Increasing access to ARVs for children

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Overview

- Existing problems
- WHO/UNICEF meeting & recommendations
- Solutions identified (short and longer term)
  - Best use for now
  - Reformulation and new formulations
- Research and programmes issues

TREAT 3 million by 5 2005

Key Barriers to Pediatric HIV ART Treatment-

Lack of:

- **Advocacy and attention to children**
- **Trained pediatric health care professionals, with expertise or experience in treatment of HIV**
- **Affordable diagnostics**
- **Affordable available ARV for ped use**
- **Data for production and demand forecasting**

Specific Challenges relating to Pediatric ARV Drugs

- No pediatric labeling for ARV drugs (originator & generic) esp. for infants.
- Lack of pediatric formulations, especially fixed dose combos and generics
- Higher costs associated of treating children
- Difficulties gaining registration, supply & procurement (e.g. lead times, order size)
- Lack of data on PK and dosage in children

FDA approved pediatric ARV formulations

Zidovudine	Oral Syrup
Didanosine	Powder (reconstitute with antacid)
Lamivudine	Oral Solution
Stavudine	Oral Solution
Abacavir	Oral Solution
Nevirapine	Suspension
Efavirenz	Capsules (50 and 100 mg)
Ritonavir	Oral Solution (contains ethanol)
Nelfinavir mesylate	Oral Powder (to be mixed with foods)
Amprenavir	Oral Solution (contains propylene glycol)
Lopinavir/Ritonavir	Oral Solution (contains ethanol)

UNICEF- HIV supplies

ARVS

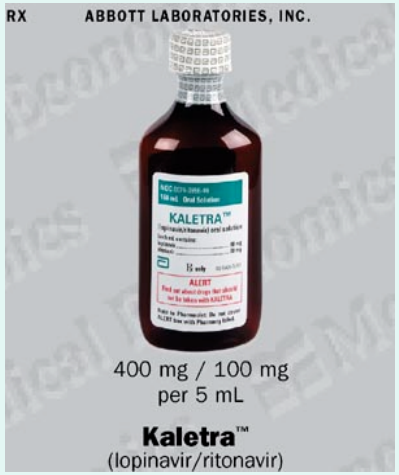
42 formulations in 75 different presentations,

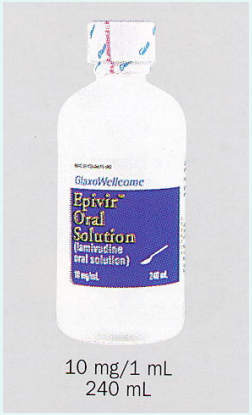
30 - 40% can be used for children

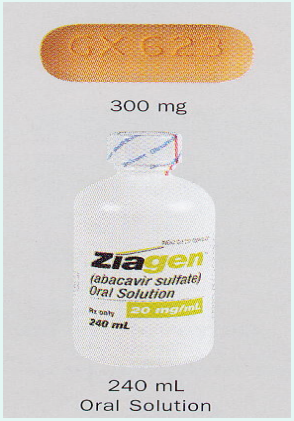
HIV Ab tests, CD4, CD8, Viral load including PCR equipment

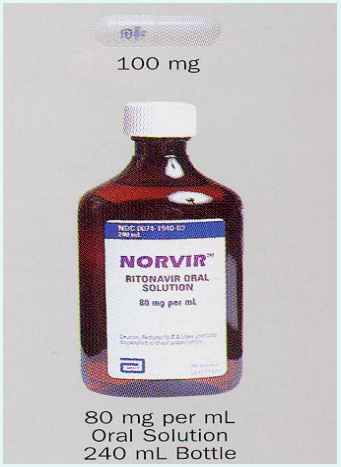
So what is the real problem?

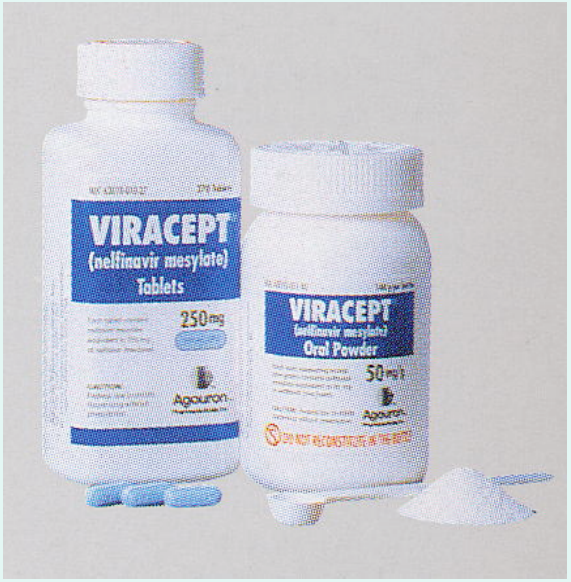
- More expensive than adult formulations
- No fixed dose combinations
- Estimating needs are problematic
- Complex dosing schedules mg/kg or mg/m^2
- Some need cold storage, shipment
- Distributing/dispensing glass bottles
- Taste of formulations
- Bulk of supplies











Obstacles for Pharmaceutical Companies

- **Lack of data for demand and production forecasting**
- **Not clear what's needed**
  - Regulatory requirements
  - Difficulties gaining PK data
  - Future ARV recommendations

- **Originators:**
  - Formulation difficulties (especially for PI's)
  - 'no business case', especially to make several formulations
  - Patent extension/restrictions (carrot by FDA) (Big sticks being proposed by EU)
  - Solid formulations – dosage requirements more challenging

- **Generic Companies:**
  - Also need a 'business case'
  - Cost (and lack of) expertise and research 'know-how'
  - Regulatory/ Pre-qualification issues

WHO/UNICEF Technical Consultation: Improving Access To Appropriate Paediatric ARV Formulations

Nov 3-4, 2004

1. Principles and practice for best use of currently available ARVs
2. Principles and priorities for design and development of modified/new ped ARVs
3. Demand forecasting & programme indicators for M & E of ped HIV care and ART.
4. Gaps, obstacles and priority operational research needs.

Experts form North & South, pharmacologists, regulators and product dev^{mt} experts

Recommendations - currently available ARV formulations in resource poor settings

Younger, smaller infants (<10kg)

- Syrups, solutions or dissolvable formulations of the following remain the best options
  - zidovudine (ZDV AZT)
  - abacavir (ABC)
  - lamivudine(3TC)
  - nevirapine (NVP)
  - lopinavir/ritonavir (LPV/r)
- Not ideally recommended in the very young due to problems in dispensing, acceptability, difficulty of use or need for refrigeration
  - stavudine (d4T) liquid
  - didanosine(ddi) sachets
  - nelfinavir powders
- Switch to available solid formulations as soon as possible or tolerated

Currently available ARV formulations –cont'd

Infants and children (usually > 10-12 kg)

- Switch to solid formulations as soon as possible or tolerated
- Use solid formulations of the first and second line drugs used for adults
- Tablets may be divided in half but not further
- Adult FDCs may result in under-dosing of individual components and this should be checked
- Adult FDCs need to be used (crushable or solid): dual FDC may reduce chances of under-dosing of NVP
- Adult FDCs can be used in combination with regular formulations either to augment one of the under dosed components of a triple combination (example additional NVP with a triple FDC based combination), or to complement a dual combination (example: AZT/3TC equivalent + nevirapine)
- Require single formulation of NVP in addition to dual or triple NRTI FDC
- Need to check for dose changes as children's growth, weight and development improve on treatment

Recommendations for future development of paediatric ARVs

- Syrups and solutions should be reserved for infants <10 -12kg.
- Where possible sachets, granules, or dispersible tablets preferred

Liquid formulations:

- Should be stable at room temperature; have small dose/volume; have long shelf life at high humidity and temperatures
- Be available in suitable dosage forms to provide appropriate dose ranges by 2-3kg weight band for smallest infants,
- Be packaged to provide for 28-30 treatment days
- Have suitable masking of bad taste (e.g. AZT)
- Have dispensing tools included

Recommendations for future development of paediatric ARVs

Solid formulations

- Preferred
- Be available in suitable dosage forms to provide appropriate dose ranges by 2-3kg weight band for smaller infants and by 10kg weight band for bigger ones
- Crushable, granulate or dispersible tablets easier
- Stable product with longer shelf life at high room temperatures and humidity
- Scored tablets
- Have suitable masking of bad taste

Single drug priorities – liquids and solids

- Reduced dosage forms of adult tablets of:
  - 3TC (40/75)
  - ZDV (75/150)
  - ABC
  - NVP (100)
  - EFV

  (some of these are currently available but not licensed for paediatric use)
- Pre-FDC formulation – co-packaging of e.g. ZDV/3TC/EFV: ddi/3TC/EFV

FDCs

Two drug FDC priorities - solids

d4T/3TC
ZDV/3TC
3TC/ABC
FTC/TDF

Three drug FDC priorities - solids

- Paediatric formulations of those FDCs already available for adults should be produced:

  ZDV/3TC/NVP
  ZDV/3TC/ABC
  d4T/3TC/NVP

- Any new product being developed for adults should be investigated for children

e.g. FTC/TDF/EFV is currently being developed for adults, paediatric formulation and established dose ranges are urgently needed.

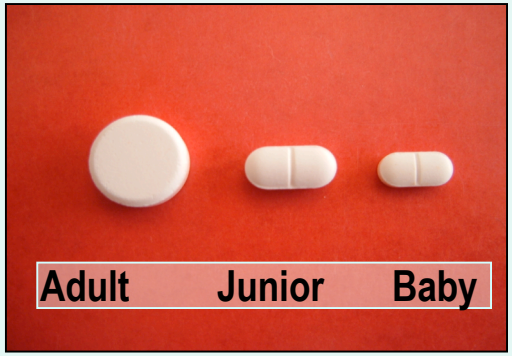
Priority FDCs

FDC for WHO first line treatment

D4T/3TC or ZDV/3TC + EFV or NVP

ZDV based triple and double FDC

- ZDV 150mg/3TC 75mg/plus EFV or NVP
- ZDV 150mg/3TC 75mg
- ZDV 75mg/3TC 40mg



D4T based triple and double FDC

– D4T-15/3TC-75 plus NVP or EFV

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Other recommendations

- Advocacy for including children
- Include ped ARVs in EOI for pre-Qual
- Dialogue with generics & originators
- Incentives and technical support to generics/originators
- Support essential research required
- Work with 'purchasers' to secure commitments to bulk purchase

Programming

Develop:

- treatment targets for children
- basic tools for programming (demand & production forecasting and coverage)
- Simplified dosing & dispensing tools

Provide technical support to:

- highest burden countries to scale up
- to 'fast track' national licensing/regulation and International pre-qualification
- To companies to support licensing/registration of emerging products

Research issues

Stimulate, encourage & coordinate the research agenda

3 Key areas identified

1. Burden of disease; (testing, diagnosis & tools)
2. Clinical – response (CD4,VL and clinical response), PK , bioavailability and current treatment practices
3. Program/operational – service delivery models, M & E and surveillance tools and practice

'The business case'

- Numbers are significant (> 50% of HIV inf. need ART by 2 years)
- Even with PMTCT, these will remain sig no's for at least 10-20 years
- Children often have parents/carers who also need ART
- Do we really need one?

Requirements for approval of ARV drugs

- Info on mechanism of action, ADME and PK profile, path to resistance
- Chemistry/manufacturing/controls info
- Adequate and well-controlled clinical trials of 24 to 48 weeks
- Demonstrated beneficial effect on HIV RNA, CD4 counts, clinical course
- For ped ARV usually must also evaluate:
  - Differences in absorption, distribution, metabolism, elimination - PK profile for age
  - Differences in side effect profile
  - Differences in therapeutic effect – if not different in HIV disease

Extra problems - use of adult formulations in children

- If splitting tablets ensure that procedure can be performed reliably by target population
- If crushing tablets or opening capsules may need PK data to support that route
- If using adult FDC must ensure each component provided in recommended dose for age range being treated

What about generic pediatric formulations

- Demonstrate bioequivalence
  - Single product - compare generic to reference drug (innovator)
  - For FDC product - compare generic FDC to individual reference drugs taken together
  - Preferred study design is randomized, single-dose, 2-way cross-over
- Monitor tolerability and safety

But -

- Bioequivalence studies need not be done in children
- If comparing 2 oral solutions no BE study required, if comparing formulations other than solutions BE study required
- If evaluating solid or suspension formulations dissolution testing required (to assure reproducible drug release)
- What if drug has no paediatric indication ?
- Registration problems in countries ?