Screening and management of HIV-associated bone loss

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Changing age distribution of HIV+ individuals living in US between 2001 and 2005

Mortality remains higher than general population despite ART (CASCADE)

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

Bhaskaran JAMA 2008

Bhaskaran JAMA 2008
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 2.23)

Dong, AIDS, 2013

Multifactorial etiology of bone loss in HIV

Chronic immune activation with HIV infection: potential effects on bone cells

Antiretroviral Agents Approved in the U.S. (contemporary agents)
Inadequate mineralization
direct effect on bone cells
potentially linked to ‘functional’ vitamin D deficiency
secondary hyperparathyroidism
effect on osteoblast gene expression (Grigsby, 2013)

Impact of vitamin D therapy on BMD in patients on TDF
McComsey et al., JID 2011

Decrease in BMD at the spine occurs by 24 weeks after ART initiation

**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>48 weeks</td>
<td>TDF/FTC + EFV ABC/3TC + EFV</td>
<td>-0.6%*</td>
<td>-0.6%*</td>
</tr>
<tr>
<td>McComsey, ACTG 5224s 2011</td>
<td>96 weeks</td>
<td>TDF/FTC ABC/3TC Atripla EFV</td>
<td>-3.3%*</td>
<td>-4.0%*</td>
</tr>
<tr>
<td>Reynea, PROGRESS 2013</td>
<td>96 weeks</td>
<td>TDF/FTC+LPV/ HVL/LPV</td>
<td>-2.5%*</td>
<td>-3.1%*</td>
</tr>
<tr>
<td>Brown, ACTG 5208s 2014</td>
<td>96 weeks</td>
<td>TDF/FTC+ATV/ TDF/FTC+ORV/ TDF/FTC+RAL</td>
<td>-4.0%*</td>
<td>-3.9%*</td>
</tr>
<tr>
<td>Sax, Gilead 104-111 2015</td>
<td>48 weeks</td>
<td>E/C/P/TDF E/C/P/TAF</td>
<td>-2.5%*</td>
<td>-3.0%*</td>
</tr>
</tbody>
</table>

ACTG 5280: Vitamin D+calcium supplementation to attenuate BMD loss with antiretroviral initiation

**Decrease in BMD at the hip occurs by 48 weeks**

**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)

**ACTG 5280: Vitamin D+calcium supplementation to attenuate BMD loss with antiretroviral initiation**

**Randomized, double-blind, placebo controlled**

**Changes in 25(OH) Vitamin D3**

<table>
<thead>
<tr>
<th>Median Value</th>
<th>Week 0</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D3</td>
<td>25.4 ng/mL (71 nmol/L)</td>
<td>55.8 ng/mL (139 nmol/L)</td>
<td>55.8 ng/mL (141 nmol/L)</td>
</tr>
<tr>
<td>Placebo</td>
<td>25.4 ng/mL (71 nmol/L)</td>
<td>76.4 ng/mL (183 nmol/L)</td>
<td>76.0 ng/mL (182 nmol/L)</td>
</tr>
</tbody>
</table>

*P < 0.001*
Percent Decline in BMD from Baseline to 48 Weeks

<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>

DXA screening for osteoporosis

- DXA indicated: Women ≥65, Men ≥70
- DXA indicated with following risk factors (partial list):
  - Fracture History
  - Glucocorticoid Use
  - Low weight
  - Smoking
  - Hypogonadal
  - Malabsorption
  - Emphysema
  - CKD
  - AED
  - PPI
  - >50 Fracture
  - Hypogonadal
  - Glucocorticoid
  - CKD
  - Alcohol
  - AED
  - Diabetes
  - FRAX without BMD for age ≥40

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

- 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.
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-vertebralFx 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

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<th>Study</th>
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<th>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</td>
<td>96 wks</td>
<td>AZT/3TC to TDF/FTC AZT/3TC to ABC/FTC</td>
<td>8.5/100py T&lt;1.0*</td>
<td>4.4/100py T&lt;1.0*</td>
</tr>
<tr>
<td>Cotter PREPARE 2013</td>
<td>N=84</td>
<td>48 wks</td>
<td>AZT/3TC to TDF/FTC Stay on AZT/FTC</td>
<td>-2.6%*</td>
<td>-0.2%</td>
</tr>
<tr>
<td>Blach TROP 2014</td>
<td>N=37</td>
<td>48 wks</td>
<td>TDF+Pis to RAL+Pis</td>
<td>+3.0%</td>
<td>+2.5%</td>
</tr>
<tr>
<td>Haskelberg SECOND LINE 2013</td>
<td>N=210</td>
<td>96 wks</td>
<td>LPV+2-3 NRTIs LPV+RAL</td>
<td>-4.9%*</td>
<td>-3.5%</td>
</tr>
<tr>
<td>Curran, SPIRAL-LIP, 2012</td>
<td>N=74</td>
<td>48 wks</td>
<td>NRTIs+LPV to NRTIs+RAL</td>
<td>+0.01 g/cm^2*</td>
<td>no change</td>
</tr>
</tbody>
</table>

FRAX®

- 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
- Does FRAX work equally well at predicting 10-year fracture risk among HIV+ and HIV-?
  - FRAX scores 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

Yin et al, CROI 2015

Modified-FRAX with HIV as cause of secondary osteoporosis

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

O/E=1.29 (95%CI: 1.19, 1.40)
O/E=1.62 (95%CI: 1.45, 1.81)
O/E=1.20 (95%CI: 1.08, 1.34)

Yin et al, CROI 2015
NOF FRAX pharmacologic treatment thresholds among HIV+ at the hip

<table>
<thead>
<tr>
<th>Hip fracture ≥ 3%</th>
<th>Hip FX</th>
<th>No Hip FX</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3%</td>
<td>3</td>
<td>71</td>
</tr>
<tr>
<td>&lt;3%</td>
<td>93</td>
<td>6900</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>3%</td>
<td>(3/93)</td>
</tr>
<tr>
<td>Specificity</td>
<td>99%</td>
<td>(6900/6971)</td>
</tr>
</tbody>
</table>

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

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

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