Zoledronic acid is superior to TDF-switching for increasing bone mineral density in HIV-infected adults with osteopenia: a randomised trial

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Potential conflicts of interest

The Alfred has received reimbursement for my involvement in Advisory Boards for Gilead, Viiv Healthcare, Merck Sharp & Dohme
ZOL vs TDF switch for low BMD

TDF lowers BMD and increases fracture risk

TDF switching and bisphosphonates both improve BMD – unknown which is superior

NRTI to abacavir or TDF

Zoledronic acid vs. Placebo

McComsey et al, AIDS 2011; Sax et al, CROI 2015
Borges et al, Clin Infect Dis 2017

Martin et al, CID 2009; Huang et al, AIDS 2009
ZOL vs TDF switch for low BMD

Hypothesis and primary outcome

- **Hypothesis**
  - bisphosphonate therapy with zoledronic acid (ZOL) will increase BMD more effectively over 2 years than switching TDF to another antiretroviral drug

- **Primary outcome**
  - Mean % change in lumbar spine (L1-L4) BMD by DXA – spine chosen in preference to hip as:
    - measurement of lumbar spine BMD and hip BMD have similar variability, but
    - lumbar spine BMD responds more rapidly to pharmaceutical intervention than hip BMD

ZOL vs TDF switch for low BMD

Inclusion criteria

- Age ≥18 years
- Stable ART including TDF for preceding 6+ months
- HIV RNA <50 copies/mL for preceding 3+ months
- eGFR >60ml/min
- T-score ≤ -1.0 at spine (L1–L4) or left femoral neck by DXA (i.e. osteopenia)
- No prior virological failure, resistance, intolerance or contraindication to proposed switch ARV drug (including HLA-B*5701+ or prior CVD for abacavir)
ZOL vs TDF switch for low BMD

Exclusion criteria

- Prior bisphosphonate
- On TDF for previously active chronic HBV
- Requiring therapy for low BMD (e.g. fragility fracture)
- Secondary causes of osteoporosis
  - hypogonadism (low total testosterone/oestrogen and LH>25% above ULN)
  - hypothyroidism (low T4 and elevated TSH)
  - hyperparathyroidism (elevated PTH / Ca)
  - inhaled fluticasone in a patient on ritonavir
  - prednisolone ≥7.5mg/day or equivalent
- Contra-indication to ZOL (hypocalcaemia, uveitis, recent or planned dental surgery)
- Concurrent use of any nephrotoxic drug
- Breast-feeding or pregnancy

ZOL vs TDF switch for low BMD

Study design

- Randomised, open-label, 2-year trial
- Eligible patients allocated to either
  - ZOL 5mg IVI at M0 and M12 and continue TDF
  - Switch TDF to alternate ARV (no ZOL)
- Stratification by
  - radiology facility
  - T-score (< or ≥ -2.0)
ZOL vs TDF switch for low BMD

Study Design

- Calcium 1500mg/day for all participants
- Vitamin D replacement to promote BMD increase and prevent ZOL-induced hypocalcaemia
  - Screening / Month 11: if <25 nmol/L, received vitamin D 100,000IU (2 tablets)
  - Screening / Month 11: if 25-50 nmol/L, received vitamin D 50,000IU (1 tablet)
  - For above patients, if still <50 nmol/L at Month 3 received vitamin D 50,000IU monthly thereafter
  - ZOL given at least 2 weeks after Vitamin D replacement

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DXA

- Sites
  - lumbar spine (L1-L4)
  - left hip
- Facilities x 3 (Sydney, Melbourne, Barcelona)
  - common protocol
  - central adjustment of BMD values for longitudinal and cross-sectional consistency based on phantom scans
- BMD results unavailable until M24 unless
  - minimal-trauma fracture or
  - BMD decline of >5% or
  - new T-score <-2.5
ZOL vs TDF switch for low BMD

Statistical analysis

- **Sample size**
  - prior studies mean 2-year change at lumbar spine
    - 6.1% (SD <4%) with a bisphosphonate
    - 1% (SD 2%) with tenofovir switching
  - if $\Delta=4\%$ and SD=6%, sample size = 36 / group
  - if LTFU is 15%, n=42 / group

- **DXA and lab parameters**
  - groups compared with t-test

- **Categorical data**
  - groups compared using Fisher’s exact test or a Chi-square test as appropriate

- **All presented analyses by ITT**
  - PP analyses yielded similar results

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ZOL vs TDF switch for low BMD

CONSORT chart

- **Screened**
  - n = 109

- **Not randomised**
  - n = 22
    - ineligible = 20
    - refused = 1
    - other = 1

- **Randomised**
  - ZOL
    - n = 43
  - TDF switch
    - n = 44
    - Revoked consent
      - n = 2
ZOL vs TDF switch for low BMD

CONSORT chart

Screened
n = 109

Randomised

ZOL
n = 43

Received ZOL
n = 43
death = 1
moved = 1
LTFU = 1
ceased TDF = 3

TDF switch
n = 44

Switched TDF
n = 42
abacavir = 26
INSTI = 12
restarted TDF = 4
received ZOL = 0

Not randomised
n = 22
ineligible = 20
refused = 1
other = 1

Revoked consent
n = 2

Analysed

ZOL
n = 43

TDF switch
n = 42

ZOL vs TDF switch for low BMD

Screening / baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>ZOL n=43</th>
<th>TDF switch n=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean yrs)</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Sex (male %)</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>Ethnicity (white, %)</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td>626</td>
<td>609</td>
</tr>
<tr>
<td>TDF duration (mean yrs)</td>
<td>5.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Boosted PI (%)</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Weight (mean kg)</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>
**ZOL vs TDF switch for low BMD**

Screening / baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>ZOL n=43</th>
<th>TDF switch n=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-scores (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>spine</td>
<td>-1.7</td>
<td>-1.6</td>
</tr>
<tr>
<td>left total hip</td>
<td>-1.4</td>
<td>-1.1</td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 nmol/L</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>25-50 nmol/L</td>
<td>40%</td>
<td>36%</td>
</tr>
<tr>
<td>eGFR (mean mL/min)</td>
<td>93</td>
<td>91</td>
</tr>
</tbody>
</table>

Changes in BMD

% change

Lumbar spine

Δ = 3.2%  
(95%CI 1.7-4.7)  
p<0.001

Mean diff. 4.4%  
(95%CI 2.6-6.3);  
p<0.001
ZOL vs TDF switch for low BMD

Changes in BMD - hip

- 1 pt in ZOL group had unevaluable hip BMD
- M12 data carried forward for 1 pt/group because of subsequent left hip replacements
- Baseline data carried forward to M12 for 1 patient in TDF switch group

Fractures

<table>
<thead>
<tr>
<th>Fractures (n, %)</th>
<th>ZOL n=43</th>
<th>TDF switch n=42</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>events*</td>
<td>1 (2%)</td>
<td>7 (17%)</td>
<td>0.03</td>
</tr>
<tr>
<td>wrist</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>spine</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ribs</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hand / foot</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients</td>
<td>1 (2%)</td>
<td>4 (10%)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* 1 fracture in each group was deemed a fragility fracture
ZOL vs TDF switch for low BMD

Other adverse events

<table>
<thead>
<tr>
<th></th>
<th>ZOL n=43</th>
<th>TDF switch n=42</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mean Δ)</td>
<td>-6.0</td>
<td>3.3</td>
<td>0.003</td>
</tr>
<tr>
<td>SAE (n, %)</td>
<td>9 (19%)</td>
<td>6 (14%)</td>
<td>0.57</td>
</tr>
<tr>
<td>RNA &gt;50 cp/mL</td>
<td>0</td>
<td>1 (2%)</td>
<td>..</td>
</tr>
</tbody>
</table>

- No SAE was deemed to be related to any study intervention

ZOL vs TDF switch for low BMD

Limitations

- Almost all white, adult men
- Follow-up for 24 months – follow-up ongoing to M36
- Pre-TAF, but switch to TAF unlikely to be superior to switch to ABC or INSTI
- Not powered for fracture events
ZOL vs TDF switch for low BMD

Conclusions

- ZOL (with Ca\(^{2+}\) ± vitamin D replacement) is more effective at increasing BMD than switching from TDF, in adult men with low BMD
- Much larger and longer studies are required to determine impact on fracture outcomes
- Clinical significance will likely depend on underlying fracture risk

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Questions