Bone Health in the context of HIV

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Disclosures

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  - **Mention may be made of therapeutic combinations not fully evaluated/approved by the FDA (‘off-label’ combinations)**
Learning Objectives

1) Describe disease burden of Osteoporosis in HIV+ population
2) Discuss pathogenesis of bone loss in HIV, including viral and drug toxicity effects
3) Review recent screening guidelines
4) List recommended steps in management of osteoporosis and osteopenia
Case:

49 yo male with h/o HIV since 1994. Multiple salvage regimens, currently suppressed on E/C/F/TAF+DRV
Labs: CD4+ 250 cell/mL, VL <20 copies
SocHx: remote meth use, currently ½ PPD
PMedHx: lipodystrophy, PJP, HTN
Weight = 62 kg, BMI 19

Should you screen this patient for Osteoporosis?

A. Yes, because of his age
B. Yes, because of HIV, ART, smoking history, BMI
C. No, because of his age
D. No, because it will not be covered
BASIC TERMS AND MEASURES

What the FRAX is Absorptiometry?
Bone Endocrinology - Definitions

- **Fragility Fracture**: resulting from fall from standing position
- **BMD**: Bone Mass/Bone Volume (as determined by DEXA)
- **T-Score**: SD difference in BMD compared to a healthy 30 yo of same gender
- **Z-Score**: SD difference in BMD compared to a healthy same-aged person of same gender
- **Osteopenia**: T-score between -1 and -2.5
- **Osteoporosis**: T-score less than -2.5
- **FRAX**: WHO fracture assessment tool incorporating clinical factors and BMD measurement to predict fracture risk
Reduced BMD - Definitions

- **T-Score: 0.0** - Normal
- **T-Score: -2.0 SD** - Osteopenia
- **T-Score: -2.5 SD** - Osteoporosis

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**Osteopenia** in HIV-positive men, women, and adolescents involves multiple factors: Effects of HIV-1 viral proteins, cytokines, and ART on bone cells and bone turnover.

**Osteoporosis** has a multifactorial etiology, including traditional risk factors such as smoking and low body weight, as well as direct effects of HIV infection.

DISEASE BURDEN OF BONE LOSS IN HIV

Key Clinical Questions:
Is it greater than the general population?
Prevalence of Bone Disease in HIV

- 884 HIV+ patients: 67% with reduced BMD, 15% osteoporosis

- Osteoporosis more likely in HIV+ than HIV- (OR 3.68)

- Among HIV+, more likely in those on ART (OR 2.38)

Brown TT and Qaqish RB AIDS 2006; 20:2165-2174
Prevalence of Fracture in HIV

• N = 8525 HIV+ patients and N = 2.2 million HIV negative

• Fracture prevalence 2.87 vs 1.77 per 100 p-y (p < 0.0001)
WHAT’S THE MECHANISM?

Key Clinical Questions:
Is it the virus, the drugs, or traditional risk factors?
HIV Itself?

- **In Vitro Studies:**
  - *Vpr* and *gp120* increase osteoclast activity; *Gag* proteins suppress osteoblast activity
  - Activated T-cells express increased Receptor-Activator NFkB (RANKL) – potent Osteoclast activator
  - HIV associated with decreased production of osteoprotegerin
  - Enhanced expression of cytokines (TNF-, IL-1, IL-6) increase Osteoclast activity
Most studies show 2-6% loss in BMD in first 1-2 years on ART, followed by relative stabilization

Individual Anti-retrovirals:

- Protease Inhibitors – Lower BMD and Increased Fracture risk; possibly through osteoblast suppression, and decreased Vit D synthesis
- Efavirenz – lower BMD; possibly through increased Vit D metabolism
- Tenofovir DF – lower BMD of 0.5-2.0% and associated with fracture; possibly through phosphate wasting

ART?

- SMART study: patients randomized to DC (drug conservation) or VS (viral suppression) groups and followed prospectively.

- Continuous ART associated with larger decreases in BMD 1.4% more at hip, 1.3% at spine (P 0.002 and 0.03, respectively)

- Continuous ART 10 fractures/2753 pts vs. 2 fractures/2720 pts (HR 4.9)
**TDF vs. TAF**

**Study Design**

Two Separate Phase 3, International, randomized, double-blind, active-controlled studies

- **Tx-Naïve Adults**
  - HIV-1 RNA ≥ 1000 c/mL
  - eGFR ≥ 50 mL/min

- **Stratification by**
  - HIV-1 RNA ≤ /≥ 100,000 c/mL
  - CD4 cell count
  - Geographic region

**Primary Endpoint**

Non-inferiority (12% margin) of E/C/F/TAF to Stribild based on HIV-1 RNA <50 copies/mL* at Week 48 by FDA Snapshot analysis†

**Secondary Endpoints**

Efficacy, safety** and tolerability observed through Week 96, Week 144

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* Taqman 2.0 assay
† Combined efficacy analysis was pre-specified. **SCr, proteinuria, hip and spine BMD were pre-specified week 48 safety endpoints.

Study 104 (North America, EU, Asia) and Study 111 (North America, EU, Latin America)

E/C/F/TAF: elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg
STB: elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir DF 300 mg

ClinicalTrials.gov Identifier: NCT01780506 and NCT01797445

TDF vs. TAF

Week 48 BMD Changes

Significantly less decrease in spine and hip BMD in the E/C/F/TAF group at Week 48

E/C/F/TAF, n=845
Stribild, n=850

Significantly less decrease in spine and hip BMD in the E/C/F/TAF group at Week 48

*Comparison of E/C/F/TAF vs Stribild at Week 48
Traditional Risk Factors?

- AGEthV cohort: N = 581 HIV+ patients and N = 520 HIV negative, > 45 yrs old

- Osteoporosis more prevalent in HIV+ than HIV- (13.3% vs. 6.7%, p<0.001)

- After adjusting for body weight and cigarette smoking, HIV status no longer independently associated with osteoporosis

- Strongest association body weight
HIV or Traditional Risk Factors?

- Veterans Aging Cohort Study (VACS) N = 581 HIV+ patients and N = 119,318, 33% HIV+

- Fragility fractures more common in HIV+ than HIV-
  - Unadjusted: 2.5/1,000 p-y vs. 1.9/1,000 p-y (P < 0.0001)
  - After adjusting for demographics, comorbid disease, smoking, and alcohol abuse, HIV remained associated (HR 1.24, 95% CI 1.11-1.39)
  - Adjusting for BMI attenuated this association (HR 1.10, 95% CI 0.97-1.25)
  - Only HIV-specific factor associated with fracture was current protease inhibitor use (HR 1.41, 95% CI 1.16-1.70)
  - Current TDF use (HR 1.29, 95% CI 0.99-1.70) and CD4 count at baseline (HR 1.02, 95% CI 0.98-1.05), NOT associated with fracture.
Multifactorial model

HIV
- The virus
- Pro-inflammatory state
  - ART

OSTEOPOROSIS and FRACTURE
  - Ageing
  - Hypogonadism
  - Glucocorticoids
  - Nutritional status
    - Tobacco, alcohol, drugs
    - Race/ethnicity
    - Genetics
    - Traditional risk factors

PAETC HIV LEARNING NETWORK
FINALLY

Key Clinical Question:
Should Osteoporosis screening be different for HIV+?
# Bone Health – Screening Recommendations

<table>
<thead>
<tr>
<th>Agency</th>
<th>Group</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>USPSTF</td>
<td>Women</td>
<td>&gt; Age 65 or ≤ 65 with FRAX &gt; 9.3% (B)</td>
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<tr>
<td></td>
<td>Men</td>
<td>(Insufficient evidence)</td>
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<tr>
<td>National Osteoporosis Foundation</td>
<td>All</td>
<td>Anyone &gt; Age 50 with fragility fracture</td>
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<tr>
<td></td>
<td>Women</td>
<td>&gt; Age 65 or Post-menopausal</td>
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<tr>
<td></td>
<td>Men</td>
<td>&gt; Age 70 or with other Risk factors</td>
</tr>
<tr>
<td>McComsey GA et al</td>
<td>HIV+ Women</td>
<td>&gt; Age 50 or Post-Menopausal or h/o fracture</td>
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<tr>
<td></td>
<td>HIV+ Men</td>
<td>&gt; Age 50</td>
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<tr>
<td>Brown TT et al (OREP)</td>
<td>HIV+</td>
<td>Age &lt; 40 – no screening</td>
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<tr>
<td></td>
<td></td>
<td>Age 40-50 – calculate FRAX</td>
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<tr>
<td></td>
<td></td>
<td>- FRAX &lt; 10% → repeat in 2-3 yrs</td>
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<tr>
<td></td>
<td></td>
<td>- FRAX 10-20% → perform DEXA</td>
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<tr>
<td></td>
<td></td>
<td>- FRAX &gt; 20% → TREAT</td>
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<tr>
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<td>Age &gt; 50 – perform DEXA</td>
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Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers

Grace A. McComsey¹, Pablo Tebas², Elizabeth Shane³, Michael T. Yin³, E. Turner Overton⁴, Jeannie S. Huang⁵, Grace M. Aldrovandi⁶, Sandra W. Cardoso⁷, Jorge L. Santana⁸, and Todd T. Brown⁹

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**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
Recommendations for Evaluation and Management of Bone Disease in HIV

HIV+ adults

- **Age < 40**
  - No screening needed

- **Age 40-50**
  - Calculate FRAX
    - **FRAX <10%**
      - Ensure adequate Ca intake
      - Ensure adequate Vit D levels
      - Lifestyle advice
    - **FRAX >10%, <20%**
      - Calculate FRAX
    - **FRAX ≥20%**
      - BMD by DEXA (or FRAX if DEXA not available)
        - **T score < -2.5**
          - Or FRAX >20% or ≥3% at the hip
          - Or Hip or vertebral fracture
        - Exclude secondary causes of osteoporosis
        - Consider Bisphosphonate therapy

- **H/o fragility fx**
  - Steroid (≥5mg X 3mos)
  - High risk of fall
  - Post-menopausal women
  - Men ≥50
FRAX

WHO Fracture Risk Assessment Tool

Calculation Tool

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

Country: US (Caucasian)  Name/ID:  

Questionnaire:
1. Age (between 40 and 90 years) or Date of Birth
   Age:   Date of Birth: 
   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  

Weight Conversion
Pounds ➔ kg

Height Conversion
Inches ➔ cm

04828273  Individuals with fracture risk assessed since 1st June 2011

https://www.shef.ac.uk/FRAX/tool.jsp
Calculation Tool

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

Country: **US (Caucasian)**  Name/ID: **HIV patient**

**Questionnaire:**

1. Age (between 40 and 90 years) or Date of Birth
   - Age: **49**
   - Year: **1957**
   - Month: **01**
   - Day: **12**

2. Sex
   - Male  Female
3. Weight (kg)  **65**
4. Height (cm)  **152.4**
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)
    - T-Score  **-2.3**

**BMI: 28.0**

The ten year probability of fracture (%) with BMD

- Major osteoporotic: **6.5**
- Hip Fracture: **2.8**

If you have a TBS value, click here: **Adjust with TBS**

https://www.shef.ac.uk/FRAX/tool.jsp
Questions?