The Global Accelerator for Paediatric Formulations (GAP-f)

Ensuring children have accelerated access to optimal drug formulations

Sébastien Morin (International AIDS Society, Switzerland)
9th EuPFI – 20 September 2017 – Warsaw (Poland)
The paediatric HIV drug market is too small and fragmented to succeed without coordinated and sustained intervention.
The Global Accelerator for Paediatric Formulations

- Builds on the HIV experience and formalizes collaboration across sectors to ensure accelerated development and uptake of the most needed drugs and formulations for children.

- Is a drug development consortium that will accelerate timelines, reduce development costs, and improve global health outcomes through a coordinated and purposeful clinical, product development, and commercialization strategy.

- Focuses on HIV, with the intention to address similar challenges in other disease areas in the near future.
Challenges for paediatric drug formulation development

- Drug absorption, distribution, metabolism and elimination changes lead to different PK/PD at different ages

- Need for taste-masked, scored tablets in dispersible, chewable or crushable forms to cover the entire age spectrum; these are difficult to develop

- Sequential enrolment of different age groups into PK studies and clinical trials delays progress

- Small market in high-income countries does not stimulate development of formulations adapted to paediatric needs

- Limited interaction between industry and research community on paediatric study plans (PIP/PSPs)
The paediatric HIV “market”

- At the end of 2015, 1.6 million children were living with HIV with an estimated **50% on treatment** (and less on optimal formulations)

- The number of new infections will drop over time with increased PMTCT coverage but there will still be a **substantial** number of children that need treatment

- The best drugs and formulations are **not available**
  - Lack of clinical evidence to define appropriate paediatric doses
  - Delayed time to market (product development and uptake) of several years compared to adult products
## Access to paediatric drugs takes too long...

<table>
<thead>
<tr>
<th>SRA approval</th>
<th>Adults</th>
<th>Children</th>
<th>DELAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>2001</td>
<td>2010</td>
<td>9 years</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>2003</td>
<td>2014</td>
<td>11 years</td>
</tr>
<tr>
<td>Darunavir</td>
<td>2006</td>
<td>2011</td>
<td>5 years</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>2007</td>
<td>2013</td>
<td>6 years</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>2011</td>
<td>NA</td>
<td>?</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>2012</td>
<td>NA</td>
<td>?</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>2013</td>
<td>2017 (partial)</td>
<td>4 years</td>
</tr>
<tr>
<td>TAF (FDC)</td>
<td>2016</td>
<td>NA</td>
<td>?</td>
</tr>
</tbody>
</table>

Burger and van Rossum. Adapted from Improved labelling of antiretrovirals for paediatric use. Lancet HIV. October 2016.

“In not a single instance, has there been an important difference in efficacy or safety between adults and children. Is it not time to change the paradigm, and assume that new drugs approved for adults can be used in children, until proven otherwise?”

*Alexandra Calmy, Plenary presentation at IAS 2017 (Paris)*

Reference: Calmy, 2017
This is not a situation unique to HIV...
Precursors to GAP-f

- Prioritization (PADO)
- Dosing (PAWG)
- Development (PHTI)
- Selection (IATT)
- Procurement (APWG)

Clinical research
Product development and introduction

Key formulations are prioritized in the context of a public health approach

Children

Priority formulations are reliably supplied to countries

Technical and research work is undertaken to support development of the priority formulations

Priority formulations are procured via a pooled mechanism

Priority formulations are included in optimal formulary for selection
Prioritizing HIV products and dosage

NVP/AZT for infant prophylaxis

DRV/r (120/20 mg)

RAL (50 mg scored)

DTG single (10 mg scored dispersible)

DTG/3TC/ABC (5/30/60 mg)

F/TAF

TAF/XTC/DTG

DTG/DRV/r

Reference: PADO 3 priorities, 2016

PADO
Paediatric ARV Drug Optimization

PAWG
Paediatric ARV Working Group
Supporting product development

- Prioritization (PADD)
- Dosing (PAWG)
- Drug optimization
- Children
- Procurement (APWG)
- Selection (IATT)
- Development (PHTI)

Paediatric HIV Treatment Initiative (PHTI)
Selecting products and strengthening supply

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Formulation</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td>EFV</td>
<td>Tablet (scored)</td>
<td>200 mg</td>
</tr>
<tr>
<td>NNRTI</td>
<td>NVP</td>
<td>Tablet (disp, scored)</td>
<td>50 mg</td>
</tr>
<tr>
<td>NNRTI</td>
<td>NVP</td>
<td>Oral liquid</td>
<td>50 mg/5mL, 100mL</td>
</tr>
<tr>
<td>PI</td>
<td>LPV/r</td>
<td>Tablet (heat stable)</td>
<td>100 mg/25mg</td>
</tr>
<tr>
<td>PI</td>
<td>LPV/r</td>
<td>Oral liquid</td>
<td>80 mg/20 mg/mL</td>
</tr>
<tr>
<td>PI</td>
<td>LPV/r</td>
<td>Oral pellets</td>
<td>40mg/10mg</td>
</tr>
<tr>
<td>FDC</td>
<td>AZT/3TC</td>
<td>Tablet (disp, scored)</td>
<td>60 mg/30 mg</td>
</tr>
<tr>
<td>FDC</td>
<td>ABC/3TC</td>
<td>Tablet (disp, scored)</td>
<td>60 mg/30 mg, 120mg/60mg</td>
</tr>
<tr>
<td>INSTI</td>
<td>RAL</td>
<td>Chewable tab</td>
<td>100mg</td>
</tr>
</tbody>
</table>

IATT
Inter-Agency Task Team for Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children

APWG
ARV Procurement Working Group

Why do we need GAP-f?

We have nice processes in place...

But we need to be FASTER, more EFFICIENT and more SUSTAINABLE!
Lessons from GAP-f precursors

What works well

- PADO priorities helps coordinate clinical research goals around priority products
- PAWG review and modeling provides approaches to dosing other than clinical trials

What we have learned

- Need for more coordination between upstream and downstream activities
- Need for acceleration: reducing lag time between steps
- Need for a portfolio approach to coordinate efforts with overall treatment needs and with donors across product lifecycles
- Need for market analytics to support decisions at various stages of program lifecycle
- Need for product commercialization plans and means for implementation
The GAP-f builds on existing efforts

GAP-f aims to promote a faster, more efficient and more focused approach to paediatric formulation development

Reference: Penazzato et al., JIAS, Under review
Stage 1 – 2017-2018 – Preliminary work
- Push forward specific recommendations and streamline regulatory activities
- Develop a research toolkit for paediatric drug formulation development
- Improve paediatric drug formulation forecasting to support industry planning

Stage 2 – 2018-2020 – Pilot phase
- Maintain a prioritized product portfolio
- Accelerate product development through incentives (potentially including strategic financing and market shaping approaches)

Stage 3 – 2020 and beyond – GAP-f formalized
- Full development of the GAP-f model to coordinate and accelerate all stages of a portfolio of products across several diseases
- Potential formalization as an independent non-profit organization
GAP-f: Stage 1 – 2017-2018 – Preliminary work
The paediatric HIV market is not declining...
Proposed recommendations by regulators to drug innovators

- Begin paediatric formulation work as soon as there is evidence of potential public health benefit
- Engage with PAWG at early stage
- Make initial PIP/PSP submissions less detailed in order to simplify and streamline subsequent revisions
- Use weight-based dosing in designing paediatric PK and safety studies
- Include adolescents in initial registrational adult efficacy trials or in parallel with adult studies
- Enrol all ages/weight bands concurrently (>4 weeks)
- Ensure acceptability and palatability data are acquired early

Ongoing conversation with SRAs and other key regulatory agencies
GAP-f: Stage 1

More formal role for Paediatric ARV Working Group (PAWG)

• To be a reference group and provide overall technical advice (clinical, PK, programmatic) to drug and formulation development

• To advise manufacturers on the development of their PIP/PSPs

• To contribute to the PK work required for informing ratio and dosing for FDCs

• Broader set of skills

• Greater responsiveness

• Greater accountability

• More transparency

• Continuity and sustainability
GAP-f: Stage 1

Research toolkit to support drug manufacturers (originators and generics) efforts in drug and formulation development

1. PK studies and PK modelling
2. Trial design
3. Pharmacovigilance
4. Pregnant and breastfeeding women
5. Co-infections
6. Acceptability
7. Community engagement
8. Target product profile
9. Modelling and forecasting
10. Regulatory filing

Official launch of the research tool at the International AIDS Conference in July 2018

The research toolkit development is coordinated by the WHO
GAP-f: Stage 1

Improving paediatric drug market forecasting

Programmatic data
Spectrum output
Observational data
Scale-up scenarios

Quantification (Now)
Forecasting (1-5 years)
R&D (> 5 years)

HIV infected children
HIV infected children diagnosed
HIV infected children started on ART
HIV infected children failing 1st line
HIV infected Switched to 2nd line
GAP-f: Stage 1

- New compound in Phase I/II age-staggered
- SRA approval (age-based mg/kg dose)
- Clinical trials to compare the new compound vs SOC
- New compound in Phase I/II simultaneous enrolment
- SRA approval (weight-based dosing)

- PK modelling to inform development of FDC
- Validation of weight-band dosing
- Introduction in Tx guidelines with weight-based dosing
- PK modelling to inform development of FDC
- Introduction in Tx guidelines with weight-based dosing

- Formulation development (bio-stability and bio-equivalence)
- Clinical studies to validate formulation
- SRA approval and in country registration
- Formulation development (bio-stability and bio-equivalence)
- SRA approval and in country registration

5-9 years from adult development
2-3 years from adult development

- Getting studies right from the very beginning
- Enrolling more rapidly (in parallel, not sequentially) and based on weight
- Maximizing the use of PK studies and PK modelling
- Innovating trial design

Reference: Penazzato et al., CID, 2017
GAP-f: Stage 2 – 2018-2020 – *Pilot phase*
Maintain prioritized portfolio

- Establish watching briefs for new products, clinical research outcomes, evolving needs of global health
- Rank opportunities against clinical, development and commercial criteria
- Communicate consistently and broadly to ensure alignment to priorities (i.e. PADO priorities for HIV)
Learning from the PHTI and taking advantage of the CHAI-UNITAID *Optimal ARVs* project as a proof of concept
GAP-f: Stage 3 – 2020 and beyond – GAP-f formalized
Hurray!
GAP-f: What will it do?

- Coordinate efforts between suppliers, innovators, research networks, regulators, procurers, MOH, MOF, etc.
- Secure funding to support entire product lifecycles
- Maintain a product portfolio that addresses treatment needs
- Develop flexible PIP/PSPs in collaboration with innovators
- Coordinate clinical research priorities
- Provide market analytics to support decisions across all stages
- Design, implement, and fund product commercialization plans
GAP-f: What will it do?

1. Sufficient safety and efficacy in innovator adult product
2. Adult product approved
3. Innovator paediatric product approved
4. Generic paediatric product approved

Paediatric clinical research

Market analytics

Generic product development
Generic SRA filing

Product access, community engagement, & uptake

Procurement
Pharmacovigilance
Supporting paediatric clinical research

- **Clinical evidence meeting the needs of patients in LMICs**
  - PIP/PSPs align in requirements and timing, and can fit new clinical evidence
  - Clinical evidence meets SRA standards
  - Master protocol for clinical studies
    - Uses WHO weight band dosing
    - Enrolls all weight bands concurrently (>4 weeks old)
    - Ensures acceptability and palatability data are obtained
Supporting product development and market analytics

• **Market analytics**  — Inform on market size and evolution for prioritized products

• **Generic R&D**
  — Account for clinical evidence, target product profile, market impact, and manufacturing requirements
  — Develop incentives for manufacturers (e.g., tech transfer support, development funding, market intelligence, and catalytic procurement)
  — Product commercialization plan

1. Sufficient safety and efficacy in innovator adult product
2. Adult product approved
3. Innovator paediatric product approved
4. Generic paediatric product approved
Supporting access, procurement, pharmacovigilance

- **Product introduction**
  - Develop product briefs and training materials for early engagement with MOH, MOF, primary care physicians, HCWs, and community activists

- **Procurement**
  - Coordinate procurement to catalyze uptake

- **Pharmacovigilance**
  - Monitor paediatric patients
In summary...

• The best drugs are often not available to treat children

• GAP-f can help us get better products quicker and cheaper
  – Prioritizes products
  – Streamlines generation of clinical evidence
  – Incentivizes manufacturers
  – Accelerates product development and introduction
  – Coordinates procurement
What next?

Next steps

• Better articulate the key financial interventions required
• Identify the right time to include other disease areas
• Define final set up of GAP-f as independent, disease agnostic organization
Thanks to GAP-f partners and supporters

Special thanks to Martina Penazzato (WHO)!
Thanks for your attention

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