Decreased bone mass in perinatally HIV-infected school-aged South African children on ART

Childhood HAART Alterations in Normal Growth, Genes, and Aging Evaluation Study (CHANGES)
Bone Study Team

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Background

• Increased risk of osteoporosis and fracture rates in HIV-infected adults

• Lower bone mineral content (BMC) and bone mineral density (BMD) also reported in HIV-infected children
  • Largest cumulative exposure to HIV and ART
  • Impaired bone accrual may compromise peak bone mass

• Little known about bone development among HIV infected children in resource-limited settings
Study Questions

Among South African pre-pubertal children:

1. Do HIV-infected children initiated on potent ART at an early age have lower bone mass compared to HIV-uninfected controls?

2. Is the lower bone mass solely due to the smaller size of the HIV-infected children?

3. Do HIV-infected children initiated and maintained on LPV/r-based ART have similar bone mass to children initiated on LPV/r-based ART and later switched to EFV?
Methods

• Analysis of baseline data from the CHANGES Bone Study

• Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa

• Pre-pubertal children aged 5-9 years
  • 220 HIV-infected: initiated ART <2 years, enrolled from a prior clinical trial (NEVEREST 3)
  • 180 HIV-uninfected: siblings or household members of HIV-infected children as well as healthy children attending the site for preventive health services
Measurements

- Demographics
- Weight and height
- CD4 and HIV RNA levels (for HIV-infected children)
- Whole body bone mineral content (BMC) by dual-energy X-ray absorptiometry (DXA)
Statistical Approach

1. Compare BMC in grams between HIV+ and HIV-

2. Compare BMC-height Z-score between HIV+ and HIV- (to see if lower bone mass is due to smaller size)
   - BMC-height distribution of the uninfected children was used to generate a gender specific Z-score for each HIV-infected child
   - Generated using quantile regression
   - Used in studies of pediatric illnesses that adversely affect growth (cystic fibrosis\(^1\), Crohn’s disease\(^2\), and sickle cell disease\(^3\))
   - Correlates well with volumetric cortical bone by QCT\(^4\)

3. Compare BMC-height Z-score between children maintained on LPV/r and switched to EFV

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\(^1\)Kelly J Clin Densitom 2008; \(^2\)Burnham JBMR 2004; \(^3\)Buison Pediatrics 2005; \(^4\)Leonard Bone 2004
## Characteristics of CHANGES Bone Study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV+ N=220</th>
<th>HIV- N=180</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>49</td>
<td>55</td>
<td>0.24</td>
</tr>
<tr>
<td>Age in years, Mean ± SD</td>
<td>6.4 ± 1.3</td>
<td>7.1 ± 1.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WAZ, Mean ± SD</td>
<td>-0.8 ± 0.9</td>
<td>-0.6 ± 1.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Underweight, %</td>
<td>11</td>
<td>5</td>
<td>0.03</td>
</tr>
<tr>
<td>HAZ, Mean ± SD</td>
<td>-1.4 ± 0.9</td>
<td>-1.2 ± 1.0</td>
<td>0.046</td>
</tr>
<tr>
<td>Stunted, %</td>
<td>26</td>
<td>19</td>
<td>0.08</td>
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</tbody>
</table>

WHO growth reference definitions: Underweight (WAZ < -2), Stunted (HAZ < -2)
1. Bone mass is lower in HIV+ compared to HIV-

Is the lower bone mass due to smaller size of the HIV-infected children?

HIV+ vs. HIV-

- HIV+ mean: 416 ± 98 g
- HIV- mean: 496 ± 123 g

p<0.01

Mean ± SD
2. Difference in whole body BMC-height Z-score* between HIV+ and HIV-

Lower z-score for HIV+ boys

Lower z-score for HIV+ girls

p=0.03

p<0.001

*adjusted for age
Overview of treatment history

Initiated and suppressed on LPV/r

Mean age at ART start 8.9 months

Randomized in Neverest 3 clinical trial (age 3-5 years)

- Remain on LPV/r
- Switch to EFV

11 switch to EFV after trial

Enrolled in CHANGES Bone Study (age 5-9 years)

- On LPV/r (N=110)
- On EFV (N=110)

- 94% with HIV RNA <400 copies/mL
- Mean CD4% 37.3

*also on two NRTIs including 3TC and ABC, d4T, or AZT but not TDF
3. Mean whole body BMC-height Z-scores by treatment group

Boys

<table>
<thead>
<tr>
<th></th>
<th>Stay on LPV/r</th>
<th>Switch to EFV</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>p=0.03</td>
<td></td>
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Switch to EFV:
- 0-2 yrs
- >2 yrs

p=0.06
3. Mean whole body BMC-height Z-scores by treatment group

Girls

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<tr>
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<th>Stay on LPV/r</th>
<th>Switch to EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
Conclusions

• Despite early initiation of ART and excellent virologic control, HIV-infected children receiving ART have decreased bone mass compared to HIV-uninfected controls

• Differences cannot entirely be accounted for by smaller body size

• Children switched to EFV have better bone mass compared to those maintained on LPV/r

• Use of bone-sparing regimens may enhance bone accrual during childhood
Acknowledgements

CHANGES Participants and Caregivers

CHANGES Bone Study Team

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Thank you!