ADDRESSING GAPS IN INNOVATION FOR NEGLECTED PATIENTS:
DNDi AND PEDIATRIC HIV/AIDS

Rachel Cohen, Regional Executive Director, DNDi North America
Proposals for a Global Innovation System that Responds to Patients Needs and Ensures Both Innovation and Access
July 22, 2012
A Fatal Imbalance

From 1975 to 2004

Tropical diseases: 18 new drugs (incl. 8 for malaria)

Tuberculosis: 3 new drugs

98.7% 1,535 new drugs for other diseases

1.3% 21 new drugs for neglected diseases

Crisis in R&D for drugs for neglected diseases

Patient Needs-Driven R&D Model

- Non-profit drug R&D organization founded in 2003
- Virtual R&D model to address the needs of the most neglected patients
- “Conductor of a virtual orchestra”: Harnessing resources and technical know-how from public research institutions, private industry, academic institutions, and philanthropic entities (emphasis on public leadership and role of ‘endemic’ countries)

Founding Partners
- Doctors Without Borders/ Médecins Sans Frontières (MSF)
- Indian Council of Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation (Fiocruz), Brazil
- Institut Pasteur, France
- WHO TDR (permanent observer)

7 worldwide offices
6 New Treatments Developed Since 2007

- ASAQ (Fixed-dose combination of artesunate + amodiaquine)
- ASMQ (Fixed-dose combination of artesunate + mefloquine)
- NECT (Nifurtimox-eflornithine combination therapy)
- SSG&PM (Sodium stibogluconate & paromomycin combination therapy)
- NEW VL TREATMENTS IN ASIA (SD AmBisome® / PM+M / A®+M /)
- Benznidazole (12.5 mg Pediatric dosage form of benznidazole)

- Easy to Use
- Affordable
- Field-Adapted
- Non-Patented
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**Legend:**
- NRTI = nucleoside reverse transcriptase inhibitor
- NNRTI = non-nucleoside RTI
- PI = protease inhibitor
- FI = fusion inhibitor
- CCR5 = CCR5 receptor inhibitor
- CCR2 = CCR2 receptor inhibitor
- IN = integrase inhibitor
- AI = attachment inhibitor
- MI = maturation inhibitor
- PK booster = pharmacokinetic booster
- FDC = fixed-dose combination
State of HIV Pharmaceutical Innovation

- “Golden decade” of ARV drug development (Source: 2011 TAG/HIV i-Base Pipeline Report)
  - > 30 approved ARVs or combination ARV products
  - Success rate for NCEs and FDCs (phase II or further) since 2003: 28.6%
  - Robust pipeline with no major signs of slowing (despite claims that HIV pipeline is drying up)
  - Increased role in innovation from generic industry

- > $13 billion market
  - But fundamental tension between innovation and access under current paradigm

- And many gaps remain
Children (<15 years) estimated to be living with HIV | 2011

Total: 3.4 million [3.1 million – 3.9 million]
Pediatric HIV

- Virtual elimination of MTCT in high-income countries...
- ...but 3.4 million children with HIV/AIDS (91% in sub-Saharan Africa)
  - 330,000 new infections per year (2011)
  - 230,000 AIDS-related deaths (2011)
- HIV disease progression in children more rapid than in adults
- ART coverage abysmal for children
  - 562,000 receiving ART as of 2011
  - ~23% compared with 54% for adults
  - Small fraction are infants or young children
- Children have no voice on the political or scientific stage and will never be a “lucrative market”
### FDA-Approved ARVs (2011)

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### FDA Approved ARVs (2011)

**Limited choices for neonates and infants**

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Not approved in neonates and infants
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 2010 Guideline Revision**:  
  - Early diagnosis and immediate ART for children <2 years, irrespective of CD4 count or WHO clinical stage  
  - Initiation of ART for children 24-59 months with CD4 count ≤750 cells/mm³ or %CD4+ ≤25, whichever is lower, irrespective of WHO clinical stage  
  - Initiation of ART for all children >5 years with CD4 count of ≤350 cells/mm³ (as in adults), irrespective of WHO clinical stage
But Treatment With What?

- New evidence suggesting PI-based therapy demonstrates superior efficacy to NNRTI-based therapy regardless of prior ARV exposure

- But...limitations of LPV/r
  - Solution contains over 40% alcohol
  - Unstable in tropical climates (not heat-stable)
  - Horrible taste
  - In some settings, up to 50% of children are co-infected with TB and need anti-TB therapy – with major negative DDI with LPV/r
  - Liquid formulations (not just of LPV/r) extremely complex for caregivers to administer
Most Urgent Treatment Needs (TPP)

- Formulations/regimens that are simple, easy to administer, and more tolerable (once daily or less, heat-stable, dispersible/sprinkles, tolerable taste)
- Durable (forgiving and minimal requirement for repeated immunological or virological testing; minimal risk for developing resistance)
- Suitable for infants (< 2 mos-3 yrs)
- TB treatment compatible
- Affordable
DNDi’s Pediatric HIV Program Goals

1. LPV/r-based first-line
   - For all newly diagnosed children who cannot swallow pills primarily (< 3 years and some older)
   - Regardless of prior NVP exposure
   - Combined with 2 NRTIs (based on risk of ABC hypersensitivity and other local factors)
     - ABC+3TC or
     - AZT+3TC

2. Efficacious super-boosting of the newly developed, PI-based first-line for treating TB co-infected children
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, store, 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.retroconference.org/2012b/PDFs/982.pdf)
Bring a “4-in-1” Sachet to Patients:
DNDi-Cipla Collaboration on Product Development & Access

- Address the need for a PI-based first-line ARV FDC
- Adaptable for use in treating TB co-infected children
Some Considerations & Constraints

- **Major programmatic challenges**
  - PMTCT ‘cascade’: Low ANC attendance, lack of access to HIV testing, poor access to optimal PMTCT/maternal ART, high loss to follow-up
  - EID: If we can’t diagnose, we can’t treat (point-of-care EID tool still not in hand)
  - Enrollment and retention in treatment programs, adherence/disclosure issues, etc.

- **WHO leadership:** Will WHO issue definitive guidance recommending PI-based first-line in next evolution of guidelines?

- **Adoption/uptake:** Will countries adopt a new/more expensive protocol?

- **Donor discourse:** Will the ‘elimination’ agenda shift attention from the need to treat children who continue to be infected?

- **Funding crisis:** Who will fund pediatric ARV procurement and treatment programs?

- **Ongoing innovation gaps:** How to accelerate R&D process for children with HIV (and other needs)?
Transforming Individual Successes into Sustainable Change?

DNDi experience and lessons:

- **Public leadership** essential to prioritize patients’ needs and ensure access
- Utilization and strengthening of **research capacity in disease-endemic countries** key (incl. tech transfer)
- Need for **increased resources** (new, sustainable funding)
- Need for **new incentives** for R&D that resolve trade-off between innovation and access (delinkage)
- Need to **decrease R&D costs** and **accelerate R&D process** (“time-to-patient”)
  - ‘Open innovation’ models to address knowledge gaps and improve efficiency
  - Pro-access IP management to ensure affordability and access
  - Harmonized regulatory strategies
Acknowledgements

• DNDi colleagues (B Pecoul, S Chang, M Lallemand, J Lee, J-R Kiechel)
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