Antiretroviral therapy and its effect on bones

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Disclosures

• Research funding from NIH (NIAID, NICHD)
• Consultant for Gilead and Abbott
Outline

• Epidemiology of bone loss and fractures in HIV-infected individuals

• Pathophysiology and risk factors

• Screening and treatment recommendations

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

- Manifest clinically by 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
Decrease in BMD at the spine occurs by 24 weeks after initiation

Decrease in BMD at the hip occurs by 48 weeks
BMD loss with ART-initiation: ~2–6% within 1–2 years

<table>
<thead>
<tr>
<th>Author, yr</th>
<th>N</th>
<th>wks</th>
<th>ART</th>
<th>Spine</th>
<th>Hip</th>
<th>Total BMD</th>
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</thead>
<tbody>
<tr>
<td>Gallant, 2004</td>
<td>602</td>
<td>144</td>
<td>TDF/3TC+EFV</td>
<td>-2.2%*</td>
<td>-2.8%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>D4T/3TC+EFV</td>
<td>-1.0%</td>
<td>-2.4%</td>
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<tr>
<td>Brown, 2009</td>
<td>106</td>
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<td>71</td>
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<td>PI non-PI</td>
<td>-4.4 to -5.1%*</td>
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<td></td>
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<td>385</td>
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<td>ABC/3TC+EFV</td>
<td>-1.9%</td>
<td>-1.6%</td>
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<td>McComsey 2011</td>
<td>269</td>
<td>96</td>
<td>TDF/FTC</td>
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<tr>
<td></td>
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<td></td>
<td>ATV/r</td>
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<td></td>
<td></td>
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<td>EFV</td>
<td>-1.7%</td>
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Greater decline in BMD with tenofovir-containing regimens

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BMD is stable in younger HIV+ men on established ART

Bone metabolism in HIV+ women

**Premenopausal**
- 2700 HIV+ and 900 HIV- women in 5 US cities (WIHS)
  - Median age=39
  - 60% African American
  - BMI: 28–30 kg/m²
  - 70% on ART

**Postmenopausal**
- 95 HIV+ and 97 HIV-postmenopausal cohort from NYC
  - Median age=57
  - 35% African American, 60% Hispanic
  - BMI: 28–30 kg/m²
  - 80% on ART
Bone density lower in HIV+ than HIV- PM women

• Yin et al. JAIDS, 2010; Yin et al JCEM, 2010

\[ P=0.002 \quad P=0.001 \quad P=0.03 \quad P=0.42 \]

<table>
<thead>
<tr>
<th>LS</th>
<th>TH</th>
<th>FN</th>
<th>1/3R</th>
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<tbody>
<tr>
<td>0.8</td>
<td>0.55</td>
<td>0.3</td>
<td>0.05</td>
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<tr>
<td>0.2</td>
<td>0.45</td>
<td>0.7</td>
<td>0.95</td>
</tr>
<tr>
<td>( P=0.09 )</td>
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</tbody>
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Premenopausal

- HIV- (N=68)
- HIV+ (N=100)

Postmenopausal

- HIV- (N=97)
- HIV+ (N=95)

Bone loss greater in postmenopausal than premenopausal HIV+ women

\begin{align*}
\text{Premenopausal} & \quad \text{Postmenopausal} \\
\text{HIV- (N=68)} & \quad \text{HIV- (N=58)} \\
\text{HIV+ (N=100)} & \quad \text{HIV+ (N=82)} \\
\end{align*}

Yin et al. JAIDS, 2010; Yin et al JCEM, 2010; Yin et al JCEM, 2011
Higher bone turnover markers & TNFα levels in postmenopausal HIV+ women

Premenopausal
- HIV- (N=68)
- HIV+ (N=100)

Postmenopausal
- HIV- (N=58)
- HIV+ (N=82)

Yin et al JAIDS, 2010; Yin et al JCEM, 2010

High Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)

- Acquires 3-D stack of 116 high resolution CT slices at distal radius and tibia
- ~ 3 min scan time
- Low radiation (< 3 µSv)
- Reproducibility:
  - density: 0.7 to 1.8%
  - structure: 1.2 - 7.4%
Tibial cortical thickness 12% lower in HIV+ postmenopausal women

![Graph showing tibial cortical thickness and bone mineral density (BMD) comparing HIV+ and HIV- groups.]

HIV- Age=61

HIV+ Age=61

Yin et al., *CTI*, 2013

Hypothetical evolution of bone mass with HIV infection and ART

![Graph showing hypothetical evolution of bone mass with HIV infection and ART.]

Does early HIV infection affect “peak bone mass” and microarchitecture?

Hypothetical evolution of bone mass with HIV infection early in life

Hypothetical evolution of bone mass with HIV infection early in life

Peak Bone Mass in men infected with HIV early in life

<table>
<thead>
<tr>
<th></th>
<th>HIV+ Perinatally infected (N=15)</th>
<th>HIV+ Infected during adolescence (N=15)</th>
<th>HIV- men (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21.9 ± 0.4</td>
<td>23.1 ± 0.3</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>Tanner 5</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Race/ethnicity*</td>
<td>73% AA 27% Hispanic</td>
<td>66% AA 34% Hispanic</td>
<td>30% AA 70% Hispanic</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25 ± 1</td>
<td>26 ± 1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>Truncal fat %</td>
<td>24 ± 1</td>
<td>19 ± 1</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>Smoking %</td>
<td>20%</td>
<td>67%</td>
<td>20%</td>
</tr>
<tr>
<td>Alcohol %</td>
<td>60%</td>
<td>87%</td>
<td>73%</td>
</tr>
<tr>
<td>Illicit drug %</td>
<td>29%</td>
<td>80%</td>
<td>27%</td>
</tr>
</tbody>
</table>


Yin et al., CROI 2013
Areal BMD (g/cm²) by Z scores

HRpQCT images of tibia in 24 year old African American men

Yin et al., CROI 2013
Percent difference in HRpQCT measures between HIV+ and HIV- at radius and tibia

Yin et al., CROI 2013

Individual Trabeculae Segmentation (ITS): plates (green) vs rods (red)
% difference in Individual Trabeculae Segmentation (ITS) and micro Finite Element Analysis (μFEA)

Is fracture risk increased with HIV-infection or ART?
Higher prevalence of fracture in HIV+

Female

Male

Higher incidence of fractures in HIV+

Shiau et al., AIDS, 2013
### Higher fracture incidence with traditional risk factors

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Cohort, sex, median age</th>
<th>Cohort, N</th>
<th>Unadjusted incidence per 1000 person-yrs</th>
<th>Predictors</th>
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<td>Hansen, 2011</td>
<td>Denmark, M&amp;W Age=37</td>
<td>4455 HIV+ 851 HIV/HCV 26,530 controls</td>
<td>7.4 (fragility) 17.7 4.8</td>
<td>HAART exposure, HCV, smoking, co-morbidities</td>
</tr>
<tr>
<td>Hasse, 2011</td>
<td>Swiss, M&amp;W Age=45</td>
<td>8444 HIV+</td>
<td>1.6 (fragility)</td>
<td>Age&gt;65, osteoporosis diagnosis</td>
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<tr>
<td>Collin, 2009</td>
<td>ANRS, M&amp;W Age=36</td>
<td>1281 HIV+</td>
<td>3.3 (all Fx)</td>
<td>HCV, ETOH</td>
</tr>
<tr>
<td>Yin, 2011</td>
<td>ACTG, M&amp;W Age=39</td>
<td>3398 HIV+</td>
<td>3.8 (all Fx)</td>
<td>Within 0-2 yrs of ART initiation, HCV, smoking</td>
</tr>
<tr>
<td>Bedimo, 2012</td>
<td>VA, M&amp;W Age=45</td>
<td>55,660 HIV+ (32439 HAART era)</td>
<td>4.1 (fragility)</td>
<td>TDF exposure in HAART era patients</td>
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### Higher fracture incidence with ART

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Higher fracture incidence early in ART initiation: ACTG ALLRT

Outline

• Epidemiology of bone loss and fractures in HIV-infected individuals

• Pathophysiology and risk factors

• Screening and Treatment recommendations
Multifactorial etiology of bone loss in HIV

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

Host

Virus

ART

Direct effect of viral proteins on bone cells
Immune activation

Direct effect on bone cells
Inadequate mineralization
Immune reconstitution

Bone Remodeling Sequence

- Osteoclast
- Osteoblast
- Resting Bone Surface
- “Activation”
- Resorption
- Reversal
- Bone Formation
- Mineralization

LC = Lining Cells  CL = Cement Line  OS = Osteoid  BRU = Bone Remodeling Unit

~3 WEEKS  ~3 MONTHS
Immune activation and increased bone resorption > formation

HIV

↑ Apoptosis

T Cell Activation

↑ TNF-α

↑ IL-6

↑ RANKL

Osteoclast Precursors

Bone Resorption

N-telopeptide
C-telopeptide

Osteoblast Precursors

Bone Formation

Role of circulating calcifying cells in the bone-vascular axis

Fadini et al, Circulation, 2012
Circulating osteogenic precursor studies

- Circulating osteoblast precursors can be sorted from PBMCs using antibodies against osteocalcin (OCN) with flow cytometry
  - OCN+ /CD34- cells in culture expressed osteoblast markers (Runx2, ALP, Osterix) and formed mineralized nodules*

- Refined process by first gating out lineage cells (LIN) then identifying osteogenic cells with antibodies against OCN, Runx2 and CD34
  - Compared proportions of mature cells (OCN+Runx2+CD34-) and telomere lengths between HIV+ and HIV- groups

*Rubin et al JCEM 2010

Replicative senescence of osteoblast precursors with HIV infection early in life

<table>
<thead>
<tr>
<th></th>
<th>Perinatal-infection (N=15)</th>
<th>Infection during Adolescence (N=15)</th>
<th>HIV-uninfected (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIN- / OCN+ /RUNX2+ (%)</td>
<td>0.15±0.1^a</td>
<td>0.22±0.1^b</td>
<td>0.39±0.3</td>
</tr>
<tr>
<td>CD34- (% of LIN-/OCN+/RUNX2+)</td>
<td>56±27^a,c</td>
<td>73±11</td>
<td>67±7</td>
</tr>
<tr>
<td>Telomere length (T/S ratio)</td>
<td>2.3±0.2^a,c</td>
<td>2.5±0.2</td>
<td>2.6±0.4</td>
</tr>
</tbody>
</table>

^a Perinatal infection vs HIV-uninfected controls, p<0.05
^b Adolescent infection vs HIV-uninfected controls, p<0.05
^c Perinatal vs adolescent infection, p<0.05
**PI effect on osteoclasts & osteoblasts**

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<tr>
<th>Protease Inhibitor</th>
<th>Osteoclast</th>
<th>Osteoblast</th>
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<tbody>
<tr>
<td></td>
<td>Fakruddin</td>
<td>Wang</td>
</tr>
<tr>
<td>ritonavir</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>saquinavir</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>indinavir</td>
<td>→</td>
<td>→</td>
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<tr>
<td>nelfinavir</td>
<td>→</td>
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<tr>
<td>lopinavir</td>
<td>→</td>
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<tr>
<td>amprenavir</td>
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**Bone loss with tenofovir**

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<th>BTMs</th>
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<td>Switch Studies</td>
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<td>Martin, 2009</td>
<td>357</td>
<td>96</td>
<td>AZT/3TC to TDF/FTC ABC/3TC</td>
<td>8.5/100py (OPO/OPE)*</td>
<td>4.4/100py</td>
<td>↑</td>
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<tr>
<td>Cotter, 2013</td>
<td>53</td>
<td>48</td>
<td>AZT/3TC to TDF/FTC AZT/3TC</td>
<td>-1.5%</td>
<td>-1.7%</td>
<td>-0.39</td>
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<tr>
<td>Bloch, CROI 2012</td>
<td>37</td>
<td>48</td>
<td>TDF to RAL</td>
<td>+3.0%</td>
<td>+2.1 to +2.7%*</td>
<td>↓</td>
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<tr>
<td>PreP</td>
<td></td>
<td></td>
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<td>Liu, 2011</td>
<td>184</td>
<td>104</td>
<td>TDF placebo</td>
<td>-0.7%</td>
<td>-0.8 to -1.9%*</td>
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<td>Mulligan, 2011</td>
<td>503</td>
<td>24</td>
<td>TDF/FTC placebo</td>
<td>-0.7 to 1.0%*</td>
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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**
  - Not all due to vitamin D deficiency; impact on BMD 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)

Osteomalacia

- **Results from inadequate mineralization of osteoid**
  - Prolonged, severe vitamin D deficiency
  - Very low calcium intake
  - Hypophosphatemia

- **Clinical manifestation**
  - Bone pain (long bones and ribs)
  - Proximal muscle weakness
  - Spontaneous fractures

- **Treatment requires long-term supplementation and removal of offending agent**
Summary

- BMD decreases 2–6% with ART initiation
  - Most bone loss in first 6–12 months then stabilizes
  - Greater loss with tenofovir, certain PI’s and AZT
- BMD stable in younger HIV+ men and women on established ART
- Rates of fragility and non-fragility fractures higher with HIV+, especially with HCV, and perhaps certain ARVs
- Fracture incidence still low (3–5 per 1000py) but will undoubtedly increase with aging of our HIV population

Outline

- Epidemiology of bone loss and fractures in HIV-infected individuals
- Pathophysiology and risk factors
- Screening and Treatment recommendations
Bone Mineral Density (g/cm$^2$)

<table>
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<tr>
<th>Age (years)</th>
<th>Fracture per 1000 person-years</th>
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<tr>
<td>&gt;1.0</td>
<td>160</td>
</tr>
<tr>
<td>0.90 - 0.99</td>
<td>80</td>
</tr>
<tr>
<td>0.80 - 0.89</td>
<td>60</td>
</tr>
<tr>
<td>0.70 - 0.79</td>
<td>40</td>
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<tr>
<td>0.60 - 0.69</td>
<td>20</td>
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<tr>
<td>&lt;0.60</td>
<td>0</td>
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</tbody>
</table>

Fracture per 1000 person-years vs. Bone Mineral Density (g/cm$^2$)


DXA screening for osteoporosis

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>DXA indicated</td>
<td>Women $&gt;$65 Men $&gt;$70</td>
<td>PM women $&gt;$65</td>
<td>Men and women $&gt;$50</td>
</tr>
<tr>
<td>DXA indicated with following risk factors (partial list)</td>
<td>$&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>Fracture Hypogonadal Glucocorticoid</td>
</tr>
</tbody>
</table>

DXA indicated with following risk factors (partial list)
Work up and treat secondary causes of osteoporosis

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Lab test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>25-hydroxyvitamin D</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>iPTH, Ca, PO4</td>
</tr>
<tr>
<td>Renal phosphate wasting in patients on tenofovir</td>
<td>Fractional excretion of phosphate</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>TSH</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Morning free testosterone Menstrual history, FSH</td>
</tr>
<tr>
<td>Idopathic hypercalciuria</td>
<td>24-hour urinary calcium</td>
</tr>
</tbody>
</table>

Who to treat (NOF, 2008)

- Hip or vertebral fractures
- DXA
  - T-scores < -2.5 at femoral neck, total hip or lumbar spine
  - T-score between -1.0 and -2.5 and 10-yr probability fracture by FRAX®
    - > 3% at the hip
    - > 20% for any osteoporosis-related fracture
Treatment Options

- **Bisphosphonates** (inhibits osteoclast resorption)
  - Reduces vertebral & non-vertebral Fx by 25-50% in non-HIV
  - 6 RCT in HIV+ in combination with Ca and VitD

<table>
<thead>
<tr>
<th>Author, yr (N)</th>
<th>T score</th>
<th>Med (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>+4.0% vs +3.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Monds, 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>Rosenberg, 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>

- **Teriparatide** (PTH analogue, stimulates osteoblasts)
- **Denosumab** (monoclonal RANKL antibody)
- **Estrogen and Raloxifene** in women

- **Bisphosphonates** (Adverse events)
  - Osteonecrosis of the jaw (<1 case per 100,000 py of exposure)
  - Sub-trochanteric fractures or atypical femoral shaft fractures (rare if < 5yrs of use)
  - FDA expert panel recommends consideration of drug interruption after 5 yrs
Summary

• Lifestyle modification recommended for everyone
• Vitamin D screening is controversial
  – indicated in patients with high fracture risk: osteoporosis, fracture or falls
  – Studies are needed define optimum 25-OHD levels, and use supplementation in specific circumstances (ART initiation and with certain antiretrovirals)
• DXA screening for age > 50, if available
• Consider avoidance of TDF for ART initiation and switching off TDF to RAL in patients with high fracture risk (previous fracture or osteoporosis)

Areas for research

• Epidemiology
  – Bone acquisition in perinatally-infected children in resource-constrained settings
  – Acquisition of peak bone mass in young adults
  – Falls and fractures in elderly HIV+
• Pathophysiology
  – Bone loss with ART initiation, mechanisms of ARVs
  – HCV co-infection
• Management
  – Vitamin D and calcium supplementation (dose, indications, outcomes)
  – Use of bone turnover markers and other predictors for fracture
  – Validation of FRAX or other fracture prediction algorithms
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