Impacts of vitamin D and calcium supplementation on bone mineral density among perinatally HIV-infected adolescents: A 48-week randomized clinical trial

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Study objective:
- To evaluate the impacts of vitamin D and calcium (VitD/Ca) supplementation on BMD and bone metabolism among perinatally HIV-infected adolescents

Study methods:
- **Design:** An ongoing, multicenter, 48-week, randomized, open-labeled study
- **Population:** Perinatally HIV-infected Thai adolescents aged 10-20 years with virologic suppression (plasma viral load <400 copies/ml)
- **Outcome measurement:**
  - **Bone mineral density (BMD):** lumbar spine dual-energy X-ray absorptiometry (DXA) technique
  - **Bone metabolism-related hormone:** 25-hydroxyvitamin D (25OHD), intact parathyroid hormone (iPTH)
  - **Bone turnover marker:** alkaline phosphatase (ALP), C-terminal cross-linked telopeptide of type I collagen (CTX), procollagen type I amino-terminal propeptide (PINP)
Study procedures and randomization

Eligible participants

Baseline BMD
Randomization

Low BMD (BMD Z-score ≤ -2)
High-dose group

Normal-dose group

Randomization

Normal BMD (BMD Z-score > -2)
High-dose group

Normal-dose group

High-dose group: Vitamin D 3,200 IU plus calcium 1.2 g daily
- FDC tablet of 200 IU of vitamin D3 and 600 mg of calcium twice daily
- Capsule of 20,000 IU vitamin D2 once weekly

Normal-dose group: Vitamin D 400 IU plus calcium 1.2 g daily
- FDC tablet of 200 IU of vitamin D3 and 600 mg of calcium twice daily

Randomization ratio 1:1 (computer-generated), open-labeled fashion, balanced within site

FDC: fixed dose combination.
Figure 1. Flow of study participants*

Screened (n = 215)

Eligible and randomly assigned (n = 166)

Ineligible (n = 49)
- Meet exclusion criteria (n = 7)
- Not meet inclusion criteria (n = 31)
- Decline to participate (n = 8)
- Other reasons (n = 3)

Low BMD (n = 67)

High-dose (n = 35)
- Completed study on treatment (n = 33)
- Failed to complete week 48
  - Loss to follow-up (n = 1)
  - Unwilling to participate (n = 1)

Normal-dose (n = 32)
- Completed study on treatment (n = 30)
- Failed to complete week 48
  - Unwilling to participate (n = 2)

Normal BMD (n = 99)

High-dose (n = 48)
- Completed study on treatment (n = 46)
- Completed study off treatment (n = 1): acne
- Failed to complete week 48
  - Unwilling to participate (n = 1)

Normal-dose (n = 51)
- Completed study on treatment (n = 49)
- Completed study off treatment (n = 1): pregnancy
- Failed to complete week 48
  - Death (n = 1)

*Preliminary data as of October 2016.
Figure 2. Changes from baseline of bone mineral density and bone biochemical markers over the 48-week study follow-up (ITT analysis)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Change from baseline to week 48</th>
<th>Change from baseline to week 48</th>
<th>Between group comparison $P_t$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low BMD (n = 67)</strong></td>
<td></td>
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</tr>
<tr>
<td>High-dose (n = 35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD z-score</td>
<td>0.71 (0.29 to 1.11)$^*$</td>
<td>0.49 (-0.40 to 1.19)$^*$</td>
<td>0.07</td>
</tr>
<tr>
<td>25OHD, ng/ml</td>
<td>5 (-2 to 12)$^*$</td>
<td>6 (3 to 12)$^*$</td>
<td>0.41</td>
</tr>
<tr>
<td>iPTH, pg/ml</td>
<td>-10 (-20 to 0)$^*$</td>
<td>-15 (-23 to -6)$^*$</td>
<td>0.04</td>
</tr>
<tr>
<td>ALP, U/l</td>
<td>-22 (-123 to 0)$^*$</td>
<td>-65 (-96 to -26)$^*$</td>
<td>0.09</td>
</tr>
<tr>
<td>CTX, ng/l</td>
<td>-170 (-450 to 0)$^*$</td>
<td>-420 (-720 to -130)$^*$</td>
<td>0.39</td>
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<tr>
<td>PIP, µg/l</td>
<td>-48 (-216 to 0)$^*$</td>
<td>-137 (-317 to -30)$^*$</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Normal BMD (n = 99)</strong></td>
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<tr>
<td>BMD z-score</td>
<td>0.10 (-0.25 to 0.66)</td>
<td>-0.07 (-0.51 to 0.43)</td>
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<tr>
<td>25OHD, ng/ml</td>
<td>5 (1 to 11)$^*$</td>
<td>6 (2 to 10)$^*$</td>
<td></td>
</tr>
<tr>
<td>iPTH, pg/ml</td>
<td>-6 (-21 to 1)$^*$</td>
<td>-12 (-22 to -3)$^*$</td>
<td></td>
</tr>
<tr>
<td>ALP, U/l</td>
<td>-44 (-81 to -9)$^*$</td>
<td>-50 (-119 to -21)$^*$</td>
<td></td>
</tr>
<tr>
<td>CTX, ng/l</td>
<td>-330 (-740 to 6)$^*$</td>
<td>-320 (-620 to 30)$^*$</td>
<td></td>
</tr>
<tr>
<td>PIP, µg/l</td>
<td>-81 (-202 to 8)$^*$</td>
<td>-73 (-249 to 16)$^*$</td>
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<td><strong>Normal-dose (n = 51)</strong></td>
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*Data is presented as median change from baseline (interquartile range).

$^*$P-value evaluates the overall difference in median change from baseline to week 48 between the two treatment groups (between group difference).

$^*$Indicates the median change from baseline to week 48 within the treatment groups (within group difference) is a statistical significant ($P < 0.05$).
Conclusions

With the preliminary results:

- **LS BMD z-scores were significantly increased** in HIV-infected Thai adolescents with low baseline BMD who received VitD/Ca supplementation over 48-week follow-up
  - With a trend of greater improvement among adolescents receiving high-dose VitD/Ca supplementation

- **Bone biochemical markers were re-established** in adolescents with low as well as normal baseline BMD in both treatment groups

- **Supplementation of high-dose VitD/Ca** did not show significant differences in the changes of BMD and bone metabolism outcomes compared to normal-dose VitD/Ca

- **A prospective study with longer follow-up** is warranted to confirm our findings
Acknowledgements

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  - Chiang Rai Prachanukroh Hospital, Chiang Rai, Thailand
  - Queen Sirikit National Institute of Child Health, Bangkok, Thailand

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