The conundrum of HIV, Antiretroviral Therapy and Bone Disease

Professor Jenny Hoy
Department of Infectious Diseases Unit,
The Alfred Hospital and Monash University

HIV Congress 2014
Mumbai, India
Disclosures

• Alfred Health has received funding for my participation in Advisory Boards for Gilead Sciences, Merck Sharp & Dohme and Viiv Healthcare
HIV and Bone Disease

• Is bone loss important in HIV?
• What is the association between bone loss and ART?
• What is the appropriate timing for assessment of fracture risk and bone mineral density?

• Should we worry about the bones?
Osteoporosis is a silent disease: clinical manifestation is fracture
Loss of architecture in osteoporotic bone

Normal

Osteoporotic

Thinning trabeculae, less well connected

Image (A) obtained from http://www.iofbonehealth.org and (B) from http://courses.washington.edu/bonephys/
Osteoporosis/osteopenia

Original WHO definitions of osteoporosis/osteopenia compare bone mineral density (BMD) to a normal population (T-score)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>T score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; –1.0</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>–2.5 to –1.0</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>&lt; –2.5</td>
</tr>
</tbody>
</table>

T score = standard deviation (SD) between measured BMD measured and mean BMD of white women at peak bone density (aged 30 years)

Z score = SD between measured BMD and mean BMD of individuals of the same age, race, and gender

Use Z Scores in those <50 years of age
If Z score < -2 – consider secondary causes of low BMD

2. NIH consensus development panel on osteoporosis prevention, diagnosis and therapy. JAMA 2001; 285:785–795
Fracture probability is age- and gender-specific

Adapted from Kanis et al., Osteoporos Int. 2000
Effect of age on 10-yr fracture probability according to BMD T score - women

Kanis et al, 2001
Fracture prevalence greater in HIV+ compared with HIV- adults

Women

MGH/Partners Healthcare System: 1996-2008
8,525 HIV-infected
2,208,792 non HIV-infected patients

Men

Triant VA et al. J Clin Endocrinol Metab 2008;93:3499-3504
Fracture prevalence greater in HIV+ compared with HIV- adults

What drives the increased fracture prevalence?

- Traditional fracture risk factors
- Role of ART in increased fracture prevalence less clear - studies show conflicting results
Bone is continuously being remodelled
Resorption = Formation → No net gain or loss of bone

The bone multicellular unit (BMU)

A  Resorption
- Lining cells
- Osteoclasts
- Normal resorption depth
- Osteoporosis resorption depth

B  Remodelling
- Osteoblasts
- Newly formed bone matrix (osteoid)

C  Mineralisation & mineral maturation
- Calcified bone matrix

D  Quiescence
- Lining cells
- Normal filling depth
- Osteoporosis filling depth
- Completed remodelling unit (new bone)
Risk factors for decreased BMD in HIV

- **Female sex**
- **Smoking**
- **White race**
- **Family history**
- **Increasing age**
- **Amenorrhoea / premature menopause**

**HIV infection related**

- Cytokines (eg TNFα, IL6)
- Decreased muscle mass
- Decreased fat mass
- Fat deposition in marrow

- **Decreased physical activity**
- **Alcohol**
- **Decreased bone acquisition**

**Bone Mineral Density**

**cART-related**

- **NRTI/mitochondrial dysfunction- tenofovir**
- **Protease inhibitors**
- **Lipodystrophy**

**Classic**

**Chronic diseases**
(e.g. hyperthyroidism, hyperparathyroidism, liver disease, rheumatological conditions, eating disorders, etc.)

- **Hypogonadism**
- **Renal dysfunction**
- **Malnutrition/low BMI**

**Secondary**

- **Medications**
  (e.g. corticosteroids, anticonvulsants, anticoagulants)

Diagram adapted from Glesby MJ. *Clin Infect Dis* 2003; 37(Suppl 2):S91–S95
Potential effects of HIV infection on bone remodelling

Multifactorial – complex interaction between traditional risk factors for low BMD and HIV infection

Uncontrolled HIV viremia and its effect on immune activation and systemic inflammation may increase bone resorption

HIV proteins increase osteoclast activity in vitro, and decrease bone formation

Low BMI consistently associated with low BMD in HIV

Hypogonadism

Lipoatrophy and central fat adiposity through complex relationships between adipocyte hormone signalling

High prevalence of Vitamin D deficiency
Effect of ART initiation on BMD
ART initiation is associated with bone loss

Individuals lose 2-6% of total BMD at the initiation of ART
- Some drugs produce more bone loss than others

Mean Percentage Changes in Lumbar Spine and Hip Bone Mineral Density (BMD) From Baseline to Week 96 (Intent-to-Treat)

- ABC/3TC: $P=0.004$, -1.3% 
- TDF/FTC: $P=0.035$, -1.7% 
- ATV/r: $P=0.025$, -2.6% 
- EFV: $P=0.59$, -3.1% 

Marked reduction in BMD in first 48 weeks with stabilisation thereafter in naïve ART studies

* -linear regression
No significant interaction of NRTI and NNRTI/PI components (p=0.63)

McComsey, G et al. 17th CROI 2010. Abstract 106LB
ART and bone Loss
ABC/3TC versus TDF/FTC

Subjects

ABC/3TC: 176 134 117 182 141 125
TDF/FTC: 180 156 138 183 165 143

ABC/3TC: -1.90%
TDF/FTC: -3.55%
Δ = -1.68; 95% CI (-2.26, -1.09)

ABC/3TC: -1.59%
TDF/FTC: -2.41%
Δ = -0.84; 95% CI (-1.61, -0.06)

Stellbrink HJ et al., EACS 2009
BMD change in patients initiating ART with PI/r versus Raltegravir regimens (ACTG A5257)

Mean Percentage Change in BMD over 96 Weeks by Treatment Regimen

- Total Hip
  - ATV/r v DRV/r: p=0.30
  - PI/r v RAL: p=0.005

- Lumbar Spine
  - ATV/r v DRV/r: p=0.42
  - PI/r v RAL: p=0.001

*error bars represent 95% confidence intervals

Brown, T et al, CROI 2014 Poster 779LB
ACTG A5257 – comparison of 3 initial regimens ATZ/r versus DRV/r versus RAL combined with TDF/FTC

• Change in BMD at the hip and spine were not different for ATZ/r and DRV/r both combined with TDF/FTC at 96 weeks

• TDF/FTC and Raltegravir was associated with significantly less bone less at hip and spine

• Change in Total BMD was greatest with ATZ/r compared to DRV/r and raltegravir

Brown, T et al, CROI 2014 Poster 779LB
Effect of other integrase inhibitors on BMD

- **Dolutegravir** – no data
- **Evitegravir**
  - %change in BMD from baseline in naïve patients

<table>
<thead>
<tr>
<th></th>
<th>Spine BMD</th>
<th>Hip BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC/ELV/Cob</td>
<td>1.96%</td>
<td>3.16%</td>
</tr>
<tr>
<td>TDF/FTC/ATZ/r</td>
<td>3.54%</td>
<td>4.19%</td>
</tr>
<tr>
<td>P value</td>
<td>0.049</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Rockstroh et al, JAIDS 2013
GS-US-292-102: % Change in BMD (DEXA) at Week 24 comparing TAF with Tenofovir DF

- Proportion of subjects with no decrease in BMD
  - Spine: E/C/F/TAF, 38%; E/C/F/TDF, 12%
  - Hip: E/C/F/TAF, 41%; E/C/F/TDF: 23%

Zolopa, et al., CROI 2013; Paper # 99LB
Stabilization or Continuous decrease in BMD
SMART: BMD Loss With Continuous vs Intermittent Antiretroviral Therapy

- Continuous antiretroviral therapy is associated with significantly larger BMD decline than intermittent antiretroviral therapy

Switch studies in virologically suppressed patients
Effect on BMD with randomized switch from AZT/3TC to TDF/FTC and ABC/3TC in virologically suppressed patients

**Significant decrease in both hip and spine BMD with TDF/FTC compared with ABC/3TC**

Rasmussen et al, 2012
TROP study: Single arm pilot study of switch from Tenofovir DF to Raltegravir
Class switching from tenofovir to raltegravir can improve low BMD

<table>
<thead>
<tr>
<th></th>
<th>Mean % Change BMD from Baseline [95% CI]</th>
<th>Week 24</th>
<th>P</th>
<th>Week 48</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip</td>
<td>1.4 [0.8, 2.0]</td>
<td>0.0001</td>
<td></td>
<td>2.5 [1.6, 3.3]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>1.5 [0.3, 2.7]</td>
<td>0.0131</td>
<td></td>
<td>2.1 [0.9, 3.2]</td>
<td>0.0011</td>
</tr>
<tr>
<td>Right hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip</td>
<td>0.6 [-0.3, 1.5]</td>
<td>0.1902</td>
<td></td>
<td>2.7 [1.9, 3.5]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.4 [-0.9, 1.7]</td>
<td>0.5402</td>
<td></td>
<td>2.3 [1.2, 3.5]</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Bloch et al, HIV Med 2014
### SPIRAL Study: Switch PI/r to RAL

Bone composition (median change from baseline to week 48)

<table>
<thead>
<tr>
<th>DEXA scan</th>
<th>RAL</th>
<th>PI/r</th>
<th>Difference (IQR) PI/r vs RAL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total BMD (g/cm²)</td>
<td>0.01 (p=0.002)</td>
<td>0</td>
<td>0.01 (-0.01 ; 0.02)</td>
<td>0.079</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²)</td>
<td>0</td>
<td>-0.01</td>
<td>0.01 (-0.02 ; 0.02)</td>
<td>0.032</td>
</tr>
<tr>
<td>Femoral neck T score</td>
<td>0.04</td>
<td>-0.10</td>
<td>0.01 (-0.18 ; 0.18)</td>
<td>0.016</td>
</tr>
<tr>
<td>Total hip BMD (g/cm²)</td>
<td>0.01 (p=0.015)</td>
<td>0</td>
<td>0.01 (-0.01 ; 0.02)</td>
<td>ns</td>
</tr>
<tr>
<td>Total hip T score</td>
<td>0.12 (p=0.004)</td>
<td>0.01</td>
<td>0.11 (-0.05 ; 0.20)</td>
<td>ns</td>
</tr>
<tr>
<td>L1-L4 BMD (g/cm²)</td>
<td>0</td>
<td>0.02</td>
<td>0 (-0.02 ; 0.04)</td>
<td>ns</td>
</tr>
<tr>
<td>L1-L4 T score</td>
<td>0.03</td>
<td>0.10</td>
<td>0.09 (-0.11 ; 0.31)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Switching to RAL led to a significant increase in femoral neck BMD (but not spine)

*Curran A, AIDS 2012;26:475-81*
Switch studies in virologically failing patients
Mean change in BMD in patients virologically failing first line NNRTI-based ART randomised to either LPV/r+2-3N(t)RTI or LPV/r + raltegravir

Mean % change (SE) in BMD from week 0 to 48

<table>
<thead>
<tr>
<th></th>
<th>Proximal Femur</th>
<th>Lumbar Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>r/LPV+2-3NtRTI</td>
<td>-2.4% (-3.5 to -1.2)</td>
<td>-2.1% (-3.3 to -0.6)</td>
</tr>
<tr>
<td>r/LPV+RAL</td>
<td>-2.0% (-3.5 to -1.2)</td>
<td>-1.9% (-3.3 to -0.6)</td>
</tr>
</tbody>
</table>

Mean difference between arms

- Proximal femur: -2.4% (-3.5 to -1.2) p=0.0001
- Lumbar spine: -2.1% (-3.3 to -0.6) p=0.0006

All analyses are adjusted for baseline imbalances in gender, BMI and smoking status.
96 week change in BMD
Secondline Study
Magnitude of BMD loss and trajectory similar to BMD changes in naïve patients

?effect of viremia

% Hip BMD Change

% Spine BMD change

2-3 NRTI + LOP/r

Raltegravir + LOP/r

Study week

0 48 96

0 2 4

0 2 4 6 8 10 12

0 48 96

Study week
ART-Associated Effects on Bone Mineral Density: Summary

• Initiation of ART and changing ART in viremic patients is associated with increased bone loss over 48 weeks.
• Decline in BMD with ART (2-6% in first 12 months) is statistically significant, but mean absolute change is small.
• Tenofovir and PI/r regimens associated with significantly greater bone loss compared with other regimens.
• Currently unable to predict which patients will experience greater loss of BMD or develop osteoporosis on ART.
• Is there sufficient data to support prevention or reversal of osteoporosis by choice of, or change in, ART regimen?
To Screen or Not to Screen….
Who and How to Screen

Which tool?

When to start screening?

How often to screen?
Bone Health in HIV

Who to Screen
Any HIV positive patient > 40 years old

Screening Frequency
3 yearly until > 60 years of age then annually

How to screen
- Calculate FRAX score (mark YES for other secondary causes of osteoporosis to account for HIV-induced bone loss)
- Measure serum Ca, PO4, Vitamin D
- Screen for testosterone deficiency (in men)

Calcium and Vitamin D Supplementation

<table>
<thead>
<tr>
<th>Definition of deficient</th>
<th>Replacement Doses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-OH Vitamin D &lt;50 nmol/L mild deficiency</td>
<td>1,000-2,000 IU daily</td>
<td>Check ALP and PTH</td>
</tr>
<tr>
<td>&lt;25 moderate-severe deficiency</td>
<td>3,000 – 5,000 IU daily for 6 – 12 weeks then as above</td>
<td></td>
</tr>
</tbody>
</table>

Calcium Intake of < 2-3 serves of high calcium food (i.e. dairy) per day

Intake of < 2-3 serves of high calcium food (i.e. dairy) per day

Encourage increased dietary intake

First line

If dietary intake not possible then supplement with 500-600mg daily

Must be taken with food

Screening for Secondary Causes of Bone Loss

Condition | Screening Test
---|---
Hyperparathyroidism | Parathyroid Hormone (PTH)
Hypogonadism | Free and total Testosterone and Luteinizing Hormone (LH)
Diabetes | Fasting glucose
Hyperthyroidism | Thyroid function tests (TFT)
Chronic Liver disease | LFTs
MGUS/ Myeloma | Serum protein electrophoresis/ and light chains

Bisphosphonate dosing

- Alendronate 70mg orally weekly
- Risedronate 35mg orally weekly
- Zoledronic acid 5mg IV yearly

Comments re Bisphosphonates:
- Should be taken on their own (i.e. 30 mins before or after food or other medications) to maximise absorption
- Sit/stand upright for 30min post taking to prevent esophagitis
- Should not be given to patients undergoing dental procedures (risk of osteonecrosis of the jaw)

PBS approved indications for bisphosphonates

<table>
<thead>
<tr>
<th>Steroid-induced osteoporosis</th>
<th>Osteoporosis</th>
<th>Established Osteoporosis</th>
</tr>
</thead>
</table>
| Patient must be on long term (≥3 months) of ≥7.5mg/day prednisolone AND Have a BMD T-score of ≤-1.5 | > 70 years old AND BMD T-Score ≤-2.5 | Had a minimal trauma fracture
- Secondary Osteoporosis
- Failure of 1 line therapy
- Severe osteoporosis on DEXA
- Suspected Hypogonadism

Endocrinology if:
- If secondary cause identified may not require treatment
- Repeat DEXA 5 years

Bisphosphonate Therapy

If secondary cause identified may not require treatment

Repeat DEXA 5 years

Repeat DEXA 1-2 years

Thoraco lumbar spine X-ray

Baseline DEXA scan

DEXA scan to determine BMD

T < -1.0 Normal

T < -1 and > -2.5 Osteopenia

T > -2.5 Osteoporosis

Consider Tamofin-induced renal bone disease
Screen for secondary causes of bone loss

Repeat DEXA 5 years

Repeat DEXA 1-2 years
<table>
<thead>
<tr>
<th>Who to Screen</th>
<th>Any HIV positive patient &gt; 40 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Frequency</td>
<td>3 yearly until &gt; 60 years of age then annually</td>
</tr>
</tbody>
</table>
| How to screen         | - Calculate FRAX score (mark YES for other secondary causes of osteoporosis to account for HIV-induced bone loss)  
                        - Measure serum Ca, PO\textsubscript{4}, Vitamin D  
                        - Screen for testosterone deficiency (in men) |
http://www.shef.ac.uk/FRAX/tool.aspx
FRAX considerations

- Fracture probabilities very low for anyone under the age of 50 years – FRAX can be used for younger patients but they will be assumed to be 40 years in the calculations.
- It is possible to estimate a 10 year fracture probability without BMD.
- FRAX has not been validated in the HIV population.
- Some experts believe HIV should be considered a secondary cause of osteoporosis and that box ticked in the FRAX calculation.
- Those with 10 yr fracture probabilities of >20% for osteoporotic fracture and >3% for hip fracture should have a DXA scan.
Calculate FRAX score in all patients > 40 years old
www.shef.ac.uk/FRAX/tool.jsp

- **Low Risk <8%**
  - Repeat FRAX yearly

- **Medium or High Risk >8%**
  - Thoraco lumbar spine X-ray
  - No fracture
    - Is the patient postmenopausal or ≥ 50 years of age or, on long term steroids ≥ 7.5mg daily
      - **NO**
      - **YES**
        - Baseline DEXA scan
        - DEXA scan to determine BMD
        - Bisphosphonate Therapy

- **Fracture**
DEXA scan to determine BMD

- **T ≥ -1.0**
  - Normal
  - Repeat DEXA 5 years

- **T ≤ -2.5**
  - Osteoporosis
  - Repeat DEXA 1-2 years

- **T < -1 and > -2.5**
  - Osteopenia
  - Repeat DEXA 5 years

**Consider Tenofovir-induced bone disease**

Screen for secondary causes of bone loss

- If secondary cause identified may not require treatment
- Repeat DEXA 5 years
- Bisphosphonate Therapy
  - Repeat DEXA 1-2 years

Fracture

- If secondary cause identified may not require treatment
- Repeat DEXA 5 years
- Bisphosphonate Therapy
  - Repeat DEXA 1-2 years
# Bone Health

## Screening for Secondary Causes of Bone Loss

<table>
<thead>
<tr>
<th>Condition</th>
<th>Screening Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>Parathyroid Hormone (PTH)</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Free and total Testosterone and Luteinizing Hormone (LH)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting glucose</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Thyroid function tests (TFT)</td>
</tr>
<tr>
<td>Chronic Liver disease</td>
<td>LFTs</td>
</tr>
<tr>
<td>MGUS/ Myeloma</td>
<td>Serum protein electrophoresis/ and light chains</td>
</tr>
</tbody>
</table>
DEXA scans

Who should have a screening DXA scan?

- All postmenopausal women
- Men over the age of 50 yrs with at least one additional risk factor
  - Intermediate or high risk FRAX score
  - History of fragility fracture
  - High risk for falls
  - Receipt of glucocorticoids at a dose of ≥7.5 mg prednisolone or equivalent daily for 3 months

Those that fit the above definition should have a DXA scan at HIV diagnosis, OR prior to initiation of cART
**DEXA scans**

How frequently should DEXA scans be performed?

- DEXA screening interval is determined by baseline scan result
- If baseline DEXA scan shows normal or mild osteopenia, screening interval should be about 5 years
- Advanced osteopenia – repeat scan in 1-2 years
- DEXA scans do NOT need to be done more frequently in those on tenofovir or PI-containing ART regimens

What is a clinically relevant change in BMD?

- 10% at femoral neck and 5% at the spine
See you in Melbourne in July!