Optimizing Vitamin D Treatment in HIV/AIDS: An RCT

The FDA and Me

Andrea Branch, Ph. D.

May 23, 2012
Thanks!

- Lori Jennex  IRB
- Kacey Feasel  IRB
- Rebecca Banchik  IRB
- Glenn Martin  IRB
- Jeff Silverstein  IRB
- Vivian Mitropoulou  Compliance
- Nancy Lowe  ClinicalTrials.gov
- Jessica Moise  GCO
- Michelle Steer  GCO
Bone Loss in HIV-positive Patients on HAART Is a Major Problem

Subjects: 671 patients with at least one DXA scan, 391 with ≥2 scans

Baseline: Low BMD in 71%; osteopenia, 48%, osteoporosis, 23%

Of 105 patients ≥ 5 yr of follow-up, 18% progressed from normal BMD to osteopenia; 29% progressed from osteopenia to osteoporosis.

T score is BMD compared to young, normal reference group
Osteopenia (-1 to -2.5 SD), osteoporosis (> -2.5 SD)

A Bonjoch et al., AIDS. 2010 Nov 27
Because vitamin D enhances calcium absorption and protects bone, vitamin D and calcium supplements may be especially important for HIV-positive patients.
Risk of mother-to-child transmission of HIV and child mortality were lowest at 28-64 ng/ml 25(OH)D

Adjusted for maternal age, CD4 cell count, HIV disease stage, and multivitamin regimen, Mehta et al., JID, 2009
Hypothesis

Vitamin D and calcium supplements will benefit HIV-infected patients by
- Improving bone and calcium metabolism
- Reducing inflammation and fatigue
- Enhancing immune function
Pilot Study

Assess vitamin D status and response to supplements in 91 HIV-positive patients

Dr. Douglas Dieterich, MD
Dr. Michael Mullen, MD
50% of Dr. Mullen’s patients were vitamin D deficient.
25(OH)D was inversely related to fatigue in Caucasian patients.
Dr. Mullen began advising his patients to increase consumption of vitamin D and calcium (1 g/day calcium citrate).

<table>
<thead>
<tr>
<th>Baseline (ng/ml)</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 10</td>
<td>2800 IU</td>
</tr>
<tr>
<td>10-20</td>
<td>1800 IU</td>
</tr>
<tr>
<td>20-30</td>
<td>800 IU</td>
</tr>
<tr>
<td>Over 30</td>
<td>0 IU</td>
</tr>
</tbody>
</table>

2800 IU is not a megadose; 10,000IU/day is safe; 20,000IU are produced by a day at the beach.

R.P. Heaney, 2005, J of Steroid Biochem and Molec Biol
CD4+ T cells rose by 112 cells/µl (p=0.012) among 15 fully adherent subjects with HIV VL ≤ 200 copies/ml and 25(OH)D ≤ 25 ng/ml.
Goals of the RCT

I. Produce an evidence-based protocol for correcting vitamin D insufficiency

Determine the dose of vitamin D needed to raise 25(OH)D levels over 32 ng/ml in HIV-positive patients on HAART who have basal 25(OH)D levels below 25 ng/ml and well-preserved kidney function.

II. Assess the global health benefits of vitamin D and calcium supplements

Measure changes in CD4⁺ T cell subsets, BMD, markers of inflammation, fatigue, depression.
Guidelines for Treating Vitamin D Deficiency in HIV-infected Patients

- The IDSA has not released guidelines
- The European AIDS Clinical Society recommends 800-2000 IU/d
- UpToDate recommends a loading dose of 50,000 IU/wk followed by a maintenance dose of at least 800-1000 IU/d

Our data show that these doses are too low for patients with basal 25(OH)D levels below 10 ng/ml
Study Design

**Protocol A**
UpToDate
High Fixed Loading Dose
50,000 IU vitamin D$_2$/week
For 8 weeks
1000 IU Maintenance Dose
For 44 weeks
N = 100

**Protocol B**
Tiered Starting Dose
Based on the Basal 25(OH)D Level
Dose Titration Based on the 25(OH)D Level at 3 mo
Maintenance Dose
N = 100

<table>
<thead>
<tr>
<th>Basal 25(OH)D</th>
<th>Vitamin D$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 ng/ml</td>
<td>4000 IU/d</td>
</tr>
<tr>
<td>&gt; 10 -15 ng/ml</td>
<td>3000 IU/d</td>
</tr>
<tr>
<td>&gt; 15 – 25 ng/ml</td>
<td>2000 IU/d</td>
</tr>
</tbody>
</table>
Study Design

Screen about 500

Enroll 200 Subjects
Randomize 1:1
Stratify by
25(OH)D Level
CD4+ T Cells
Sex and Race

Expect to Exclude 300
25(OH)D > 25 ng/ml
GFR < 60 ml/min/1.73m²
Osteoporosis
Not HIV VL Undetectable

Protocol A
High Fixed Loading Dose
1000 IU Maintenance Dose
N = 100

Protocol B
Tiered Starting Dose
Titrated Maintenance Dose
N = 100
Hi, Lori, How are you on this sun-filled Monday morning? I am writing with a question about the vitamin D trial that was submitted on Friday. Since the FDA previously declined to give an IND for our past vitamin D study, do you think the IRB will require another IND application? If so, should I start the paperwork now, or wait to hear from the IRB?

Thanks! Andrea
From: Jennex, Lori
Sent: Monday, August 30, 2010 1:02 PM
To: Branch, Andrea
Cc: 'Catherine Constable'

Subject: RE: Vitamin D and FDA question

If it’s a new project, I’m guessing yes. If it’s a continuation for the project I know that Catherine worked on, then nope. :-) enjoy the day!
How Academic Research Balances Pharmaceutical Research

Tenofovir and Secondary Hyperparathyroidism

A Story about Gilead Pharmaceuticals
TDF reduces BMD at the L-spine, despite a 3 kg weight gain at 144 weeks

Gallant et al JAMA, 2004

DF indicates disoproxil fumarate. The range of variability (SD) of percentage change in lumbar spine and hip bone mineral density was from 2.5% to 5.2%.
HAART can dramatically reduce bone mineral density (BMD) in children

Child #11

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Baseline 25(OH)D ng/ml</th>
<th>TDF dose</th>
<th>Puberty</th>
<th>BMD Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>72</td>
<td>213</td>
<td>3</td>
<td>1-5%</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>34</td>
<td>208</td>
<td>3</td>
<td>1-5%</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>26</td>
<td>265</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>Not done</td>
<td>270</td>
<td>1</td>
<td>1-5%</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>23</td>
<td>345</td>
<td>1</td>
<td>27%</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td>17</td>
<td>275</td>
<td>1</td>
<td>10%</td>
</tr>
</tbody>
</table>

Purdy et al. J. Pediatrics 2008
PTH maintains serum calcium at the expense of bone

Low Vitamin D

Decreased Serum Calcium

Increased Parathyroid Hormone

Supply Calcium at Cost to Bone

Secondary Hyperparathyroidism
Secondary hyperparathyroidism occurred with Tenofovir (TDF)

30 ng/ml 25(OH)D = Low optimal

Many patients on TDF with low vitamin D had secondary hyperparathyroidism

87 pg/ml iPTH = ULN

- Tenofovir/FTC
- ART no-Tenofovir
Newsflash from Gilead: TDF causes significant increases in PTH

903 Study

DF indicates disoproxil fumarate. The range of variability (SD) of percentage change in lumbar spine and hip bone mineral density was from 2.5% to 5.2%.

Omitted from Gallant et al JAMA, 2004; Package insert and PDR
What Happened to My IND Applications?
Dear Dr. Branch,

Please submit a copy of the product labels (package insert and/or packaging labels) and representative certificates of analysis to show test results for the identity, content, and purity of the products. These certificates can be obtained from the manufacturer.

A prompt response is requested because this information is required for our safety review of your IND.

If you have any questions, please call me at (301) 796-5332.

Sincerely,

Pooja Dharia, Pharm. D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Hi, Lisa,

My IRB requires me to apply to the FDA to use vitamin D2, vitamin D3, and placebo from Tishcon.

The FDA requires information about manufacturing practices, purity, and quality control.

Can you please send me this information for vitamin D2, vitamin D3, and placebo (in capsule form)?

It would be wonderful if you can send this information ASAP.

Many thanks! Andrea
Dear Andrea,
Thank you for your email.
Based on the information which you have requested in the email below, we are not interested in pursuing this project if it is being done under an IND.
Sorry, we cannot be of help.
Regards,

Arun K. Chopra - Sr. VP / Chief Operating Officer - Tishcon Corp.
Email: Arun@Tishcon.com; Tel: 410 860 0046 Ext. 126;
Tishcon Corp. 2410 N. Zion Road, Salisbury, MD 21801
What Happened to My IND Applications?

- Lost the vitamin D supplier
- Applied for three INDs
  - Vitamin D$_2$
  - Vitamin D$_3$
  - Half a gram of calcium (25% of the RDA)
- Vitamin D$_2$ and D$_3$ were declared exempt by the Division of Metabolism and Endocrinology Products
- An IND for calcium citrate was issued by the Division of Reproductive and Urologic Products
- After days of negotiations, the consent form was revised
Academic Medicine Saves Lives

- The regulatory burdens are driving academic investigators out of research

- How can you help?
  - Ensure that the regulatory burden is in proportion to the research risk
  - Strengthen ties to the FDA and other regulatory agencies
  - Keep lines of communication to PIs open