Challenges for paediatric ARVs development
What’s in the pipeline?

Marc Lallemand
Antiretroviral drug discovery

- 1981: AIDS
- 1983: HIV
- 1985: tests
- Virus
  - Drug targets

- 1987 – today: 25 years of incessant antiretroviral drug discovery
The number of approved drugs decreases with children’s age

Polly Clayden

2012 Pipeline report I-BASE & TAG
<table>
<thead>
<tr>
<th>Drug</th>
<th>Calendar years</th>
<th>Time in years between adult approval and PD</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine</td>
<td>1991–2001</td>
<td>9.9</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>1995–2001</td>
<td>5.7</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>Saquinavir</td>
<td>1995–2010</td>
<td>14.9</td>
<td>Roche</td>
</tr>
<tr>
<td>Stavudine</td>
<td>1995–2001</td>
<td>5.7</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>1996–2001</td>
<td>5.5</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>1997–2003</td>
<td>6.5</td>
<td>Agouron</td>
</tr>
<tr>
<td>Abacavir</td>
<td>1998</td>
<td>&lt;1</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>2000–2007</td>
<td>7.5</td>
<td>Abbott</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>2003–2005</td>
<td>2.9</td>
<td>Gilead</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>2005–2007</td>
<td>2.7</td>
<td>Boehringer Ingelheim</td>
</tr>
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</table>

P. Clayden
2011 Pipeline report I-BASE & TAG.
Pediatric Planning in the Drug Development Process Timing

**US**

- Preclinical testing
- Phase 1: Peds plans discussed-maybe
- Phase 2: Written Request (BPCA) maybe issued
- Phase 3: PREA requirements agreed before approval (pediatric plan)
- PIP process begins
- Adult PK
- PIP modifications
- Pre-NDA/BLA
- Submission & Review
- Marketing Approval
- PMR
- Post Marketing Requirements
- Approved PIP required for MAA submission

**EU**

AAADV Workshop May 2011
Pediatric indications in 2011-2012

- **Darunavir** (DRV) oral suspension formulations for children ages 3–<5 and >6 years unable to swallow tablets
- **Raltegravir** (RAL) chewable tablets for children 2–18 years old;
- **Tenofovir** (TDF) oral powder and tablets of for children 2–<18 years old
- **Etravirine** (ETR) tablets for 6–18 years old;
- **Fosamprenavir** (FOS) oral suspension for children 4 weeks to <6 years old.
Staggered age de-escalation studies

- **ATV** powder & capsules +/- RTV 3 months to 6 years of age (PRINCE1 and 2 and IMPAACT P1020A)
- **EVG/COBI** reduced-strength tablets and suspension in all age groups (PIP)
- **EVG/COBI/TDF/FTC** reduced strength tabs 6–18 years (PIP)
- **ETR** dispersible tablets 2 months to 6 years (P1090)
- **MVC** CCR5 antagonist oral suspension 2–8y (A4001031)
- **RAL** granules for suspension 6 mg/kg for less than 2 (P1066 & P1097)
- **RIL** 25 mg once daily 12 to 18 y, more than 32 kg (PAINT), and granules 0–12 years (TMC278-C220)
ARV & TB Pipeline highlights (PIPs)

- **tenofovir prodrug** (GS-7340) improved PK and cellular penetration, low doses (10-24 mg/d vs 300 mg/d TDF)
  - GS-7340/FTC/EVG/COB studied
  - GS-7340/FTC/DRV/COB, first PI-based single-tablet FDC

- **Dolutegravir** (DTG), OD in naïve, no boosting, resistance profile distinct from raltegravir? low dose, UGT1A1 (CYP3A minor route) i.e. manageable interactions; pediatric granule formulation (p1093)
  - DTG/ABC/3TC (572-Trii) studied

- **Bedaquiline** (TMC 207) evaluated in DR-TB and DR-TB/HIV co-infected children (p1108)
Caveat 1: Registration ≠ Access

- For 95% of HIV infected children worldwide who live in Africa, Asia and Latin America access, beyond FDA tentative approval, requires:
  - In country regulatory approval
  - Country program adoption (national guidelines)
  - Affordability
  - Efficient supply chain
  - (in addition to timely HIV diagnosis and appropriate monitoring)
Caveat 2: Generic competition, IP & prices

- 100 fold price decrease of 1st line therapy in 6 years
- Will this repeat itself with newer drugs?
  - Widespread patenting in Developing Countries
  - Basic patent expiry date for ETR: 2019; RAL: 2022
- Licenses negotiated from a public health perspective through the Medicine Patent Pool may be a key mechanism
Caveat 3: Generic market fragmentation

- Advocacy to manufacturers has resulted in many formulations of the same drugs
  - Many products (45!) but few options (2 lines!) and still no adapted PI formulation
  - Top 4 (of 45) represent more than 50% of the total market value (UNITAID/CHAI)
- No demand for the WHO prequalified combination (ABC+3TC+ZDV 60/30/60mg tablet)
- Need for consolidated orders to reach manufacturer batch size
  - Up to 9 months delays before order are fulfilled
Caveat 4: Shrinking pediatric HIV population

Projected annual no. of newly infected children and no. receiving early HIV diagnosis and ART during infancy

- Newly infected children
- Diagnosed and access to ART <12mo
Beyond new drugs
Treatment optimisation: WHO Treatment 2.0

- **Re-formulation** (improve drug bioavailability; stability; acceptability; extended release formulations)
- **Co-formulation** (FDCs or co-blister pack)
- **Dose adjustment/reduction** (reduce toxicity & pill burden/size)
- **Sequencing strategies**, induction-maintenance; intensification
  - NEVEREST (LPV->EFV);
  - ARROW (NNRTI+2 or 3 NRTIs-> NNRTI+2NRTIs or 3NRTIs)
- **Drug manufacturing process** (improve synthesis/reduce cost)
- **Management of TB/HIV co-infection** (RIF PI & NNRTI interactions)
  - Additional RTV to reach a 1:1 superboostin LPV/RTV ratio
  - Evaluation of alternative options: Rifabutin, RAL
  - Appropriately dosed pediatric FDCs (TB Alliance)
Adapting doses and formulations to children

- Smaller size = Smaller absolute dose
  - Growth requires a wide range of doses (difficult with solid dosage forms)
  - Dose relative to size (mg/kg, mg/m², mg/kg^{3/4}) is not proportional and very difficult to predict
  - Developmental changes in drug absorption, distribution, metabolism, excretion, pharmacogenetics
Requirements for pediatric drug dosage forms

- ensure sufficient bioavailability taking into account children's particularities
  - Reach efficacy target (may undergo a maturation process; for antiretrovirals is assumed to be the same as adults)
  - Remain below toxicity target (not necessarily well known)
- contain nontoxic excipients for the age group
  - Limit of inactive ingredients per the dosing regimen
- acceptable and palatable
  - Taste/Sweetness preference differ around the world
- acceptable dose uniformity

Requirements for pediatric drug dosage forms

- easy and safe to administer
  - Flexible dosage: dispersible or chewable tablets, sprinkles, granules
  - Minimum dosing frequency
- socio-culturally acceptable (stigmatization)
- have precise and clear product information
- appropriate for caregivers / setting
  - Stability in Zone IV climatic conditions (30°C, 65 or 70% RH)
  - No clean water required for dispensing medication
  - Heat stable – no refrigeration required

Solid formulations


Advantages
- Nontoxic excipients
- Lower price
  - switch from liquids to solid FDCs
    = US$100 shipment/storage
- Various options for taste masking
- Modified release options
- Stability (storage & in-use & different climates)
- Reduces storage space
- High content uniformity
- Easy administration

Disadvantages
- Dimensions: swallowing
- Requires liquid for swallowing
- Aspiration (safety)
- Difficult dose adaption
- Varying bioavailability
- Dissolution rate impact

Acceptability of 3 mm minitabs in young children
Solid formulations vs. liquid formulations

- **Licensed**

- **Off label use**

From off-label use of Adult formulations to Pediatric FDCs

A drug dosage table is a useful tool to facilitate prescriptions of antiretroviral drugs for children in Thailand

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¹Médecins Sans Frontières, Bangkok; ²Prachomklao Hospital, Department of Paediatrics, Petchaburi; ³Technical and Information Unit, R&D Institute, Government Pharmaceutical Organization, Bangkok, Thailand; ⁴Médecins Sans Frontières, Operational Research, Medical Department, Brussels, Belgium

- MSF pediatric drug dosage table (splitting tablets, adding NVP)
- Weight band dosing table created by WHO experts to enable generic production of paediatric FDC
- First paediatric FDC WHO prequalified in 2008, 4 years after adult FDC.
Pediatric Fixed Dose Combinations

- Current pediatric FDCs are NVP based and have been mostly used in older children
- CHER trial
  - HIV diagnosis in the first months of life
  - treatment initiated immediately
- Change in the pediatric HIV treated population
  - Higher viral load & ARV exposed viral population
- P1060 trial
  - regardless of exposure to NVP for PMTCT LPV/r superior to NVP based therapies
Switching from NVP to LPV/r first-line?

**LPV/r + 2 NRTIs**
- Liquid only currently
- Bitter taste
- Neurotoxic excipients
  - 42% ethanol
  - 15% propylene glycol
- Needs cold chain
- Heavy to carry, hard to hide
- Difficult dosing
- Need for RTV super-boosting in TB/HIV co-infected children

**NVP based ART**
- FDCs available
- Baby and junior dosing
- Scored tablets
- Can be crushed
- Easy dosing
Lopinavir-Ritonavir challenges

- According to the Biopharmaceutics Classification System (BCS) absorption of oral drugs predictable knowing:
  - its intrinsic permeability across the intestinal mucosa
  - its concentration at absorption site
  - and assuming dose form rapid dissolution
    - ≥85% API dissolution from formulated product in 30 minutes

<table>
<thead>
<tr>
<th></th>
<th>High solubility</th>
<th>Low solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Particle size, polymorphic forms, solubility enhancers</td>
</tr>
<tr>
<td>High permeability</td>
<td>ZDV, FTC</td>
<td></td>
</tr>
<tr>
<td>Low permeability</td>
<td>3TC, ABC</td>
<td>RTV, LPV</td>
</tr>
<tr>
<td>transit time, GI transporters and metabolic enzymes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

highest dose soluble in 250 mL at pH 1 to 7.5

more permeable than co-dosed drug at least 85% absorbed (WHO).
Lopinavir-Ritonavir challenges

- LPV requires RTV boosting
  - RTV is a CYP3A4 substrate and inhibitor.
  - Inhibits GI metabolism by enterocytes CYP3A4 and Pgp efflux transporters (Cmax)
  - Inhibits liver CYP3A4 and Pgp thus maintaining LPV half-life
  - Boosting effect may be affected by GI and liver enzyme maturation

- Lopinavir absorbed in the beginning portion of the GI tract
  - Effect of gastric Ph, GI development on absorption

Initial explorations

- Original LPV and RTV formulations were alcohol based (LVP/r and RTV liquid and soft gel capsules; Abbott)
- Replaced for adults and older children with LPV/r tablets (Abbott)
- Tablets cannot be used in young children as crushed they lose up to 50% bioavailability
- Alternative options explored by DNDi
  - Prodrugs (eg. RTV)
    - Nano particles
    - Nano dispersions

Encouraging PK in animals
Poor taste; 5 years time line (NCE)
Cipla meltrex sprinkles lopimune

[Image: Results of adult bioequivalence study presented at CROI 2012]

Pharmacokinetic parameters

Table 2: Pharmacokinetic parameters of Lopinavir and Ritonavir administered as oral solution and as sprinkles.

<table>
<thead>
<tr>
<th></th>
<th>AUC_{0-1} (hr·μg/ml)</th>
<th>AUC_{0-∞} (hr·μg/ml)</th>
<th>C_{max} (μg/ml)</th>
<th>T_{max} (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lopinavir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprinkles</td>
<td>86.98±19.95</td>
<td>92.99±21.96</td>
<td>6.82±1.3</td>
<td>6.26±2.17</td>
</tr>
<tr>
<td>Solution</td>
<td>84.57±26.48</td>
<td>89.26±27.83</td>
<td>6.28±1.77</td>
<td>5.99±0.85</td>
</tr>
<tr>
<td>Ln-transformed 90%</td>
<td>91.19−126.53</td>
<td>87.75−122.54</td>
<td>01.31−121.02</td>
<td></td>
</tr>
<tr>
<td>Confidence intervals (T/R)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Ritonavir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprinkles</td>
<td>6.69±2.45</td>
<td>6.86±2.51</td>
<td>0.78±0.23</td>
<td>6.88±1.95</td>
</tr>
<tr>
<td>Solution</td>
<td>6.23±2.22</td>
<td>6.38±2.24</td>
<td>0.77±0.34</td>
<td>5.72±0.59</td>
</tr>
<tr>
<td>Ln-transformed 90%</td>
<td>98.23−123.15</td>
<td>96.63−124.6</td>
<td>08.4 −139.96</td>
<td></td>
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<tr>
<td>Confidence intervals (T/R)</td>
<td></td>
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<tr>
<td><strong>Ratio of Least square means T/R</strong></td>
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<tr>
<td>Ln-transformed</td>
<td>102.51</td>
<td>103.71</td>
<td>109.38</td>
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<tr>
<td><strong>Ratio of Least square mean T/R</strong></td>
<td></td>
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<tr>
<td>Ln-transformed</td>
<td>105.08</td>
<td>105.09</td>
<td>104.55</td>
<td></td>
</tr>
</tbody>
</table>

Jaideep A Gogtay Milind Gole Abhishek Khanna Raghu Naidu Geena Malhotra Shrinivas Purandare
Cipla Limited, Mumbai, India; Sitec Labs, India

[Images: Mean Plasma Concentration vs. Time Profile of Lopinavir (Linear) and Mean Plasma Concentration vs. Time Profile of Ritonavir (Linear)]
- Exposure LPV in sprinkles comparable to the Abbott oral solution and historical data
- High variability
  - CV%: 62-66%

Pharmacokinetics and acceptability of a new generic lopinavir/ritonavir sprinkle formulation compared with syrup/tablets in African, HIV-infected infants and children according to WHO weight-band dose recommendations.
R Keishanyu, Q Fillekes, P Kasirye, et al., on behalf of the CHAPAS 2 trial team; 4th Pediatric workshop 2012
Cipla – DNDi – MRC partnership

- DNDi has joined MRC to add to Chapas-2 the key cohort of 1 to 4 years of age
- Further develops with Cipla two LPV/r fixed dose combinations
4-in-1 LPVr FDCs basic questions

- Twin sachets or LPVr + NRTIs granules of the same size in a single sachet/capsule?
  - Are all components compatible? At all ratios?
- Can all components be adequately taste masked?
- Given less than 20% loading for LPV/r and 50% for NRTIs, will the amount of excipients remain within acceptable limits?
- Will bioequivalence of all components be confirmed?
  - Consequences on the clinical development?
- What LPV/r : NRTIs ratio? What dosage strengths? For what weight bands?
Ratios, strengths, weight bands

WHO weight bands dosing is a compromise utilizing existing formulations. FDCs must assemble drugs with different metabolic pathways of different maturation kinetics.

**ZDV**: glucuronyl transferase + renal excretion

**3TC**: 5% transsulfoxide; unchanged renal elimination

**ABC**: alcohol dehydrogenase and glucuronyl transferase

**LPV**: CYP3A enzymes oxidation

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[Graphs and charts showing acquisition of renal function and changes in metabolic capacity over different ages and time periods.]
Which targets? Modeling exposures

- LPV-AZT-3TC combination
  - LPV: Cmin 1 – 8 mg/L (efficacy-toxicity)
  - 3TC: reported AUCs in adults (8.9 to 16.6 mg.h/L)
  - AZT: reported AUC in adults (3 to 5 mg.h/L)

- AUC = Fraction of dose absorbed / clearance function of age and weight
- Weight band dosing
  - Pooling existing PK data and modeling drug exposure according to age and weight bands
Preliminary results in 6 to 20 Kg
In summary

- Pediatric drug development is challenging, generally.
- The context in which new drugs, new formulations, new combinations will be introduced cannot be ignored:
  - Shrinking pediatric population
  - Fragmented market
  - Intellectual property rights obstacles
- We need to think strategically to give HIV infected infants the best chances to reach adulthood safely while keep all their treatment options.
Thank you for your attention

Acknowledgments
Janice Lee
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Stephen Robinson
Ed Capparelli
Jean Marc Treluyer
Saik Urien
Formulation, gastro-intestinal maturation and absorption

- Acceptability of the pediatric formulation is key
- Early gastro-intestinal maturation further modulates absorption
  - Gastric Ph (ionisation, solubility, stability, coating)
  - Gastric emptying time
  - Gastro-intestinal motility
  - Intestinal integrity