Existing and most needed paediatric ARV formulations

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Paediatric coverage still lags behind

Source: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS); Proportion of HIV-exposed infants receiving virological testing by their second month of age.

BUT THE REAL GAP IS 68%
2015 WHO ARV Consolidated Guidelines

- Test earlier
- Test closer
- Treat earlier

- Treat more newborns
- Decentralise Treatment
- Treat All children
Starting ART early is not easy

- Dealing with limited options for newborns
- Optimising options with the best formulation available
- Monitoring closely and adjusting dosing*
- Introduction of LPVr pellets
  (guidance for administration and procurement)

<table>
<thead>
<tr>
<th></th>
<th>0-2 weeks</th>
<th>2 weeks - 3 months</th>
<th>3 – 36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred</strong></td>
<td>AZT + 3TC + NVP</td>
<td>ABC or AZT + 3TC +</td>
<td>ABC or AZT + 3TC +</td>
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<tr>
<td></td>
<td></td>
<td>LPV/r syrup</td>
<td>LPV/r pellets</td>
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<tr>
<td><strong>Alternative</strong></td>
<td></td>
<td>AZT + 3TC + NVP</td>
<td>ABC or AZT + 3TC +</td>
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<td></td>
<td></td>
<td></td>
<td>LPV/r pellets</td>
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<tr>
<td><strong>Special circumstances</strong></td>
<td>AZT + 3TC + NVP</td>
<td></td>
<td>ABC or AZT + 3TC +</td>
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<td></td>
<td></td>
<td></td>
<td>RAL (from 4 weeks)</td>
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# Starting ART in children

- Using the most potent regimen available for young children (LPVr)
- Simplifying where feasible (substitute LPVr with EFV)
- Using RAL-based regimen in special circumstances
- Keeping ABC + 3TC as preferred NRTIs
- Maintaining EFV-based regimen to harmonise with adults

<table>
<thead>
<tr>
<th>Children &lt; 3 years</th>
<th>Children 3 years to &lt; 10 years</th>
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<tbody>
<tr>
<td><strong>Preferred</strong></td>
<td>ABC + 3TC + LPV/r or AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>AZT + 3TC + NVP</td>
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**In summary ...NO CHANGE**
### Offering better options for 2\(^{nd}\) line

<table>
<thead>
<tr>
<th>Children including adolescents</th>
<th>First-line ART regimen</th>
<th>Second-line ART regimen</th>
</tr>
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<tbody>
<tr>
<td>LPV/r-based first line</td>
<td>Younger than 3 years</td>
<td>ABC + 3TC + LPV/r</td>
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<tr>
<td></td>
<td></td>
<td>AZT + 3TC + LPV/r</td>
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<tr>
<td></td>
<td>3 years and older</td>
<td>ABC + 3TC + LPV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td>NNRTI-based first-line regimen</td>
<td>All ages</td>
<td>ABC + 3TC + EFV (or NVP)</td>
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<tr>
<td></td>
<td></td>
<td>TDF + 3TC + EFV (or NVP)</td>
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<tr>
<td></td>
<td></td>
<td>AZT + 3TC + EFV (or NVP)</td>
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</tbody>
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- Introducing more potent options for children failing on LPV/r
- Promoting use of once daily bPI such as ATV
- Preserving DRVr as a 3\(^{rd}\) line drug
## Starting ART in adolescents

<table>
<thead>
<tr>
<th>First-line ART</th>
<th>Preferred first-line regimens</th>
<th>Alternative first-line regimens&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>TDF + 3TC (or FTC) + EFV</td>
<td>AZT + 3TC + EFV (or NVP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF + 3TC (or FTC) + DTG&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF + 3TC (or FTC) + EFV&lt;sub&gt;400&lt;/sub&gt;&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF + 3TC (or FTC) + NVP</td>
</tr>
<tr>
<td>Adolescents</td>
<td>TDF + 3TC (or FTC) + EFV</td>
<td>AZT + 3TC + EFV (or NVP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF (or ABC) + 3TC (or FTC) + DTG&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF (or ABC) + 3TC (or FTC) + EFV&lt;sub&gt;400&lt;/sub&gt;&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF (or ABC) + 3TC (or FTC) + NVP</td>
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</tbody>
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- Introducing more potent and tolerable regimens as alternatives
- Simplifying regimens adolescents who started Tx in childhood
- Maintaining harmonisation with adults
Enhanced Prophylaxis

- For “low risk” – keep current recommendations
- For “high risk” – use two drugs together in infants for 6 weeks after delivery
- For “high risk” – in breastfed infants continue prophylaxis (either 1 drug or 2) for 12 weeks until maternal ART drops the viral load

**Birth**

- **FORMULA FEEDING**
  - AZT/NVP 6 weeks

- **BREAST FEEDING**
  - AZT/NVP 6 weeks
  - AZT/NVP 6 weeks AND NVP 6 weeks
  - 2 to 1 option
  - 2 to 2 option
What do we need NOW?

• We need better drugs and formulations for newborns for Tx and PnP (ie. AZT/NVP)
• We need FDCs for 1st line regimens
  – LPVr 4-IN-1
  – EFV/ABC/3TC
• We need better formulations for 2nd and 3rd line regimens
  – ATVr
  – RAL (chewable as dispersible)
  – DRVr

NONE OF THESE ARE AVAILABLE!
PADO 2 priorities

Identifying priority regimens for optimal sequencing which include **newer compounds** for which paediatric development has not been completed.

<table>
<thead>
<tr>
<th></th>
<th>0-3 yrs</th>
<th>3-10 yrs</th>
<th>10 yrs +</th>
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<tbody>
<tr>
<td><strong>FIRST LINE</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mid-term (5 yr)</td>
<td>ABC/3TC/DTG</td>
<td>TAF/3TC/DTG</td>
<td></td>
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<tr>
<td>Long term (10 yr)</td>
<td>TAF/3TC/DTG</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SECOND LINE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-term (5 yr)</td>
<td>AZT/3TC/RAL or LPV/r</td>
<td>AZT/3TC/DRV/r</td>
<td>TAF/3TC/DRV/r</td>
</tr>
<tr>
<td>Long term (10 yr)</td>
<td>AZT/3TC/LPV/r</td>
<td>RPV/DRV/r or AZT/3TC/DRVr</td>
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New formulations of **existing drugs** that already have registration for children or in advanced paediatric development.
LPVr 4-in-1: first line for under 3 years to address the lack of optimal formulations

EFV triple: first line 3-10 years to provide an FDC to maximise adherence and simplify procurement

ATVr and DRVr: use in 2nd and 3rd line formulations and overcome issue with separate administration of RTV

NVP 20 mg: better dosage form to facilitate dosing for PnP

RAL better formulation: use in infants and young children to enable rapid introduction of INI for use in 1st line regimen

DTG single or FDCs: identified as key drug to introduce INI in first line with potential for harmonisation across the full age spectrum

TAF: key drug for future use in 1st line to minimise toxicity with potential for harmonization across the full age spectrum

Rationale for prioritisation
Progress made since Dec 2014

- **New Guidelines**: more prominent role of integrase inhibitors and ATVr as an alternative to LPVr in 2nd line use.
- **New products**: LPVr pellets FDA approved
- **Better access**: Merck agreement with MPP on RAL
- **Advances in FDC development**: PHTI projects
- **Progress of ongoing research**: P1093 and new protocols
- **More communication**: SRAs consulted to advocate for PADO priorities and to explore regulatory pathways for key FDC
- **More guidance**: IATT policy briefs on LPVr pellets
- **Impact in countries**: PAPWG commitment has resulted in most countries with high burden to procure optimal products

MPP= Medicine Patent Pool; PHTI= Paediatric HIV Treatment Initiative; SRAs: stringent regulatory agencies; IATT= Interagency Task Team; PAPWG= Paediatric ARV Procurement Working Group; CTA=Commitment To Action.
Thinking strategically about 1st line

**0-4 weeks**
- RAL
- DTG single or DTG/ABC/3TC
- DTG/TAF/XTC

**4 wks-3 years**
- LPVr 4-in-1
- RAL better formulation
- DTG single or DTG/ABC/3TC
- DTG/ABC/3TC

**3-10 years**
- EFV/ABC/3TC
- DTG single or DTG/ABC/3TC
- DTG/TDF/XTC
- DTG/TAF/XTC

**10-18 years**
- DTG/ABC/3TC or DTG/TDF/XTC
- DTG/TAF/XTC

**NOW**

**FUTURE**
Q2: SHORT TERM (now): Considering need, feasibility and timeline for development, please rank the importance of the following formulations, 1 being the most critical and 8 the least critical?

Respondents: 36

1. EFV/ABC/3TC
2. LPV/RTV/3TC/ABC or AZT...
3. RAL for infants and...
4. DTG
5. DRV/rtv
6. DTG/ABC/3TC
7. ATV/rtv
8. NVP dispersible...
Q3: MID TERM (within 2-5 years): Considering need, feasibility and timeline for development, please rank the importance of the Following Formulations, 1 being the most critical and 9 the least critical?

1. DTG / ABC / 3TC
2. DTG
3. DTG / TAF / XTC
4. EFV / ABC / 3TC
5. LPV / RTV / 3TC / ABC or...
6. RAL for infants and...
7. MIVP / AZT dispersible...
8. DRV / rtv
9. ATV / RTV
How does PAWG support this?

**EFV triple**
- PK modelling
- Dialogue with SRA

**ATVR and DRVr**
- Weight band dosing developed
- Dosing reviewed to account for originators modelling

**RAL**
- Interaction with study teams and originators (weight-bands)
- PK study needed to assess BE of chewable as dispersible

**DTG**
- Preliminary weight-band dosing based on 1093
- Plan for PK modelling to support FDC development

**NVP/AZT**
- Dosing and ratio being discussed
- Advice from SRA to be sought
Continuous dialogue with regulators

Members of **PADO/PAWG** were invited to provide advice to EMEA/PDCO on paediatric development of FDC. This included:

- Any drug should be investigated down to birth (unless strong rationale).
- WHO weight-bands should be formally part of PIPs
- Palatability and acceptability data should be added to the requirements for paediatric formulations
- Submission of adolescents data WITH adults should be required and no delays should be accepted

While existing age groups considered by SRAs stem out from international regulations which cannot be changed, diversion from those standards to align with WHO age groups and include weigh-bands can be considered when designing PIPs.
Moving forward

• ILF/CIPHER remains a critical platform to ensure the PADO priorities are promptly communicated to manufacturers
• PADO/PAWG can be formally consulted for any technical question that manufacturers may have
• Dialogue with regulators to continue
• PADO3 tentatively planned for December 6\textsuperscript{th}-7\textsuperscript{th} potentially in conjunction with other meetings (ie. PHTI, IATT, PAPWG)
  – Review of priority list
  – Research innovations
  – New treatment strategies: NRTI sparing and long-acting
  – Learning from HIV to inform other diseases: TB and hepatitis