PADO-HIV: History, successes and lessons learned

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The development of pediatric products lags unacceptably behind that of adults – by nearly a decade

Key challenges that hamper the rapid development and introduction of optimal paediatric formulations include:

<table>
<thead>
<tr>
<th>Market fragmentation</th>
<th>Lack of child-friendly formulations</th>
<th>Complexity and cost of the projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal prioritization within companies</td>
<td>Lack of market incentives ad small markets</td>
<td>Difficult and slow market uptake</td>
</tr>
</tbody>
</table>
Developing medicines for children requires addressing unavoidable complexities

- Disease natural history
- Growth and puberty: dosing the same drug in changing body and a changing brain
- Drug metabolism is different from adults and can heavily depend on genetic polymorphisms (i.e. EFV)
- Key comorbidities that impact drug use, tolerability, and toxicity in SSA (HIV, TB, malaria, malnutrition, anemia, etc.)
- Palatability and ease of administration are critical to support adherence
...while promoting simplification and harmonization across the age spectrum

**Care taker**
- Same regimen for all family members may be helpful
- Avoid inappropriate drug sharing

**Health care Provider**
- More familiar with adult regimens
- But different formulations still need to be available
- Dosing changes still necessary as child grows/ages

**Programme /supply manager**
- Streamline procurement
- Simplify forecasting and ordering

**Manufacturers**
- Ensure API availability
- Lower cost of production

Harmonization is critical but when formulations are different benefits of harmonization are potentially limited

Development of scored dispersible adults tablets becomes essential
Paediatric ARVs Drug Optimization (PADO) general objectives

• Define the **target product profile** to address the specific needs of HIV treatment and prevention in LMICs

• Identify **medium- and long-term priorities** for the development of new paediatric ARV drugs and formulations for paediatric HIV treatment and prevention.

• Identify **research gaps** to be addressed and inform optimal use of ARVs in infants, children and adolescents to enable future development and uptake of priority products

• Provide a vision on drug optimization and **feed into the WHO Guidelines** revision process
Developing and delivering paediatric formulations through collaborative and coordinated action

Key formulations are prioritised in the context of a public health approach.

- PADO
- PROGRAMS
- PAWG
- PAPWG
- PHTI
- IATT

Drug optimization

Priority formulations are prioritised in the context of a public health approach.

- Priority formulations are reliably supplied to countries.
- Priority formulations are included in optimal formulary for selection.
- Technical/research work is undertaken to support development of the priority formulations.
- Priority formulations are procured via a pooled mechanism.
Enabling alignment with policy development

GDG
Develops evidence based recommendations accounting for product development

PADO
Prioritize based on existing WHO Guidelines but also provide a vision for policy change

Guidance on product development to Industry

IMPLEMENTATION
## PADO list evolution

<table>
<thead>
<tr>
<th>PADO 1-2013</th>
<th>PADO 2-2014</th>
<th>PADO 3-2016</th>
<th>PADO 4-2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPVr 4-in-1</td>
<td>LPVr 4-in-1 (30/15/40/10 mg)*</td>
<td>In advanced development</td>
<td></td>
</tr>
<tr>
<td>ABC/3TC/EFV</td>
<td>ABC/3TC/EFV (150/75/150 mg)*</td>
<td>In advanced development</td>
<td></td>
</tr>
<tr>
<td>ATVr</td>
<td>ATVr (100/33 mg)*</td>
<td>Removed §</td>
<td></td>
</tr>
<tr>
<td>NVP 20 mg</td>
<td>NVP/AZT</td>
<td>NVP/AZT</td>
<td>Removed</td>
</tr>
<tr>
<td>RAL</td>
<td>RAL</td>
<td>RAL (50 mg scored)*</td>
<td>Removed</td>
</tr>
<tr>
<td>DRVr</td>
<td>DRVr</td>
<td>DRVr (120/20 mg)*</td>
<td>DRVr (120/20 mg)</td>
</tr>
<tr>
<td>DTG single</td>
<td>DTG paeds single</td>
<td>DTG paeds single (5 mg)*</td>
<td>DTG paeds single (10 mg scored) dispers tab</td>
</tr>
<tr>
<td>DTG/3TC/ABC</td>
<td>DTG/3TC/ABC</td>
<td>DTG/3TC/ABC (5/30/60 mg)*</td>
<td>DTG/3TC/ABC (5/30/60 mg) dispersible tab</td>
</tr>
<tr>
<td>F/TAF</td>
<td>F/TAF</td>
<td>F/TAF</td>
<td>XTC/TAF dispersible tablets</td>
</tr>
<tr>
<td>DTG/XTC/TAF</td>
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<td>DTG/XTC/TAF dispersible tablets</td>
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</tbody>
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- Over time most long term priorities have graduated to short/mid term priorities demonstrating the PADO coherence.
- Policy change has guided PADO thinking but also reflected PADO vision.
- Some difficult decisions were required in order to streamline R&D efforts for the biggest gain.
Key principles to accelerate research to inform development

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

Penazzato et al., CID, 2017
Closing the loop on paediatric development plans

PAWG to provide technical opinion on PIP/PSPs to regulators and promote further focus and alignment between agencies

Industry to seek PAWG technical advice to inform submission and implementation of PIP/PSPs that address real need

Better paediatric development plans completed and approved more quickly
GAP-f: Formal collaboration across sectors to ensure accelerated development and uptake

The Global Accelerator for Paediatric Formulations (GAP-f)

Prioritize and Evaluate
- Prioritization
- Evaluation

Develop
- Business Development
- Product Development
- Regulatory Affairs

Deliver
- Procurement
- Adoption
- Rollout & Uptake
- Monitor

Accelerating priority paediatric drug formulation development and uptake

A collaboration platform supported by an innovative financing mechanism that promotes a faster, more efficient and more focused approach to paediatric clinical and formulation development and introduction.
GAP-f will be implemented via stakeholders operating in the different disease areas and building on existing platforms and ongoing work.
Thank you

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Switzerland

www.who.int
www.gap-f.org/
www.who.int/hiv/pub/paediatric/aids-free-toolkit/en/