Treating HIV in children with tuberculosis

Helen McIlleron, Division of Clinical Pharmacology

University of Cape Town
Challenges of combined treatment

Large pill burdens, complex dosing schedules
Overlapping drug toxicities
Drug-drug interactions
Development of the immune reconstitution syndrome (IRIS)
Drug-drug interactions

NVP, nevirapine; PIs, protease inhibitors; EFV, efavirenz; ABC, abacavir; AZT, zidovudine; CYP, cytochrome P450; PGP, p-glycoprotein; UGT, UDP glucuronosyltransferases
### WHO ART guidelines for children with TB

<table>
<thead>
<tr>
<th>ART</th>
<th>TB treatment</th>
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<tbody>
<tr>
<td><strong>&lt; 2 years &amp; ARV exposure</strong></td>
<td>3NRTIs&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>&lt; 3 years; no ARV exposure</strong>&lt;br&gt;(or ARV exposure unknown)</td>
<td><strong>Nevirapine</strong> +&lt;br&gt;2NRTIs&lt;sup&gt;2&lt;/sup&gt;&lt;br&gt;or 3NRTIs</td>
</tr>
<tr>
<td><strong>&gt; 3 years</strong></td>
<td><strong>Efavirenz</strong> +&lt;br&gt;2NRTIs&lt;br&gt;or 3NRTIs</td>
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<tr>
<td><strong>On PI-based regimen, or 2nd-line regimen with PI indicated</strong></td>
<td>super-boosted PI&lt;br&gt;(LPV/RTV=1:1)+2NRTIs</td>
</tr>
</tbody>
</table>

<sup>1</sup>ABC+3TC+AZT/d4T; <sup>2</sup>3TC+ABC/AZT/d4T

WHO, 2010
NRTI-only regimens

• Inferior efficacy, especially when viral load is high
  • Berenguer et al. JAIDS 2006; 41:154-9

• High rates of NRTI mutations and virological failure in children
  • Bobat et al., 4th IAS Conf HIV Pathogen Treat Prev, Sydney 2007
  • Neely et al., 17th Conf Retroviruses Opportunistic Infect, San Francisco 2010

• Not evaluated in children with TB

• Rifampin may reduce ABC and AZT concentrations
**Nevirapine +2NRTIs in children with TB**

21 Zambian children aged 1.6 (0.7-3.2) years on TB treatment and paediatric Triomune®

<table>
<thead>
<tr>
<th></th>
<th>Children with TB (n=21)</th>
<th>Controls without TB (n=16)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>AUC&lt;sub&gt;0-12h&lt;/sub&gt; (mg.h/l)</td>
<td>52.0 (22.6, 159.7)</td>
<td>90.9 (40.4, 232.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C&lt;sub&gt;0&lt;/sub&gt; (mg/l)</td>
<td>2.93 (1.06, 11.40)</td>
<td>5.93 (3.28, 18.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/l)</td>
<td>6.33 (2.61, 14.5)</td>
<td>9.59 (5.28, 21.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number with C&lt;sub&gt;0&lt;/sub&gt; &lt; 3.0 mg/l</td>
<td>11</td>
<td>0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

_Oudijk et al. 5th IAS Conf Pathogen Treat Prev, Cape Town, July 2009_
Adjusted doses of lopinavir (LPV) & ritonavir (RTV)

- double dose LPV/r
  - LPV/RTV = 800/200 mg 12 hly

- super-boosted LPV
  - LPV/RTV = 400/400 mg 12 hrly

adequate LPV concentrations in adults on rifampin; concerns about hepatoxicity

- Nijland et al., AIDS 2008;22:931–935

Young children are different:

– doubled doses of LPV/r do not overcome the effect of TB treatment;
– super-boosting is not feasible in many settings

McIlleron et al., Antivir Ther. 2011;16(3):417-21
Chao Zhang et al., 2012, unpublished

-72% children
-48% adults

-73% children
-21% adults

+54% children
+68% adults

+19% children
+29% adults

Dose (LPV)

CLPV, VLPV/F

Dose (RTV)

F in children just 12% of adults

F in children just 12% of adults

bioavailability

bioavailability

bioavailability

bioavailability
Rifabutin (5 mg/kg, 3 x/week) with LPV/r in young children

Moultrie et al., ABSTRACT S-177; Poster board 993; Session 169; Thursday 2-4 PM.
Rifabutin (5 mg/kg, 3 x/week) with LPV/r in young children

Moultrie et al., ABSTRACT S-177; Poster board 993; Session 169; Thursday 2-4 PM.

Median (IQR) in adults on RIFABUTIN 150 mg 3 x/week and LPV/r
Naiker et al., CROI 2011
Rifabutin (5 mg/kg, 3 x/week) with LPV/r in young children

GRADE 4 neutropenia in 2 of 6 children

Moultrie et al., ABSTRACT S-177; Poster board 993; Sesson 169; Thursday 2-4 PM.
Children ≥3 years-old:
mid-dose interval concentrations of EFV (mdi-EFV)

Submitted to 13th Int workshop on Clin. Pharmacology of HIV Therapy, Barcelona, April 2012

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (IQR)</th>
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<tbody>
<tr>
<td>During TB treatment</td>
<td>1.64 (1.21, 4.40)</td>
</tr>
<tr>
<td>After TB treatment</td>
<td>1.96 (1.32, 2.93)</td>
</tr>
<tr>
<td>Control</td>
<td>1.7 (1.14, 2.27)</td>
</tr>
</tbody>
</table>
Children ≥3 years-old: mid-dose interval concentrations of EFV (mdi-EFV)

OVERALL: TB treatment had NO SIGNIFICANT EFFECT on EFV concentrations

Submitted to 13th Int workshop on Clin. Pharmacology of HIV Therapy, Barcelona, April 2012
Conclusions

- There are considerable concerns about the available treatment options for young HIV infected children with TB:
  - inferior efficacy; increased toxicity; complexity of regimens, large pill burden, and a lack of suitable formulations.

- PK, safety and efficacy studies are needed to define the best approaches:
  - Adjusted doses of LPV (or alternative PI) and RTV
    - Adequately powered studies, across ages
    - Alternative dosing approaches & alternative formulations
  - Optimized NVP dose
  - Efficacy (& Resistance mutations) with triple nucleoside regimen
  - EFV-based regimen in children <3 y
  - RALTEGRAVIR-based ART
  - Optimal RIFABUTIN dose with PI/r (& development of formulation)

- Novel TB regimens
  - RIFAMYCIN-SPARING

- Affordable FORMULATIONS suited to high burden settings are urgently needed
Acknowledgements


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