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

Interim results

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Background

- 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

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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

Ren JAIDS 2008

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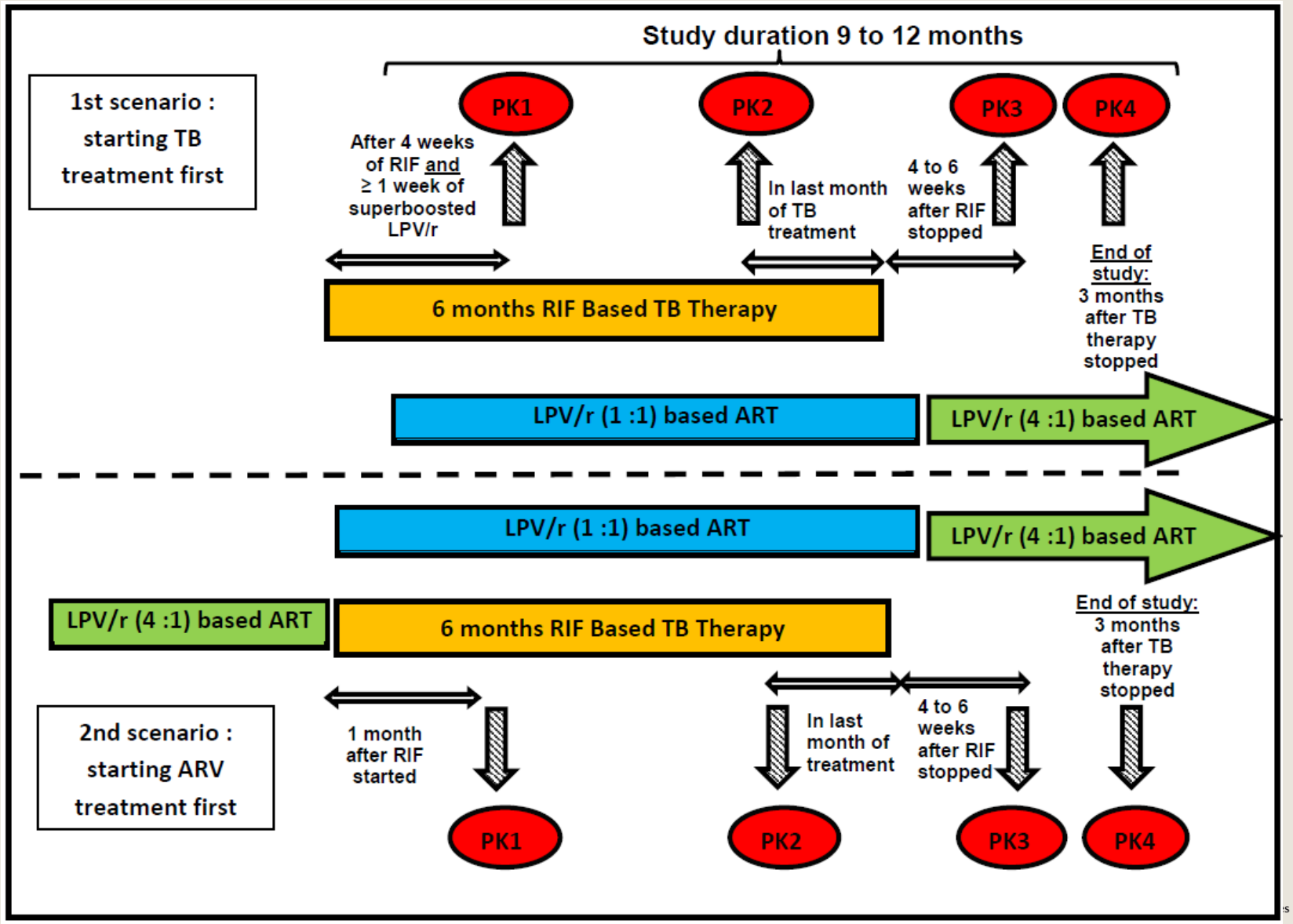
Study Design: Multicentre, open label, non-randomized, prospective, non-inferiority study - 2 scenarios



Primary Objective: To demonstrate that

- The proportion of subjects achieving modelled LPV $C_{0/\text{morning trough}}$ > 1mg/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%

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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

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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

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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

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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

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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).

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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 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

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DSMB meetings / interim analysis

- 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

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Enrolment status 1 May 2015

Screened	256
Enrolled	89
On study	22
Completed	59
Death	3
LTF	3
Withdrew	4

TB therapy started 1st: **66**

ART started 1st: **21**

TB/ART start together: **2**

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PK status 1 May 2015

PK	Expected	Performed	
1	85	84	217 Intensive PK 154 on RIF
2	71	70	
3	63	63	
4	56	56	Single $C_{0/\text{morning trough}}$

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Basic data

	Enroll	PK1 (n=80)	PK2 (n=68)	PK3 (n=56)
Age* (m)	18.2 (9.1 - 26.8)	19.1 (10.0 - 28.8)	22.9 (3.5 - 33.4)	23.7 (15.2 - 33.5)
Age <1y	29 (33%)	26 (31%)	14 (20%)	7 (11%)
Weight (kg)*	8.4 (6.9 - 10.7)	8.8 (7.2 – 11.1)	9.8 (8.7 - 12.2)	10.1 (9.1 - 12.3)
CD4 % / Cells/mm^3	19 (11.2 - 25.4) 880 (459 - 1710)			
Log Viral load	5.8 (4.7 - 6.3)			

*Median and IQR

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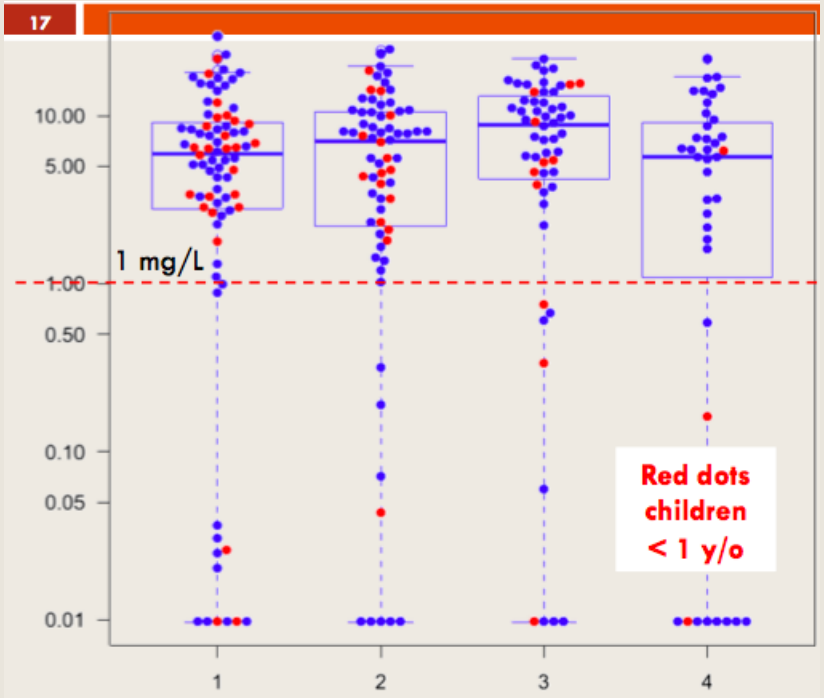
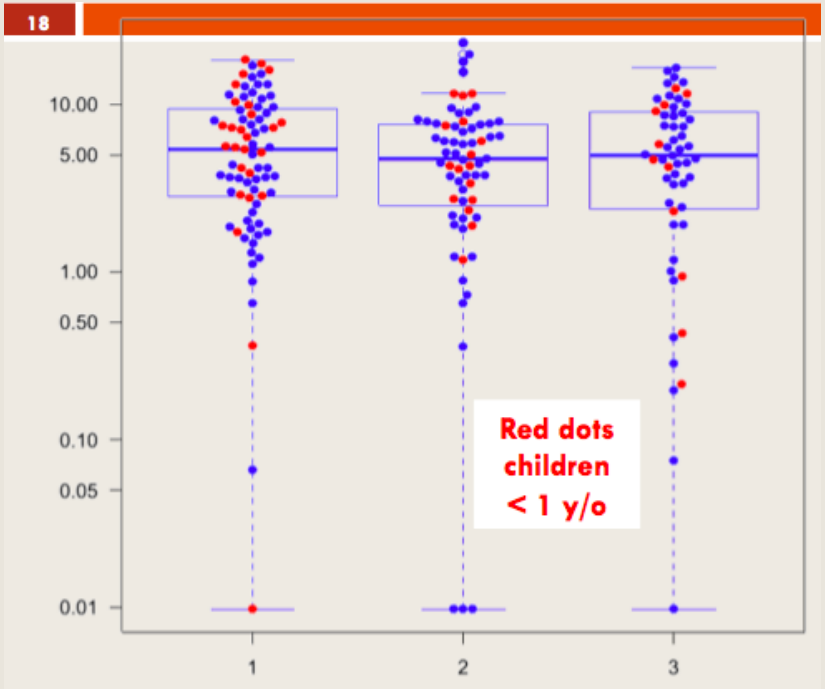
Observed LPV levels- PK1

C_0 hr



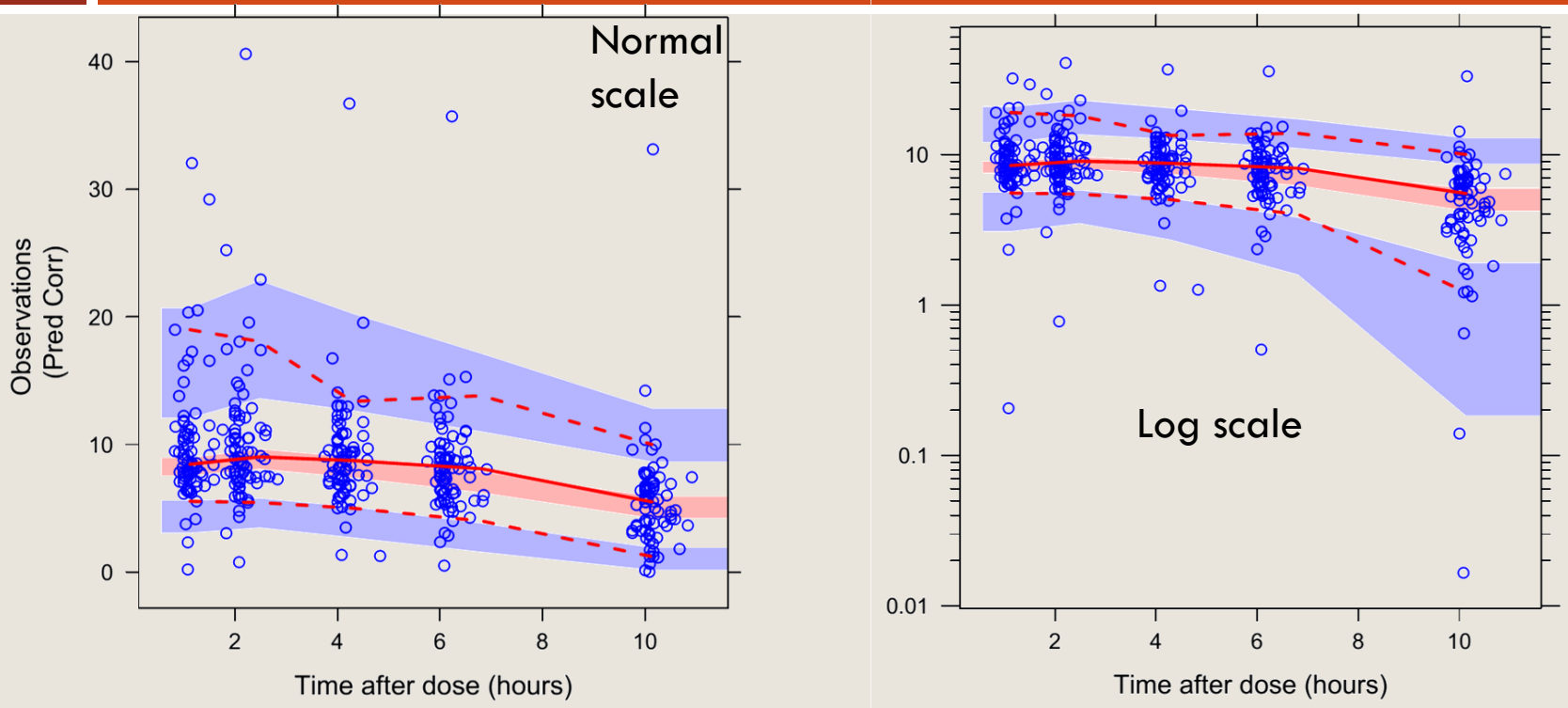
Heavily influenced by adherence in days before PK. Preceding evening **dose taken at home** with time reported

C_10 hr



After a **supervised** dose - trend different & higher than C_0

Visual predictive check – model for PK1



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

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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%)**

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- RIF+superboosted regimen has **lower** % of children below target than standard regimen.

- 10% is outside the 95% CI for the difference, proving non-inferiority

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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

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Virologic response

End of study (24 – 36 weeks)	N=30
<1000	24 (80%)
<400	22(73%)
<50	6(20%)

No major PI mutations in children not suppressing

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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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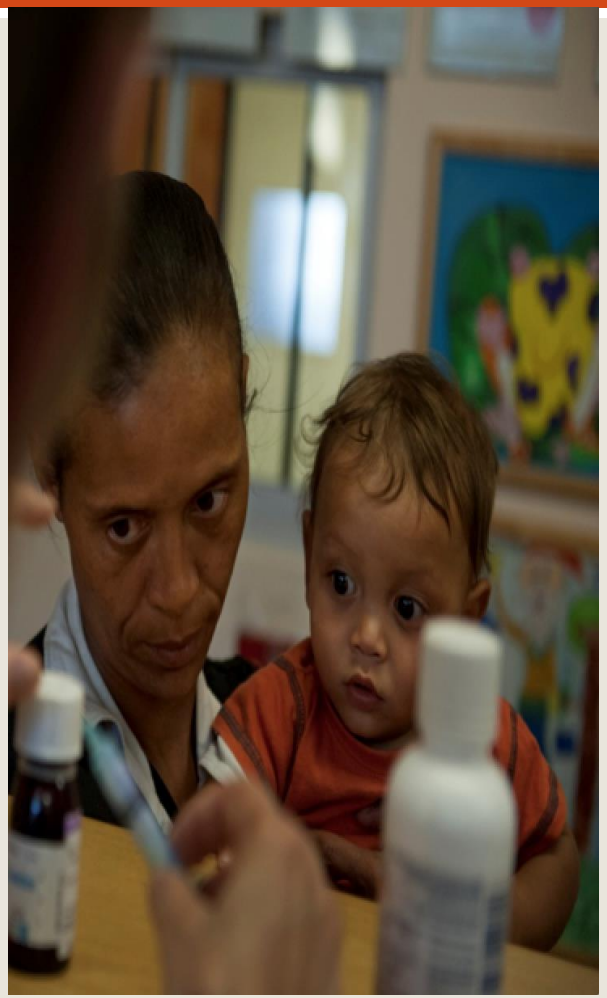

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