Bone: To DEXA or not to DEXA

Michael Yin, MD MS
Associate Professor of Medicine
Columbia University Medical Center
Learning Objectives

Upon completion of this presentation, learners should be better able to:

• Review the increased risk of osteoporosis and fracture in HIV-infected individuals

• Explain the rationale for DEXA screening and risk stratification with FRAX as well as the limitations
Faculty and Planning Committee Disclosures

Dr Yin serves as a consultant for Gilead Sciences and AbbVie

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
Changing age distribution of HIV+ individuals living in US between 2001 and 2005

Figure 1. Age distribution of HIV-infected individuals living in the United States. Adapted from Luther and Wilkin, Clin Geriatr Med, 2007.
Osteoporosis

• Systemic skeletal disease of aging
  – Low BMD
  – Microarchitectural deterioration
  – Reduced bone strength

• Fragility fractures (Vertebrae, hip, wrist)

• Diagnosis by DXA
  T scores
  – Normal > -1.0
  – Osteopenia -1.0 to -2.49
  – Osteoporosis ≤ -2.5

  – In older populations, risk of fracture increases 2-3 fold for each SD decrease in BMD
Prevalence of osteoporosis by HIV

Brown et al., AIDS, 2006

(a) Study

- Bruera (2003)
- Huang (2002)
- Knobel (2001)
- Loiseau-Peres (2002)
- Tebas (2000)
- Teichman (2003)
- Yin (2005)

Odds ratio (95% CI)
- 5.03 (1.47, 17.27)
- 4.26 (0.22, 82.64)
- 4.51 (0.26, 79.27)
- 2.11 (0.54, 8.28)
- 3.52 (0.15, 81.92)
- 5.13 (1.80, 14.60)
- 4.28 (0.46, 39.81)
- 29.84 (1.80, 494.92)
- 3.40 (0.19, 61.67)
- 17.41 (0.97, 313.73)
- 2.37 (1.09, 5.16)

Overall (95% CI)
- 3.68 (2.31, 5.84)

(b) Study

- Bruera (2003)
- Garcia (2005)
- Knobel (2001)
- Konishi (2005)
- Vescini (2003)

Odds ratio (95% CI)
- 2.41 (0.77, 7.58)
- 4.81 (0.60, 38.74)
- 1.60 (0.13, 19.84)
- 2.68 (0.70, 10.33)
- 0.84 (0.03, 22.43)
- 11.06 (0.65, 187.76)
- 0.54 (0.05, 5.68)

Overall (95% CI)
- 2.38 (1.20, 4.75)

Brown, AIDS, 2006

ACTHIV 2015: A State-of-the-Science Conference for Frontline Health Professionals
Higher prevalence of fracture in HIV+

Triant et al., *JCEM*, 2008
Incidence of fractures higher in HIV+ (RR=1.36 to 1.56)

Shiau, AIDS, 2013
Fracture incidence higher in HIV+/HCV+ than HIV+ (RR=1.70 to 2.05)

Dong, AIDS, 2013
Multifactorial etiology of bone loss in HIV

- Weight loss
- Decreased activity
- Hypogonadism
- Smoking/alcohol
- Glucocorticoids
- HCV infection
- Lipodystrophy
- CKD
- Vitamin D deficiency

**Virus**
- Direct effect of viral proteins on bone cells
- Immune activation

**Host**
- Direct effect on bone cells
- Inadequate mineralization
- Immune reconstitution

**ART**

ACTHIV 2015: A State-of-the-Science Conference for Frontline Health Professionals
Decrease in BMD at the spine occurs by 24 weeks after ART initiation.

McComsey et al., JID 2011
Decrease in BMD at the hip occurs by 48 weeks

McComsey et al. JID 2011
BMD decreases 2-4% with initiation of contemporary ART regimens: TDF > ABC or RAL or TAF; PI/r > RAL

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size/Duration</th>
<th>ART regimens</th>
<th>Change in LS BMD</th>
<th>Change in TH or FN BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stellbrink, ASSERT 2010</td>
<td>N=385 48 weeks</td>
<td>TDF/FTC + EFV ABC/3TC + EFV</td>
<td>-3.6%*</td>
<td>-2.4%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1.9%</td>
<td>-1.6%</td>
</tr>
<tr>
<td>McComsey, ACTG 5223s 2011</td>
<td>N=269 96 weeks</td>
<td>TDF/FTC ABC/3TC ATV/r EFV</td>
<td>-3.3%*</td>
<td>-4.0%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1.3%</td>
<td>-2.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-3.1%*</td>
<td>-3.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1.7%</td>
<td>-3.1%</td>
</tr>
<tr>
<td>Reynes, PROGRESS 2013</td>
<td>N=206 96 weeks</td>
<td>TDF/FTC+LPV/r RAL+LPV/r</td>
<td>-2.5%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+0.7%</td>
<td></td>
</tr>
<tr>
<td>Brown, ACTG 5260s 2014</td>
<td>N=328 96 weeks</td>
<td>TDF/FTC+ATV/r TDF/FTC+DRV/r TDF/FTC+RAL</td>
<td>-4.0%*</td>
<td>-3.9%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-3.6%*</td>
<td>-3.4%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-2.4%</td>
<td>-1.8%</td>
</tr>
<tr>
<td>Sax, Gilead 104-111 2015</td>
<td>N=1733 48 weeks</td>
<td>E/C/F/TDF E/C/F/TAF</td>
<td>-2.9%*</td>
<td>-3.0%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1.3%</td>
<td>-0.7%</td>
</tr>
</tbody>
</table>
Tenofovir and bone loss: putative mechanisms

- **Inadequate mineralization**
  - Proximal tubular dysfunction and hyperphosphaturia occurs in 5-30%; but hypophosphatemia and clinical osteomalacia are rare.

- **Secondary hyperparathyroidism**
  - Potentially linked to ‘functional’ vitamin D deficiency
  - Impact of vitamin D therapy on BMD in patients on TDF-containing regimens is uncertain: Vitamin D treatment decreases PTH but not BTMs in adolescents on TDF (Havens, *CID* 2012)

- **Direct effect on bone cells**
  - Effect on osteoblast gene expression (Grigsby, *BBRC* 2010)
Case

- A 55-year-old HIV/HCV co-infected postmenopausal woman
- HIV infection 10 years ago PCP, started on TDF/FTC and ATV/r
- Most recent CD4=550 cells/µl, VL<50
- She is a current smoker and uses >2 servings of alcohol/day
- **No history of falls or fractures**, no bony pain
- BMI=26.0 kg/m²
- No parental history of hip fracture and does not have diabetes or rheumatoid arthritis.
- She currently takes 800 IU of vitamin D3 and calcium carbonate 1000mg daily for supplementation.
Should you screen for fracture risk? And if so, what would you use for screening?

• Option 1: Dual energy xray absorptiometry (DEXA)

• Option 2: Calculate FRAX® score

• Option 3: No screening necessary
## DXA screening for osteoporosis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA indicated</td>
<td>Women ≥65, Men ≥70</td>
<td>PM women ≥65</td>
<td>Men and women ≥50</td>
<td>PM women or Men ≥50</td>
<td>Men and women ≥50</td>
</tr>
<tr>
<td>DXA indicated with following risk factors (partial list)</td>
<td>&gt;50 Fracture RA Glucocorticoid Low weight smoking Hypogonadal Malabsorption Emphysema CKD AED PPI</td>
<td>&gt;50 Fracture Hypogonadal Glucocorticoid CKD Alcohol AED Diabetes</td>
<td>FRAX without BMD for age &gt;40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Bone Mineral Density (g/cm²)

Fracture per 1000 person-years

Age (years)

80+
75-79
70-74
65-69
60-64
55-59
50-54
45-49
<45

Hui et al, JCI, 1988
# DXA results

<table>
<thead>
<tr>
<th>Site</th>
<th>g/cm²</th>
<th>T-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>0.692</td>
<td>-2.9</td>
</tr>
<tr>
<td>Total Hip</td>
<td>0.584</td>
<td>-2.8</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>0.535</td>
<td>-2.7</td>
</tr>
<tr>
<td>1/3 Radius</td>
<td>0.400</td>
<td>-2.1</td>
</tr>
</tbody>
</table>
## Laboratory results

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
<td>45 pg/dL</td>
<td>8-51 pg/dL</td>
</tr>
<tr>
<td>25-hydroxyvitamin D</td>
<td>28 ng/mL</td>
<td>30-80 ng/mL</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>3.0 mg/dL</td>
<td>2.5-4.3 mg/dL</td>
</tr>
<tr>
<td>% Tubular Reabsorption PO4</td>
<td>90%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>TSH</td>
<td>1.2 IU/ml</td>
<td>0.3-3 IU/ml</td>
</tr>
</tbody>
</table>
FRAX calculation with BMD results

Calculation Tool

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

Country: US (Black)  Name/ID: 

**Questionnaire:**

1. Age (between 40 and 90 years) or Date of Birth
   - Age: 55
   - Date of Birth: Y: _ M: _ D: _

2. Sex
   - Male
   - Female

3. Weight (kg)
   - 75

4. Height (cm)
   - 170

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: -2.7

**BMI: 26.0**

The ten year probability of fracture (%) with BMD

- Major osteoporotic: 6.7
- Hip Fracture: 2.7
What would you do?

1. Treat with high dose vitamin D supplementation

2. Start bisphosphonate therapy

3. Change tenofovir to either abacavir or raltegravir and evaluate with DXA in 1 year
What would you do?

Option 1. Treat with high dose vitamin D supplementation

Option 2. Start bisphosphonate therapy

Option 3. Change tenofovir to either abacavir or raltegravir and evaluate with DXA in 1 year
Bisphosphonates

• First line therapy in general population
  – Reduces vertebral & non-vertebral Fx by 25-50%
• 6 RCTs in HIV patients with alendronate (70 mg/wk) or zoledronic acid (4-5mg IV/year)
  – Well tolerated and similar short-term effect on BMD as in general population
• Rare but serious adverse events limit long-term use
  – Sub-trochanteric fractures or atypical femoral shaft fractures and osteonecrosis of the jaw
  – FDA expert panel recommends consideration of drug interruption after 5 yrs
Greater BMD loss with switch to TDF than ABC; BMD improves with switch from TDF or LPV/r to RAL

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample/ Duration</th>
<th>ART regimens</th>
<th>Change in LS spine</th>
<th>Change in FN or TH BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin, STEAL 2009</td>
<td>N=357 96 wks</td>
<td>AZT/3TC to TDF/FTC AZT/3TC to ABC/FTC</td>
<td>8.5/100py T&lt;-1.0* 4.4/100py T&lt;-1.0</td>
<td></td>
</tr>
<tr>
<td>Cotter PREPARE 2013</td>
<td>N=84 48 wks</td>
<td>AZT/3TC to TDF/FTC Stay on AZT/FTC</td>
<td>-2.0%* -0.2%</td>
<td></td>
</tr>
<tr>
<td>Bloch TROP 2014</td>
<td>N=37 48 wks</td>
<td>TDF+PI/r to RAL+PI/r</td>
<td>+3.0%</td>
<td>+2.5%</td>
</tr>
<tr>
<td>Haskelberg SECOND LINE 2013</td>
<td>N=210 96 wks</td>
<td>LPVr+2-3 NRTIs LPVr+RAL</td>
<td>-4.9%* -3.5%</td>
<td>-4.1%* -2.2%</td>
</tr>
<tr>
<td>Curran, SPIRAL-LIP, 2012</td>
<td>N=74 48 wks</td>
<td>NRTIs+LPVr to NRTIs+RAL Stay on NRTIs+LPVr</td>
<td>+0.01 g/cm²* no change</td>
<td></td>
</tr>
</tbody>
</table>
What would you do?

**Option 1.** Treat with high dose vitamin D supplementation

**Option 2.** Start bisphosphonate therapy

**Option 3.** Change tenofovir to either abacavir or raltegravir and evaluate with DXA in 1 year
Does FRAX® work as well at predicting fracture risk in HIV+ individuals?

• FRAX® is a computer based algorithm developed by WHO using easily obtained clinical risk factors to calculate 10-year probability of:
  – Major osteoporotic fracture (hip, spine, humerus, wrist)
  – Hip fracture

• Smaller studies show FRAX not predictive of osteoporosis by DXA or prevalent fractures in HIV+ individuals

Calmy et al, *JID* 2009
Gazzola et al, *JID* 2010
Short et al, *Arch Osteoporos*, 2014
Does FRAX work equally well in HIV+

Age
Sex
Race
Weight / Height
Previous Fracture
Current smoking
Glucocorticoid use
Alcohol use
Rheumatoid Arthritis
Parental hip fracture
Secondary Osteoporosis
(type 1 diabetes, osteogenesis imperfecta, untreated hyperthyroidism, chronic malnutrition, malabsorption or chronic liver disease)
Study sample

- Veterans Aging Cohort Study Virtual Cohort (VACS-VC)
  - 50-70 year-old men
  - Complete data from 2000 to approximate all but 2 factors for modified-FRAX calculation (secondary osteoporosis & parental hip fracture)
  - Data from 2001-2010 for ICD-9 coded incident fracture at hip, spine, upper arm and wrist
  - Resulting analytic sample: 24,451
    - HIV+: 7,064 (29%)
    - HIV-: 17,387 (71%)

Womack et al *PLOS* 2011
Womack et al *CID* 2013
Methods

- **Estimates of fracture by modified-FRAX**
  - Use of automated program to input and retrieve data from the web-based FRAX® calculator specific for U.S. and stratified by race/ethnicity
  - “No” entered for parental hip fracture & secondary osteoporosis

- **Accuracy**
  - Agreement between observed fractures and modified-FRAX estimated fractures by observed/estimated ratios (O/E).
  - Accuracy is perfect if O/E=1.0

- **Accuracy of modified-FRAX evaluated in**
  - HIV+ vs. HIV-
  - In HIV+ when HIV is considered a cause of secondary osteoporosis in modified-FRAX calculation
Observed and estimated rates of incident fracture

Observed fractures

Estimated fractures by modified-FRAX

% Fracture over 10-years

Major osteoporotic fracture

Hip fracture

Major osteoporotic fracture

Hip fracture

p<0.0001

p=0.0008

p<0.0001

p<0.0001

HIV+

HIV-

Yin et al, CROI 2015
Modified-FRAX with HIV as cause of secondary osteoporosis

- Estimated % fracture over 10 years
  - Major osteoporotic fracture: 31%
  - Hip: 67%

Yin et al, CROI 2015
Accuracy of modified-FRAX worse in HIV+ than HIV-

HIV-uninfected (N=17,387)  

HIV-infected (N=7064)

HIV-infected with HIV as cause of secondary osteoporosis

Yin et al, CROI 2015
Pharmacologic treatment thresholds for FRAX

National Osteoporosis Guideline Group (NOGG) in United Kingdom

- FRAX used in patients with low BMD/osteopenia (T score between -1.0 and -2.5) by DXA

National Osteoporosis Foundation (NOF) in United States

- FRAX used in patients with low BMD/osteopenia (T score between -1.0 and -2.5) by DXA
- Major osteoporosis fracture ≥20%
- Hip fracture ≥3%
FRAX pharmacologic treatment thresholds among HIV+ at the hip

Hip fracture $\geq$ 3% (NOF)

1.1% (N=74) when HIV is considered a cause of secondary osteoporosis

<table>
<thead>
<tr>
<th></th>
<th>Hip FX</th>
<th>No Hip FX</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq$3%</td>
<td>3</td>
<td>71</td>
</tr>
<tr>
<td>&lt;3%</td>
<td>90</td>
<td>6900</td>
</tr>
<tr>
<td></td>
<td>93</td>
<td>6971</td>
</tr>
</tbody>
</table>

Sensitivity = 3% (3/93)
Specificity = 99% (6900/6971)

Using this threshold, 71 men would be unnecessarily treated to prevent 1 fracture
And 97% of men who will get fracture remain untreated
Limitations of VACS FRAX study

• Missing 2 FRAX variables (secondary osteoporosis and parental hip fracture)
• No femoral neck BMD
• Data only in men, which limits generalizability
• Only 10% of study sample over 65
• We are exploring the impact of HCV on FRAX estimates
Summary for FRAX

- In this study of men >50, modified-FRAX underestimates fracture rates more in HIV+ than HIV- men.

- Consideration of HIV as a cause of secondary osteoporosis in modified-FRAX calculation improves accuracy, but does not fully correct the underestimation of risk.

- Modified-FRAX threshold of >3% at the hip has poor predictive value for incident fracture; other thresholds should be evaluated.
Overall summary

• DXA screening
  – DXA screening of HIV+ men and women>50 is a rational extrapolation from general guidelines
  – However, will result in clinical management dilemmas for patients with osteoporosis but low absolute risk of fracture

• ART Management in patients with high fracture risk
  – Avoid TDF and PI/r containing regimens for ART initiation; use RAL, ABC or TAF. Data for other integrase inhibitors (dolutegravir) pending
  – In patients on established regimens who fracture or are diagnosed with osteoporosis, consider switching from TDF to RAL, ABC, TAF and getting follow up DXA to delay bisphosphonate therapy
Acknowledgements

- Columbia University
  - Elizabeth Shane
  - Scott Hammer
  - Stephen Arpadi
  - Sanil Manavalan
  - Jayesh Shah
  - Kathy Harwood

- Veterans Aging Cohort (VACS)
  - Julie Womack
  - David Rimland
  - Cynthia Gibert
  - Maria Rodriguez-Barradas
  - Roger Bedimo
  - Amy Justice

- Funding
  - NIH/ NIAID
    - R01 HD073977
    - R01 AI096089
  - Irving Scholars Award