HIV and Osteoporosis

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Aims

• Healthy bone
• Definition of osteoporosis
• Diagnosis of osteoporosis
• Risk factors
• Vitamin D and osteomalacia
• Guidelines for screening
• Management of osteoporosis
Healthy bone

- Most bones have a basic structure composed of:
  - an outer cortical zone (resists deformation)
  - an inner trabecular or spongy zone (complex system of internal supports)
- Bone marrow fills the spaces within the trabeculae

- Bone undergoes constant remodelling with bone formation by osteoblasts and resorption by osteoclasts
Age related changes in bone mass

Compston JE. Clin Endocrinol 1990; 33:653–682
Definition of Osteoporosis

‘A disease characterised by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk’

Normal bone

Osteoporosis

World Health Organisation (WHO), 1993
Clinical Manifestations

- Fracture
- Hip / vertebrae / Colles’
- Humerus / pelvis / ankle
- Vertebral fracture is sub-clinical in 60-70% of cases
  - Height loss
  - Kyphosis
  - Back pain
Relative Risk of Death Following Clinical Fractures Fracture Intervention Trial (FIT)*


*6459 postmenopausal women ages 55-81 years followed for an average of 3.8 years.
Prior fracture and subsequent fracture risk

<table>
<thead>
<tr>
<th>Prior fracture</th>
<th>Subsequent fracture (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wrist</td>
</tr>
<tr>
<td>Wrist</td>
<td>3.6</td>
</tr>
<tr>
<td>Spine</td>
<td>1.4</td>
</tr>
<tr>
<td>Hip</td>
<td>-</td>
</tr>
<tr>
<td>Pooled</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Pooled risks: 34 studies

*Klotzbuecher et al. JBMR 2000;15:721*
Epidemiology of osteoporosis in the UK

- Approximately 250,000 fragility fractures annually in the UK
- Lifetime risk for 50 year old woman: 1:2 and 50 year old man 1:5
- Cost fractures: £1.7 billion in UK
- 70,000 hip fractures occur each year
  - Occupy 20% of orthopaedic beds
  - Totals up to 800,000 bed-days
  - 50% of hip fracture patients lose the ability to live independently
  - Up to 20% hip fracture patients die during the subsequent year as a result of fracture
Incidence rates of common osteoporotic fractures

Aetiology of fracture

Bone quantity and quality

High- or low-impact trauma
Osteoporosis is a condition for which prevention, rather than cure, is clearly desirable.
Preventive strategies for osteoporosis

A

Mean

Bone density
Target those with a low bone density

B

Bone density
Move entire distribution by intervening in everyone

The Diagnosis of Osteoporosis
DEXA: Definitions of osteoporosis

- **T scores** = standard deviation comparisons with the mean of a female population at peak bone mass
- **MINUS T score** indicates less than young adult mean
- Osteoporosis is defined as T score < -2.5 (WHO)
- Osteopenia is defined as T score < -1.0 (WHO)
- Z scores are age- and sex-matched reference scores
About DEXA

- Usually measured at spine (L1-L4) and proximal femur (axial and appendicular)
- Can be estimated throughout the skeleton
- Lumbar spine readings may be inaccurate in the presence of: scoliosis; osteophytes; extra-skeletal calcification; vertebral deformity
- Estimates areal bone mineral mass only – cannot take into account FALLS or structural or geometric factors
- Has been validated for estimating subsequent risk of fracture among men and women aged > 50 years (but not in those aged < 50 years)
Risk Factors for Low BMD in HIV-Infected Patients

Traditional
- Female gender
- Smoking
- Caucasian
- Family history
- Increasing age
- Alcohol

Secondary
- Decreased physical activity
- Decreased bone acquisition
- Amenorrhoea/premature menopause
- Opiates

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

Hypogonadism

Renal dysfunction

Malnutrition/low BMI

Medications
(e.g. glucocorticoids, anticonvulsants, anticoagulants)

Vitamin D deficiency

Bone
Mineral Density

Antiretroviral therapy
(e.g. PIs, NRTIs)

Viral factors
(e.g. p55 gag, gp120)

Immunologic effects
(e.g. cytokines - TNFα, IL-6)

HIV-related

Ageing

Diagram adapted from Glesby MJ. Clin Infect Dis 2003; 37(Suppl 2):S91–S95
Prevalence of Low BMD is Higher in HIV-Infected Patients

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of patients</th>
<th>Overall prevalence of low BMD, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+</td>
<td>HIV−</td>
</tr>
<tr>
<td><strong>Tebas et al 2000</strong></td>
<td>95</td>
<td>17</td>
</tr>
<tr>
<td><strong>Knobel et al 2001</strong></td>
<td>80</td>
<td>100</td>
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<tr>
<td><strong>Huang et al 2002</strong></td>
<td>15</td>
<td>9</td>
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<tr>
<td><strong>Loiseau-Peres et al 2002</strong></td>
<td>47</td>
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<tr>
<td><strong>Bruera et al 2003</strong></td>
<td>111</td>
<td>31</td>
</tr>
<tr>
<td><strong>Teichman et al 2003</strong></td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>Amiel et al 2004</strong></td>
<td>148</td>
<td>81</td>
</tr>
<tr>
<td><strong>Brown et al 2004</strong></td>
<td>51</td>
<td>22</td>
</tr>
<tr>
<td><strong>Dolan et al 2004</strong></td>
<td>84</td>
<td>63</td>
</tr>
<tr>
<td><strong>Madeddu et al 2004</strong></td>
<td>172</td>
<td>64</td>
</tr>
<tr>
<td><strong>Yin et al 2005</strong></td>
<td>31</td>
<td>186</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>884</td>
<td>670</td>
</tr>
</tbody>
</table>

Derived from Brown TT & Qaqish RB. AIDS 2006; 20:2165-2174
Bone mineral and HIV infection

• Generally small studies (<1000 patients in total)
• Grouped osteoporosis and osteopenia together (‘low bone mass’)
• Heterogeneous populations: infected males and females, different acquisition HIV
• Variable attention to confounding risk factors e.g. use of glucocorticoids, cigarette smoking

Osteopenia: 33-65% (OR 6.4, 95% CI 3.7-11.3)
Osteoporosis: 6-16% (OR 3.7, 95% CI 2.3-5.9)

Derived from Brown TT & Qaqish RB. AIDS 2006; 20:2165-2174
HIV and fracture

• Growing evidence that the increased prevalence of osteopenia and osteoporosis is associated with the expected effect on fracture rates in HIV patients

Triant VA et al. JCEM 2008;93:3499-3504
Grund et al, AIDS, 2009
FRAX® WHO Fracture Risk Assessment Tool

- Determines 10 year absolute risk of fracture
- Risk factors used in FRAX® calculation
  - Femoral neck T-score (BMD)
  - Age
  - Sex
  - Low body mass index
  - Previous low trauma fracture
  - Family history of hip fracture
  - Current cigarette smoking
  - Steroid exposure
  - Rheumatoid arthritis
  - Secondary causes of osteoporosis
  - High alcohol intake ($\geq 3$ units/day)

NOGG guidance algorithms

WITH A BMD MEASUREMENT

WITHOUT A BMD MEASUREMENT
Antiretroviral therapy and bone
Longitudinal studies of naïve patients commencing HAART

Lumbar spine BMD measured by DEXA

\[ \text{g/cm}^2 \]

![Graph showing the change in Lumbar spine BMD over time with two lines representing different treatments: NVP/Kaletra and Combivir/Kaletra. The graph indicates a statistically significant difference between the two treatments.}

\[ p<0.0001 \]

Van Vonderen et al, AIDS 2009
Longitudinal comparison of BMD among those using ART continuously vs. intermittently (SMART sub-study)

Spine (DXA)

- Intermittent
- Continuous

<table>
<thead>
<tr>
<th>Years</th>
<th>Change From Baseline (%)</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
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<td>3</td>
<td>0.5</td>
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<tr>
<td>4</td>
<td>2.1</td>
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</tbody>
</table>

- Est. diff.: 1.7
- P values: 0.003

Hip (DXA)

- Intermittent
- Continuous

<table>
<thead>
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<tr>
<td></td>
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<td>1.0</td>
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</tbody>
</table>

- Est. diff.: 1.3
- P values: 0.002
BMD: Effect of ART

Truvada reduces BMD more than Abacavir: Results of a 96 week trial in ART-experienced patients

Right hip T score

P<0.0001  P<0.0001

Spine T score

P=0.002  P=0.023

Cooper D et al. 16th CROI 2009. Abstract #576
Long term cART

• Bone loss appears to slow beyond 2 years after commencement of cART
• Rate of bone loss after 96 months cART still greater than that seen in non-HIV controls (unmatched participants in long term follow-up studies)
• BMD fell by mean -1.01% at lumbar spine and -1.56% at hip in HIV cases as compared with changes of +0.04% spine and -0.31% hip in HIV-negative patients (significantly greater at spine but not hip)
• People with higher baseline CD4+ counts lost less BMD on cART commencement

Management of low bone mass in HIV

- Cochrane review
- 3 RCTs Alendronate
- Heterogeneity!!
- Alendronate, calcium and vitamin D well-tolerated and improved BMD after 1 year vs. calcium/D alone\(^1\)
- Two studies showing that Zoledronate infusions increase bone mass\(^2,3\)

Lin & Rieder, 2007

Huang et al, AIDS 2009 and Bolland et al, JCEM, 2007
Side effects of bisphosphonates

- Osteonecrosis of the jaw
- Oesophageal cancer
- Atypical femoral shaft fractures

- All RARE in people taking ‘osteoporosis’ treatment levels of bisphosphonates (exaggerated by use in cancer for bone metastases)

- Drug holiday?
- 5 years therapy then re-assess DEXA/risk factors
Other drugs for osteoporosis

- HRT
- Raloxifene
- Strontium ranelate
- Denosumab
- Parathyroid hormone (teriparatide)

Do work with your local osteoporosis specialist.
Treatment of low bone mass in HIV

- Always check vitamin D status (DXA does not separate osteomalacia) and supplement if deficient
- Calcium and vitamin D should be prescribed in anybody treated with bisphosphonates
- No evidence as yet that bisphosphonates or any other treatment modality prevent fractures in HIV patients
Conclusion

- Osteoporosis is yet another comorbidity
- Fragility fractures occur age > 60 years in women and > 70 years in men in general population
- Falls
- People with one fragility fracture are at the GREATEST risk of others
- Vertebral osteoporosis usually sub-clinical
- Effects of cART recognised but probably should not unduly influence decision-making except in unusual cases
- Bisphosphonates are cheap but NOT risk-free!
- There are expanding options for the treatment of osteoporosis
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