Lopinavir/Ritonavir Super-boosting Overcomes Interactions In Children Treated With Rifampicin: A Model-Based Approach For Non-Inferiority Trials

Paolo Denti (1), Helena Rabie (2), Janice Lee (3), Helen McIlleron (1), Mark Cotton (2), Mats Karlsson (4), France Mentre' (5), Marc Lallemant (3)

(1) Division of Clinical Pharmacology, University of Cape Town, South Africa - (2) Department of Pediatrics and Child Health University of Stellenbosch, Tygerberg Hospital and Children's Infectious Diseases Clinical Research Unit, Cape Town, South Africa - (3) Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland
(4) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden (5) Inserm, IAME, UMR 1137, Université Paris Diderot, Paris, France.

Email: paolo.denti@uct.ac.za

Background and Objectives

1st-line HIV treatment in infants includes **lopinavir/ritonavir in dose ratio 4:1** (LPV/r) in association with NRTIs.

Target exposure for LPV is morning Cmin > 1 mg/L [2]

Rifampicin (RIF) **co-treatment for tuberculosis** (TB) **lowers LPV exposure**.
Extra ritonavir (RTV) to achieve a **4:4 ratio** (super-boosting) seems effective, but PK was only studied in 15 children [1] and with RIF dosed at 5 mg/kg.

A rigorous study is necessary to show non inferiority of LPV/RTV 4:4 during TB treatment vs. LPV/r 4:1 without TB treatment.

Methods

A study in South Africa compared the PK of super-boosted LPV/RTV whilst on concurrent RIF, with LPV/r alone in **children weighing 3-15 kg**.

The objective was to **prove non-inferiority defined as no more than 10% difference** (with one-sided 95% confidence) in the **proportion of children NOT achieving the therapeutic target,** i.e. all children with LPV morning Cmin<1 mg/L [2].

Blood was taken before and 1, 2, 4, 6, 10 h after dosing at 3 visits (Fig 1):
- on LPV/r super-boosting after 1-2 months of RIF (**PK1**),
- on LPV/r super-boosting in the last month of RIF (**PK2**),
- on normal LPV/r 4:1 at 4-6 weeks after stopping RIF (**PK3**).

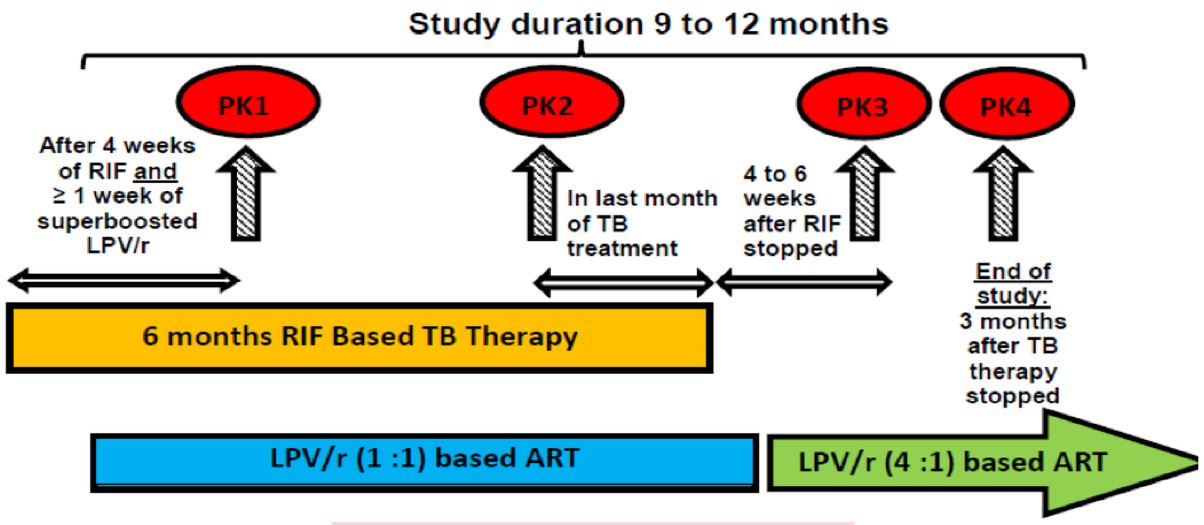

Figure 1 Study design

Modelling procedure in NONMEM 7.3, using PsN.

1. **Structural model** developed based on PK1 results.
   Pre-dose concentrations modelled with by initialising compartments using a baseline approach, B2 from [3] to handle poor information on prior doses and dosing procedure (see variability in Fig 2).

2. Same model used for the **comparison of PK2 and PK3**, after adding flexibility whenever possible **irrespectively of statistical significance**
   a. **separate typical values** for all parameters at each PK visit
   b. **BSV and BOV** whenever possible

3. Simulations for non-inferiority
   a. A **nonparametric bootstrap (n=500)** assessed uncertainty.
   b. For each of the (n=500) sets of bootstrap parameter estimates simulations of PK profiles (n=10 000) assuming 100% adherence, 12 hourly dosing, and a 30% slower clearance overnight accounting for the diurnal variation [4].
   c. **The percentage of model-simulated morning Cmin<1 mg/L** at PK2 and PK3 was compared to obtain a 95% CI and assess non-inferiority.

Results

Of 96 children enrolled, 80 completed the study.

Table 1 Patient info. n and (%) or median (and IQR)

	Enroll n=96	PK1 n=93	PK2 n=84	PK3 n=80
Age* (m)	18.2 (9.6-26.8)	19.1 (10.4-27.6)	23.3 (15.2-34.4)	25.0 (16.7-34.3)
Female	52 (54%)			
Age <1y	30 (31%)	27 (29%)	15 (18%)	7 (9%)
Weight* (kg)	8.4 (6.7-10.3)	8.8 (7.1-11.1)	9.8 (8.5-12.2)	10.1 (8.9-12.3)
Clinical stage 4	60 (62%)			
CD4%	19.5 (11.6 – 25.7)		27.3 (20.5 – 32.6)	
Viral load Log	5.7 (4.6-6.3)		2.1 (<1.6-2.9)	
Viral load <Log2.6	6 (6%)		67 (82%)	
TB therapy started first	70 (73%)			
TB therapy 4 drugs EMB	77 (80%)			
NRTI ABC + 3TC	91 (95%)			

Results

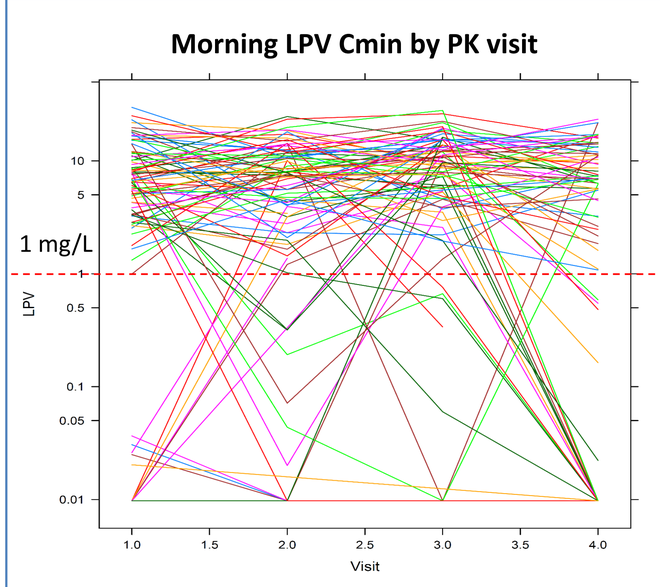

Figure 2 Observed Cmin (pre-dose)

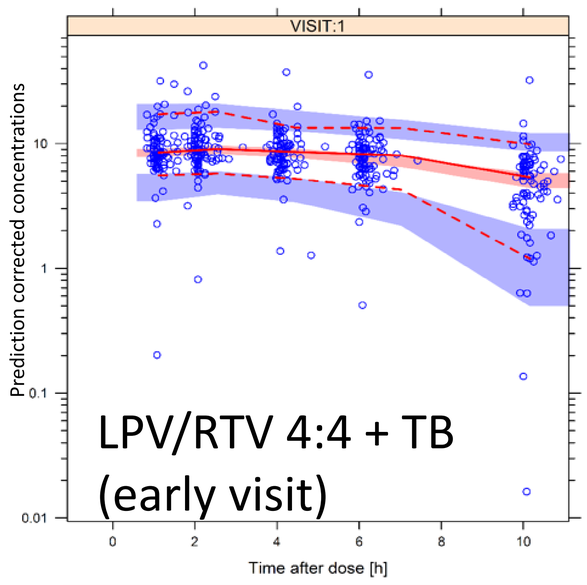

Figure 3 Pred-corrected VPC **PK1**

1-compartment model with 1st-order absorption and elimination

Allometric scaling adjusted for weight, and **no effect of age** could be identified.

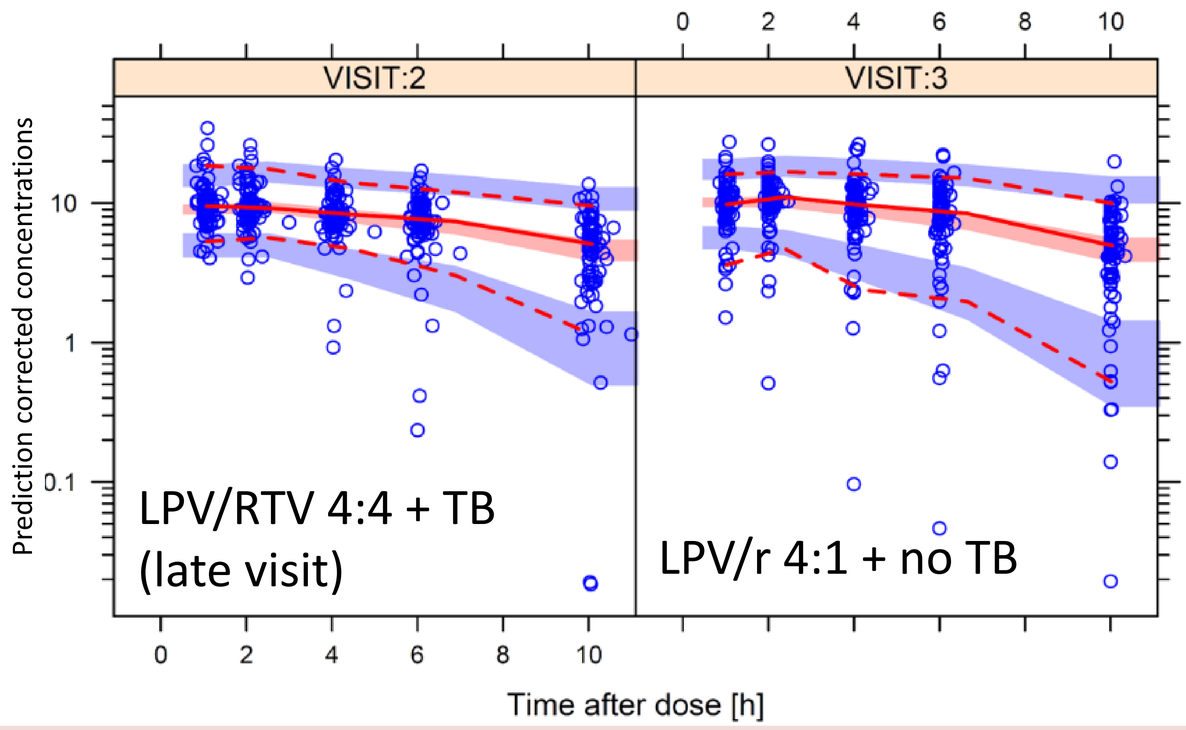

Figure 4 Prediction-corrected visual predictive check.
On the left **PK2** (second visit on LPV/RTV 4:4 during TB treatment), on the right **PK3** (visit one month after the end of TB treatment and switching back to LPV/r 4:1)

Table 2 Parameter estimates (95% CI from bootstrap)

Parameter	Typical value PK2	Typical value PK3	BSV	BOV
CL [L/h]	2.48 [2.13, 3.01]	2.33 [1.88, 2.95]	37.5% [12.7%, 50.6%]	46.6% [17.8%, 68.7%]
V [L]	22.9 [18.1, 35.5]	16.1 [12.7, 21.6]	*	*
Ka [1/h]	0.629 [0.442, 1.195]	0.438 [0.358, 0.583]	*	52.8% [31.4%, 74.8%]
F	1 FIXED		*	45.4% [28.3%, 58.3%]
Prop Err [%]	16.5% [9.1%, 19.2%]			
Add Err [mg/L]	0.174 [0.010, 1.035]			

CL and V scaled to a 10 kg child.
*When included, this random effect provided no improvement in the fit and made the model unstable

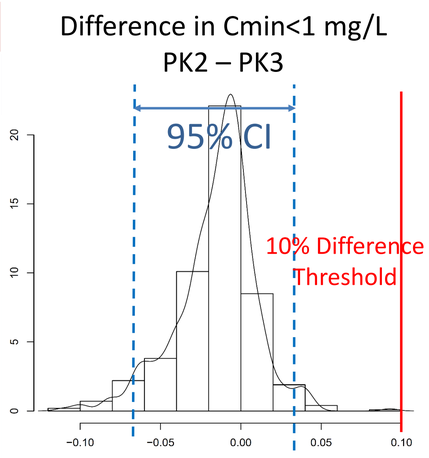

Figure 5 Simulated difference in children failing to achieve Cmin of 1mg/L

The simulated percentage of children below target with super-boosting (PK2) was 7.6% (95% CI: 0.4%, 16.2%) and on normal dose (PK3) was 8.8% (0.6%, 19.8%),

The difference PK2-PK3 was -1.1% (-6.9%, 3.2%) and **confirming the non-inferiority** of LPV exposure during super-boosting compared with standard LPV/r.

Conclusions

LPV super-boosting during RIF treatment is as **effective** as standard dosing alone to achieve the therapeutic target.

We suggested and successfully implemented **a model-based approach to evaluate non-inferiority (or other comparisons) of PK exposure**.

References

[1] C. Zhang, H. McIlleron, Y. Ren, J.-S. van der Walt, M. O. Karlsson, U. S. H. Simonsson, and P. Denti, "Population pharmacokinetics of lopinavir and ritonavir in combination with rifampicin-based antitubercular treatment in HIV-infected children.," Antivir. Ther., vol. 17, no. 1, pp. 25–33, Jan. 2012.
[2] J. Ananworanich, P. Kosalaraksa, A. Hill, U. Siangphoe, A. Bergshoeff, C. Pancharoen, C. Engchanil, K. Ruxrungtham, D. Burger, and HIV-NAT 017 Study Team, "Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children.," Pediatr. Infect. Dis. J., vol. 24, no. 10, pp. 874–9, Oct. 2005.
[3] C. Dansirikul, H. E. Silber, and M. O. Karlsson, "Approaches to handling pharmacodynamic baseline responses," J. Pharmacokinet. Pharmacodyn., vol. 35, no. 3, pp. 269–283, Jun. 2008.
[4] C. Zhang, P. Denti, E. Decloedt, Y. Ren, M. O. Karlsson, and H. McIlleron, "Model-based evaluation of the pharmacokinetic differences between adults and children administered lopinavir and ritonavir in combination with rifampicin," in PAGE. Abstracts of the Annual Meeting of the Population Approach Group in Europe. ISSN 1871-6032, 2012, p. Abstr 2400.