LOPINAVIR/RITONAVIR 1:1 SUPER-BOOSTING OVERCOMES RIFAMPICIN INTERACTIONS IN CHILDREN

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Background

- LPV/r (4:1) preferred 1\textsuperscript{st} line ARV regimen for infants
- TB is common in HIV-infected children
- Rifampicin (RIF) induces cytochrome (CYP) p450 3A4 and p-glycoprotein → ± 90% ↓LPV/r
- Doubling the LPV/r dose does not work in children
- “Superboosting” - i.e. increasing the dose of ritonavir (RTV) to obtain a 1:1 LPV:RTV ratio counteracts the RIF effect in children - BUT
  - Small studies
  - RIF dose increased in revised WHO guidelines
Multicenter, open label, non-randomized, study

Primary Objective:
- To determine whether the proportion of subjects achieving modelled LPV C\textsubscript{0/morning trough} > 1mg/L during RTV superboosting (1:1 ratio) on RIF-based anti-TB treatment is inferior to LPV/r 4:1 without RIF
- Non-inferiority threshold -10%

- Standard weight-band dosing
- Using liquid LPV/r and RTV
Sample size

- Calculated to provide at least 80% power to prove that LPV/r trough levels during superboosting for RIF therapy are not inferior to those after superboosting and RIF discontinuation (critical delta 10%)

- 90 evaluable subjects provide adequate power to test for non-inferiority
Study plan

Intensive pharmacokinetic visits: PK1, 2, and 3; PK4 trough levels only
6 samples: Hr 0 = (pre observed dose), then 1, 2, 4, 6, & 10 hours
Inclusion / exclusion criteria

Inclusion

- Confirmed HIV-1 infection
- Weight 3.0 kg - 15.0 kg
- > 42 weeks post-conception age
- On or about to start LPV/r-based ART
- Clinically diagnosed TB requiring RIF in anti-TB therapy
- Written informed consent

Exclusion

- Concomitant potent enzyme-inducing/inhibiting drugs
- Need for anti-TB or ARVs other than from protocol
- Anticipated anti-TB treatment duration > 9 months
## Screening, Enrollment and Follow-up

<table>
<thead>
<tr>
<th>PK</th>
<th>Expected</th>
<th>Performed</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>82</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Returned late for PK2 n=2)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

- Lost to follow-up N = 5
- Withdrew consent N = 6
- Death N=3
- Other N= 2

N=16

254 Intensive PK performed 174 on Rif
# Subjects characteristics (1)

<table>
<thead>
<tr>
<th></th>
<th>Enroll n=96</th>
<th>PK1 n=93 PK Data for 92</th>
<th>PK2 n=84 Data for 82</th>
<th>PK3 n=80 Data for 80</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (months)</strong></td>
<td>18.2 (9.6-26.8)</td>
<td>19.1 (10.4-27.6)</td>
<td>23.3 (15.2-34.4)</td>
<td>25.0 (16.7-34.3)</td>
</tr>
<tr>
<td>Female</td>
<td>52 (54%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;1y</td>
<td>30 (31%)</td>
<td>27 (29%)</td>
<td>15 (18%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>8.4 (6.7-10.3)</td>
<td>8.8 (7.1-11.1)</td>
<td>9.8 (8.5-12.2)</td>
<td>10.1 (8.9-12.3)</td>
</tr>
<tr>
<td><strong>WAZ</strong></td>
<td>-2.15 (-3.36 -1.19)</td>
<td>-2.00 (-2.86 -0.87)</td>
<td>-1.34 (-2.15 -0.43)</td>
<td>-1.37 (-2.22 -0.45)</td>
</tr>
<tr>
<td><strong>WHZ</strong></td>
<td>-0.64 (-1.61 -0.31)</td>
<td></td>
<td></td>
<td>-0.26 (-1.1 -0.52)</td>
</tr>
<tr>
<td>Clinical stage 4</td>
<td>60 (62%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4% *</td>
<td>19.5 (11.6 – 25.7)</td>
<td></td>
<td>27.3 (20.5 – 32.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Median and IQR
## Subjects characteristics (2)

- TB treatment started 1\textsuperscript{st}: 70 (73%)
- < 3 Months ART Before TB: 12 (12.5%)
- TB therapy 4 drugs (including EMB): 77 (80%)
- ABC + 3TC: 91 (95%)

<table>
<thead>
<tr>
<th></th>
<th>Enroll n=96</th>
<th>PK1 n=93</th>
<th>PK2 n=84</th>
<th>PK3 n=80</th>
</tr>
</thead>
<tbody>
<tr>
<td>*BSA</td>
<td>0.39 (0.34-0.46)</td>
<td>0.40 (0.35-0.47)</td>
<td>0.44 (0.40-0.52)</td>
<td>0.45 (0.41-0.52)</td>
</tr>
<tr>
<td>*LPV Dose mg/m\textsuperscript{2}</td>
<td>322.9 (297.5 – 339.45)</td>
<td>309.86 (287.21-330.51)</td>
<td>308.14 (286.37-329.12)</td>
<td></td>
</tr>
<tr>
<td>*RIF Dose mg/kg</td>
<td>12.45 (11.1-13.48)</td>
<td>12.63 (11.68-13.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load Log</td>
<td>5.7 (4.6-6.3)</td>
<td>2.1 (&lt;1.6-2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load &lt;Log 2.6</td>
<td>6 (6%)</td>
<td>67 (82%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Median and IQR
Model-based analysis

- PK1 was used to develop PK model
- The model was used to compare the data from PK2 (LPV/RTV superboosting with RIF) and PK3 (LPV/r normal dose)
  - Separate PK estimates for each visit
- Model-based simulations were used to compare exposures between superboosting or normal dose:
  - To account for diurnal variation overnight clearance was assumed 30% slower
  - The % of children with Cmin < 1mg/L was compared for each regimen
  - The 95% confidence interval for this difference was checked for non-inferiority
Observed LPV $C_0$ and $C_{10}$ levels

### Dosing unobserved

<table>
<thead>
<tr>
<th>PK</th>
<th>Median (IQR) LPV $C_0$, mg/L</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.21 (2.86 – 10.1)</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>7.34 (2.43 – 11.0)</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>9.12 (4.60 – 11.4)</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>6.33 (0.957 - 11.2)</td>
<td>72</td>
</tr>
</tbody>
</table>

### Dosing observed at clinic

<table>
<thead>
<tr>
<th>PK</th>
<th>Median (IQR) LPV $C_0$, mg/L</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.38 (2.81 – 9.12)</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>5.01 (2.45 – 7.84)</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>5.35 (2.82 – 8.62)</td>
<td>80</td>
</tr>
</tbody>
</table>
Visual predictive check – Model PK 1
The percentiles are consistently within the 90% confidence intervals

Log Scale

Observed concentrations
- 5th & 95th centile observed value
- 50th centile observed value

5th & 95th centile modeled value
- 50th centile modeled value

Dose
Bioavailability (F)
Absorption Compartment
ka
Central Compartment
CL/V
Visual predictive check – Model PK 2-3

The percentiles are consistently within the 90% confidence intervals

Log Scale

<table>
<thead>
<tr>
<th>Observed concentrations</th>
<th>5th &amp; 95th centile observed value</th>
<th>5th &amp; 95th centile modeled value</th>
<th>50th centile observed value</th>
<th>50th centile modeled value</th>
</tr>
</thead>
</table>

- **VISIT:2**
- **VISIT:3**
Percentage modeled $C_0$ below target

- **Superboosting** % $C_{\text{min}} < 1 \text{ mg/L} = 7.6\% (0.4\% - 16.2\%)
- **Standard dose** % $C_{\text{min}} < 1 \text{ mg/L} = 8.8\% (0.6\% - 19.8\%)
- **Difference:** -1.1\% (-6.9\% to 3.2\%)

The 10\% delta threshold is outside the 95\% confidence interval for the difference, confirming non-inferiority.
Adverse events and safety

- 29 Serious adverse events
  - 3 deaths
  - 16 infections (7 respiratory tract infections)
  - 1 obstructive jaundice (temporary discontinuation of therapy all reintroduced)
  - 4 neutropenia (no therapy changes required)
  - 1 type 1 Diabetes (islet cell antibody positive)

- No ECG abnormalities requiring therapy change
# Hepatic enzymes monitoring

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PK1</th>
<th>PK2</th>
<th>PK3</th>
<th>Exit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT (U/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>25.0</td>
<td>25.0</td>
<td>26.0</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>(18.0 - 40.0)</td>
<td>(19.0 - 32.0)</td>
<td>(19.5 - 35.5)</td>
<td>(16.0 - 26.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>68 (72%)</td>
<td>79 (86%)</td>
<td>62 (78%)</td>
<td>72 (91%)</td>
<td></td>
</tr>
<tr>
<td><strong>ALT Gr 1</strong></td>
<td>21 (22%)</td>
<td>9 (10%)</td>
<td>13 (16%)</td>
<td>6 (8%)</td>
<td></td>
</tr>
<tr>
<td>1.5-2.5 ULN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALT Gr 2</strong></td>
<td>6 (6%)</td>
<td>4 (4%)</td>
<td>5 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6-5 ULN</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
At PK 2
- 69 (84%) < Log 3
- 67 (82%) < log 2.6

22 resistance test performed
- 7 No mutations
- No lopinavir resistance
- M184V in 10/15 children
- NNRTI mutations seen in 10/15 children (9/10 significant)
Discussion and conclusion

- LPV trough levels on superboosting were NOT inferior to those on standard LPV/r without RIF
- Viral suppression <400 copies was comparable to published cohort data
  - No major LPV/r resistance documented
  - 9 of 15 children with resistance had significant NNRTI resistance
- Logistical complexity and tolerability may remain obstacles – Mothers assessment and children reactions do not necessarily match
- Taste masked LPV/r granules and RTV powder may help
Acknowledgements

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