Optimizing treatment for children and adolescents: The power of NOW

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OUTLINE

Yesterday
  - WHO 2016 ARV guidelines (2\textsuperscript{nd} edition)
  - Evidence used and challenges
  - Key treatment recommendations

Today
  - Introduction of better drug options
  - Need for priority formulations
  - Support development of better formulations

Tomorrow
  - The challenges of testing sooner and closer
  - Dealing with the adolescent wave
  - Innovative therapeutic strategies for investigation
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Paediatric coverage still lags behind

The treatment GAP continues to exist

Source: Global Plan report 2016
2015 WHO ARV Consolidated Guidelines

Critical tool to reach the Treatment targets
Which evidence did we use in 2015?

• IeDea\(^1\) casual modelling added to the body of evidence suggesting that earlier ART is better
• P1060\(^2\) demonstrated that infants and young children need more potent regimens.
• NEVEREST\(^3\) and MONOD\(^4\) supported the substitution of LPVr with EFV to simplify treatment
• PENPACT-1\(^5\), CHAPA-3\(^6\) and ARROW\(^7\) all contributed to inform the current 1\(^{st}\) line approach in older children
• Registrative trials\(^8\) and pharmacovigilance studies\(^9\) reassured us on the use of 2\(^{nd}\) and 3\(^{rd}\) line drugs

Where did we struggle?

- Adults trials do not include subjects below 18 years
- Lack of age-stratified and time-updated analysis
- Head to head comparisons are rare
- New drugs are either not approved or limited evidence exist on their use
- Critical trials became more challenging with the fast-changing policies
- Adult data drives the policy change and extrapolation is not always possible nor appropriate (ie infants)
- Programmatic needs became the biggest driver
Offering optimal regimens in age-appropriate formulations

<table>
<thead>
<tr>
<th>Children including adolescents</th>
<th>First-line ART regimen</th>
<th>Second-line ART regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r-based first line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 3 years</td>
<td>ABC + 3TC + LPV/r</td>
<td>AZT or ABC + 3TC + RAL</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + LPV/r</td>
<td></td>
</tr>
<tr>
<td>3 years and older</td>
<td>ABC + 3TC + LPV/r</td>
<td>AZT + 3TC + EFV or RAL</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + LPV/r</td>
<td>ABC or TDF + 3TC + EFV or RAL</td>
</tr>
<tr>
<td>NNRTI-based first-line regimen</td>
<td>All ages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC + EFV (or NVP)</td>
<td>AZT + 3TC + ATV/r or LPV/r</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC + EFV (or NVP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + EFV (or NVP)</td>
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</tbody>
</table>

Complexity is unavoidable but some optimal formulations exist and more are needed to deliver the preferred regimens that maximise efficacy and minimise toxicity.
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Shift to Treat All children is happening

But suboptimal regimens are still being used.
Introduction of better options doesn’t happen over night

LPVr pellets

- LPV/r pellet was USFDA tentatively approved in May 2015. Approved for use from 2 weeks but no dosing for <5kg
- Palatability still not optimal
- Acceptability data from CHAPAS2
- Administration in exclusive BF and young infants below 3 months is problematic
- Feasibility data being gathered
- In country registration undergoing but happening slowly

RAL

- Full paediatric programme now almost down to neonates
- Granules formulation is not practical in resource limited settings
- Chewable tablets could be used as dispersible but bioequivalence to be demonstrated
- Limited experience in first line use for infants and young children
- No generic production and price remains relatively high

Research to address these unknowns and support introduction in countries
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

MORE DRUGS and FORMULATIONS ARE URGENTLY NEEDED (PADO PRIORITY)
HOW do we GET THEM?

New compound in Phase I/II age-staggered → SRA approval (age-based mg/kg dose) → Clinical trials to compare the new compound vs SOC → PK modelling to inform development of FDC → Validation of weight-band dosing → 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.
What can we do NOW?

• Innovate trial design
• Move away from age-cohort approach
• Investigate directly weight band dosing
• Optimize the generation and use of PK data
• Include TB/Hep infected children
• Address acceptability/feasibility
• Simplify regulatory requirements
• Focus efforts on priority formulations

Integration and better coordination can be our key to success
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Testing infants earlier and closer

- Birth testing and POC introduction will lead to more neonates initiating ART
- ARV dosing in neonates still largely unknown
- Complex ART to prescribe and administer in neonates
- The right treatment is delivered where children are identified

Fewer new infections will make it harder to conduct efficacy trials and PK studies will become increasingly important
An adolescent wave to deal with

- Children started on treatment are surviving into adolescence with complex treatment histories and limited ARV options
- Adolescents have poor access to services and are at higher risk for lost to follow-up, poor adherence and rapid selection of HIVDR with limited treatment options
- Implementation of Adolescents Friendly Health Services (AFHS) is critical but probably not enough
- Injectable and implants can be attractive delivery systems to overcome inadequate adherence
- Increasing numbers of adolescents are at risk of acquiring HIV: important to consider the role new ARVs for PreP

Innovations to adolescents first and not “second” - this requires early inclusion of adolescents in drug development studies
Innovative strategies are needed

**Simplification strategies**
- Dual therapy (ie. DTG+3TC)
- NRTI sparing (ie. DTG/DRV)

**Long-acting and injectable**
- Cabotegravir
- Rilpivirin LA

**Immunotherapy**
- Neutralizing antibodies
- Therapeutic vaccine

**Remission**
- Early treatment
- Combination strategies

Life-long triple antiretroviral cannot be our long-term goal (particularly in children)
The power of NOW

• **New efforts** are urgently needed: drug optimization is unfinished business

• Research networks continue to play a **critical role**

• **Strategic study design** to address multiple questions and respond to the needs of HIV-infected children where they live

• **Joining forces** can help us reach our goals faster

• **Focus and innovative** thinking about tomorrow and the strategic response required by the shifting landscape of the HIV epidemic
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Thank you