Addressing The Drug Development Needs Of Infants And Young Children: DNDi’s Pediatric HIV Program

The virus:
• High viral load, rapid progression to AIDS
• Resistant viruses – Pre-exposure through PMTCT

The drugs:
• Fewer options, limited safety data, fewer available formulation/FDCs,
• Only 2 (LPV/r & fosamprenavir) approved for infants/young children

The patients:
• Rapid developmental changes can significantly affect drug metabolism
• Dosing by weight and BSA with polypharmacy
• TB co-infection

The Pediatric HIV Challenge
Children Are Not Just Small Adults

<table>
<thead>
<tr>
<th>% of Total Body Weight</th>
<th>Newborn</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>Skin</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Skeleton</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Heart</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Liver</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Kidneys</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Brain</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

Benefit of PI-based ARV and formulation challenges

** Benefit **
- Replacing NNRTI due to prior exposure through PMTCT
- RCT data suggest superiority
- More forgiving in settings where stock-outs common
- Reduction in malaria
- Less resistance even with failing regimen
- After achieving viral suppression, switching back to NVP-based ART is possible **

** Challenges **
- Drug-drug interactions – mainly CYP3A4
- Complication of concomitant TB meds
- Low solubility for PIs
- Liquid formulation (alcohol/taste/stability/stock out)
- Pro-drugs are more soluble, but taste remains an issue

** Ashraf Coovadia et al., JAMA. 2010;304(10):1082-1090 **
Innovative PI formulation – The Cipla-MRC collaboration

- LPV/r sprinkles by Cipla*
- CHAPAS-2: Pharmacokinetics and acceptability of sprinkle formulation compared with syrup/tablets**

- Sprinkles preferred: better to swallow, storage/transport, important advantage for caregivers. 71% (<1 y.o.) chose to continue sprinkles over syrup after study.
- Inspired DNDi, leading to the concept of “4-in-1” sachet

* http://www.retroconference.org/2012b/PDFs/982.pdf
** http://www.controlled-trials.com/isrctn/pf/01946535; 4th Pediatric HIV Workshop, 2012 DC

Bring the “4-in-1” sachet to patients – DNDi-Cipla Collaboration on product development and access

1. Addressing the need for a PI-based first-line ARV FDC
2. Adaptable for use in treating TB-coinfection
TB-HIV challenge

- High rate of co-infection:
  - The true burden of disease in children remains uncertain due to diagnostic challenges and limited surveillance data.
  - HIV-infected pregnant women are at increased risk of transmitting both TB and HIV to their children

- Intensifying case finding:
  - GeneXpert TB diagnostics taking off in low-resource countries
  - The PMTCT/Pediatric HIV Technical Working Group recommends that intensified TB case finding be implemented in all PMTCT programs (PEPFAR July 2012)

- ARV and TB meds – challenges
  - Pill burden
  - Overlapping toxicity
  - Drug-drug interactions

Rifampin and PI: drug-drug interactions

- CYP3A4 metabolize LPV and RTV; elevated CYP3A4 levels reduce effectiveness of ARV therapy
- RTV is a potent inhibitor of CYP3A4 – used to “boost” LPV serum concentrations (LPV/r 4:1 ratio)
- Rifampin is a potent inducer of the enzyme CYP3A4
- With co-administration of rifampin, LPV/r (4:1) fails to reach effective trough level for efficacy

Overcoming drug-drug interactions with “superboosting”

- Increasing RTV to the “4-in-1” sachet for “superboosting”
- In parallel, to conduct PK study on the co-administration to validate “superboosting”
Bring to patients a “4-in-1” FDC in 2015 – working together with many partners

- **Product development:**
  - Cipla team
  - 4-in-1 sachet
  - Adapted 4-in-1 sachet: LPV/r at 1:1 for superboosting

- **Clinical validation of concept**
  - Chapas-2 (LPV/r sprinkles in 1-4 y.o.) & improvements
  - Additional partners for PK and efficacy studies using currently available ARV formulations (sprinkles of LPV/r and dispersible tablets of NRTIs)

More work......
More partners.....

**Acknowledgment**

- Chapas-2 team (MRC; Di Gibb; Uganda investigators)
- Cipla Manufacturing and R&D
- South-Africa-DNDi partnership (Cape Town, Johannesburg, Durban)
- DNDi-pediatric HIV And Pharmacology Expert Committee
END