Alendronate improves bone mineral density in HIV-infected children and adolescents

IMPAAACT P1076

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• Team members have no conflicts of interest to disclose.
Background and Significance

- Puberty is a time of rapid bone mineral accrual. Within the five years surrounding peak height velocity in adolescence, 39% of adult total body bone mineral content is accrued.

- Detriments in bone accrual during this critical period could lead to lower peak bone mass which increases the risk of osteoporosis later in life.

- Several factors may contribute to poor bone accrual including inflammation, poor linear growth and weight gain, malabsorption, medications, endocrinopathies, low vitamin D concentrations, etc.
Background and Significance

• HIV-infected children/youth have lower bone mineral density (BMD) than their HIV-uninfected peers, which may be more pronounced in boys.

• While the bisphosphonate alendronate has been shown to increase BMD or slow down loss of bone in adults with osteopenia or osteoporosis, it has not been extensively studied in HIV-infected children and adolescents.
IMPAACT P1076

• Randomized, placebo-controlled, double-blind, crossover study

• Assess safety and efficacy of 48/96 weeks of once-weekly alendronate in HIV-infected children and adolescents
Key Inclusion/Exclusion Criteria

**Inclusion:**
- Age 11 - < 25 years
- Acquired HIV before puberty
- On same ART ≥12 weeks (or not on ART ≥ 12 weeks)
- Lumbar spine (LS) BMD z-score < -1.5 OR history of a fragility fracture within 12 months of study entry
- If on tenofovir disoproxil fumarate (tenofovir) or medroxyprogesterone, on ≥ 6 months

**Exclusion:**
- 25-hydroxy vitamin D (25-OHD) concentrations < 10 ng/mL in combination with elevated intact parathyroid hormone (PTH) above upper limit of normal for local laboratory

Recruited at sites in the US (including Puerto Rico) and Brazil
Treatment Sequences

Participants randomized equally to three groups (N=51 total)
A/A – Alendronate treatment for 96 weeks
A/P – Alendronate treatment 48 weeks followed by placebo for 48 weeks
P/A – Placebo for 48 weeks followed by alendronate for 48 weeks

DXA scans were performed at 0, 24, 48, 72, 96 and 144 weeks
Presentation of Week 48

- A/A and A/P groups combined for week 48 analysis

- Modified intent-to-treat analysis only including those who started study treatment
Treatment

- **Alendronate treatment** - Once weekly alendronate tablet
  - 70 mg if > 30kg or 35 mg if ≤ 30 kg
- **Placebo** – Once weekly placebo tablet

All participants throughout follow-up

**Calcium carbonate (600 mg) and vitamin D (400 IU)**

- Once daily if 25-OH-vitamin D levels ≥20 ng/mL
- Twice daily if 25-OH-vitamin D levels <20 ng/mL

- **Weight-bearing exercise** – Asked to perform 60 minutes daily
Primary Safety Outcome Measures and Analysis

Proportion (95%CI) of participants experiencing new:

- Grade $\geq 3$ hematology or chemistry laboratory values, signs or symptoms*
- Cases of jaw osteonecrosis (JON), atrial fibrillation or non-healing fractures

*Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events, Dec 2004
Primary and Secondary Efficacy Outcome Measures and Analysis

Outcome measures

• **Primary:**
  - % change in lumbar spine (LS) BMD (g/cm$^2$)

• **Secondary:**
  - Change in LS BMD z-score*
  - % change in whole body (WB) BMD (g/cm$^2$)
  - Change in WB BMD z-score*

Unadjusted analysis

• Mean (95% CI) week 0 to 48

*z-scores for age, sex and race
Effect modification

- Evaluate if effect of alendronate varies across levels of factors at week 0 (effect modification)
  - Age, Tanner stage, bone age
  - Ethnicity
  - Tenofovir use
  - Vitamin D concentrations, nadir CD4 count, BMD

- Fit individual slopes (average change in outcome over one year including weeks 0, 24, 48)
- Linear regression to test effect modification term: treatment group*covariate
Screened N=75

Not enrolled N=23*
- LS BMD z-score > -1.5: 11
- Dental issues: 7
- Change ARVs/Depo: 2
- Non-adherence ARVs: 1
- Problems with labs: 2
- Anemia: 1
- HIV-RNA > 10,000 cp/mL: 1
- Recent surgery: 1
- Co-enrollment not allowed: 1

Randomized N=52

Alendronate N=34 (A/A: 17, A/P: 17)
- Started trt: N=32
- Did not start trt (N=2)
  - Entry LS BMD z-score > -1.5: N=2

Placebo N=18
- Started trt: (N=18)

Completed 48 weeks on study trt: (N=31)
Completed 48 weeks but off study trt: (N=1)
Adherence issues: (N=1)

Completed 48 weeks on study trt: (N=18)

49/50 who started treatment completed at least 48 weeks of study
## Characteristics at Entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alendronate (N=32)</th>
<th>Placebo (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (66%)</td>
<td>13 (72%)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (34%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Non-Hispanic</td>
<td>6 (19%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Black Non-Hispanic</td>
<td>6 (19%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Hispanic (Any Race)</td>
<td>20 (63%)</td>
<td>16 (89%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>16.1 (11.1, 23.4)</td>
<td>16.3 (11.2, 22.4)</td>
</tr>
<tr>
<td><strong>Tanner stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>6 (19%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (19%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>4-5</td>
<td>20 (62%)</td>
<td>12 (67%)</td>
</tr>
<tr>
<td><strong>Smoker at entry</strong></td>
<td>2 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td><strong>CDC stage/cat</strong></td>
<td>3 (9%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>A/B</td>
<td>9 (11%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>29 (91%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td><strong>CD4 count (cells/mm(^3))</strong></td>
<td>693 (543, 777)</td>
<td>876 (599, 1,152)</td>
</tr>
<tr>
<td><strong>HIV-1 RNA</strong></td>
<td>&lt;400 copies/mL</td>
<td></td>
</tr>
<tr>
<td>26 (81%)</td>
<td>15 (83%)</td>
<td></td>
</tr>
</tbody>
</table>
## Characteristics at Entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alendronate (N=32)</th>
<th>Placebo (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On tenofovir</td>
<td>14 (44%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>Perinatally HIV-infected*</td>
<td>31 (97%)</td>
<td>18 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS BMD (g/m$^2$)</td>
<td>0.7 (0.6, 0.8)</td>
</tr>
<tr>
<td>LS BMD Z-score</td>
<td>-2.4 (-3.1, -1.9)</td>
</tr>
<tr>
<td>WB BMD with head (g/m$^2$)</td>
<td>0.9 (0.8, 1.0)</td>
</tr>
<tr>
<td>WB BMD with head Z-score</td>
<td>-2.6 (-3.3, -1.9)</td>
</tr>
</tbody>
</table>

* 1 child infected through cross-contaminated breastmilk
No cases of jaw osteonecrosis, atrial fibrillation or non-healing fractures. All grade 3 and not related to treatment.

<table>
<thead>
<tr>
<th>Group</th>
<th>ID</th>
<th>Week</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>1</td>
<td>4</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>24</td>
<td>Total bilirubin</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>48</td>
<td>Total bilirubin</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>48</td>
<td>Platelets</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>48</td>
<td>Phosphorus/Phosphate</td>
</tr>
<tr>
<td>Placebo</td>
<td>6</td>
<td>24</td>
<td>Difficulty swallowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Midline chest pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain swallowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight loss (disseminated)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>47</td>
<td>Total bilirubin</td>
</tr>
</tbody>
</table>
### Number of Participants Experiencing At Least One Safety Event

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Trt</th>
<th>Participants with events</th>
<th>Total</th>
<th>Had event % (95% CI)</th>
<th>Alendronate - placebo % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary safety events</strong></td>
<td>A</td>
<td>5</td>
<td>32</td>
<td>15.6 (5.3, 32.8)</td>
<td>4.5 (-24.2, 33.0)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>2</td>
<td>18</td>
<td>11.1 (1.4, 34.7)</td>
<td></td>
</tr>
<tr>
<td><strong>New events &gt; grade 2</strong></td>
<td>A</td>
<td>15</td>
<td>32</td>
<td>46.9 (29.1, 65.3)</td>
<td>8.0 (-21.2, 35.9)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>7</td>
<td>18</td>
<td>38.9 (17.3, 64.3)</td>
<td></td>
</tr>
</tbody>
</table>

All Fisher’s exact p-values > 0.77
LS Outcomes: Mean (95% CI)

LS BMD

LS BMD z-score
Percent Change in BMD Outcomes From Week 0: Mean (95% CI)

% change LS BMD
12.7 (6.8, 18.6), P < 0.001*

% change WB BMD
6.1 (2.1, 10.0), P = 0.004*

*T-test
Changes in Z-score Outcomes From Week 0: Mean (95% CI)

Change LS BMD z-score
0.73 (0.41, 1.05), P <0.001*

Change WB BMD z-score
0.64 (0.29, 0.98), P <0.001*

*T-test
Alendronate Had a Larger Effect on LS Outcomes in Younger Children*

% change LS BMD

Change LS z-score

*P-value for effect modification
Trends were similar by Tanner stage and bone age, and for whole body
Conclusions

• No indications of safety issues with alendronate in HIV-infected youth treated for 48 weeks
• Significantly greater improvements in BMD and BMD z-scores on alendronate
  • compared to vitamin D/calcium/exercise alone
  • in less mature (age, Tanner, bone age) participants
• Mean z-scores at week 0 and 48 weeks
  A: -2.6 to -1.7   P: -2.8 to -2.6

• Impact on fractures and peak bone mass unknown
• Limitations include a small sample size
Durability of Alendronate treatment

Does an additional 48 weeks of alendronate further improve BMD?
How long is efficacy maintained after stopping alendronate?

A/A
A/P
P/A

Weeks 0 48 96 144

- Alendronate (A)
- Placebo (P)
- Follow-up (no treatment)
IMPAACT P1076 Protocol Team

- George Siberry
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- Patrick Jean-Phillipe
- Paul Sato
- Hans Spiegel
- Rohan Hazra
- Kimberly Hudgens
- Kathy George
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- Jane Benson
- Yvonne De Souza
- Catherine Gordon
- Dan Colosi
- Fred Ferguson
- Jessica Pagano-Therrien
- Dorothy Shaw
- Eric Stets
- Arthur Santora

Study sites

Brazil:
- Federal University Minas Gerais
- University of Sao Paulo

US:
- UCLA Medical Center
- Chicago Children’s
- University of Miami South Florida
- San Juan City Hospital
- Johns Hopkins University
- St Jude
- U Mass Medical School
Thank you

- IMPAACT P1076 participants and guardians

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References for z-scores

Lumbar spine:
• Kelly et al (1990): 3-6 years (white)
• Bone Mineral Density in Childhood Study (BMDCS Kalkwarf et al, 2007): females 7-16 years and males 7-17 years (black and non-black)
• Kelly et al (2005): > 17 years

Whole Body with head:
• NHANES, Kelly et al 2009: 8-85 years (black, white and Hispanic)