Addressing Pediatric Needs of the Most Neglected: next steps

An updated overview of DNDi Pediatric Focus

Nathalie Strub Wourgaft (Medical Director)
Janice Lee (HIV Pediatric Clinical Manager)
A Fatal Imbalance

Tropical diseases (including malaria) and tuberculosis account for:
• 12% of the global disease burden
• But only 1.3% of new drugs developed

A Needs-Driven Model for Drug Development: DNDi

- Non-profit drug research & development (R&D) organization founded in 2003
- Addressing the needs of the most neglected patients
- Harnessing resources from public institutions, private industry and philanthropic entities

7 Founding Partners

- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation Brazil
- Medecins Sans Frontieres (MSF)
- Institut Pasteur France
- WHO/TDR (permanent observer)

7 support offices

- USA
- DRC
- Japan
- Brazil
- Kenya
- India
- Malaysia

Coordination team
Geneva + consultants
2011 DNDi Disease Portfolio

- **Leishmaniases**
  - HAT
  - Chagas

- **Helminths**

- **Paediatric HIV**

- **Malaria**

**Discovery**

- “Mini portfolios”
  - New in 2011
  - Completed; phasing out by 2014

**Pre-clinical**

**Clinical**

**Reg.**

**Access**
Pediatric needs for specific diseases

- **Malaria:**
  - Accounts for 20% of pediatric mortality in Africa
  - 200,000 deaths/year in newborns

- **Visceral Leishmaniasis:** fatal if untreated
  - 10 to 47% < 5 years and 48% to 69% < 15 years (depending on geographical region)

- **Human African Trypanosomiasis (sleeping sickness):** stage 2: fatal if untreated
  - 25% are children < 15 and 4% < 4 years old

- **Chagas Disease:**
  - > 15,000 annual incidence of congenital transmission

- **Pediatric HIV:** will be fully developed

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1 [http://www.who.int/malaria/high_risk_groups/pregnancy/fr/index.html](http://www.who.int/malaria/high_risk_groups/pregnancy/fr/index.html)
3 Source MSF, total: 31,817 cases
## Neglected Diseases & needs (for children)

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>ASAQ and ASMQ include paediatric formulation based on age bands</td>
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<tr>
<td>Visceral Leishmaniasis (VL)</td>
<td>No adapted formulation (except miltefosine), doses are mostly based on weight</td>
</tr>
<tr>
<td>Sleeping Sickness (HAT)</td>
<td>No age adapted formulation, doses are essentially based on weight, no oral treatment</td>
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<tr>
<td>Chagas Disease</td>
<td>Developed a 12.5mg dispersable tablet for newborns</td>
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</table>
More concretely …

- **HAT:**
  - 1 new treatment for HAT should enter Phase 2/3 in 2012, PIP to develop … (type of possible data to collect to define)
  - NECT: adult co-administration on EML - field study data will be available …
  - An NCE should enter phase I in 2012

- **VL:**
  - An NCE should enter phase I in 2012 (questions around timing and type of required PK data in different age band groups, adaptive design with inclusion of children as data become available …, basis for dose calculation with variable weights/age …)
  - PK data on miltefosine (on EML) in children will be collected from an ongoing study in Africa

- **Chagas:**
  - Benznidazole 100mg tablet on EML – development of dispersable 12.5mg tablet – pop pk children (incl newborns) ongoing
GLOBAL HEALTH

Pediatric HIV — A Neglected Disease?

Marc Lallemand, M.D., Shing Chang, Ph.D., Rachel Cohen, M.P.P., and Bernard Pecoul, M.D., M.P.H.

PAEDIATRIC HIV = NEGLECTED DISEASE?

DNDI’S ENTRY INTO HIV FIELD
Paediatric HIV

2.5 million children (<15 yrs) living with HIV in 2009

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Newly infected</td>
<td>370,000</td>
</tr>
<tr>
<td>Treated</td>
<td>355,000</td>
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<tr>
<td>AIDS deaths</td>
<td>260,000</td>
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</table>
New estimates 2010: more children infected, better survival, less coverage

<table>
<thead>
<tr>
<th></th>
<th>End 2009</th>
<th>End 2010 new estimate</th>
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<tbody>
<tr>
<td>Number of children in need</td>
<td>1.27 million</td>
<td>2.01 million</td>
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<tr>
<td>Number of children on ART</td>
<td>356,000</td>
<td>450,000</td>
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<tr>
<td>Coverage</td>
<td>28%</td>
<td>21.5%</td>
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</table>

2010 data, new estimates resulted in more children infected and less ART coverage.

WHO PAWG 2011: Shaffiq Essajee
Paediatric HIV

• Virtual elimination of paediatric HIV in high-income countries…

• …but 370,000 new infant infections each year and 2.5 million children with HIV/AIDS (92% in sub-Saharan Africa)
  – > 1,000 new pediatric HIV infections daily
  – > 700 deaths in HIV+ children daily

• HIV disease progression in children more rapid than in adults if no treatment is given
  – 1/3 of HIV+ infants will die by 1 yr old
  – 50% of HIV+ children will die by 2 yrs old
  – 80% of HIV+ children will die by 5 yrs old
A Tale of 2 Paediatric Epidemics

High-resource countries
- New perinatal infections are rare
- Effective treatment available
- Aging cohort of infected children
- Concerns long-term complications of treatment

Low-resource countries
- 1,000 infants are newly infected each day
- Diagnosis of infection in infants problematic
- Treatment when available is started late
- Problems with drug access

1. Lack of incentive for manufacturers to conduct paediatric studies or improve paediatric formulations
2. Small market
Scientific/Clinical Challenges

• HIV concentration in babies and infants 10-100 times higher than in adults – more aggressive therapy needed

• Many infected babies/infants are exposed to nevirapine through infant or maternal treatment or prophylaxis – viral resistance

• Pharmacokinetic parameters change considerably with age – complicates weight band dosing for certain drugs for fixed dose combination

• Tuberculosis, malnutrition, childhood morbidity is part of the picture
PI vs. NNRTI-based ART

- IMPAACT P1060 trial: LPV/r-based therapy demonstrated superior virological efficacy over NVP regardless of NVP exposure for PMTCT (Palumbo et al. IMPAACT P1060 Trial, Presented at CROI 2011)
P1060: LPV/r superior to NVP-Based HAART in sdNVP exposed children

Palumbo P et al. IAS, Capetown, South Africa, July 2009, Abs. LBPEB12

Week 24 failure rate

Week 24 difference across age strata:
NVP - LPV/r: 18.6% (p=0.015)
P1060: LPV/r superior to NVP-Based HAART in Children not exposed to sdNVP

In October 2010, the Data Safety Monitoring Board recommended unblinding the study results.

Median age at enrollment was 1.7 years (73% ≥12 months), baseline HIV RNA 535,632 copies/mL and CD4 percentage 15%.

The 24-week primary endpoint differences were 22.0% (<12 months) and 21.3% (≥12 months) in favor of LPV/r and 21.5% overall (p < 0.001).
Treatment Recommendations

- CHER trial: 76% reduction of mortality when children < 2 years initiate ART immediately vs. after immunologic decline or clinical symptoms (Violari et al. N Engl J Med 2008;359:2233-44)

- WHO Guideline revised Apr 2008 and 2010:
  - Early diagnosis and immediate ART for children <2 years, irrespective of CD4 count or WHO clinical stage
  - Infants and children < 2 yo exposed to NVP or NNRTIs either directly or via maternal treatment, use protease inhibitor (lopinavir/ritonavir) bd
## 25 FDA-Approved ARVs (as of Nov 2011)

<table>
<thead>
<tr>
<th>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</th>
<th>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</th>
<th>Protease Inhibitors (PIs)</th>
<th>Integrate Inhibitor</th>
<th>Fusion Inhibitor</th>
<th>CCR5 Antagonist</th>
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<tr>
<td>Abacavir (ABC)/ Ziagen</td>
<td>Delavirdine (DLV)/ Rescriptor</td>
<td>Atazanavir (ATV)/ Reyataz</td>
<td>Raltegravir (RAL)/ Isentress</td>
<td>Enfuvirtide (T20)/ Fuzeon</td>
<td>Maraviroc (MVC) Selzentry</td>
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<td>Saquinavir (SQV)/ Invirase</td>
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Implementation Challenges

Horrible tasting solution
6 months shelf life

Horrible tasting solution
40% alcohol
Require refrigeration until dispensing
1 day stability at >25°C

Multiple co-infections eg. TB, malaria requiring treatment, lack of co-formulations
Scope of DNDi Pediatric HIV Projects

- First-line ART for under 3-year-olds
- Short-term (<3 yr) and medium-term (<5 yr) projects
- Guided by target product profile (TPP) developed in consultation with expert advisors
# Target Product Profile

<table>
<thead>
<tr>
<th>Profile</th>
<th>Ideal</th>
<th>Acceptable</th>
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<tbody>
<tr>
<td>Target population</td>
<td>Both NVP-exposed and non-exposed HIV+ children under 3 years old</td>
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<tr>
<td>Dosing frequency</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Formulation</td>
<td>Water-soluble, dispersible tablet dosage form that can be used with small amount of liquid (suitable for 2-36 months old)</td>
<td>Sprinkles dosage form may work.a Crushable pill that can be used in “food” may be acceptable</td>
</tr>
<tr>
<td>Pill burden</td>
<td>1 (scored) pill - usable across broad weight bands (WHO table)</td>
<td>If 2 pills, must be same tablet count (or same fraction) for both</td>
</tr>
<tr>
<td>Durability&lt;sup&gt;d&lt;/sup&gt;</td>
<td>High genetic barrier (PI-like). Long plasma half-life.</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>Same as for adults</td>
<td></td>
</tr>
<tr>
<td>Safety/tolerability</td>
<td>Well tolerated and no laboratory monitoring needed</td>
<td>No laboratory monitoring needed</td>
</tr>
<tr>
<td>Palatability (taste)</td>
<td>No taste or nice taste for children</td>
<td>Palatable</td>
</tr>
<tr>
<td>Drug-drug interaction (TB Rx)</td>
<td>No drug-drug interaction with TB medicines, particularly rifampicin or rifabutin</td>
<td>Some drug-drug interaction with TB medicines, but can be used with proper dose adjustments</td>
</tr>
<tr>
<td>Stability</td>
<td>No cold chain requirement, minimum 2 years shelf life at room temperature</td>
<td></td>
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<tr>
<td>Cost</td>
<td>≤50 USD/patient/year (consistent with adult ART)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>To be investigated&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Summary of Actions Planned

1. Develop an improved PI formulation (LPV/r)
2. Evaluate different NRTI backbone options for use in first line (ABC & TDF)
3. Assess feasibility of resolving incompatibility between PIs and TB medicines
4. Investigate “induction-maintenance” concept (integrase inhibitors) and potential for special regimen for infants
Projects Under Consideration (1)

• Improved forms of LPV/r
  – Prodrugs: for ritonavir (RTV) & lopinavir (LPV)
    • Synthesis commissioned
    • Characterization planned (PK, stability formulation, etc.)
  – Improved formulation with existing LPV and RTV API
    • Nanodispersion formulation at IOTA
    • Nanoparticles at WuXi
  – Uncertainties:
    • Taste
    • Cost
    • IP
  – Consider atazanavir (ATV) as alternative
Projects Under Consideration (2)

Incompatibility between ARV & TB medicine

- Rifampicin induced CYP3A4 expression
- PIs and some NNRTIs are metabolized mainly by CYP3A4
- RTV inhibits CYP3A4, thus enhances PI exposure
- Extra RTV (superboosting) is required when rifampicin is given

- TB medicine that is compatible with ARVs
  - Rifabutin or rifapentine as alternative for rifampicin
  - To hold expert meeting with TB Alliance
  - To facilitate the development (long-term)

- ARV regimen that is compatible with TB treatment
  - RTV for super-boosting
  - Raltegravir + TDF/3TC adult trial in Brazil (Merck-Gilead/ANRS), planned in children (IMPAAACT)
Projects Under Consideration (3)

• Improved forms of ritonavir for super-boosting
  
  – Prodrug of ritonavir (RTV)
    • Involves chemical modification
    • Potential for dispersible tablet
  
  – Nanodispersion formulation of RTV
    • Technology is based on the formation of a dry, solid blend of insoluble material within a soluble matrix without chemical modification

• Nanoparticles
  
  • Field evaluation of super-boosting
Projects Under Consideration (4)

- “Induction-maintenance” scheme
  - HIV+ children have higher viral load, and disease progression is more aggressive
  - Adding an extra ARV drug (from new class) to 1st-line regimen during “induction” phase should lead to rapid reduction in viral load, which may result in patient benefit
  - Integrase inhibitors are known to achieve HIV RNA levels below detection at a more rapid rate
  - Merck drug raltegravir (RAL) is the furthest along, but not yet approved for infants (also need to explore ViiV integrase inhibitor)
  - Proof of concept study now?
Conclusions

• Every effort must be made to “eliminate” MTCT
• But utopia will not arrive tomorrow – infants will continue to fall through cracks
• Children with HIV/AIDS do not constitute lucrative “market” so are excluded from the pharmaceutical R&D agenda
• Appropriately adapted and affordable treatments are urgently needed
• Innovative, collaborative, not-for-profit models for developing pediatric formulations can fill gap
• Policy pre-conditions:
  – Access to IP and facilitation of open innovation
  – Innovative regulatory pathways
  – New incentives
  – Sustainable financing