition – continuum in which “multiple pathogenic processes converge to cause a loss of bone mass and deterioration of skeletal microarchitecture”

Raisz LG. J Clin Invest. 2005
Bone remodeling overview

Hematopoietic Stem Cell

T lymphocytes

Cytokines

RANK/L OPG PTH

Osteoblast Stromal Cell

BMPs

Osteoblast Precursor

Mesenchymal Stem Cell

Osteoclast

Osteoblasts

Osteocytes

Activation

Resorption 2-4 weeks

Reversal

Formation 4-6 months

Raisz LG. J Clin Invest. 2005
Osteoporosis: tipping the balance

Promotion of Activation & Bone Resorption

- Cytokines (IL-1, IL-6, TNF, others)
- PTH
- 1,25-dihydroxy vitamin D₃
- Estrogen, androgen, glucocorticoids, and thyroid hormone

Suppression (or delay) of Bone Formation

- Sex hormones
- Proliferation (senescence)
- IGF-1 & TNF-β (steroids)

Raisz LG. J Clin Invest. 2005
Manolagas SC. Endocrine Rev. 2000
Risk factors for Osteoporosis

TRADITIONAL
- Age
- Non-black or white race
- Latitude furthest from equator
- Family history
- Low BMI
- Prior fragility fracture
- Alcohol abuse
- Tobacco use
- Glucocorticoids
- Proton pump inhibitors
- Anticonvulsants
- Falls

CO-MORBIDITY RELATED
- Hepatitis C & B viruses
- Male hypogonadism, premature menopause
- Substance abuse
- Growth hormone deficiency
- Diabetes
- Chronic liver disease
- Chronic renal disease
- COPD
- HIV

Why HIV+ adults are at increased risk for osteoporosis

↑ Traditional Risk Factors

↑ Co-morbidity Risk Factors

HIV Virus

ART

Immune System
HIV viremia & bone mineral density

- HIV viremia → stimulates bone turnover
- Increased markers of bone resorption and formation in the setting of HIV viremia

Mallon PW. *Curr Opin HIV AIDS*. 2014
Differences in blood biomarkers

### Before & After HIV Infection

<table>
<thead>
<tr>
<th>Parameter (median)</th>
<th>Activity</th>
<th>Pre-HIV infection</th>
<th>Pre-ART initiation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-telopeptide</td>
<td><img src="image" alt="C-telopeptide" /></td>
<td>0.300</td>
<td>0.265</td>
<td>0.31</td>
</tr>
<tr>
<td>P1NP</td>
<td><img src="image" alt="P1NP" /></td>
<td>47.37</td>
<td>43.40</td>
<td>0.21</td>
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<tr>
<td>Osteocalcin</td>
<td><img src="image" alt="Osteocalcin" /></td>
<td>7.02</td>
<td>4.60</td>
<td>0.04</td>
</tr>
<tr>
<td>Sclerostin</td>
<td><img src="image" alt="Sclerostin" /></td>
<td>0.031</td>
<td>0.031</td>
<td>0.93</td>
</tr>
<tr>
<td>25-OH vitD$_3$</td>
<td>Deficiency linked with resorption</td>
<td>36.58</td>
<td>33.10</td>
<td>0.06</td>
</tr>
</tbody>
</table>

\( ^a \) Procollagen type-1N terminal propeptide
ART initiation (in viremic patients) is associated with a 2-6% loss of bone mineral density in the first year.

Mallon PW. *Curr Opin HIV AIDS*. 2014
LPVr/AZT/3TC vs. EFV/AZT/3TC

Subjects in the LPV/r group discontinued ZDV/3TC between week 24 and week 48.
Bone Mineral Density

Differences in traditional risk factors

Normal age-related changes

ART initiation

ART switch

ART interruption

2nd line ART

HIV-

HIV+

Time

Mallon PW. Curr Opin HIV AIDS. 2014
Tenofovir disoproxil fumarate (TDF) has been associated with BMD loss

- In HIV+ initiating ART
- In ART therapy switches
- In HIV- adults on PrEP

Stellbrink HJ et al. *Clin Inf Dis.* 2010
Cotter AG et al. *J Clin Endocrinol Metab.* 2013
Glidden DV et al. *JAIDS.* 2017
And many more...
ACTG 5224s (substudy of A5202): TDF/FTC+(ATVr or EFV) vs. ABC/3TC+(ATVr or EFV)

Spine BMD

Hip BMD

NRTI Component Primary Analysis

Spine BMD percent change from week 0

Visit Week from Randomization

No. of subjects

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC</th>
<th>ABC/3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>128</td>
<td>130</td>
</tr>
<tr>
<td>24</td>
<td>111</td>
<td>122</td>
</tr>
<tr>
<td>48</td>
<td>105</td>
<td>106</td>
</tr>
<tr>
<td>96</td>
<td>97</td>
<td>101</td>
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<tr>
<td>144</td>
<td>87</td>
<td>80</td>
</tr>
<tr>
<td>192</td>
<td></td>
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</tbody>
</table>

p = .004

NRTI Component Primary Analysis

Hip BMD percent change from week 0

Visit Week from Randomization

No. of subjects

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC</th>
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</tr>
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<tbody>
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<td>0</td>
<td>126</td>
<td>128</td>
</tr>
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<td>24</td>
<td>109</td>
<td>119</td>
</tr>
<tr>
<td>48</td>
<td>104</td>
<td>104</td>
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<tr>
<td>96</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>144</td>
<td>85</td>
<td>79</td>
</tr>
<tr>
<td>192</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p = .024*

* - two-sample t-test

McComsey GA et al. J Infect Dis. 2011
Also noted...

**Spine BMD**

**Hip BMD**

Protease inhibitors & BMD

- A5257
- ATV/r vs. DRV/r vs. RAL, all paired with TDF/FTC
- BMD results at 96 wks
- L-spine results similar

**Hip BMD**

<table>
<thead>
<tr>
<th></th>
<th>ATV/r</th>
<th>DRV/r</th>
<th>PI pooled</th>
<th>RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>-3.9%</td>
<td>-3.4%</td>
<td>-3.7%</td>
<td>-2.4%</td>
</tr>
</tbody>
</table>

P = 0.36

Proposed mechanisms of ART & bone changes

- Poorly defined mechanisms for how ARVs cause differential bone effects

<table>
<thead>
<tr>
<th>ARV</th>
<th>Proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td>↑ osteoclastgenesis, inhibition of osteoblasts</td>
</tr>
<tr>
<td>AZT</td>
<td>↑ osteoclastgenesis</td>
</tr>
<tr>
<td>TDF</td>
<td>Renal tubular dysfunction (hypophosphatemia)</td>
</tr>
<tr>
<td>EFV</td>
<td>↓ Vitamin D due to CYP P450 inhibition</td>
</tr>
</tbody>
</table>

Compston J. BoneKEy Rep. 2015
Tenoforvir alafenamide (TAF)

EVG/c/TDF/FTC vs. EVG/c/TAF/FTC @ 144 weeks

Arribas JR et al. JAIDS. 2017
# Reversible ART effects: Switch studies

<table>
<thead>
<tr>
<th>Design</th>
<th>Original ARV</th>
<th>Switched to</th>
<th>Results of switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label, randomized trial (n=86)</td>
<td>PI/r</td>
<td>RAL vs. no switch</td>
<td>Statistically significant ↑ in femoral neck BMD after 48 wks</td>
</tr>
<tr>
<td>Open-label, non-randomized trial of pts with low BMD (n=37)</td>
<td>TDF + PI/r</td>
<td>RAL + PI/r</td>
<td>Statistically significant ↑ in femoral neck BMD after 24 and 48 wks</td>
</tr>
<tr>
<td>Pooled data from 2 clinical trials (n=214 pts with low BMD)</td>
<td>TDF-containing regimen</td>
<td>EVG/c/F/TAF</td>
<td>Statistically significant ↑ in L-spine and hip BMD after 96 wks</td>
</tr>
</tbody>
</table>

Brown TT et al. *CROI poster 683*. 2017
Bone metabolism is driven by an interacting balance of resorption and formation.

HIV+ adults have many traditional risk factors for low BMD.

HIV infection independently alters bone metabolism.

ART initiation leads to drop in BMD.
- TDF and PIs are associated with greatest effects.
- ART switch from these can reverse BMD loss.
Epidemiology & Clinical Considerations
Clinical Definitions

- **Osteopenia**: mild thinning of the bone. DXA T-score (compared to young healthy adult) between -1 and -2.5 standard deviations
- **Osteoporosis**: severe thinning of bone. DXA T-score $\leq -2.5$
- **Fragility Fracture**: any fall from a standing height or less, that results in a fracture. Most common sites: hips, spine, and wrist.
Epidemiology

- HIV+ men and women have consistently been found to have high rates of low BMD

- Similarly, they also have been found to have higher rates of osteoporosis


Anastos K et al. *Antivir Ther.* 2007

Amiel C et al. *J Bone Miner Res.* 2004
### HIV+ & fragility fracture risk

- VACS cohort study – HIV+ (n=40,115) and HIV- (n=79,203) males

<table>
<thead>
<tr>
<th></th>
<th>Model 1 HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>1.32 (1.20-1.47)</td>
</tr>
<tr>
<td>Age (per 10yrs)</td>
<td>1.33 (1.26-1.41)</td>
</tr>
<tr>
<td>White race</td>
<td>1.74 (1.56-1.94)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>1.81 (1.53-2.15)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.33 (1.08-1.63)</td>
</tr>
<tr>
<td>Current steroid use</td>
<td>1.57 (1.28-1.92)</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.44 (1.25-1.66)</td>
</tr>
<tr>
<td>Any PPI use</td>
<td>1.64 (1.47-1.84)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.82 (0.79-0.85)</td>
</tr>
</tbody>
</table>

Risk of fractures in HIV+/- women

HIV+ aHR = 1.32 (95% CI 1.04-1.69)

*Adjusting for age, race, prior fracture, and prior drug use*

Sharma A et al. *JAIDS*. 2015
Key risk factors for bone outcomes in HIV+ adults

Osteoporosis (or low BMD)

Older age
White race
BMI
ART initiation (esp TDF and PI use)
Low CD4 & high VL at ART start
Early ART initiation

Hoy JF et al. J Bone Miner Res. 2017
# Key risk factors for bone outcomes in HIV+ adults

<table>
<thead>
<tr>
<th>Osteoporosis (or low BMD)</th>
<th>Fractures</th>
<th>HR or RR range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Age (per 10 yrs)</td>
<td>1.3 – 1.5</td>
</tr>
<tr>
<td>White race</td>
<td>White race</td>
<td>1.4-1.9</td>
</tr>
<tr>
<td>BMI</td>
<td>BMI</td>
<td>0.9</td>
</tr>
<tr>
<td>ART initiation (esp TDF and PI use)</td>
<td>Previous fracture</td>
<td>1.7-3.8</td>
</tr>
<tr>
<td>Low CD4 &amp; high VL at ART start</td>
<td>Drugs /cigs/ EtOH</td>
<td>1.3-1.6</td>
</tr>
<tr>
<td>Early ART initiation</td>
<td>Smoking</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>HCV / liver disease</td>
<td>1.4-1.6</td>
</tr>
<tr>
<td></td>
<td>CD4 nadir &lt;200 or ADI</td>
<td>1.6-3.1</td>
</tr>
<tr>
<td></td>
<td>Current PI</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Current /cum TDF*</td>
<td>1.1-1.3</td>
</tr>
<tr>
<td></td>
<td>History of falls</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Grant PM et al. *Clin Inf Dis*. 2013  
Hoy JF et al. *J Bone Miner Res*. 2013  
Borges AH et al. *Clin Inf Dis*. 2017  
Sharma A et al. *JAIDS*. 2015  
Gedmintas L et al. *Osteoporos*. 2017
HIV clinical application

Who should be screened?
When & how should they be screened?
How should they be treated based on those results?
How can BMD loss be prevented?
How can fractures be prevented?
Recommendations for Evaluation and Management of Bone Disease in HIV

Todd T. Brown, Jennifer Hoy, Marco Borderi, Giovanni Guaraldi, Boris Renjifo, Fabio Vescini, Michael T. Yin, and William G. Powderly
Screening

Adult with HIV infection

No risk factors

- History of fragility fracture
- Glucocorticoids (≥5mg x 3mo)
- High risk of falls at any age

< 40 years
- No screening necessary

40-50 years
- Calculate FRAX®

All postmenopausal women
- DXA (or FRAX®)

Men ≥ 50 years
- DXA
FRAX® - 10 year fracture risk

Questionnaire:
1. Age (between 40 and 90 years) or Date of Birth
   Age: [ ] [ ] [ ] [ ] [ ] Y: [ ] M: [ ] D: [ ]

2. Sex
   [ ] Male [ ] Female

3. Weight (kg)
   [ ] [ ] [ ]

4. Height (cm)
   [ ] [ ] [ ]

5. Previous Fracture
   [ ] No [ ] Yes

6. Parent Fractured Hip
   [ ] No [ ] Yes

7. Current Smoking
   [ ] No [ ] Yes

8. Glucocorticoids
   [ ] No [ ] Yes

9. Rheumatoid arthritis
   [ ] No [ ] Yes

10. Secondary osteoporosis
    [ ] No [ ] Yes

11. Alcohol 3 or more units/day
    [ ] No [ ] Yes

12. Femoral neck BMD (g/cm²)
    Select BMD
    [ ] Clear [ ] Calculate

*not required

Assessment & Management

- **40-50 years**
  - Calculate FRAX®
  - Score <10%
  - Score >10%
  - Score >20%
  - Ca / vit D - lifestyle

- **All postmenop. women**
  - Men > 50 years

- **History of fragility fracture**
  - Glucocorticoids (>5mg x3mo)
  - High risk of falls at any age

- **DXA**
  - No fractures - T > -2.5
  - H/o fractures - T < -2.5
  - Eval for secondary causes
  - Consider bisphos. tx
  - Ca / vit D - lifestyle

- **Score <10%**
- **Score >10%**
- **Score >20%**
# Monitoring

<table>
<thead>
<tr>
<th>Group</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOW</strong></td>
<td></td>
</tr>
<tr>
<td>40-50 years of age</td>
<td>Repeat FRAX® every 2-3 years</td>
</tr>
<tr>
<td>FRAX® &lt; 10%</td>
<td></td>
</tr>
<tr>
<td>Postmenop. Women</td>
<td>Repeat DXA in</td>
</tr>
<tr>
<td>Men ≥ 50 years</td>
<td>• 1-2 years if advanced osteopenia (Tscore, -2.0 to -2.49)</td>
</tr>
<tr>
<td>FRAX® &gt; 10%</td>
<td>• 5 years if mild-moderate osteopenia (Tscore -1.01 to 1.99)</td>
</tr>
<tr>
<td>DXA with osteopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MODERATE</strong></td>
<td></td>
</tr>
<tr>
<td>DXA with osteoporosis</td>
<td>Repeat DXA in 2 years, reassess indication for continuation in 3-5 years</td>
</tr>
<tr>
<td>Started on bisphosphonate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIGH</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Prevention

<table>
<thead>
<tr>
<th>Group</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50 years of age</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| FRAX® < 10%                                | - smoking, EtOH avoidance  
- regular exercise  
- check 25-OH vitamin D if at risk | | |
| Postmenop. Women                           |      |           |      |
| Men ≥ 50 years                             | - smoking, EtOH avoidance  
- regular exercise (weight-bearing)  
- check 25-OH vitamin D, goal = 30 ng/mL  
- consider ART switch off TDF & PIs | | |
| DXA with osteopenia                        |      |           |      |
| DXA with osteoporosis                      |      |           |      |
| Started on bisphosphonate                  | - smoking, EtOH avoidance  
- regular exercise (weight-bearing)  
- check 25-OH vitamin D, goal = 30 ng/mL  
- ART switch off TDF & PIs  
- falls prevention (Sedating meds? Stairs? Dementia/depression? Balance?) | | |
165 ART adults starting EFV/TDF/FTC
Randomized to Ca/vitD₃ vs. placebo
Outcome: BMD @ 48 wks

Conclusions

- HIV+ adults are at increased risk for low BMD and osteoporosis
  - Traditional risk factors & HIV/ART effects
- ART initiation is associated with a 2-6% BMD loss
- New ARVs (II, TAF) have less effects on BMD
- Screening for osteoporosis and fracture risk begins at age 40-50 years
- Prevention of low BMD and fractures is relevant for all ages
Thank you!