Pediatric Drug Pipeline: New Drugs, New Strategies

Dr. Martina Penazzato
Paediatric HIV Advisor
HIV Department, WHO-Geneva
July 15th 2016
OUTLINE

• What do we have now?
• What to expect “tomorrow”?
  – Formulations pipeline
  – New drugs pipeline
• What to do differently?
• Where next?
OUTLINE

• What do we have now?
• What to expect “tomorrow”?
  – Formulations pipeline
  – New drugs pipeline
• What to do differently?
• Where next?
2016 WHO ARV Consolidated Guidelines

Test earlier and closer

Treat earlier and better

Tailor service delivery

Treat more newborns

Introduce new drugs

Simplify strategies
Offer optimal regimens in age-appropriate formulations

<table>
<thead>
<tr>
<th>Age at first line failure</th>
<th>First-line ART regimen</th>
<th>Second-line ART regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPV/r-based first line</strong></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></td>
</tr>
<tr>
<td><strong>NNRTI-based first-line regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</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>
<td></td>
</tr>
</tbody>
</table>

- Simplification strategy: substitute LPV/r with EFV at 3 years
- RAL first line in special circumstances
- DRV/r and DTG most appropriate for 3rd line use.
Introduction of better options doesn’t happen overnight

**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
OUTLINE

• What do we have now?

• What to expect “tomorrow”?
  – Formulations pipeline
  – New drugs pipeline

• What to do differently?

• Where next?
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/AZT: FDC to facilitate dosing for enhanced 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
Progress...despite several hiccups

LPVr 4-in-1
- Fully taste masked granules developed
- Clinical studies to be undertaken for establishing dosing

ABC/3TC/EFV
- Development by 3 manufacturers based on PK modelling
- Regulatory guidance provided completion by Q4 2017

DRVr
- Dosing and ratio agreed upon based on PK modelling
- Work undergoing to address regulatory requirements

RAL
- Scored dispersible tablet based on PK modelling
- Two generic manufacturers have started development

ATVr
- Dosing recommendations available (1/3 of adult tablet)
- Modest interest by generics

NVP/AZT
- Dosing and ratio being discussed by the PAWG
- Interest by generics to be generated
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

Some good news …and some “not so good”
The good news is...

**Dolutegravir (DTG)**

- DTG and TAF are approved > 12 y
- DTG for 6-12y submitted to FDA which approved it for >30 kg
- P1093 and ODYSSEY will generate data on weight-band dosing
- E/C/F/TAF and F/TAF studies in children <12 ongoing

**TAF (Tenofovir Alafenamide)**

- Changes in Renal Tubular Biomarkers by Study Week
- Changes in Bone Mineral Density by Study Week

---

**References**

- Wiznia et al. CROI 2016
- Gaur et al. CROI 2016
But studies are taking longer than we would like…

**DOLUTEGRAVIR**

**DTG: Pregnancy and Paediatric Overview**

- **PREGNANT WOMEN**
- **INFANTS (0-2YRS)**
- **YOUNG CHILDREN (2-6YRS)**
- **CHILDREN (6-12YRS)**
- **ADOLESCENTS (12-<18YRS)**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>50mg tablet</th>
<th>5mg FDT</th>
<th>25mg tab</th>
<th>10mg tab</th>
<th>50mg tablet</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIV: Pregnancy study IX: ODE, DOR, PPAR, ODYSSEY (PENTA 2A) Treatment strategy study (1st and 2nd arms) (incl. TB PK sub-study)</td>
</tr>
<tr>
<td>IMPACT: P1923 Cohort IV (screening)</td>
</tr>
<tr>
<td>IMPACT: P1923 Cohort I &amp; II</td>
</tr>
<tr>
<td>IMPACT: P1923 Cohort II &amp; III</td>
</tr>
</tbody>
</table>

**Reg’Y Label**

- FDA: Category B
- EMA: Not licensed

**Reg’Y Plans**

- FDA: Category B
- EMA: Not licensed

Most recent approval >30 kg only

The paediatric plan designed on age rather than weight: potential adjustments needed. This is resulting in delays with ODYSSEY

---

**TAF**

**GS-US-292-0106: E/C/F/TAF Pediatric Study**

**Schema: Cohort 2 (6 to 12 years) Virologically Suppressed**

**Part A:**

- Screening
- E/C/F/TAF Ne=18-24
- Extension Phase

**Part B:** To be determined

Key Enrollment Criteria:
- Virologically suppressed
- Stable ARV regimen for ≥ 6 months
- Weight ≥ 25 kg

Study drug for those ≥ 25 kg: the same as adult E/C/F/TAF tablet

**GS-US-311-1296: F/TAF Pediatric Study**

**Schema: Cohort 2 (6 to 12 years) Virologically Suppressed**

Part A to Initiate after Review of Cohort 1 PK Data

Cohort 2 (part B)

- Screening 5 to 12 yrs
- FtFaf + antiretroviral agent (≥30)
- Week 96
- 30 day Follow-up or Extension Phase

Key Enrollment Criteria:
- Virologically suppressed (subjects do not have to be on TDF-containing regimen)
- Stable ARV regimen for ≥ 6 months
- Weight ≥ 14 kg

Enrolment not completed for ECFTAF and to be started for FTAFT
And the newborn pipeline is still lagging behind

<table>
<thead>
<tr>
<th></th>
<th>Preterm</th>
<th>Term</th>
<th>2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>P1106 &lt;2500g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>P1106 &lt;2500g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>P1106 &lt;2500g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir AF</td>
<td>P1026s-washout</td>
<td>P1026s-washout</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>P1026s-washout</td>
<td>P1026s-washout</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>P1026s-washout</td>
<td>P1026s-washout</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>P1106 &lt;2500g</td>
<td>P1115 &gt; 34 wks GA</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doravirine</td>
<td>P1026s-washout, v10</td>
<td>P1026s-washout, v10</td>
<td></td>
</tr>
<tr>
<td><strong>PROTEASE INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>P1026s-washout</td>
<td>P1026s-washout</td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td>P1026s-washout</td>
<td>P1026s-washout</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>P1026s-washout, P1106 &lt;2500g</td>
<td>P1026s-washout</td>
<td></td>
</tr>
<tr>
<td><strong>INTEGRASE INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>P1026s-washout</td>
<td>P1026s-washout, P1093 – in development</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>P1026s-washout</td>
<td>P1026s-washout</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>P1097-washout, P1110-dosing</td>
<td>P1097-washout, P1110-dosing</td>
<td></td>
</tr>
<tr>
<td><strong>ENTRY/FUSION INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td></td>
<td></td>
<td>In Development</td>
</tr>
</tbody>
</table>

Source: Polly Clayden and Ted Ruel
OUTLINE

• What do we have now?
• What to expect “tomorrow”?
  • Formulations pipeline
  • New drugs pipeline
• What to do differently?
• Where next?
Innovative strategies are needed

**Simplification strategies**
- Dual therapy
- NRTI sparing

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

**Immunotherapy**
- Neutralizing antibodies
- Therapeutic vaccine

**Remission**
- Early treatment
- Combination strategies

Life-long triple antiretrovirals should not be our long-term goal
Only one ongoing study: SMILE trial (virologically suppressed children >6 years switching to DRVr +EVG).

“NEVEREST 4” start with RAL and substitute with DTG?

INSTI+PIs for 2\textsuperscript{nd} line (NRTI sparing strategies, 7 randomized trials in adults as a switch)

INSTI+3TC in switching strategies

INSTI+3TC in naive (2 studies investigating DTG+3TC following positive results from the PADDLE trial)

Weekends off: is there still a role for this with new regimens? Breather 2.0?
Where next?

• Drugs and formulations for infants (enhanced prophylaxis and treatment)
• Importance of formulations suitable to LMIC
• New drugs will be largely used for an experienced population: Shift focus from 1\textsuperscript{st} line to 2\textsuperscript{nd} and 3\textsuperscript{rd} line and to optimise sequencing and adherence
• Adolescents wave: Innovations to adolescents first and not “second”
• Strategic study design: address multiple questions and respond to the needs of children where they live
• Speeding up the pipeline is not trivial but ...
WHO GDG members
PADO and PAWG members
PHTI partners
WHO colleagues

Thank you