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>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>ABC + 3TC + EFV (or NVP)</td>
<td>AZT + 3TC + ATV/r or AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td>All ages</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 LPVr with EFV at 3 years
- **RAL first line in special circumstances**
- **DRV/r and DTG most appropriate for 3rd line use.**
## Paediatric treatment needs and coverage in South Africa

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>20260</td>
<td>14992</td>
<td>13435</td>
<td>11585</td>
<td>10107</td>
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<tr>
<td>1</td>
<td>33471</td>
<td>26168</td>
<td>20621</td>
<td>19514</td>
<td>17712</td>
</tr>
<tr>
<td>2-4</td>
<td>126625</td>
<td>115060</td>
<td>100861</td>
<td>84448</td>
<td>72178</td>
</tr>
<tr>
<td>5-9</td>
<td>171883</td>
<td>173809</td>
<td>173126</td>
<td>171625</td>
<td>166110</td>
</tr>
<tr>
<td>10-14</td>
<td>98017</td>
<td>109857</td>
<td>119901</td>
<td>127810</td>
<td>134556</td>
</tr>
</tbody>
</table>

| On ART | | | | | |
| <1     | 2693  | 3470  | 3422  | 3126  | 2586  |
| 1      | 4099  | 4812  | 4881  | 4649  | 4084  |
| 2-4    | 22419 | 27076 | 28021 | 25364 | 21930 |
| 5-9    | 49317 | 63371 | 74071 | 81084 | 83488 |
| 10-14  | 29338 | 42332 | 54871 | 65660 | 75143 |

| Coverage | | | | | |
| <1       | 0.13  | 0.23  | 0.25  | 0.27  | 0.26  |
| 1        | 0.12  | 0.18  | 0.24  | 0.24  | 0.23  |
| 2-4      | 0.18  | 0.24  | 0.28  | 0.30  | 0.30  |
| 5-9      | 0.29  | 0.36  | 0.43  | 0.47  | 0.50  |
| 10-14    | 0.30  | 0.39  | 0.46  | 0.51  | 0.56  |

In 2014: 18% of children were reported to be on LPV/r first line. Of children on second line, 91% were on a LPV/r base regimen.
From nevirapine (NVP) to lopinavir (LPV/r)

NVP based ART

- Fixed dose combinations (FDCs) available
- Baby and junior dosing
- Scored tablets
- Can be crushed/dispersed
- Easy dosing

But

- Sub-optimal
- Resistance mutations

LPV/r + 2 NRTIs

- Liquid only currently
- Bitter taste
- Neurotoxic excipients
  - 42% ethanol
  - 15% propylene glycol
- Needs cold chain
- Heavy to carry, hard to hide
- Difficult dosing
- Need for RTV super-boosting in TB/HIV co-infection
Tablets vs. liquid formulations

- **Licensed**
- **Off label use**

Lopinavir/ritonavir tablets cannot be used in young children as crushed they loose up to 50% bioavailability.

**Pharmacokinetics of Lopinavir/Ritonavir Crushed Versus Whole Tablets in Children**

Brooke M. Best, PharmD, MAS, *† Edmund V. Capparelli, PharmD, *† Huy Diep, BS, *Steven S. Rossi, PhD, †Michael J. Farrell, RN, †Elaine Williams, RN, MSN, ‡§ Grace Lee, BS, ‡John N. van den Anker, MD, PhD, ‡§ and Natalla Rakhmanina, MD, PhD ‡§

Adult bioequivalence study presented at CROI 2012


Cipla Limited, Mumbai, India; Sitec Labs, India
DNDi-Cipla Target Product

The Right Dose, The Right Taste

- 4 products in 1: granules (FDC) in a capsule
- Capsule simple to open and use with water, milk, food
- Well taste masked
- No cold chain
- Suitable for infants < 2 mos-3 yrs (& children who cannot swallow pills)
- TB-treatment manageable (additional RTV booster)
- Affordable

Modular format allows flexibility to replace drug in the combination

To be added during HIV/TB therapy

4-in-1 in Fixed-Dose Combinations
4-in-1 initial questions

**R&D questions**
- Are the four molecules compatible?
- What amount of each drug is needed per unit dose to cover all weight bands?
- How to taste mask without losing bioavailability?
- How likely is the new formulation bioequivalent to originator products?
- What paediatric clinical data will be necessary for registration?

**IP and Market shaping questions**
- How to deal with IP issues, for research and for market?
- What needs to be done to assist in country registration?
- How to facilitate adoption in national guidelines and procurement by national treatment programs
Lopinavir based fixed dose combinations: ratios, strengths, weight bands

- Four drugs that are absorbed and metabolized through different mechanisms which mature at different paces
  
  **ZDV**: glucuronyl transferase + renal excretion
  **3TC**: 5% transsulfoxide; unchanged renal elimination
  **ABC**: alcohol dehydrogenase and glucuronyl transferase
  **LPV**: Oxidation by CYP3A enzymes
Lopinavir based fixed dose combinations: ratios, strengths, weight bands

- PK analysis of 25 datasets (INSERM, IMPAACT and PENTA)
- Nonlinear mixed effect modelling

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>No. of capsules (2x per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV</td>
<td>40 mg</td>
<td></td>
</tr>
<tr>
<td>AZT or ABC</td>
<td>30 mg</td>
<td></td>
</tr>
<tr>
<td>3TC</td>
<td>15 mg</td>
<td></td>
</tr>
</tbody>
</table>

- 4 – 5.9 kg: 2
- 6 – 9.9 kg: 3
- 10 – 13.9 kg: 4
- 14 - 19.9 kg: 5
- 20 - 24.9 kg: 6
Taste masking lopinavir
The challenge of taste masking: loss of bioavailability and high variability of lopinavir plasma levels

Screen new formulations in dogs in order to select formulations to be evaluated in adult volunteers
5% or 8% coated pellets vs. Solution – Fed state
1:3 TMP granules vs. Liquid - Fed state

Mean plasma concentration vs. time curve for Lopinavir
(Upper Panel: Linear Plot; Lower Panel: Semilog Plot)
Selection criteria for the final LPV/r formulation relevant for the targeted patient group

- Simplicity of the formulation process (compare minitablets, coated granules and plain granules)
- Bioavailability
- Taste masking
- Size of granules versus minitablets
- Volume of dose to administer to babies
- "Mouthfeel"
- Visual aspect of the 4 in 1
- Food effect
LTFU at 12 months: 20%, increased from 11.9% in 2004 to 24.5% in 2012. Retention on ART at M12: 73.5%.

Levels of pre-treatment HIVDR in LMIC have increased between 2004 and 2010, primarily driven by raised levels to NNRTIs in Africa. (14% in SA)

The proportion of HIV new infections due to transmission from people with previous exposure to ARV drugs through PMTCT or previous treatment will increase. Therefore the risk of transmitted HIVDR among new-borns will increase. How do we anticipate this? In terms of early warning indicators, in terms of sequencing?
With increasing NNRTI HIVDR combined to use of Prep based on tenofovir /FTC, which are backbone components of first line ART, do we set up the scene for functional monotherapies or de facto suboptimal first line regimen?

Can we develop other Prep components issued from other classes to preserve the NRTIs efficacy?

Children will need more treatment options than adults, especially if the get infected with MDRHIV, this needs to be anticipated now.
To all the patients and their families, the Cipla and DNDi staff.

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