Pharmacokinetics of lopinavir/ritonavir super-boosting in infants and young children co-infected with HIV and TB
HIVPED001

Interim results

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TB is common in HIV-infected children

Rifampicin (RIF) causes drug-drug interactions by:

- Inducing cytochrome (CYP) p450
- Also increased:
  - p-glycoprotein
  - multiple drug resistance protein 2
  - organic-anion transporting polypeptide
  - UDP-glucuronyl- & sulfotransferase
Background

- LPV/r (4:1) is preferred drug in infants
- RIF reduces LPV/r exposure by ± 90%
- Doubling LPV/r works in adults but not children
- “Super-boosting” with ritonavir (RTV) for 1:1 parity with LPV is the only strategy to counteract the RIF effect
  - Small study, mainly older children
  - RIF dosage subsequently increased by WHO
Study Design: Multicentre, open label, non-randomized, prospective, non-inferiority study - 2 scenarios

1st scenario: starting TB treatment first

2nd scenario: starting ARV treatment first
Primary Objective: To demonstrate that

- The proportion of subjects achieving modelled LPV $C_{0/morning \, trough} > 1\text{mg/L}$ during RTV super-boosting (1:1 ratio) on RIF-based anti-TB treatment is not inferior to LPV/r 4:1 without RIF

- Non-inferiority threshold -10%
Secondary Objectives

- Safety and tolerability
- Effects of age, sex, initial severity of TB and anthropometric measurements on PK parameters
- PK of anti-TB meds
- To assess adherence
- To describe viral load evolution
- To compare abacavir exposure with and without super-boosting
- To explore pharmacogenetic influences on anti-TB drugs and ARV exposure during co-treatment
Inclusion criteria

- Confirmed HIV-1 infection
- Weight >3kg ≤15 kg at enrolment
- > 42 weeks post-conception age
- On or about to start LPV/r-based ART
- Clinical diagnosis of TB requiring RIF-based therapy
- Written informed consent
Exclusion criteria

- <42 weeks gestation/14 days old
- Concomitant/chronic use of potent enzyme-inducing/inhibiting drugs (steroids low dose excluded)
- Anticipating anti-TB treatment duration > 9 months
- Known malignancies
- Contraindications to LPV/r
- Treatment with experimental drugs within 30 days
- Children requiring dosing of either anti-TB or ARVs other than from protocol
Safety

- EKG at baseline & after super-boosting X2W
  - Central cardiologist – John Lawrenson, SU/UCT
- AST/ALT; lipids; hematology
Dosing and pharmacokinetic visits

- Standard weight band dosing for ART & TB Rx
- Liquid LPV/r and RTV
- Pharmacokinetic visits
  - 6 samples over 10-hours
  - 0- (pre observed dose), then 1, 2, 4, 6, & 10 hours post dose

PK1: RIF X4W & super-boosted LPV/r (1:1) ≥1W
PK2: RIF & super-boosted LPV/r (1:1) - Month 6 for TB Rx
PK3: LPV/r (4:1) – 4-6W post RIF & super-boosting
PK4: 3M after TB Rx
Pharmacokinetics Analysis:

- PK 1 data used to develop structural model
  - Pre-dose concentrations modeled with baseline approach to minimize effect of adherence/incorrect dosing information
  - Comparison of modeled and real levels through visual predictive checks

- Model applied to PK2 (super-boost) and PK3 (standard dose) data
  - Separate estimation of PK parameter for PK2 and PK3
  - Bootstrapping to obtain confidence intervals (CI)
    - Simulation of predicted concentrations for 10,000 subjects using bootstrap estimates (and imputing 30% lower clearance overnight).
Sample size for non inferiority testing

- Calculated to give at least 80% power to compare the predicted number of children with \( C_{0/\text{morning trough}} < 1 \text{ mg/L} \) between PK3 and PK2 for non inferiority

- If upper limit of 95% CI of the difference PK3 - PK2 is below 10%, non-inferiority can be declared
Request from WHO to update data on PK outcomes for new guidelines

Gave permission for additional analysis

We present the interim analysis of the primary outcome until May 2015

PRIOR to required sample size

Only for primary objective
Enrolment status 1 May 2015

<table>
<thead>
<tr>
<th>Screened</th>
<th>256</th>
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</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>89</td>
</tr>
<tr>
<td>On study</td>
<td>22</td>
</tr>
<tr>
<td>Completed</td>
<td>59</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
</tr>
<tr>
<td>LTF</td>
<td>3</td>
</tr>
<tr>
<td>Withdrew</td>
<td>4</td>
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</tbody>
</table>

TB therapy started 1st: 66
ART started 1st: 21
TB/ART start together: 2
## PK status 1 May 2015

<table>
<thead>
<tr>
<th>PK</th>
<th>Expected</th>
<th>Performed</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85</td>
<td>84</td>
<td>217 Intensive PK 154 on RIF</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>56</td>
<td>Single C₀/morning trough</td>
</tr>
<tr>
<td></td>
<td>Enroll</td>
<td>PK1 (n=80)</td>
<td>PK2 (n=68)</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td><em><em>Age</em> (m)</em>*</td>
<td>18.2 (9.1 - 26.8)</td>
<td>19.1 (10.0 - 28.8)</td>
<td>22.9 (3.5 - 33.4)</td>
</tr>
<tr>
<td><strong>Age &lt;1y</strong></td>
<td>29 (33%)</td>
<td>26 (31%)</td>
<td>14 (20%)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong>*</td>
<td>8.4 (6.9 - 10.7)</td>
<td>8.8 (7.2 - 11.1)</td>
<td>9.8 (8.7 - 12.2)</td>
</tr>
<tr>
<td><strong>CD4 % / Cells/mm³</strong></td>
<td>19 (11.2 - 25.4)</td>
<td>880 (459 - 1710)</td>
<td></td>
</tr>
<tr>
<td><strong>Log Viral load</strong></td>
<td>5.8 (4.7 - 6.3)</td>
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</tbody>
</table>

*Median and IQR
Observed LPV levels- PK1

Heavily influenced by adherence in days before PK. Preceding evening dose taken at home with time reported

After a supervised dose - trend different & higher than C_0
Visual predictive check: the model was used to re-simulate the dataset.

**Observed concentrations**
- 50th centile
- 5th & 95th centiles

**Modeled from simulation**
- 50th centile
- 5th & 95th centiles
Percentage modeled $C_0$ below target:

- Super-boosting: 10.7% (3.3% to 19.6%)
- Standard dose: 15.1% (5.1% to 27.7%)
- Difference: = -4.4% (-12.1% to 1.4%)
- RIF+superboosted regimen has *lower* % of children below target than standard regimen.

- 10% is outside the 95% CI for the difference, proving non-inferiority.
Serious Adverse events

- 3 Deaths – None thought directly associated with intervention
- No interruptions for abnormal ECG
- 1 interruption for hepatitis with obstructive jaundice, thought unassociated with study therapy, then reintroduced
- Other SAEs due to HIV and related illness
Virologic response

<table>
<thead>
<tr>
<th>End of study</th>
<th>N=30</th>
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<td>(24 – 36 weeks)</td>
<td></td>
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<tr>
<td>&lt;1000</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>&lt;400</td>
<td>22(73%)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>6(20%)</td>
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No major PI mutations in children not suppressing
Discussion and conclusion

- Interim results – enrolment continues
- Super-boosting at C_0 NOT inferior to standard LPV/r without RIF
  - Virologic efficacy also comparable
- Safety not a concern at this stage
- Logistical complexity and tolerability remain obstacles – LPV/r pellets/granules and RTV granules may help
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