Long Term Complications of Treatment in Children

By

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Concerning Long Term Complications of Treatment in HIV-Infected Children and Adolescents

- Lipodystrophy, esp. facial lipoatrophy
- Metabolic complications that may result in cardiovascular diseases/coronary heart diseases/stroke, DM
- Kidney dysfunction
- Fractures risk/osteopenia/vitamin D deficiency
- Neuro/psychiatric problems
Let’s start with the look

Some would lead teens to give up ARV
A 14 year-old boy with lipodystrophy, dyslipidemia and DM

- At 3 yo, start d4T/3TC/EFV
- At 5.5 yo, switched to AZT/3TC/IDV/r due to failure
- At 9 yo, lipodystrophy, obese, impair FBS, OGTT, insulin-R, and hypercholesterolemia (TC = 230 mg/dl)
  - Treated with metformin, lifestyle modification
  - Switched to TDF/3TC/ATV/r
- Despite Rx, became DM at 14 yo
  - Treated with insulin
Lipodystrophy in HIV-infected children

- Incidence vary 10-30% due to lack of consensus for definition
- Associated with PI and stavudine
  - PI: Predominate with truncal obesity, buffalo hump, and less peripheral lipoatrophy
  - d4T: Predominate with facial lipoatrophy, associated with HLA-B*4001 and Fas gene
- Likely to appear in early adolescence

Characteristics of Lipodystrophy from Protease Inhibitors

• Fat gain on abdomen, breast, and dorsocervical hump
• Fat loss from peripheral extremities
• Fat gain in visceral organs

Areas of possible fat gain (lipohypertrophy)

- neck
- back
- breasts
- abdomen

before after
Facial and peripheral lipoatrophy following >6 months of stavudine treatment, found in 38% of d4T Rx, occur around early adolescence. Associated with HLA-B*4001 and Fas gene

Facial lipoatrophy may improve after stopping d4T.

Improvement found in 23%, at mean duration of 45 months after stopping d4T, around early adolescence.

Need to stop d4T before reaching adolescence.

Body fat abnormality in HIV-infected children and adolescents: *The difference of regions*

**Study Population**

- **Lipoatrophy**: 23%
  - Europe, N=426, LD = 42%
    - Receiving PI 60%, Exposed to d4T 10%
  - Thailand, N=202, LD = 25%
    - Receiving PI 41%, Exposed to d4T 60%
- **Lipohypertrophy or combine**: 2.5%
- **No fat maldistribution**: 75%

*Alam NM. J Acquir Immune Defic Syndr. 2012 March 1; 59(3): 314–324*

Metabolic complications:

>> Start from lipodystrophy,

>> dyslipidemia, insulin resistance

End up with cardiovascular diseases, stroke, DM
Development of HIV and PI associated lipodystrophy/ IR


11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; FFA, free fatty acids; ROS, reactive oxygen species;
Dyslipidemia found 40%-80% in children, associated with receiving PI and lipodystrophy\textsuperscript{1-3}

Prevalence of Dyslipidemia in a European cohort of HIV-infected children and adolescents (N=426), 60% receiving PI\textsuperscript{4}

- Fasting Hypertriglyceridemia: 66%
- Hyper-cholesterolemia: 49%
- Glucose intolerance: 5%

## Frequency of abnormal lipid profile in Thai adolescents

Siriraj, Bangkok, 2013

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected N = 100</th>
<th>Healthy Total = 50</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOL $&gt; 200$ mg/dl</td>
<td>25 (25%)</td>
<td>12 (24%)</td>
<td>0.867</td>
</tr>
<tr>
<td>LDL $&gt; 130$ mg/dl</td>
<td>16 (16%)</td>
<td>8 (16%)</td>
<td>0.733</td>
</tr>
<tr>
<td>HDL $&lt; 35$ mg/dl</td>
<td>8 (8%)</td>
<td>0 (0)</td>
<td>0.017</td>
</tr>
<tr>
<td>TG $&gt; 150$ mg/dl</td>
<td>37 (37%)</td>
<td>1 (2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

49% receiving PI

V. Poomlek. 7\textsuperscript{th} IAS 2013, KL, MOPE047
Should we just leave it for the adult doctors to take care of the business when the children grown-up?

- They are important risk factors for CVD in adults
  - Atherosclerosis starts in childhood, esp. if TC>200 and LDL-C >130 mg/dl, or with metabolic syndrome

- DM interrupt normal life
  - Treatment is difficult for a regular teen
  - Complications of uncontrolled DM are serious
  - Can be delayed/prevented by early intervention

Metabolic Syndrome in children and adolescents: The clusters of metabolic risk factors (International Diabetes Federation)

- Waist circumference > P90
- FBS > 100 mg/dl
- TG > 150 mg/dl
- HDL < 40 mg/dl (<50 mg/dl in female >16 yo)
- BP > 130/85 mmHg

Presence of metabolic syndrome increases the risk of DM and CVD.
Exercise and Metformin can prevent DM

A randomised study of 3432 subjects with IFG or IGT

- At 3 years
  - Lifestyle gr.: reduced the risk of converting to DM by 58%
  - Metformin gr.: reduced the risk of converting to DM by 31%
  - Incidence of DM in lifestyle gr.: 39% lower than metformin gr.

Lifestyle modification include 7% weight loss and 150 minutes physical activities/week

Impaired FBS

Oral Glucose Tolerance Test (OGTT)
- Glucose 1.75g/kg/dose (Max 75g)
- Blood for Blood sugar and insulin
  - (at 0, 60, 120 min)

Impaired OGTT

Hyperinsulinemia
- Start Metformin
- DM education
- Life style modification
- ART modification

Dyslipidemia
- Life style modification
- ART modification
- Lipid lowering agent if not response

Physical exam/wt/ht/wc
Check FBS, Lipid q 6 mo.

Impaired FBS

F/U FBS, HbA1C q 3 M
Start Insulin SC if:
- HbA1C > 9 or
- FBS > 200 mg/dl

normal
- F/U FBS q 3-6 months

Dyslipidemia
- Life style modification
- ART modification
- Lipid lowering agent if not response

Check FBS, Lipid q 6 mo.
Management of Metabolic Complications in HIV-Infected Children and Adolescents

• Step 1
  • Lifestyle modification with diet and exercise
  • Weight control
  • Change PI to NNRTI or use ATV/r or DRV/r, may consider unboosted ATV
  • Metformin (for ≥10 yo) if impair FBS, OGTT

• Step 2
  • Insulin injection if HbA1C>9 or FBS >200 mg/dl
  • Fibrate if TG>400 mg/dl
  • Lowest dose statin (pravastatin or atorvastatin) if TC > 200 mg/dl (for ≥ 8 yo)

Need psychological and family support
How to treat LD?

• Stop using d4T (do not use d4T for > 6 months) >>

Phasing out d4T

• Avoid PI (may not be possible, or use ATV/r or DRV/r

• Medical: None is really effective and practical

• Liposuction for severe buffalo hump

• Filling therapy for facial lipoatrophy: may consider in adults

Before

After
Cardiac dysfunction

Cardiomyopathy associated with severe HIV diseases and improved with HAART.

However, long term ART may associated with increased cIMT.
3 year-old girl with pneumonia and cardiomyopathy

- **Echocardiogram** before ART (14/6/2010)
  - Severe MR
  - LV dilatation with hypokinesia LV wall, LVEF 16%
  - Minimal pericardial effusion
  - Imp: Dilated cardiomyopathy with severe MR
- **CD4= 1,346 (14%), VL 1.5x10^6**
- **Treatment**
  - ATB, Lasix, aldactone, dobutamine
  - Start AZT/3TC/NVP
- At 10 yo still have abnormal LVEF

CXR before HAART, CT 0.65 LVEF = 16%
CXR 6 M after HAART, CT 0.5 LVEF 39%
Structural and Functional Vasculature Changes in HIV-Infected Children

- Carotid intima-media thickness (IMT):
  - Increased in HIV-infected vs control uninfected children (p<0.001).
  - In infected children, PI treatment associated with increased carotid IMT.
  - Suggests both HIV & antiretroviral drugs play role.

Charakida M et al. Circulation 2005;112:103-9
The cIMT in association with on PI > 6 months in HIV-infected Thai adolescents

<table>
<thead>
<tr>
<th>cIMT (mm)</th>
<th>Receiving PI &gt; 6 months (n=53)</th>
<th>Receiving PI &lt; 6 months or never (n=47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal CCA</td>
<td>0.393 (0.284-0.478)</td>
<td>0.369 (0.289-0.448)</td>
<td>0.019</td>
</tr>
<tr>
<td>Distal CCA</td>
<td>0.40 (0.273-0.475)</td>
<td>0.381 (0.311-0.441)</td>
<td>0.022</td>
</tr>
<tr>
<td>ICA</td>
<td>0.353 (0.283-0.514)</td>
<td>0.345 (0.26-0.431)</td>
<td>0.179</td>
</tr>
<tr>
<td>Overall cIMT</td>
<td>0.379 (0.284-0.451)</td>
<td>0.372 (0.287-0.423)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

The values were presented in median (range)

V. Poomlek. 7th IAS 2013, KL, MOPE047
Low bone mass, Osteopenia and Vitamin D deficiency
A 15 years old Thai boy with growth failure

- At 1 year-old, he had recurrent severe pneumonia, delayed development, and growth failure.
- At 5 year-old, he had pulmonary TB
- He always be very small despite successful antiretroviral therapy

<table>
<thead>
<tr>
<th>Age</th>
<th>Regimen</th>
<th>CD4</th>
<th>VL</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 y</td>
<td>AZT+3TC+EFV</td>
<td>45</td>
<td>&gt;75,0000</td>
</tr>
<tr>
<td>8 y</td>
<td>“</td>
<td>461</td>
<td>26,400</td>
</tr>
<tr>
<td>11 y</td>
<td>AZT+3TC+TDF+LPV/r</td>
<td>638</td>
<td>163</td>
</tr>
<tr>
<td>12 y</td>
<td>“</td>
<td>784</td>
<td>&lt; 40</td>
</tr>
</tbody>
</table>
**DXA scan of lumbar spine (L2-L4)**

**Bone densitometry (Dual-energy x-ray absorptiometry; DXA) performed at 15 year-old**

<table>
<thead>
<tr>
<th></th>
<th>BMD</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjust to height age</td>
<td>0.721</td>
<td>-0.9</td>
</tr>
<tr>
<td>(12 y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjust to Thai</td>
<td>0.721</td>
<td>-2.1</td>
</tr>
<tr>
<td>reference (15 y)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Height age = 12**
Both HIV and ARV Associated with Osteopenia: A meta-analysis


Of 884 HIV-infected
- 67% had reduced BMD
- 15% had osteopenia

Initiation of ART is associated with a 2%-6% decrease in BMD over the first 2 years, a decrease that is similar in magnitude to first 2 years of menopause.
Bone Mass Accumulate From Childhood and Loss in Adulthood

Greatest bone mass gain at spine and hip is at:
- Girls: 11-14 yo. Tanner 2-4
- Boys: 13-17 yo. Tanner 4

Therefore, prevention of osteoporosis and fracture must be started in childhood

Bone mineral content is lower in prepubertal HIV-infected children

Age versus total body bone mineral content (TBBMC) adjusted for sex, race, height, and weight in HIV-infected (squares) and healthy (diamonds) prepubertal children.

Prevalence of low BMD measured by spine BMD (L2-L4) in Thai HIV-infected adolescents: The first study in Asia

Adjusted for Thai reference

N=98

<table>
<thead>
<tr>
<th>Z-score percentage</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z &lt; -1.5</td>
<td>36%</td>
</tr>
<tr>
<td>Z &lt; -2.0</td>
<td>24%</td>
</tr>
<tr>
<td>Z &lt; -2.5</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Pathogenesis of osteoporosis in HIV-infected patients

- Low calcium intake
- Vit D deficiency

HIV (gp120)

HIV (Tat)
RANKL
M-CSF

CD4 T cells

Protease inhibitors

Other cells

RANKL↑, OPG↓

TDF associated PRTD

Increased bone turnover

- Osteoclast differentiation

- Osteoclast activity

- Bone resorption

Osteopenia
Osteoporosis
Kaplan–Meier estimation of progression. Kaplan–Meier estimation of progression to (a) AIDS-defining events, (b) all-cause mortality, and (c) non-AIDS-defining events according to 25(OH)D concentration tertile at baseline.

Association of Vitamin D Insufficiency with Carotid Intima-Media Thickness in HIV-Infected Persons

Choi AI. CID 2011;0:1-4.
Association between initiation of antiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D

Mean change in 25(OH)D 6–12 months after initiating ART with and without efavirenz

[Graph showing mean change in 25(OH)D with and without efavirenz]

EFV induces CYP3A4 and CYP24, reducing CYP2R1, the enzyme involving in Vit D metabolism

Error bars represent ±SE. *P=0.0003 within group change and P=0.002 for between-group difference. ART, antiretroviral therapy; 25(OH)D, 25-hydroxyvitamin D.

In healthy children 19% were <20 ng/ml, and 60% were 20-30 ng/ml

% Vitamin D category
In HIV-infected adolescents

- **Deficiency**
  - Male: 50%
  - Female: 50%

- **Insufficiency**
  - Male: 30%
  - Female: 70%

- **>30 ng/ml**
  - Male: 20%
  - Female: 20%
Kidney Dysfunction

Screening is important because early renal diseases are asymptomatic.
Incidence of Persistent Renal Dysfunction in HIV-Infected Children in PACTG 219/219c

Occurrence of renal laboratory abnormality (N = 2068)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistently elevated creatinine*</td>
<td>307</td>
<td>(14.9%)</td>
</tr>
<tr>
<td>PP (≥ trace)</td>
<td>160</td>
<td>(7.7%)†</td>
</tr>
<tr>
<td>Persistent proteinuria and persistently abnormal creatinine and/or eGFR</td>
<td>21</td>
<td>(1.0%)</td>
</tr>
<tr>
<td>At least 1 persistent renal laboratory abnormality</td>
<td>446</td>
<td>(21.6%)</td>
</tr>
</tbody>
</table>

Incidence of new renal lab abnormalities was 3.7 events/100 child-years, with rates increasing between 1993-2005

CKD defined as confirmed (persisting for 3 months) decrease in eGFR to 60 ml/min per 1.73m² or less if eGFR at baseline above 60 ml/min per 1.73m² or confirmed 25% decrease in eGFR if baseline eGFR 60 ml/min per 1.73m² or less).

Mocroft A. AIDS 2010;24:1667-78.
13 year-old girl died from CRF

- At 5 yo, presented with nephrotic syndrome responded well to HAART and steroid
- She has been virologic suppressed with normalized CD4 for more than 6 years
- At 12 yo, presented with renal failure required renal replacement with CAPD
- Experienced several peritonitis events and failed CAPD
- She was refused for hemodialysis and renal transplantation

An episode of HSV stomatitis

No chance for HIV-infected children with renal failure
Neuro-psychiatric issues
Impact of HAART on HIV encephalopathy among perinatally infected children and adolescents.

Incidence of HIV encephalopathy and percentage of children on HAART from 1994 to 2006.
Mental Health Disorders in HIV-Infected Children and Adolescents

- Review of 8 studies including 328 HIV-infected children age 4-21 years; prevalence compare with overall population.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percent</th>
<th>Increased Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>24%</td>
<td>6x</td>
</tr>
<tr>
<td>Anxiety Dis.</td>
<td>29%</td>
<td>3.8x</td>
</tr>
<tr>
<td>Depression</td>
<td>25%</td>
<td>7.1x</td>
</tr>
</tbody>
</table>

Scharko AM. AIDS Care 2006;18:441-5
Impact of HIV Severity on Cognitive and Adaptive Functioning During Childhood and Adolescence

% impairment

![Bar chart showing cognitive impairment percentages for different categories: FSIQ, Perceptual Reasoning, Processing Speed, Verbal Comp, and Working Memory. The chart compares PHEU (Exposed uninfected), PHIV+/NoC (Infected w/o stage C), and PHIV+/C (Infected w stage C).]

**FIGURE 1.** Unadjusted rates of cognitive impairment: % scoring 2 SD below the mean. PHIV+/NoC indicates, perinatal HIV infection with no CDC Class C event; PHIV+/C, perinatal HIV infection with a prior CDC Class C event; PHEU, perinatally HIV-exposed but uninfected; FSIQ, full-scale intelligence quotient.

**A 13 Year-old Girl who suddenly became furious and angry with everything**

<table>
<thead>
<tr>
<th>Date</th>
<th>Age</th>
<th>Regimen</th>
<th>CD4</th>
<th>VL</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/3/2003</td>
<td>8 yrs. 11 mo.</td>
<td>Start AZT+3TC+EFV</td>
<td>25</td>
<td>0.9</td>
<td>40,400</td>
</tr>
<tr>
<td>10/2/2004</td>
<td>9 yrs. 10 mo.</td>
<td>“</td>
<td>596</td>
<td>19</td>
<td>&lt;400</td>
</tr>
<tr>
<td>8/1/2008</td>
<td>13 yrs. 9 mo.</td>
<td>“</td>
<td>1,052</td>
<td>42</td>
<td>&lt;40</td>
</tr>
<tr>
<td>16/6/2009</td>
<td>15 yrs. 2 mo.</td>
<td>“</td>
<td>912</td>
<td>35</td>
<td>&lt;40</td>
</tr>
<tr>
<td>5/1/2010</td>
<td>16 yrs. 9 mo.</td>
<td>“</td>
<td>1,171</td>
<td>44</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>
High levels of NVP and EFV may be found in 10% of Thai children.

Nevirapine plasma exposure and CYP2B6 516 G>T polymorphisms after administration of GPO-VIR Z30 in HIV-infected Thai children.

Chokephaibulkit K. Antivir Ther 2011;16:1287-95
Without good screening and early intervention, it may end up with premature age-related comorbidities.
Premature Age-Related Comorbidities Among HIV-Infected Persons Compared With General Population

Comparative risk of hypertension, diabetes mellitus, renal failure, cardiovascular disease, and fracture, by age, among patients versus control subjects.

Prevention of long term treatment complications

- Start ARV early, prefer NNRTI for 1st regimen
- Support adherence to the 1st line NNRTI regimens as long as possible >> delayed PI use
- Avoid long-term d4T
- Use TDF only when no other alternative NRTI
- Healthy life style
  - Regular exercise, control weight
  - Get enough sun light or vit D supplement
  - Eat healthy, low saturated fat diet, eat fish and veggies
  - Get enough calcium
  - No addiction to drugs, games, tobacco, alcohol, etc
- Screen and early treat for metabolic complications, kidney (esp. TDF), liver, neuropsychiatric, and bone health (esp. TDF)
Which children should be monitored BMD?

- May be before or during treatment regimens with TDF or PI, especially with risks:
  - Lean, small, or growth failure
  - Have history of fracture with minimal trauma

But make sure to know how to interpret. Best is to use ethnic specific reference. The different machine do not give same results, may need conversion

GE-Lunar = 1.195 x Hologic – 0.023

Thank you for your attention.