Will HIV-Infected Patients Make Old Bones?

Bone Health in HIV Patients: Impact of HAART and HCV Co-Infection

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Objectives

• Identify HIV infection as risk factor for osteoporosis and osteoporotic fractures.

• Explore the contribution of HCV co-infection and antiretroviral therapy in fracture risk of HIV-infected patients.

• Apply recommended best practices to evaluate and manage an HIV-infected patient with increased risk of osteoporotic fracture.
Faculty and Planning Committee Disclosures

Please consult your program book.

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
60 y/o WM, establishing care. No new complaints.

PMH:
- HIV disease diagnosed in 1998 (developed PCP); CD4 count: 688; Viral Load undetectable.
- HCV: untreated
- HTN, Hyperlipidemia
- CAD s/p MI

Social history:
- EtOH, Tobacco, IVDU

Meds:
- Tenofovir/Emtricitabine, Lopinavir/Ritonavir
- ASA, Lisinopril, Metoprolol, Rosuvastatin, Fenofibrate,

Physical exam
- Thin (BMI: 19); lipoatrophy, otherwise unremarkable
Case 1: An HIV-Infected Patient Initiating Care

- All the following have been associated with increased risk of osteoporosis and/or osteoporotic fractures in this patient, except:
  - HIV Infection
  - Hepatitis C co-infection
  - White race
  - Low BMI
  - Tenofovir exposure
  - Smoking
  - Statin use
  - Age
Case 1: An HIV-Infected Patient Initiating Care

All the following have been associated with increased risk of osteoporosis and/or osteoporotic fractures in this patient, except:

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- Smoking
- Statin use
- Age
Osteoporosis

- “A systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture”

Consensus Development Conference. American Journal Medicine, 1993, 94:646–
Odds of osteoporosis in HIV-infected patients

Comparing HIV-infected to HIV-uninfected

Among HIV-infected, comparing patients receiving ART with ART-naïve patients

(a) Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<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, 82.64)</td>
</tr>
<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>
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<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>
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(b) Study

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</tr>
</thead>
<tbody>
<tr>
<td>Amiel (2004)</td>
<td>2.41 (0.77, 7.58)</td>
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<tr>
<td>Bruera (2003)</td>
<td>4.81 (0.60, 38.74)</td>
</tr>
<tr>
<td>Garcia (2005)</td>
<td>1.60 (0.13, 19.84)</td>
</tr>
<tr>
<td>Knobel (2001)</td>
<td>2.68 (0.70, 10.33)</td>
</tr>
<tr>
<td>Konishi (2005)</td>
<td>0.84 (0.03, 22.43)</td>
</tr>
<tr>
<td>Madeddu (2004)</td>
<td>11.06 (0.65, 187.76)</td>
</tr>
<tr>
<td>Vescini (2003)</td>
<td>0.54 (0.05, 5.68)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>2.38 (1.20, 4.75)</td>
</tr>
</tbody>
</table>

ACTG 5224

Mean (95% CI) Percent Change in Spine and Hip BMD (ITT)

<table>
<thead>
<tr>
<th>Week</th>
<th>FTC/TDF</th>
<th>3TC/ABC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td>p=0.004</td>
</tr>
<tr>
<td>48</td>
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<tr>
<td>72</td>
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<td>96</td>
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<td>120</td>
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<td>144</td>
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<td>168</td>
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<tr>
<td>192</td>
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</tbody>
</table>

- **Lumbar Spine**
  - FTC/TDF
  - 3TC/ABC
  - p=0.004

- **Hip**
  - FTC/TDF
  - 3TC/ABC
  - p=0.025

- Bone fractures
  - 5.6% had ≥ 1 fracture (all traumatic)
  - No statistically significant differences between NRTI components or NNRTI/PI components in fracture rate (Fisher’s exact) or time to first fracture (log-rank test)

McComsey G. JID 2011;203(12):1791-801
Fracture Prevalence by Site and Age Group

A females

B males

C (overall comparison)

D (overall comparison)

Triant et al., JCEM. 2008,93:3499-3504
Fracture Risk in HIV – Cohort Studies

• WIHS Study: 1728 HIV+ (66% on ART), 663 HIV-; median f/u 5.4 years.
  – No ≠ in fracture incidence (1.8 vs. 1.4/100 PY, P = 0.18)
  – HIV infection was not a significant predictor of incidence of new fracture [hazard ratio (HR) = 1.28; 95% CI: 0.93–1.78].

• VA Aging Cohort Study: 119,318 men (33% HIV+)
  – HIV assoc. with ↑ fracture risk [HR: 1.10 (95% CI: 0.97, 1.25)]. Effect attenuated by adjusting for BMI [HR: 1.10 (95% CI: 0.97, 1.25)].

• HOPS: 5026 HIV+; Median age 40; 79% male; 73% on ART
  – Fracture rates > general population (NHAMCS-OPD).

Young et al., Clin Infect Dis 2011; 52:1061–1068
Fracture Risk in HIV

OSTEOPOROSIS and FRACTURE RISK

HIV

HAART

Hypogonadism

Glucocorticoids

Low BMI, Malnutrition

Race/Ethnicity, Genetics

Advancing age, Improved Survival

Tobacco, EtOH, Drugs
## Factors Predicting Osteoporotic Fracture in HIV Patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate Analysis</th>
<th>Multi-variable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative ART Use (per year)</td>
<td>1.05 (1.01 – 1.10; p=0.02)</td>
<td>0.99 (0.95 – 1.04; p=0.77)</td>
</tr>
<tr>
<td>CKD (eGFR &lt;60)</td>
<td>1.48 (1.04 – 2.09; p=0.03)</td>
<td>1.05 (0.72 – 1.53; p = 0.79)</td>
</tr>
<tr>
<td>White Race</td>
<td>1.76 (1.46 – 2.13; p &lt; 0.0001)</td>
<td>1.88 (1.54 – 2.30; p&lt; 0.0001)</td>
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<td>Age (per 10 year increase)</td>
<td>1.51 (1.39 – 1.63; p &lt;0.0001)</td>
<td>1.50 (1.37 – 1.64; p&lt; 0.0001)</td>
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<td>Tobacco Use</td>
<td>1.25 (1.06 – 1.47; p=0.01)</td>
<td>1.31 (1.09 – 1.56; p=0.003)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.27 (1.05 – 1.53; p=0.01)</td>
<td>1.10 (0.90 – 1.34; p=0.34)</td>
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<td>BMI &lt; 20</td>
<td>1.61 (1.29 – 2.00; p&lt;0.0001)</td>
<td>1.48 (1.18 – 1.87; p=0.007)</td>
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What Happened in the HAART Era?

- Higher % of patients on ARVs, low viremia.
- Increased survival (and time at risk) and increased fracture rates

Fracture Rate by Year

- Pre-HAART Era: 1.61 Events/1000 PY
- HAART Era: 4.09 Events/1000 PY

Antiretroviral Exposure and Risk of Osteoporotic Fractures: HAART Era

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.

Exposure to Specific Protease Inhibitors and OF Risk: HAART Era

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.

Fracture Risk in HIV

Potential mechanisms of TDF-induced effect on bone:
Renal insufficiency with 2ry hyperparathyroidism
Fanconi-like syndrome- phosphate wasting, metabolic acidosis
HAART and Fracture Risk: ALLRT Data

- Median age was 39 y; 83% men, 48% white,
- 116 fractures reported in 106 participants with median time-to-first fracture of 2.3 years.
- Independent predictors of fracture: current smoking, steroid use, but not with exposure to specific antiretrovirals.

Yin et al. AIDS. 2012 Nov 13;26(17):2175-2184
Role of HCV in Fracture Risk in HIV – Cohort Studies

- ANRS CO8 APROCO-COPILOTE cohort: 1,281 HIV+
  - Predictors of fracture: Alcohol consumption: HR: 2.9 (95% CI: 1.3–6.5) and HCV co-infection: HR: 3.6 (95% CI: 1.6–8.1)

- WIHS Study: 1728 HIV+ (66% on ART), 663 HIV-).
  - Predictors of fracture in MV model: Age [HR: 1.24 (1.02 - 1.51); p=0.033], White race [HR: 1.56 (1.02 - 2.39); p= 0.041, HCV co-infection [HR: 1.86 (1.33 - 2.61); p<0.001]

- HOPS: 5026 HIV+; Median age 40; 79% male; 73% on ART
  - Predictors of fractures in MV analysis: increasing age (adjusted HR [aHR], 1.43 per 10 years; 95% CI, 1.03–1.98), HCV infection [aHR, 1.99 (1.01–3.90)], and BMI ,18.5 [aHR, 3.72 (1.14–12.09)].

Collin et al., AIDS. 2009 May ; 23(8): 1021–1024. 
Yin et al., AIDS 2010; 24:2679–2686; Young et al., Clin Infect Dis 2011; 52:1061–1068
# Factors Predicting Osteoporotic Fracture in HIV Patients

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Risk of Fractures in HIV and HIV/HCV Patients – Danish Cohort

Fig. 1. Cumulative incidence of low-energy fractures (left) and high-energy fractures (right) in HIV-monoinfected patients, HIV/HCV-coinfected patients and population controls.

Fracture Risk in HIV

OSTEOPOROSIS and FRACTURE RISK

HCV
HIV
HAART (TDF)

Hypogonadism
Glucocorticoids

Low BMI, Malnutrition
Race/Ethnicity, Genetics

Advancing age, Improved Survival
Tobacco, EtOH, Drugs
Osteoporosis in HIV

OSTEOPOROSIS and FRACTURE RISK

Advancing age, Improved Survival

Tobacco, EtOH, Drugs

Low BMI, Malnutrition

Race/Ethnicity, Genetics

Hypogonadism

Glucocorticoids

HCV

HIV

HAART (TDF)

Fibrosis? Cirrhosis?
Osteoporosis in HIV

Mechanisms?

HCV → Fibrosis Cirrhosis

HIV → HAART (TDF)

OSTEOPOROSIS and FRACTURE RISK

Hypogonadism
Glucocorticoids

Low BMI, Malnutrition
Race/Ethnicity, Genetics

Advancing age, Improved Survival
Tobacco, EtOH, Drugs
Interaction of low BMD and increased bone turnover in predicting fracture risk.

Cohort of 7598 healthy women more than 75 years of age. 126 women who sustained a hip fracture during a mean 22-month follow-up were age-matched with three controls who did not fracture.

BMD: Bone Mineral Density
CTX: urinary C-terminal collagen crosslink excretion
D-Pyr: free deoxypyridinoline excretion

Increased Bone Turnover Markers in Post-Menopausal HIV+ Women

95 HIV- and 92 HIV+ women (79% on ART [39% on PI])

Yin et al., *J Clin Endocrinol Metab*, February 2010, 95(2):620–629
Changes in Bone Turnover Occur Early after ART Initiation

Figure 2. Change in markers of bone resorption. Estimated means±SEM (adjusted for baseline differences, ITT). # p<0.05 within arm 0-24 months.

Figure 3. Change in markers of bone formation. Estimated means±SEM (adjusted for baseline differences, ITT). # p<0.05 within arm 0-24 months.
Changes in BMD and BTM in HIV Clinical Trials

- **STEAL**: 301 patients; 98% male, mean age 45 years, 5.7 y prior NRTI exposure. Randomized to ABC/3TC vs. TDF/FTC
  - Randomized to switch to ABC vs. TDF-based regimens.
  - Predictors of ↓ BMD at week 96: TDF-FTC (p≤0.013), lower B/l BMD lower fat mass (p-trend ≤ 0.009), lower P1NP (p = 0.015)
  - TDF-FTC increased P1NP and CTx through Wk 96 (p<0.01).

- **ASSERT**: 385 HAART-naïve; Random. to ABC/3TC vs. TDF/FTC
  - Greater BMD ↓ in TDF/FTC (-3.6%) vs. ABC/3TC (-1.9%); p<0.001
  - BTM (P1NP and CTx) increased by Week 24 and; Greater ↑ in TDF/FTC.
  - Changes in biomarkers negatively correlated with change in BMD from baseline.

Osteoporosis in HIV

OSTEOPOROSIS and FRACTURE RISK

Advancing age, Improved Survival
Tobacco, EtOH, Drugs

Low BMI, Malnutrition
Race/Ethnicity, Genetics

Hypogonadism
Glucocorticoids

Fibrosis Cirrhosis

HCV
HIV

HAART (TDF)

↑ BTM; OPG/RANKL
Case 1: An HIV-Infected Patient Initiating Care

- 60 y/o WM, establishing care. No new complaints.
- PMH:
  - HIV disease diagnosed in 1998 (developed PCP); CD4 count: 688; Viral Load undetectable.
  - HCV: untreated
  - HTN, Hyperlipidemia
  - CAD s/p MI
- Social history:
  - EtOH, Tobacco, IVDU
- Meds:
  - Tenofovir/Emtricitabine, Lopinavir/Ritonavir
  - ASA, Lisinopril, Metoprolol, Rosuvastatin, Fenofibrate,
- Physical exam
  - Thin (BMI: 19); lipoatrophy, otherwise unremarkable
What should you do next?

1. Continue current management
2. Measure the patient’s BMD by DXA scan
3. Give the patient supplementation for calcium and vitamin D
4. Prescribe bisphosphonate therapy
What should you do next?

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Case 1: An HIV-Infected Patient Initiating Care

- Should this patient be screened with DEXA scan?
Approach to Bone Disease in HIV

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

IDSA Guidelines. McComsey et al., CID 2010; 51(8):937–946
Case 1: An HIV-Infected Patient Initiating Care

• Should this patient be screened with DEXA scan? Yes

• DEXA Scan Findings:
  – Lumbar Spine (L1-L4): BMD: 0.942 g/cm²; T-score: -1.5
  – L femoral neck : BMD: 0.632 g/cm²; T-score: -1.9

• How would you manage this patient?
  – No treatment
  – Calcium + Vitamin D
  – Calcium + Vitamin D + Alendronate
T and Z Score Measurements

T-score: compares result to younger “normal” value.
Z-score: compares individual results to age matched “normal” value

T-score ≤ -2.5 = osteoporosis
T-score ≤ -1.0 = osteopenia

Example: T-score: -2.0; Patient is 60 y/o: Z-score: -0.5
Approach to Bone Disease in HIV

http://www.shef.ac.uk/FRAX/tool.jsp?country=9

IDSA Guidelines. McComsey et al., CID 2010; 51(8):937–946
FRAX Score Calculation

**Calculation Tool**

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

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth
   - Age: 64
   - Date of birth: Y: 1948 M: 03 D: 31

2. Sex
   - Male

3. Weight (kg)
   - 58.97

4. Height (cm)
   - 172.72

5. Previous fracture
   - No

6. Parent fractured hip
   - No

7. Current smoking
   - No

8. Glucocorticoids
   - No

9. Rheumatoid arthritis
   - No

10. Secondary osteoporosis
    - No

11. Alcohol 3 or more units per day
    - No

12. Femoral neck BMD (g/cm²)
    - 0.632

**BMI 19.8**

The ten year probability of fracture (%)

- without BMD
  - Major osteoporotic: 5.9
  - Hip fracture: 1.6

**Weight Conversion**

- Pounds to kg: 130

**Height Conversion**

- Inches to cm: 68

http://www.shef.ac.uk/FRAX/tool.jsp?country=9
Work-up of HIV patient with osteoporosis: Secondary causes

- Most common secondary causes in women: premenopausal estrogen deficiency and glucocorticoid exposure; accounting for 35%–40% of cases

- Most common secondary causes in men: vitamin D deficiency, hypogonadism, alcoholism, and glucocorticoid use; together account for 40%–60% of cases
  - Meds: Steroids, PPIs, SSRI, HAART, hormonal agents

- Labs to order: CBC, BMP, Testosterone, +/- TSH, 25-OH-D, PTH, urine and serum phosphorus if on TDF

- Management of secondary causes if found; consider referral to endocrinology

IDSA Guidelines. McComsey et al., CID 2010; 51(8):937–946
Bisphosphonates in the Management of Osteoporosis in HIV

- 82 HIV patients (71% men, 77% white), median age: 48 years; Lumbar spine t-score <2.1

McComsey AIDS. 2007 Nov 30;21(18):2473-82.
Approach to Bone Disease in HIV

IDSA Guidelines. McComsey et al., CID 2010; 51(8):937–946
Management of Osteoporosis

- **Calcium**: All patients with osteopenia or osteoporosis
  - RDA: 1,000 – 1,200 mg/d; Preferred: Ca Carbonate (with food)
  - 300 mg in: yogurt (6 oz), milk (8 oz), fortified OJ (8 oz), cheese (large slice), spinach (1 cup).
  - Calcium carbonate not well absorbed with PPIs (use citrate)
- **Vitamin D**: 800-1000 IU/d for patients >50
  - Additional vitamin D if baseline 25-OH vit D <30: 50,000 IU/week x 8-12 weeks until replete.
- **Bisphosphonates**
  - Osteoporosis or history of osteoporotic fracture
  - FRAX score: 10-year risk of major fracture is >20% or risk of hip fracture is >3%

FRAX Not Yet Validated in HIV

- FRAX validated for men and women >50 years
- DM associated with higher BMD, but also higher fracture risk; BMD and FRAX underestimate fracture risk in DM
- FRAX underestimates fracture risk in HIV+ men
  - Combination of FRAX (without BMD) and “Ageing Male Symptoms” score improved sensitivity of FRAX alone in identifying HIV patients at fracture risk, at the expense of reduced specificity.

Future Directions: Treatment of HIV-infected Patients with Osteoporosis

- NRTI-free regimens
- Anti-resorptives early post-HAART initiation
  - Role of Ca/vitamin D
  - Few studies with bisphosphonates
  - Others: teriparatide (a PTH analogue) and denosumab (a monoclonal antibody against RANKL)
- Anti-HCV therapy
- Anti-Inflammatory Agents (statins)