Addressing The Drug Development Needs Of Infants And Young Children:

DNDi's Pediatric HIV Program

SATELLITES SESSION AT AIDS 2012

JULY 22, 2012

CATCHING CHILDREN BEFORE THEY FALL:

Addressing Urgent Needs In Developing Drugs For Young Children Living With HIV

Industry Liaison Forum

DNDi

Drugs for Neglected Diseases *initiative*

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The Pediatric HIV Challenge

The virus:

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

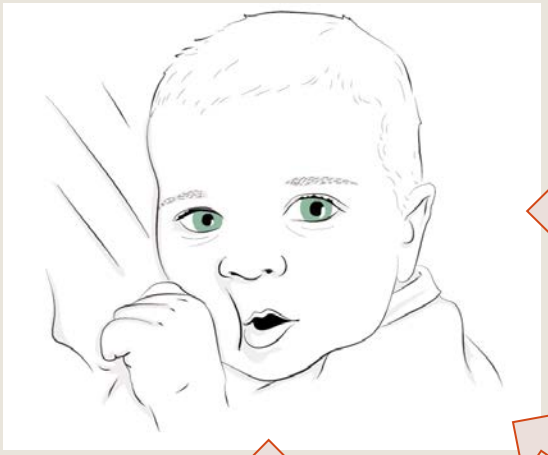
The drugs:

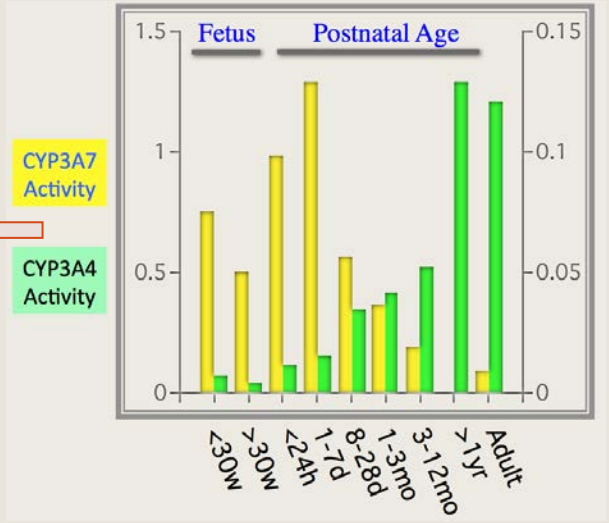
- Fewer options, limited safety data, fewer available formulation/FDCs,
- Only 2 (LPV/r & fosamprenavir) approved for infants/young children

The patients:

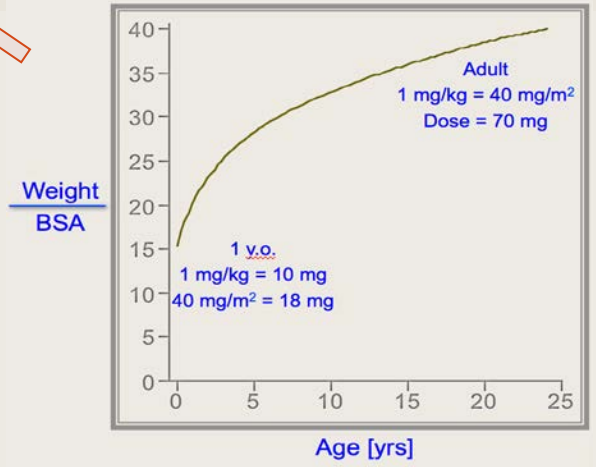
- Rapid developmental changes can significantly affect drug metabolism
- Dosing by weight and BSA with polypharmacy
- TB co-infection

Children Are Not Just Small Adults





	% of Total Body Weight	
Organs	Newborn	Adult
Skeletal muscle	25	40
Skin	4	6
Skeleton	18	14
Heart	0.5	0.4
Liver	5	2
Kidneys	1	0.5
Brain	12	2



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**

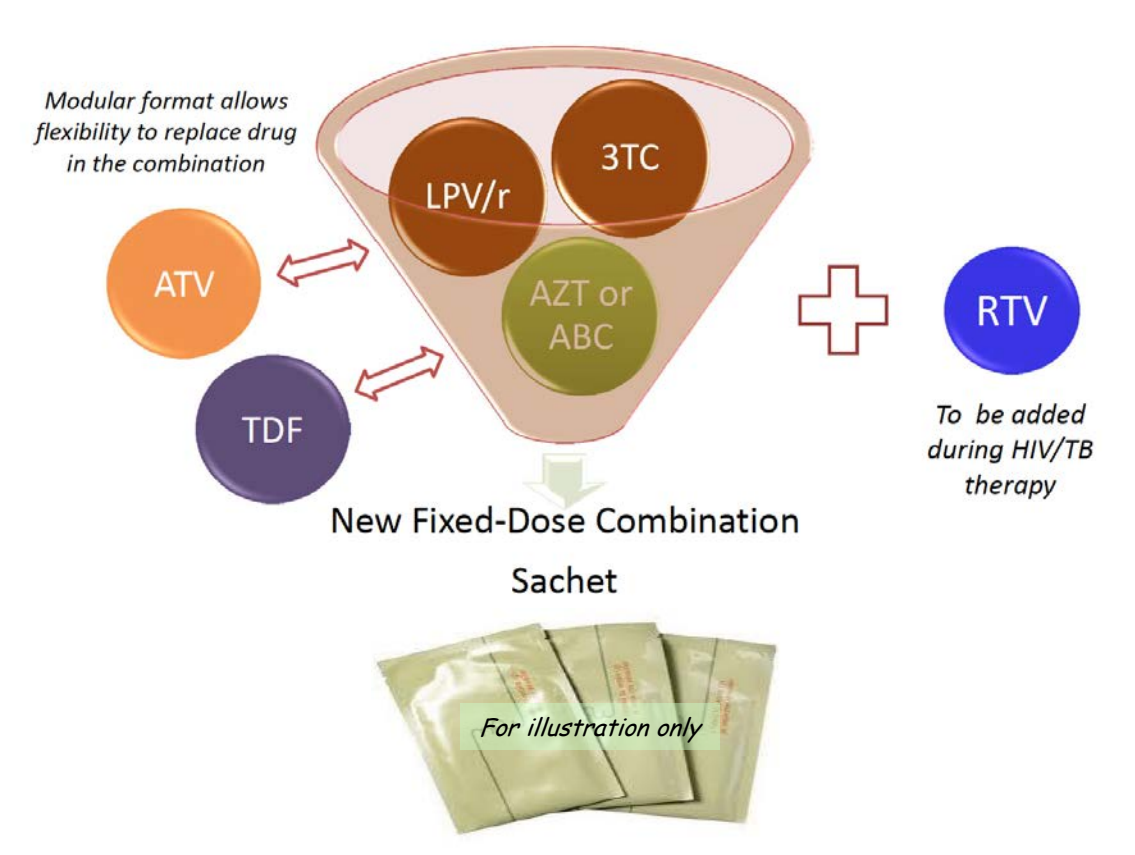
- Sprinkles preferred: better to swallow, storage/transport, important advantage for caregivers. 71% (<1 y.o.) chose to continue sprinkles over syrup after study.
- Inspired DNDi, leading to the concept of “4-in-1” sachet

* 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



Cipla
Caring for life

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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

TB-HIV challenge

- 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…..

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Acknowledgment

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

END