Forum for Collaborative Research

Accessing Drugs for Clinical Research in Resource-Limited Settings

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Barriers to ARV Research in Children

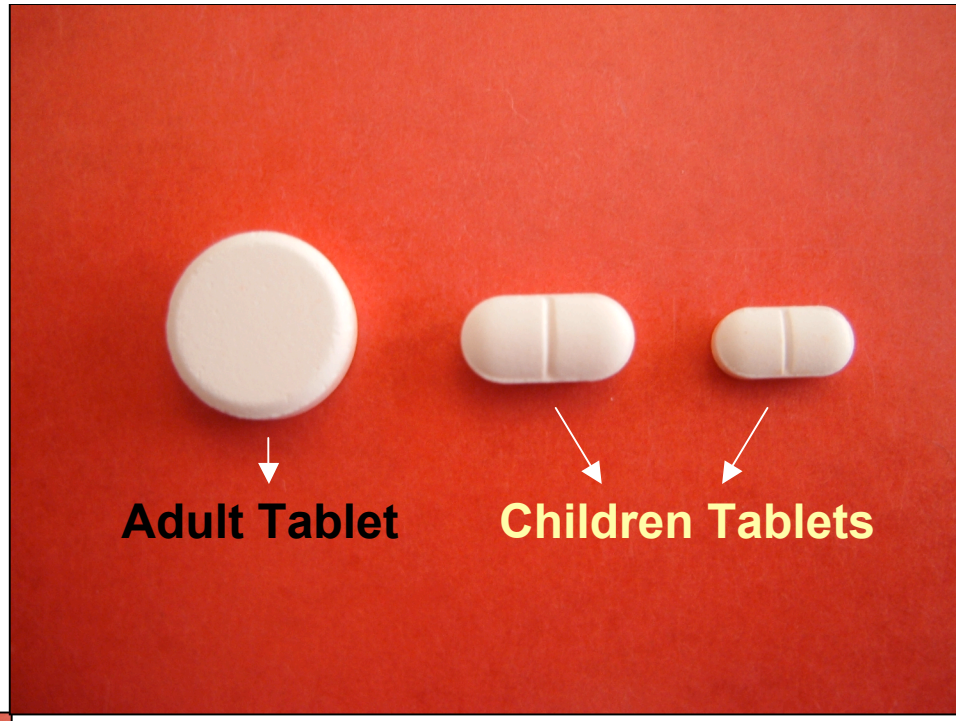
- Lack drugs with pediatric formulation
- Often lack dosing information for available drugs
- When have dosing information, is complex and changes as child ages
- Drug company issues:
  - Pediatric formulation: interest, incentive
  - Pediatric studies: interest, incentive
  - Generic company incentive for FDA submission
- Government issues:
  - Lack pediatric guidelines and don't purchase pediatric drugs – ethical issues when study over

Barriers to ARV Research in Children

- Of 21 approved ARV drugs, only 12 have approved pediatric indication.
- Lack of appropriate pediatric drug formulation for many ARVs:
  - Liquid actually not choice for children in resource-limited settings
  - Issues of weight, stability, transportation
  - Scored tablets with smaller dosing units, sprinkles, dissolvable tabs preferred
  - High cost
  - Lack financial incentive (even for generic companies – who need to submit to FDA for approval if to be used in studies under US regulatory supervision)

ART IN FIXED DOSE COMBINATIONS:

d4T + 3TC + NVP



FORMULATIONS

Adult: d4T (30 mg or 40mg), 3TC 150mg, NVP 200 mg)

Children
- **"Junior" (10 - 30 Kg):d4T 12mg, 3TC 60mg, NVP 100 mg**
- **"Baby" (3 – 10 Kg): d4T 6mg, 3TC 30mg, NVP 50mg**

Barriers to ARV Research in Children

- Lack of pediatric dosing information for many ARVs:
  - Age-related differences in body composition, renal excretion, liver metabolism, GI function leads to differences in dosing requirements
  - Drug pharmacokinetics varies by age
  - Studies in children lag behind adults and studies in infants are particularly lacking
  - Requirement to adjust dose as child grows makes treatment more complicated dosing schemes:
    - Need for weight-band based tables

Antiretroviral Drugs in Children

Drug	Pediatric formulation	Infant dosing
ABC	Yes	Yes (but only >3 mos)
AZT	Yes	Yes
3TC	Yes	Yes
d4T	Yes	Yes
ddC	No	No
ddI	Yes	Yes
FTC	No	No
TFV	No	No
NVP	Yes	Yes
DLV	No	No
EFV	No	No

Red = approved pediatric indication (although may not be all ages)

Antiretroviral Drugs in Children

Drug	Pediatric formulation	Infant dosing
APV	Yes	No (liquid contraindicated)
ATV	No	No
fosAPV	No	No
IDV	No	No
LPV/r	Yes	Yes (but only >6 mos)
NFV	Yes (powder, difficult to use)	Yes
RTV	Yes	Yes
SQV	No	No
TPV	No	No
T20	No (injection)	No

Red = approved pediatric indication (although may not be all ages)

Example of Weight-Based Table of Dosing Recommendations: NVP

Weight (kg)	Nevirapine syrup		Nevirapine tablets	
	Lead-in dose Weeks 1 & 2 (10mg/ml)	Full dose syrup (10mg/ml)	*Lead-in dose* Weeks 1 & 2 200mg tablets	Full dose 200mg tablets
5-6.9	2.2	4.5		
7-9.9	3.5	7		
10-11.9	4	8		
12-14.9	5	10	1/2 am only	1/2 am and pm
15-19.9	7	14	1 am or 1/2 am and pm	1 am and 1/2 pm
20-29.9			1/2 am and pm	1 am and pm
30-34.9				1 am and pm

Choice of over- vs under-dosing: toxicity vs resistance

Additional Barriers to Pediatric Studies

- High cost of pediatric formulations
  - Low priority for brand and generic drug companies to develop
  - Low priority for governments leads to
    - Lack of pediatric treatment guidelines
    - Lack of pediatric drug availability
  - If no pediatric treatment available after study, is it ethical to do study?
- Even if generic formulation is available, company must submit data to FDA for expedited approval to be able to use in US studies
  - Only one generic pediatric formulation approved to date (AZT – this month!)

Generic Drugs Available for Children in Some Countries But Not Approved by FDA

- **PACTG 390/PENPACT 1: US and PENTA collaboration**
  - **Strategy study of NNRTI vs PI-based initial therapy and when to switch (different RNA levels)**
  - **Drugs not provided by study, clinician choice**
  - **Collaboration with resource-limited countries became major problem due to generic drug issues:**
    - **Brazil: had to change from US regulatory to PENTA regulatory supervision**
    - **South Africa: ended up not participating**

Will Prior Single-Dose NVP Exposure Effect Subsequent Response to NNRTI-Based Therapy? CHILDREN: P1060

- **Compares viral response to NNRTI vs PI-based therapy in infants with CD4 <20%:**
  - **Infants with prior SD NVP (N=240)**
  - **Infants with no prior NVP exposure (N=240)**
- **Infant regimen difficulty:**
  - **S. Africa generic drugs not approved by FDA**
  - **Need for mutiple pharmaceutical company support, and only 2 of 3 companies agreed**
  - **Had to change initial regimen from d4T/3TC to AZT/3TC after months of negotiation**
- **Infant regimens (randomized):**
  - **A: d4T/3TC/NVP changed to AZT/3TC/NVP**
  - **B: d4T/3TC/LPV/rtv changed to AZT/3TC/LPV/r**