Paediatric ARV Drug Optimization 4

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Children continue to acquire HIV despite high PMTCT coverage.
Half of the children living with HIV receive ART

![Graph showing child and adult ART coverage from 2010 to 2017](World Health Organization logo)
New WHO policies promote more effective regimens for children

- INSTI based first line to be the preferred regimens
- Moving away from NNRTIs as soon as possible
- Potent non NNRTI options to be used while dosing for DTG is approved down to 4 weeks
- DTG included in all lines of treatment for treatment and for PEP

But...Implementation of WHO policies remain challenging to implement for infants, children, adolescents and women of reproductive potential
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<tr>
<th>PADO 1-2013</th>
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<td>Neutralizing antibodies</td>
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The **PADO list** is our tool to target global efforts on the most needed formulations and is the foundation of the **GAP-f HIV product portfolio**.
Formal collaboration across sectors to ensure acceleration

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.
PADO 4 objectives

• Review 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.

• Identify evidence gaps and key principles to guide investigation of ARVs in adolescents and pregnant and lactating women.
PADO 4 participants and structure

- PAWG members
- CADO representatives
- Research networks
- Regulators (FDA, EMA)
- Implementers
- GAP-f partners
- Civil society (AFROCAB)
Agenda

- ARV pipeline
- Specificities of the 3 populations
- Community perspective
- Principles for accelerated investigation
- Drug delivery systems in children
- Optimal ARV sequencing
- Alternative ART strategies
- HIV-associated infections
Key themes discussed (1)

Pregnant women
• Need for faster completion of preclinical studies
• Earlier investigation of drugs in pregnant and lactating women (safety and PK)
• Clearer standards for PK studies (timing, design and interpretation)
• Better engagement of women

Adolescents
• Need for earlier investigation of ARVs in adolescents
• Inclusion of adolescents in adult trials or in parallel to phase 3 studies
• Importance to engage adolescents in the design and conduction of studies
• Value of specific ART strategies to address adolescents’ needs
Key themes discussed

Children

• Need to account for current transition to more optimal regimens and its challenges
• Timelines for introduction of new ARV formulations
• Focus on babies: postnatal prophylaxis and early treatment
• Selection of HIVDR and implications for sequencing and dual regimen strategies
• Importance to think about prevention and treatment of HIV-associated diseases
• Need to innovate drug delivery systems to match the needs of LMIC context
DTG single: 10 mg scored dispersible tablets remain the priority meantime 50 mg scored tablet could accelerate generic availability to children >15 kg.

DRVr: 120/20 mg tablet remains a priority and incentives are being explored.

DTG/ABC/3TC: 5/60/30 mg most likely dosing to be validated by the end of the year once 1093 is completed.

F/TAF and DTG/XTC/TAF: urgent review of originator timelines, preliminary feasibility work on the FDC to be undertaken.

RAL: 5 mg (instead of 50 mg) scored dispersible to better reflect its added value for neonates and infants.

AZT/NVP: still a priority, but probably less urgently needed than other products.

DTG/DRVr: Concerns on the size and feasibility of the FDC (confirmed by CADO3) de-prioritized until further clinical trials support the strategy.
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### Rationale for removals

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| **NVP/AZT**      | Despite its consistent presence in the PADO list no uptake  
|                  | NVP/AZT can be provided using separate products that are currently available  
|                  | Need for frequent dosing changes a challenge for an AZT/NVP FDC  
|                  | Expected future shift towards presumptive treatment for HIGH RISK infants |
| **RAL**          | Despite its consistent presence in the PADO list no uptake  
|                  | Considering upcoming introduction of DTG in infants and young children, this is now of limited added value |
| **DTG/DRVr**     | Concerns on the size and feasibility of the FDC (confirmed by CADO3)  
|                  | De-prioritized until further clinical trials support the strategy. |
| **DTG/3TC**      | High risk of viral breakthrough associated with poor adherence (esp adolescents)  
|                  | May requirement baseline viral load in the context of limited access to routine viral load monitoring  
|                  | Cannot use in hepatitis B co-infections (under-detected in LMICs) |
PADO 4 LIST

1. DRVr (120/20 mg)
2. DTG (10 mg scored)
3. DTG/ABC/3TC (5/60/30 mg)
4. XTC/TAF
5. XTC/TAF/DTG
Implementation considerations (PADO list)

• **DRVr (120/20 mg)**: critical formulation to provide a robust PI option for 2\(^{nd}\) and 3\(^{rd}\) line use after failure on DTG-based regimens (Dosing and ratio clear).

• **DTG (10 mg scored)**: key product to expand DTG-based regimens to children as young as 4 weeks.

• **DTG/ABC/3TC (5/60/30 mg)**: critical formulation to provide preferred first line in FDC (dosing and ratio now confirmed).

• **XTC/TAF and XTC/TAF/DTG**: remains desirable for full harmonization in the future (dosing and ratio to be clarified as TAF investigation plans are completed).
MK 8591
Doravirine
bNabs
Long acting
Novel delivery technologies

PADO 4
WATCH
LIST
Implementation considerations (PADO watch list)

- **MK8591** and **Doravirine** were considered of interest and active review of paediatric investigation plans in collaboration with GAP-f partners is encouraged.

- **bNabs**: Potential use for postnatal prophylaxis and early treatment, with potential for enhancing HIV-specific immune response, and reduction of viral reservoir.

- **Long Acting**: Treatment of neonates, infants and children with current formulations is unlikely but some could represent a suitable opportunity for prevention in neonates and treatment of adolescents.

- **Novel delivery technologies** (ie. microneedle patches and Gastric residence system/ drug-polymer matrix): these technologies are forward looking and could be very amenable to paediatric populations, with the potential to be reversible, simplify administration, and improve adherence.

* More details on the TPP will be provided in the PADO4 meeting report.
Research gaps (1)

A. Neonatal Prophylaxis, Presumptive treatment for high risks and newborn treatment

- HIGH PRIORITY: 4 in 1 evaluated for safety/PK amongst infants 0-4 weeks (for ABC and LPVr)
- Long acting including bNabs for prophylaxis
- Products for LBW infants
- Do we need extended infant prophylaxis in settings with extended breastfeeding?
- Optimal ways to conduct pharmacovigilance for fetal and neonatal exposure to ARVs through maternal treatment or infant prophylaxis
- In the context of presumptive treatment in high risk infants, what are the optimal infant diagnosis algorithms?
Research gaps (2)

B. Drugs and formulations
• New formulations – (e.g., patches, implants)
• Adult doses in children (e.g., DTG 50 mg down on weight band)
• TB-HIV trials: nest PK studies in all ongoing trials to gather data in children that acquire TB while on studies
• LATs -injectables/patches: 2 mo vs >2 months
• Malnutrition (PK/PD)
• Long-term safety and efficacy (TAF, DTG)
• Co-infections (Hep C)

C. Sequencing strategies
• Future third line : DTG/DRV ± NRTIs
• Resistance surveillance

D. Innovative strategies
• Dual therapy (e.g., DTG/TAF, DRV/r/3TC, DRV/r/DTG) in naïve and experienced children
• Simplification/drug holidays strategies
• Contraception combined with ART

E. Implementation and Quality of Life research

F. High quality service delivery for peds/adolescent treatment
What's next?
Next steps (Dissemination)

- GAP-f webinar for dissemination of outcomes to industry and regulators
- New EOI to reflect PADO 4 list will be issued in early 2019 (ERP to be adjusted at the next round of revision)
- Dissemination of the PADO list at the upcoming Buyers-Suppliers meeting in India (CHAI/Unitaid)
- Outcomes will be shared with participants of the Rome High level dialogue for high level outreach
- A draft report will be made available on WHO website by the end of Q1 (peer-review manuscript being prepared)
Next steps (Implementation)

• PAWG to discuss dosing and ratio for PADO priorities on the first call of the year in January

• At CROI
  • Presentation of key principles for adolescents and PLW at the WHO Think Tank for feedback and input by adults colleagues with joint papers to be developed shortly after
  • PAWG face to face catch up for “implementation of PADO4” and integration of 2019 workplan

• Routine calls with industry to follow up specific products

• ILF/CIPHER forum on PLW around AMDS in March/April 2019

• Meeting with regulators FDA/EMA/PQ to discuss potential alignment on PADO priorities (tentatively planned in Q2 2019)
Thank you

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