Pharmacokinetics and acceptability of a new generic lopinavir/ritonavir sprinkle formulation compared with syrup/tablets in African, HIV-infected infants and children according to WHO weight-band dose recommendations (CHAPAS-2)

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Introduction

• Protease Inhibitor based ART in children is used:
  − Second-line following NNRTI+2NRTI
  − First line in infants (particularly following perinatal exposure to nevirapine for PMTCT) [1]

• Use of second-line ART remains low (<4%) [2] but is increasing in resource-limited settings:
  − Limited experience
  − Lack of appropriate formulations
  − Lopinavir/ritonavir (LPV/r) is only co-formulated PI:
    o Ritonavir liquid is very unpalatable and smallest solid formulation is 100mg

1. WHO Paediatric ART guidelines (2010)
2. UNAIDS/UNICEF (2010)
Lopinavir/ritonavir formulations

- Liquid formulation (80/20mg per ml)
  - Requires refrigeration
  - Has unpleasant taste
  - Expensive

- Tablet formulation
  - Adult (200/50mg) and paediatric (100/25mg) tablets are large
  - They must not be crushed/split (lose 45-47% bioavailability) [3]
    - Some children cannot swallow whole tablets

- Few PK data in infants or in African children

Lopinavir/ritonavir sprinkles

- Using melt extrusion technology, Cipla Pharmaceuticals, India, developed LPV/r (40/10mg) as a sprinkle formulation
  - Appropriate for even the smallest children, as it allows the drug to be easily mixed in with food
  - Stored in capsules for easy administration; no need for refrigeration
  - Bioavailability proven in healthy adults (CROI 2012 poster 982)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Number of tablets/sprinkle capsules/ml by weight band (kg) twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3-&lt;4kg</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Sprinkle 40/10mg</td>
<td>-</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Tablets 100/25mg</td>
<td>-</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Syrup 80/20 mg/ml</td>
<td>1.5ml</td>
</tr>
</tbody>
</table>

*tablets cannot be broken
The CHAPAS 2 trial: objectives

1. To determine and compare the PK of LPV/r in a twice daily paediatric co-formulated fixed dose sprinkle (Cipla) combination:
   - Versus twice daily paediatric co-formulated fixed dose tablet (Cipla) in 24 HIV-infected children aged 4-12 years
   - Versus twice daily paediatric co-formulated syrup (Abbott) in 16 HIV-infected infants under 1 year of age
     - All formulations given with food

2. To compare the formulation preferences of:
   - Sprinkle versus tablets among older children and carers
   - Sprinkle versus syrup among infants’ carers
CHAPAS 2 trial design
PK Studies 1 and 2

PK Study-1
HIV-1 infected children
aged 4 -13 years
(<25kg)* (n=24)

PK Study-2
HIV-1 infected infants
3 months - <12 months** (n=16)

* Children on or about to start Tablets and can definitely swallow them
** Infants on or about to start Syrups

PK day: time = 0, 1, 2, 4, 6, 8 & 12 hours after observed intake with food

At week 8, children/carers chose which formulation to continue
# Results

## Baseline characteristics

### Child Demographics

<table>
<thead>
<tr>
<th></th>
<th>PK study-1 (n=29)</th>
<th>PK study-2 (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>6.2 (5.8-8.0)</td>
<td>0.5 (0.4-0.6)</td>
</tr>
<tr>
<td><strong>Male, n</strong></td>
<td>13 (45%)</td>
<td>6 (43%)</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>113 (107-118)</td>
<td>62 (60-65)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>19.3 (17.9-20.9)</td>
<td>6.4 (6.1-6.7)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>15.2 (14.2-15.7)</td>
<td>17.1 (15.3-17.6)</td>
</tr>
<tr>
<td><strong>CD4%</strong></td>
<td>32 (26 to 38)</td>
<td>25 (17 to 29)</td>
</tr>
<tr>
<td><strong>Height-for-age z-score</strong></td>
<td>-1.24 (-2.06 to -0.33)</td>
<td>-1.86 (-2.57 to -0.78)</td>
</tr>
<tr>
<td><strong>Weight-for-age z-score</strong></td>
<td>-0.82 (-1.81 to -0.13)</td>
<td>-1.10 (-1.44 to -0.71)</td>
</tr>
</tbody>
</table>

Continuous values are median (interquartile range, IQR), categorical values are n (%)
Pharmacokinetic results
Tablets vs Sprinkles (4-13 years)

- LPV exposure in **sprinkles** comparable to historical data in children
- LPV exposure in **tablets** is higher than in sprinkles
- Variability all PK parameters is moderately high; CV%: 29 - 49%

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Tablets</th>
<th>Sprinkles</th>
<th>GMR (90% CI)</th>
<th>Historical data in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_{0-12h} ) (h.mg/L)</td>
<td>115.6 (103.3-129.8)</td>
<td>83.1 (66.7-103.5)</td>
<td>0.72 (0.60-0.86)</td>
<td>72.6 (41.5-103.7)</td>
</tr>
<tr>
<td>( \text{Cmax} ) (mg/L)</td>
<td>13.9 (12.9-15.1)</td>
<td>10.3 (8.6-12.2)</td>
<td>0.74 (0.64-0.85)</td>
<td>8.2 (5.3-11.1)</td>
</tr>
<tr>
<td>( \text{C12h} ) (mg/L)</td>
<td>4.4 (3.3-5.9)</td>
<td>2.6 (1.7-4.1)</td>
<td>0.59 (0.43-0.81)</td>
<td>3.4 (1.3-5.5)</td>
</tr>
</tbody>
</table>
### Pharmacokinetic results

**Syrup vs Sprinkles (<1 year)**

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Syrup</th>
<th>Sprinkles</th>
<th>GMR (90% CI)</th>
<th>Historical data in children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GM (95% CI)</td>
<td>GM (95% CI)</td>
<td>Sprinkle:tablet</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-12h}$ (h.mg/L)</td>
<td>62.5 (35.6-109.7)</td>
<td>70.9 (41.8-120.2)</td>
<td>1.13 (0.62-2.06)</td>
<td>72.6 (41.5-103.7)</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>9.3 (6.2-13.9)</td>
<td>9.1 (6.1-13.7)</td>
<td>0.98 (0.65-1.49)</td>
<td>8.2 (5.3-11.1)</td>
</tr>
<tr>
<td>C12h (mg/L)</td>
<td>2.1 (0.9-5.1)</td>
<td>3.4 (2.1-5.7)</td>
<td>1.62 (0.67-3.96)</td>
<td>3.4 (1.3-5.5)</td>
</tr>
</tbody>
</table>

- Exposure LPV in sprinkles comparable to the Abbott oral solution and historical data.
- Variability is high; CV%: 62-66%
Subtherapeutic PK values

- Sub-therapeutic trough levels in:
  - 4 (16%) sprinkles versus 1 (4%) tablets (p-value=0.35)
  - 0 (0%) sprinkles versus 3 (27%) syrup (p-value=0.21)
For older children already established on tablets:

- Tablets had better taste
- 22/29 (76%) chose to continue tablets
Sprinkles were:

- Better to swallow
- Storage/transport important advantage for caregivers
- 10/14 (71%) chose to continue sprinkles

Acceptability
Percent reporting problems (<1 year n=14)

Syrup:
- taste
- swallowing
- storing the medicine
- transporting bottles
- vomiting the medicine
- conspicuous
- weight of bottles
- volume of medicine
- opening the bottles
- number of bottles
- taking whole dose
- knowing which bottle contains which drug
- losing/breaking capsule/tables
- losing/breaking bottles

Sprinkles:
- Better to swallow
- Storage/transport important advantage for caregivers
- 10/14 (71%) chose to continue sprinkles
Discussion and conclusions

• Exposure to LPV/r from sprinkles was comparable with syrup in infants and with historical data
• Exposure to LPV/r from tablets was higher than sprinkles in older children
• Variability in LPV/r PK parameters was high in all formulations
  – High prevalence of sub-therapeutic levels, but no sign of difference between formulation groups
  – Virological response data not available (awaited)
• For infants, sprinkles were more acceptable than syrups
• For older children already able to swallow tablets, tablets were more acceptable than sprinkles
  – Taste of sprinkle was a concern
Next steps for CHAPAS 2

- Two further cohorts ongoing/planned in CHAPAS 2:
  - Young children aged 1-4 years on or starting syrups
  - Acceptability of improved granule formulation with better taste masking
Acknowledgements

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