Bone Health and Vitamin D Deficiency in HIV+ patients

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Vitamin D deficiency can be detected and readily managed.

25(OH)D Vitamin D status in a London cohort:
- 91.3% <30 µg/L (suboptimal)
- 73.5% <20 µg/L (deficient)
- 34.8% <10 µg/L (severely deficient)

Table 1. Vitamin D deficiency in HIV-positive versus HIV-negative patients.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Location</th>
<th>Study type</th>
<th>Study population</th>
<th>Control population</th>
<th>Prevalence of vitamin D deficiency (cutoff)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeyemi et al. [6]</td>
<td>USA</td>
<td>Cross-sectional</td>
<td>1268 HIV-positive women (WIHS)</td>
<td>510 HIV-negative women (WIHS)</td>
<td>60% (&lt;20 ng/ml) 72%</td>
</tr>
<tr>
<td>Dao et al. [5]</td>
<td>USA</td>
<td>Cross-sectional</td>
<td>672 HIV-positive adults (SUN)</td>
<td>US general population (NHANES)</td>
<td>70% (&lt;30 ng/ml) 79%</td>
</tr>
<tr>
<td>Stein et al. [12]</td>
<td>USA</td>
<td>Cross-sectional</td>
<td>89 HIV-positive women</td>
<td>95 HIV-negative women</td>
<td>~49% (&lt;20 ng/ml) ~46%</td>
</tr>
</tbody>
</table>

EFV, efavirenz; NVP, nevirapine; RTV, ritonavir; VDD, vitamin D deficiency; VL, viral load.

AIDS 2010; 24:1923–1928
Low bone mass is not easily detected. Vitamin D deficiency may contribute to low bone mass.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Patients (n)</th>
<th>Reduced BMD, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+</td>
<td>HIV-</td>
</tr>
<tr>
<td>Amiel et al 2004</td>
<td>148</td>
<td>81</td>
</tr>
<tr>
<td>Brown et al 2004</td>
<td>51</td>
<td>22</td>
</tr>
<tr>
<td>Bruera et al 2003</td>
<td>111</td>
<td>31</td>
</tr>
<tr>
<td>Dolan et al 2004</td>
<td>84</td>
<td>63</td>
</tr>
<tr>
<td>Huang et al 2002</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Knobel et al 2001</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Loiseau et al 2002</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Madeddu et al 2004</td>
<td>172</td>
<td>64</td>
</tr>
<tr>
<td>Tebas et al 2000</td>
<td>95</td>
<td>17</td>
</tr>
<tr>
<td>Teichman et al 2003</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Yin et al 2005</td>
<td>31</td>
<td>186</td>
</tr>
</tbody>
</table>

(a) Study

<table>
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<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
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<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>Madeddu (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>

AIDS 2006; 20:2165-74
Low bone mass may contribute to fracture risk. Vitamin D deficiency may contribute to low bone mass. Fractures may be more common.
Vitamin D deficiency can be detected. Vitamin D deficiency can be readily managed. Vitamin D deficiency may contribute to low bone mass. Low bone mass may contribute to fracture risk.

Vitamin D 400-2000 IU/day

BMD
Low bone mass is common
Low bone mass is not easily detected

DXA

Vitamin D deficiency may contribute to low bone mass

FRAX

Fractures
Fractures may be more common
Low bone mass may contribute to fracture risk

25(OH)D
Vitamin D deficiency is common
Vitamin D deficiency is associated with:

- Cardiovascular disease
- Cancer
- Impaired immunity
- HIV disease progression and MTCT

Vitamin D deficiency can be detected

Vitamin D deficiency can be readily managed

Vitamin D 400-2000 IU/day

Low bone mass is common

Low bone mass may contribute to low bone mass

Low bone mass is not easily detected

Vitamin D deficiency may contribute to low bone mass

Low bone mass may contribute to fracture risk

Fractures may be more common

Fractures

BMD

DXA

FRAX
Guidelines for vitamin D testing

**US Endocrine Society**
- If at risk of VDD
  - Black ethnicity
  - “AIDS medications”

**EACS**
- If at risk of VDD
- If diagnosed with
  - Osteomalacia
  - Osteopenia
  - Osteoporosis

**Risk factors for low vitamin D status in HIV positive patients**

*HIV parameters:*
- CD4 cell count < 200 cells/mm³
- Current use of cART
- Undetectable / detectable HIV RNA
- Longer time since HIV diagnosis
- IV drug use

*Non-HIV parameters:*
- Black or Hispanic ethnicity
- Reduced UV exposure / winter season
- Increased BMI / low exercise level
- Hypertension
- Higher eGFR

# Vitamin D deficiency and cART

**Table 1. Risk factors for severe vitamin D deficiency [25(OH)D <10 μg/l] in HIV patients.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>(a) All patients (N = 1073)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black ethnicity</td>
<td>3.1 (2.3–4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.4 (1.1–1.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Winter season</td>
<td>2.0 (1.6–2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 cell nadir &lt;200 cells/μl</td>
<td>1.7 (1.3–2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current HIV RNA ≥400 copies/ml</td>
<td>0.7 (0.5–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Current cART use</td>
<td>1.6 (1.1–2.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(b) Patients on cART (N = 843)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black ethnicity</td>
<td>2.7 (2.0–3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.4 (1.04–1.8)</td>
<td>0.03</td>
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<tr>
<td>Winter season</td>
<td>2.2 (1.6–2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 cell nadir &lt;200 cells/μl</td>
<td>1.5 (1.1–2.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Current EFV use</td>
<td>1.9 (1.4–2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current NVP use</td>
<td>0.7 (0.6–1.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Current PI use</td>
<td>0.7 (0.5–0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Current TDF use</td>
<td>0.8 (0.6–1.0)</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

cART, combination antiretroviral therapy; CI, confidence interval; EFV, efavirenz; NS, not significant; NVP, nevirapine; OR, odds ratio; PI, protease inhibitor; TDF, tenofovir.
Efavirenz and vitamin D biosynthesis

Skin
- Pro-vitamin D₃
- Pre-vitamin D₃
- Vitamin D₃ (cholecalciferol)

Diet/supplements
- Vitamin D₂ (ergocalciferol)
- Vitamin D₃ (cholecalciferol)

Liver
- Vitamin D (D₂/D₃)
- 25(OH)D (Calcidiol)

Kidney
- 25(OH)D
- 1,25(OH)₂ D (Calcitriol)

Key enzymes
- 25-hydroxylases (CYP27A, CYP2R1)
  EFV reduces CYP2R1
- 1α-hydroxylase (CYP27B1)

Trans-activation of vitamin D-responsive elements in the regulatory region of target genes:
- Bone mineralization
- Calcium absorption
- Immune modulation

Degradation
- 25(OH)D
- 1,25(OH)₂ D
- 24,25(OH)₂ D
- 1,24,25(OH)₃ D

Calcitroic acid

24-hydroxylase (CYP24)
  EFV induces CYP24
VDD, cART and $1,25(OH)_2D$

- The relationship between $25(OH)D$ and $1,25(OH)_2D$ levels is not linear.

- Two studies observed no relationship, or a weak positive correlation ($r^2=0.19$), between $25(OH)D$ and $1,25(OH)_2D$.

- Progressively lower $1,25(OH)_2D$ levels in patients with normal, insufficient and deficient $25(OH)D$ status:
  - $1,25(OH)_2D$ levels were unaffected by NNRTI exposure.
  - Tenofovir use was associated with increased $1,25(OH)_2D$ levels.

AIDS Res Hum Retroviruses 2009; 25:9–14
AIDS 2010; 24: 1127-34
Most studies have reported a **negative correlation** between 25(OH)D and PTH levels ($r^2 = 0.31-0.48$)

- **Tenofovir** has been associated with **secondary hyperparathyroidism** in cross-sectional and longitudinal studies.

- TFV-associated hyperparathyroidism appears largely restricted to patients with reduced 25(OH)D levels (<20–30 ng/mL).

- Hyperparathyroidism in HIV-positive patients is not restricted to those taking tenofovir (or those with VDD).

VDD, cART and BMD

- VDD / lower 25(OH)D levels
  - not associated with BMD in 2 studies
  - associated with lower total hip BMD in 1 study
  - associated with greater reductions in femoral neck BMD during follow up

- Higher PTH levels have been associated with greater reductions in BMD

VDD, cART and BMD

- VDD / lower 25(OH)D levels
  - not associated with BMD in 2 studies
  - associated with lower total hip BMD in 1 study
  - associated with greater reductions in femoral neck BMD during follow up

- Higher PTH levels have been associated with greater reductions in BMD

- Exposure to cART (OR 2.5 [1.8, 3.7]) and PIs (OR 1.5 [1.1, 2.0]) associated with low BMD

- Several antiretrovirals including tenofovir, didanosine, and PIs have been associated with greater reductions in BMD in cohort studies

- Continuous versus intermittent cART was associated with greater reductions in BMD (SMART)

- A switch to TFV/FTC is associated with a reduction and to ABC/3TC with improvement in BMD (STEAL)

BMD in the SMART study

Grund, AIDS 2009; 23: 1519-29
BMD in the STEAL study

- Hip
  - ABC/3TC: P<0.0001
  - TDF/FTC: P<0.0001

- LS
  - ABC/3TC: P=0.002
  - TDF/FTC: P=0.023

Cooper et al, 16th CROI 2009
VDD, cART and BMD

AIDS 2009; 23: 1367-76

J Infect Dis 2011; 203:1791–1801
VDD, cART and fractures

• Incidence of fractures in HIV-positive patients:
  – 0.03-0.9/100py in predom. men
  – 1.8/100py in women

• 3 studies reported ≈60% higher fracture rate in HIV+ patients

• 3 other studies found similar fracture rates after adjustment for potential confounders

• The majority of fractures were traumatic rather than fragility

• None of these studies reported data on vitamin D status

• cART per se has not been associated with an increased incidence of fractures

• Somewhat higher fracture rates have been reported with:
  – continuous vs. intermittent cART
  – with Tenofovir and/or PI/r

• Other factors associated with fractures in HIV-positive patients include older age, white ethnicity, low body mass index, smoking, alcohol abuse, low CD4 cell count, AIDS, diabetes, hepatitis C co-infection, use of proton pump inhibitors or corticosteroids, and osteoporosis on dual X-ray absorptiometry (DXA)

Vitamin D supplementation

- Vitamin D supplementation (800–2800 IU/day) in HIV-positive patients with suboptimal 25(OH)D levels may reduce PTH levels

- Small pilot RCT of vitamin D (2000/1000 IU qd) for 48w
  - Normalisation of 25(OH)D levels (from 26 to 80–102 nmol/L)
  - Transient improvement in 1,25(OH)\(_2\)D and PTH
  - No effects on BMD or inflammatory markers

Vitamin D and calcium supplementation

- Vitamin D 200 IU and CaCO$_3$ 500 mg
  - Hip and lumbar spine BMD increased by 1.1-1.3% at 48w

- Vitamin D 400 IU and CaCO$_3$ 1000 mg
  - Hip and lumbar spine BMD increased by 1.3-2% at 48w
  - Bone resorption was not reduced with Ca/Vitamin D alone

AIDS 2007; 21:2473–2482
Summary

- Vitamin D deficiency, (secondary) hyperparathyroidism and low BMD are common in HIV-positive patients
  - Efavirenz is associated with a reduction in 25(OH)D levels
  - cART is associated with low BMD
  - Tenofovir is associated with secondary hyperparathyroidism, greater initial reductions in BMD, and possibly with fractures

- The clinical significance of reduced BMD remains unclear, especially in younger patients

- While the incidence of fractures may be increased, the contribution of low BMD and vitamin D deficiency to these fractures is uncertain

- Limited data on vitamin D supplementation in HIV-positive patients have shown transient, beneficial effects on PTH but no effects on BMD
My personal view

- With the majority of patients <50 years, the benefits of a universal vitamin D deficiency “test and treat” strategy in terms of fracture prevention are questionable (especially if vitamin D is given without daily calcium supplements*)

  * Cochrane Database Syst Rev 2009:CD000227

- To base decisions regarding vitamin D testing and supplementation on fracture risk rather than the risk of vitamin D deficiency

- To use the FRAX score to estimate the risk of skeletal complications, and to optimise vitamin D status in those at increased risk of fractures
Three random patients

- 35 yrs
- Male
- White
- CD4 157
- VL 83,000
- HBV/HCV-

- 45 yrs
- Female
- Black
- CD4 257
- VL 83,000
- HBV/HCV-

- 55 yrs
- Male
- White
- CD4 357
- VL 83,000
- HBV/HCV-
### Three random patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>Smoking Status</th>
<th>BP</th>
<th>LDL-C</th>
<th>DM</th>
<th>Creat</th>
<th>PCR</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 yrs</td>
<td>Male</td>
<td>White</td>
<td>Smoker</td>
<td>145/76</td>
<td>4.6</td>
<td>No</td>
<td>108</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>45 yrs</td>
<td>Female</td>
<td>Black</td>
<td>Non-smoker</td>
<td>134/85</td>
<td>3.6</td>
<td>No</td>
<td>108</td>
<td>65</td>
<td>26</td>
</tr>
<tr>
<td>55 yrs</td>
<td>Male</td>
<td>White</td>
<td>Non-smoker</td>
<td>148/94</td>
<td>5.1</td>
<td>No</td>
<td>108</td>
<td>35</td>
<td>28</td>
</tr>
</tbody>
</table>
Cardiovascular risk

- 35 yrs
- White male
- Smoker
- BP 145/76
- LDL-C 4.6
- No DM

- 45 yrs
- Black female
- Non-smoker
- BP 134/85
- LDL-C 3.6
- No DM

- 55 yrs
- White male
- Non-smoker
- BP 148/94
- LDL-C 5.1
- No DM

10 year CHD risk:
- 9%
- 3%
- 18%
<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>Smoking Status</th>
<th>Blood Pressure</th>
<th>LDL-C</th>
<th>Diabetes</th>
<th>eGFR</th>
<th>PCR</th>
<th>BMI</th>
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<tr>
<td>35</td>
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What’s the fracture risk (FRAX)?

- 2.5% (0.1%)
- 2.6% (0.1%)
- 3.0% (0.2%)
Fracture risk

- 35 yrs
- White male
- Smoker
- BP 145/76
- LDL-C 4.6
- No DM
- eGFR 67 mL/min
- PCR 25
- BMI 24

- 45 yrs
- Black female
- Non-smoker
- BP 134/85
- No DM
- eGFR 58 mL/min
- PCR 65
- BMI 26

- 55 yrs
- White male
- Non-smoker
- BP 148/94
- No DM
- eGFR 62 mL/min
- PCR 35
- BMI 28

What’s the fracture risk (FRAX)?
2.5% (0.1%)  2.6% (0.1%)  3.0% (0.2%)
### Risk of Fracture (FRAX)

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Smoking Status</th>
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</tr>
</tbody>
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The DXA shows osteopenia (T score -1.3)

What’s the fracture risk (FRAX)?

- **2.5% (0.1%)**
- **2.6% (0.1%)**
- **3.0% (0.2%)**
- **3.7% (0.7%)**
- **3.4% (0.3%)**
- **4.3% (0.6%)**
• 35 yrs
• White male
• Smoker
• BP 145/76
• LDL-C 4.6
• No DM
• eGFR 67 mL/min
• PCR 25
• BMI 24

• 45 yrs
• Black female
• Non-smoker
• BP 134/85
• LDL-C 3.6
• eGFR 58 mL/min
• PCR 65
• BMI 26

• 55 yrs
• White male
• Non-smoker
• BP 148/94
• LDL-C 5.1
• eGFR 62 mL/min
• PCR 35
• BMI 28

What’s the fracture risk (FRAX)? (intervention threshold)

2.5% (0.1%)  2.6% (0.1%)  3.0% (0.2%)
3.7% (0.7%)  3.4% (0.3%)  4.3% (0.6%)
5.5% (1%)  6% (1%)  10% (1.5%)

The DXA shows osteopenia (T score -1.3)