Osteoporosis and HIV: Optimal Evaluation and Management to Prevent Fractures

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Disclosures

• Dr Brown has served as a consultant to Gilead Sciences, Inc, GlaxoSmithKline, Janssen, Merck & Co, Inc, Theratechnologies, EMD Serono, and ViiV Healthcare.
The Aging of the HIV Population: Netherlands

Smit, Lancet Inf Diseases, 2015
Multimorbidity will increase markedly in PWH over the next 10 years

- Older age-groups experience an increase in population size and prevalence of multimorbidity.
- Among those ≥ 70yrs, the projected prevalence of multimorbidity increases from 58% (in 2020) to 69% (in 2030), corresponding to an additional 71,000 individuals living with 2+ physical comorbidities beside HIV by 2030.

Kasaie, CROI 2021, Abstract 102
Comorbidity distribution

% of participants

- Hypertension
- Angina pectoris
- Myocardial infarction
- Periph. arterial insufficiency
- Cerebrovascular disease
- Diabetes mellitus type 2
- COPD
- Chronic liver disease
- Reduced renal function
- Fracture / osteoporosis

HIV negative
HIV positive

p<0.0001
p=0.005
p=0.003
p=0.006
p<0.0001
p=0.022
p=0.001

Schouten, IAS, 2012
Why worry about osteoporosis?

- Osteoporosis is common among older populations and more common in PWH compared to matched HIV SN
- Osteoprotic fractures are a major source of morbidity & mortality
- Osteoporosis is a silent disease until fractures occur
- Osteoporosis can be detected in a pre-clinical stage and fractures can be prevented
Fragility Fractures in Women and Men over 50 years

Wasnich RD, Osteoporos Int. 1997
Compared to Other Health Issues

Annual occurrences

- Breast Cancer: 232,924
- Heart Attacks: 735,000
- Strokes: 800,000
- Fractures: 2,000,000

Centers for Disease Control & Prevention 2016
Centers for Disease Control & Prevention, 2015
Centers for Disease Control & Prevention, 2015
National Osteoporosis Foundation, 2015
Relative influence on peak bone mass (men): 40% to 83% genetic; 27% to 60% environmental

0.5% to 1.0% reduction in bone volume/year

Change in Bone Volume (%)

Men

Women

Age (Yrs)

Increase Mortality After Fragility Fractures

Haentjens, Annals Int Medicine, 2010
Physical & cognitive function generally declines over time.
Decline in Function May Not Be Gradual

Quality of Life/Physical & Cognitive Function

- Heart Attack
- Pneumonia
- Hip Fracture
- Stroke

Age

50

100
Preventing comorbid events, including fracture, is critical to maintain function.

Quality of Life/Physical & Cognitive Function

- Heart Attack
- Pneumonia
- Hip Fracture
- Stroke

Women

Fracture Prevalence/100 Persons

HIV Non-HIV

P=0.002
(overall comparison)

Men

Fracture Prevalence/100 Persons

HIV Non-HIV

P<0.0001
(overall comparison)

8,525 HIV-infected
2,208,792 non HIV-infected patients

Triant, JCEM, 2008
Prevalence of Osteoporosis in HIV-infected Patients vs HIV-uninfected Controls: A Meta-analysis

Overall prevalence of osteoporosis in HIV-infected patients 15%

<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>
</tr>
<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>Madeedu (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>
</table>
Definitions

Osteoporosis:
“systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and fracture”

Consensus Conference Am J Med. 1993
Vertebral body: Normal vs Osteoporosis

normal

osteoporotic
Operational Definition (DXA)- WHO Definition

- Osteoporosis: T-score ≤ -2.5
- Osteopenia: T-score = -1.0 to -2.4
- Normal: T-score > -1.0

↑ Risk of fracture by 1.5-3.0 x for each SD decrease

Caveats:
- Z-score (≤-2.0) used in men < 50 years and premenopausal women
- BMD explains only about 50% of fracture risk
DXA Scanning

- Lumbar Spine
- Hip
  - Femoral neck
  - Total hip
- Forearm (distal 1/3)

Sites differ in proportions of cortical and trabecular bone
Fractures Happen at all BMDs
Multifactorial Etiology of Bone Loss in HIV
Bone Loss Occurs First 6 Months after ART Initiation

No significant interaction of NRTI and NNRTI/PI components (p=.63)

* = two-sample t-test

McComsey et al., JID 2011
Bone Loss with ART Initiation: TDF

<table>
<thead>
<tr>
<th>Study</th>
<th>ART regimens</th>
<th>Change in LS BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stellbrink, ASSERT 2010</td>
<td>TDF/FTC + EFV</td>
<td>-3.6%*</td>
</tr>
<tr>
<td></td>
<td>ABC/3TC + EFV</td>
<td>-1.9%</td>
</tr>
<tr>
<td>McComsey, ACTG 5224s 2011</td>
<td>TDF/FTC</td>
<td>-3.3%*</td>
</tr>
<tr>
<td></td>
<td>ABC/3TC</td>
<td>-1.3%</td>
</tr>
<tr>
<td></td>
<td>ATV/r</td>
<td>-3.1%*</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>-1.7%</td>
</tr>
<tr>
<td>Reynes, PROGRESS 2013</td>
<td>TDF/FTC+LPV/r</td>
<td>-2.5%*</td>
</tr>
<tr>
<td></td>
<td>RAL+LPV/r</td>
<td>+0.7%</td>
</tr>
<tr>
<td>Sax, Gilead 104-111 2015</td>
<td>E/C/F/TDF</td>
<td>-2.9%*</td>
</tr>
<tr>
<td></td>
<td>E/C/F/TAF</td>
<td>-1.3%</td>
</tr>
</tbody>
</table>
Bone Loss After ART Initiation: PIs vs RAL

Mean Percentage Change in BMD over 96 Weeks by Treatment Regimen*

**Total Hip**
- ATP/r vs DRV/r: p=0.36
- PI/r vs RAL: P=0.005

**Lumbar Spine**
- ATP/r vs DRV/r: p=0.42
- PI/r vs RAL: P<0.001

*error bars represent 95% confidence intervals

Brown, JID, 2015
Starting ART without TDF or PIs: 0.5-1.0% Bone Loss

Gallant, Lancet, 2017
BMD improves with ART switch

TDF → TAF or raltegravir

Ritonavir-boosted protease inhibitor → raltegravir

<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>Pozniak JAIDS 2017</td>
<td>N=242 eGFR 30-69 ml/min 48 wks</td>
<td>TDF/FTC/EVG/Cobi to TAF/FTC/EVG/Cobi</td>
<td>+2.3%*</td>
<td>+1.5%*</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>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/cm²^2*</td>
<td>no change</td>
</tr>
</tbody>
</table>
How can we prevent fractures in PWH?

• ART switching
  – avoid TDF & PIs in individuals with higher fracture risk

• Appropriate screening
  – DXA: Men ≥ 50 y & all post-menopausal women
    • Caveat: Explains only about 50% of fracture risk

Brown, CID, 2015
US Bone Health and Osteoporosis Foundation (BHOF) Guidelines for DXA Screening

- Those with a fragility fracture after age 50
- Women ≥ 65 yrs, Men ≥ 70 yrs
- Younger postmenopausal women and men 50-69 years with clinical risk factors for fracture
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for ≥ three months) associated with low bone mass or bone loss
Other Modalities to Assess Fracture Risk

• Skeletal
  – Spine X-rays
2/3 of those with subclinical vertebral fractures did not have osteoporosis.
Other Modalities to Assess Fracture Risk

• Skeletal
  – Spine X-rays
  – Trabecular Bone Score
Trabecular Bone Score as Noninvasive Measure of Bone Microstructure

- TBS is an indirect measure of bone microstructure: higher score = better microstructure
- Derived from standard LS DXA images
  - Bone texture inhomogeneity determined by pixel variations (ie, trabecular textural index)
  - Software installed on existing DXA scanner, so no extra scan time or radiation exposure
  - Archived LS DXA images can be assessed retrospectively
- FRAX can adjust for TBS

<table>
<thead>
<tr>
<th>TBS Value</th>
<th>Bone Microstructure Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.35</td>
<td>Normal</td>
</tr>
<tr>
<td>&gt; 1.20 to &lt; 1.35</td>
<td>Intermediate</td>
</tr>
<tr>
<td>≤ 1.20</td>
<td>Degraded</td>
</tr>
</tbody>
</table>

How can we prevent fractures in PWH?

- ART switching
  - avoid TDF & PIs in individuals with higher fracture risk

- Appropriate screening
  - DXA: Men ≥ 50 y & all post-menopausal women
    - Caveat: Explains only about 50% of fracture risk

- Identifying appropriate candidates for treatment
US BHOF Guidelines: Whom to Treat*

- Those with hip or vertebral fractures
- Those with BMD T-scores $\leq -2.5$ at the femoral neck, total hip, or spine by DXA
- Those with T-score b/t -1 and -2.5 (osteopenia) at above sites AND 10-year hip fracture probability $\geq 3\%$ or 10-year all major osteoporosis-related fracture $\geq 20\%$ based on FRAX model

*applies to post-menopausal women and men $\geq 50$ years
FRAX underestimates fracture risk in PWH
Yang, AIDS, 2018

Should treatment thresholds be any different in PWH?

http://www.shef.ac.uk/FRAX/
What treatment should be given?

- alendronate
- teriparatide
- zoledronic acid
General Recommendations

• Calcium
  – goal: 1200 mg daily, preferably from diet

• Vitamin D supplementation
  – at least 800 IU or target 25OHD > 20 ng/mL (50 nmol/L)

• Smoking cessation

• Alcohol reduction

• Weight-bearing exercise

• Discontinuation of medications associated with osteoporosis (eg, steroids, TZDs, proton pump inhibitors)
Pharmacologic Therapies for Osteoporosis

**Antiresorptive**
(Osteoclast Directed)

- bisphosphonates
- SERMs (raloxifene)
- denosumab
- hormone replacement therapy

**Anabolic**
(Osteoblast Directed)

- PTH/PTHrP Analogs (teriparatide, abaloparatide)
- romosozumab
### Bisphosphonates

– Reduce vertebral & non-vertebral fractures by 25-50% in non-HIV

<table>
<thead>
<tr>
<th>Author, year (N)</th>
<th>T-score</th>
<th>Medication (duration)</th>
<th>Spine</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guaraldi, 2004 (N=41)</td>
<td>&lt; -1.0</td>
<td>Alendronate 70 mg/wk (1 yr)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mondy, 2005 (N=31)</td>
<td>&lt; -1.0</td>
<td>Alendronate 70 mg/wk (1 yr)</td>
<td>+5.2% vs +1.3%*</td>
<td>NS</td>
</tr>
<tr>
<td>McComsey, 2007 (N=82)</td>
<td>&lt; -1.5</td>
<td>Alendronate 70 mg/wk (1 yr)</td>
<td>+3.1% vs +1.1%*</td>
<td>+4.0% vs +1.4%†</td>
</tr>
<tr>
<td>Rozenberg, 2012 (N=44)</td>
<td>&lt; -2.5</td>
<td>Alendronate 70 mg/wk (2 yrs)</td>
<td>+7.4% vs +4.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Bolland, 2007 (N=43 )</td>
<td>&lt; -0.5</td>
<td>Zoledronic acid 4 mg/year (2 yrs)</td>
<td>+8.9% vs +2.6%†</td>
<td>+3.8% vs -0.8%†</td>
</tr>
<tr>
<td>Huang, 2009 (N=30)</td>
<td>&lt; -1.5</td>
<td>Zoledronic acid 5 mg/year (1 yr)</td>
<td>+3.7% vs +0.7%*</td>
<td>+3.2% vs -1.8%*</td>
</tr>
</tbody>
</table>

* P < 0.05; †P < 0.001; NS = not significant

Switch off TDF vs Bisphosphonate: ZEST Study

Hoy, AIDS, 2018

3% Women
Oral vs IV Bisphosphonate

**Oral (alendronate)**
- Lower Cost
- GI problems
- Poor bioavailability
- Poor compliance/persistence

**IV (zoledronic acid)**
- Clinic administered
- Acute phase reaction (20-30% with first dose)
- Hypocalcemia
- Directly observed therapy
Antiresorptives: Long Term Adverse Events

Osteonecrosis of the Jaw
1 to 10 cases per 100,000 person-years

Atypical Femoral Fracture
3.2 to 50 cases per 100,000 person-years
Declining Use of Bisphosphonates

Jha, JBMR, 2015
## Bisphosphate Holiday

### Table 2: Recommendations for Drug Holiday from Bisphosphonates

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk: T-score still $\leq -2.5$ at the hip, previous fracture of the hip or spine or ongoing high-dose glucocorticoid therapy.</td>
<td>Drug holiday not justified.</td>
</tr>
<tr>
<td>Moderate risk: Hip bone mineral density value is now $&gt; -2.5$ (T-score), and no prior hip or spine fracture.</td>
<td>Consider drug holiday after 3-5 years of alendronate, risedronate, or zoledronic acid therapy. No information about ibandronate and drug holidays.</td>
</tr>
<tr>
<td>Low risk: Did not meet current treatment criteria at the time of treatment initiation.</td>
<td>Discontinue therapy</td>
</tr>
</tbody>
</table>

**Questions:**
- How long?
- How to monitor?
- What medications after the holiday?

McClung, Am J Medicine, 2013
Fragility Fracture v Atypical Femoral Fracture

Black, NEJM, 2020
Denosumab

- Monoclonal to RANKL
- Decrease osteoclast activation
- Increase BMD, decrease fracture risk
- ? Risk of infection: use judiciously in HIV, particularly in those with low CD4
- Given q 6 months
- Vertebral fracture after discontinuation -> follow with BPs
- Can be given in those with low GFR; concern for hypocalcemia
Pharmacologic Therapies for Osteoporosis

**Antiresorptive**
(Osteoclast Directed)
- bisphosphonates
- SERMs (raloxifene)
- denosumab
- hormone replacement therapy

**Anabolic**
(Osteoblast Directed)
- PTH/PTHrP Analogs (teriparatide, abaloparatide)
- romosozumab
PTH/PTHrP Analogs

- Generally given after BP failure
- Can be first line in severe osteoporosis
- 18-24 month duration of therapy
- Need to follow with an antiresorptive
- Daily SC injection

Teriparatide increases BMD more than alendronate in glucocorticoid-induced osteoporosis

Saag, NEJM, 2007
Romasozumab

- Monoclonal antibody to sclerostin
- Increases osteoblast activity; Inhibits osteoclast activity
- Given for 1 year; monthly injections
- Greater BMD gains vs ALN vs TRPT
- Greater fracture risk reduction vs ALN
- For severe osteoporosis or intolerance to other meds
Preventing falls will prevent fractures

**Risk Factors for Falls**

- Sedative use
- Cognitive or visual impairment
- Lower-extremity disability
  - Neuropathy
- Muscle Weakness
- Frailty

http://courses.washington.edu/bonephys
Strategies to Prevent Falls

• Assess Fall Risk (Are you worried about falling?)
• Physical Therapy Assessment for Strength and Balance
• Environmental Assessment/Modification
  – keep bathroom lights on
  – avoid loose rugs
  – remove clutter
  – keep wires behind furniture
• Behavioral Assessment/Modification
  – avoid excess alcohol, drugs
  – consider de-prescribing
  – wear sturdy shoes
  – avoid slippery/uneven surfaces
Conclusions

- Fractures likely to be a major source of morbidity for aging PWH.
- DXA screening should be more aggressive in PWH
- Bisphosphonates should be considered first line therapy
- Adherence to treatment is a major challenge
- Many questions remain re: the optimal duration of treatment & sequencing of medications
- Fall prevention is essential to prevent fractures.
HIV Treatment Cascade: Identifying and Closing the Gaps in Care
Closing the Gaps for Fracture Prevention in PWH

For Illustration Only; numbers are fictional
Preventing Comorbid Events is Critical to Maintain Function

Quality of Life/
Physical &
Cognitive
Function

Heart Attack
Pneumonia
Hip Fracture
Stroke

Age
50
100
Preventing Comorbid Events is Critical to Maintain Function

Quality of Life/Physical & Cognitive Function

Age

50

100
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