Population Pharmacokinetics of Lopinavir and Ritonavir in Combination with Rifampicin-based Antitubercular Treatment in HIV-infected Children

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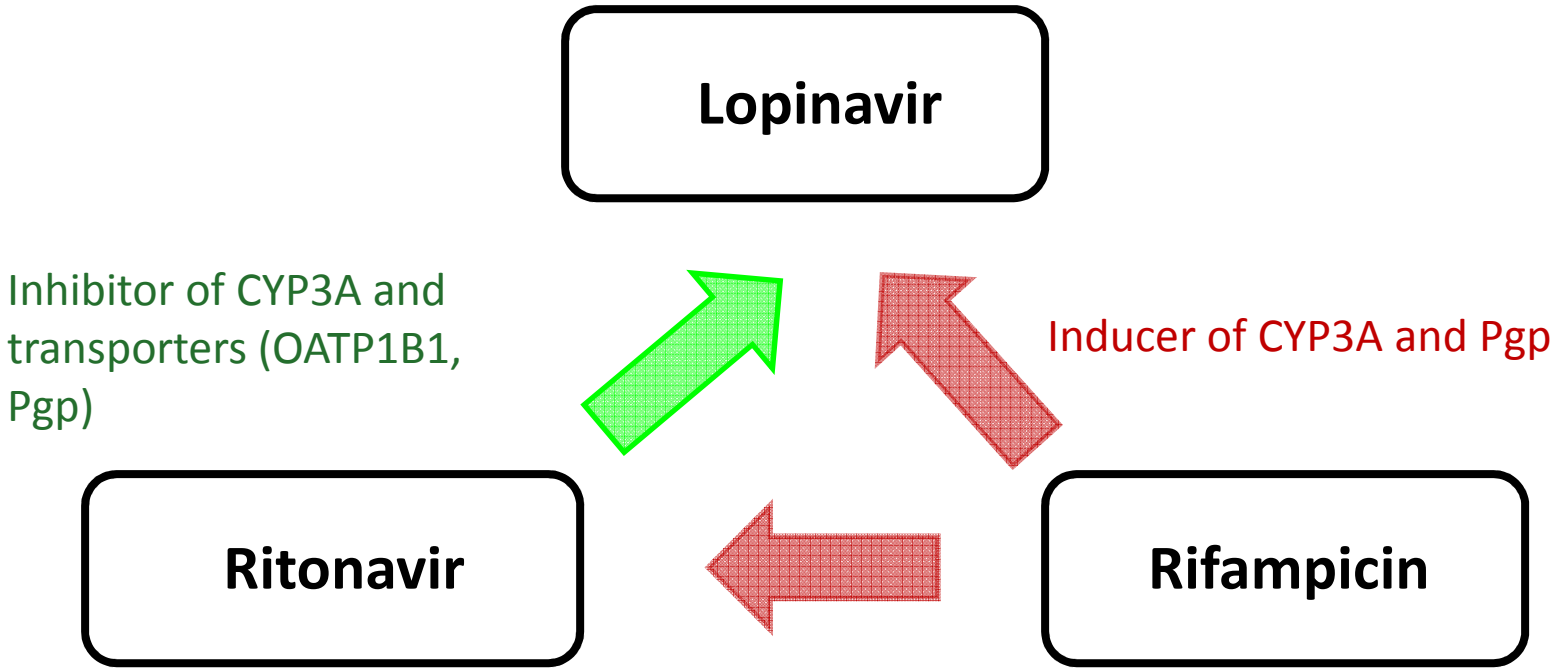
Background

- Tuberculosis (TB) is one of the most common opportunistic infection in HIV patients. Up to a third of all the new TB cases in South Africa are dually infected with HIV.
- Co-administration of antiretroviral and antitubercular therapy is frequently indicated.
- Lopinavir/ritonavir (LPV/RTV) is the first-line antiretroviral therapy for young children in South Africa.

(The South African Antiretroviral Treatment Guideline 2010).

Complicated drug-drug interaction



The concomitant administration of RIF with lopinavir/ritonavir (Kaletra®) reduces the bioavailability and Cmin of lopinavir by approximately 75% and 99% respectively.

La Porte CJL, et al. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampicin in healthy volunteers. Antimicrob Agents Chemother. 2004;48:1553-1560.

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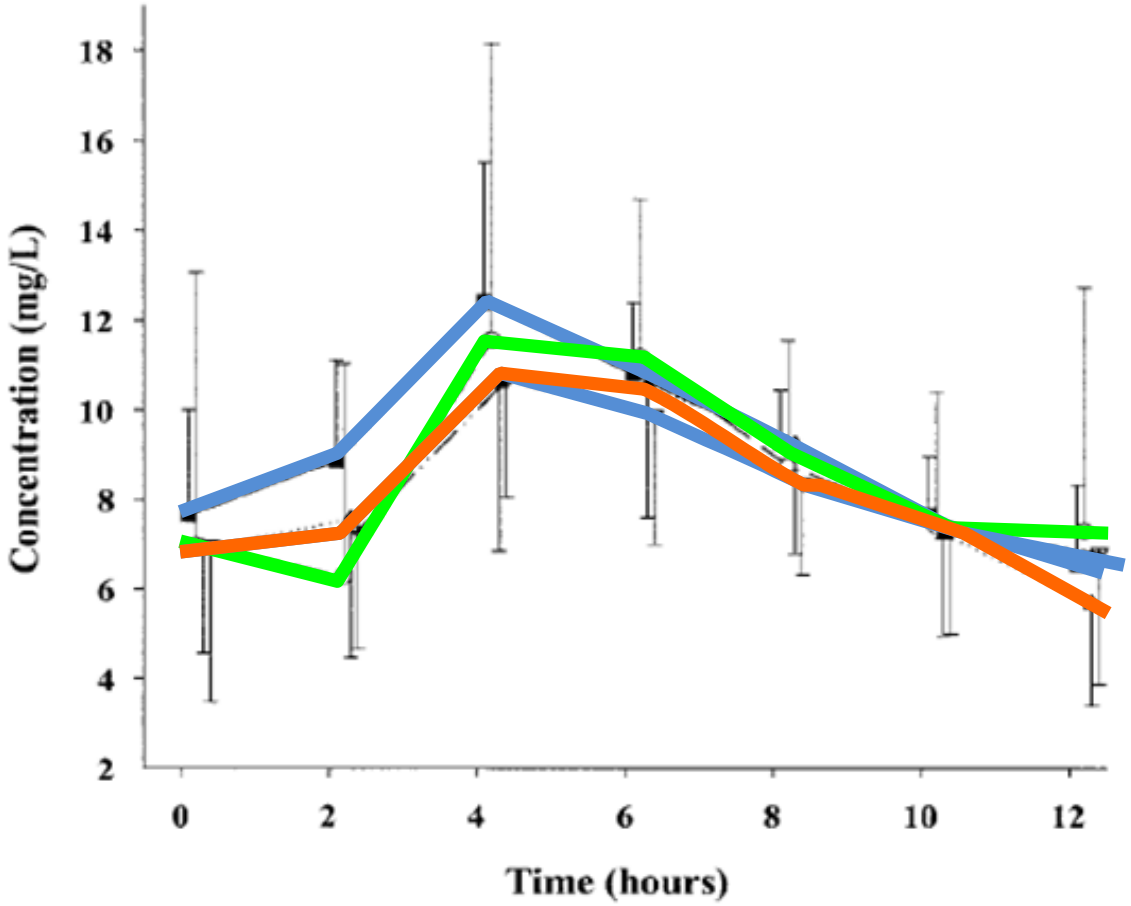
Two strategies

1. Super-boosting:
   more RTV
   (LPV:RTV=4:4)

2. Doubling the dose
   (LPV:RTV=8:2)



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Objectives

- Develop an integrated population PK model describing the interactions of LPV, RTV and rifampicin (RIF) in children.
- Evaluate the effect of patient and treatment factors (age, BSA, weight, gender, haemoglobin, albumin, ALT) on LPV and RTV PK in children.
- Suggest dose recommendations in children receiving LPV/RTV and RIF-based TB therapy concurrently.

Study Design

Oral solution of LPV/RTV=4:1 + oral solution RTV, when necessary

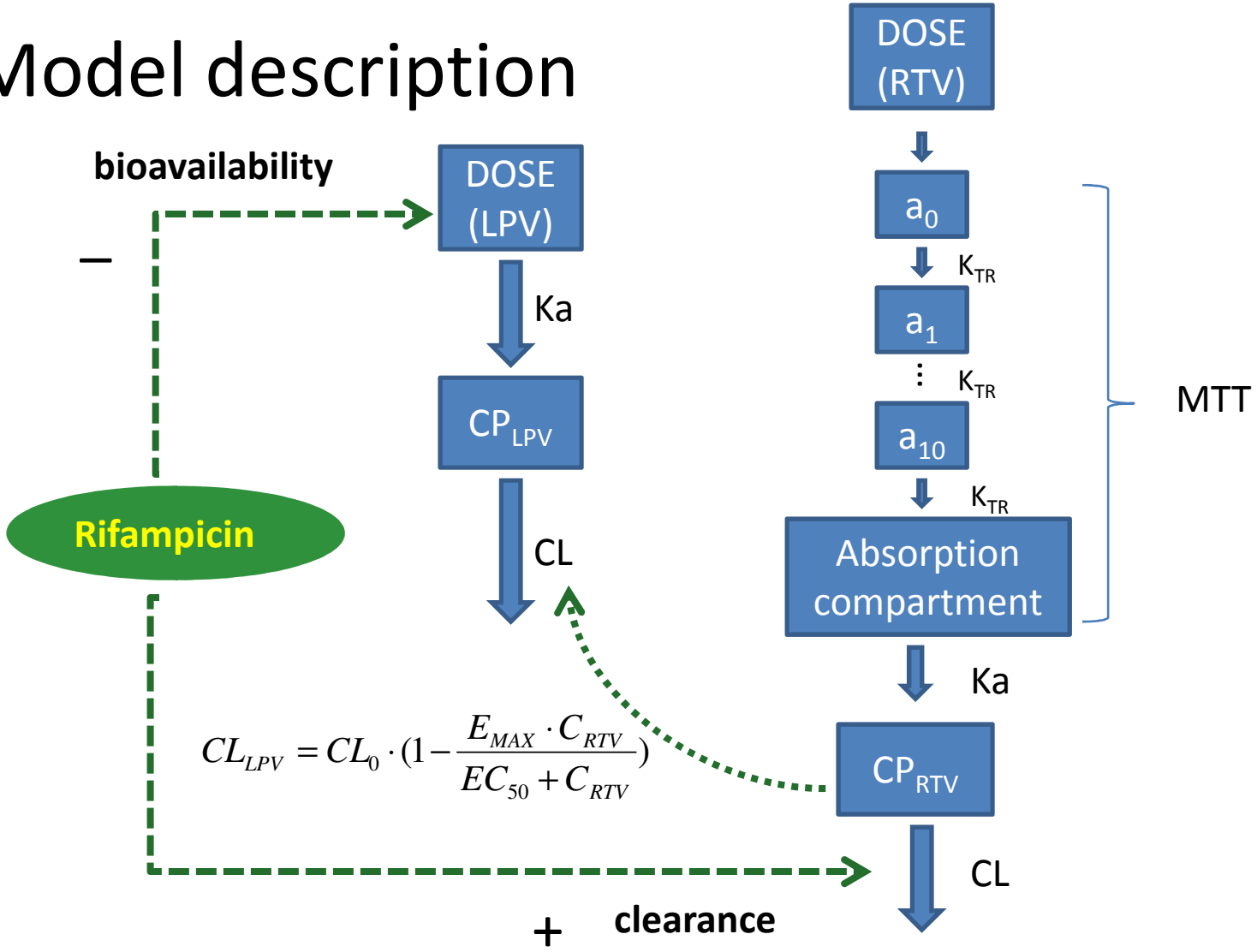
	HIV patients Control group	HIV/TB patients During RIF treatment		HIV/TB patients After RIF treatment
Dose ratio (LPV:RTV)	Normal dose 4:1	Super-boosted dose 4:4	Double dose 8:2	Normal dose 4:1
Number of subjects	39	15	20	11
Number of samples	216	120	95	88

4~8 samples from each patient, up to 12h after dose

Population

Demography	Median	Range
Age (month)	21	6 months - 4.5 years
Body weight (kg)	10.2	5 – 17
Gender (M/F)	34/40	
Height (cm)	79	58-103
BSA (m^2)	0.48	0.28-0.69
Haemoglobin (g/L)	10.7	5.7-29.7
Albumin (g/L)	38	29-47
ALT ($U \cdot L^{-1}$)	19	9-43

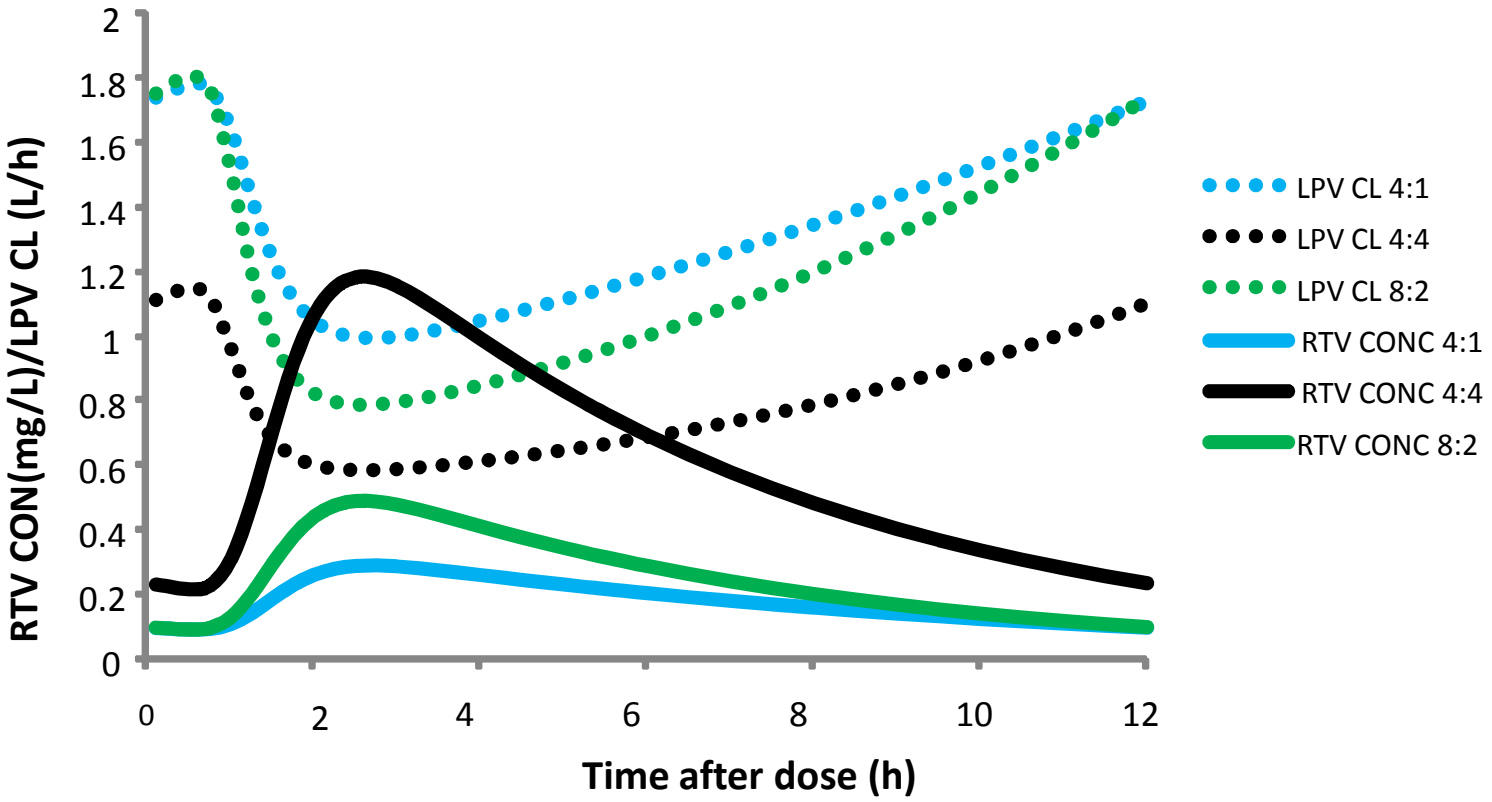
Model description



Allometric scaling of weight on CL and V for both drugs

$$CL = CL_0 \cdot \left(\frac{WT}{10kg}\right)^{3/4} \qquad V = V \cdot \left(\frac{WT}{10kg}\right)$$

Dynamic effect of concentration of RTV on clearance of LPV in the typical patient (10kg, 21 months)



Parameter estimates

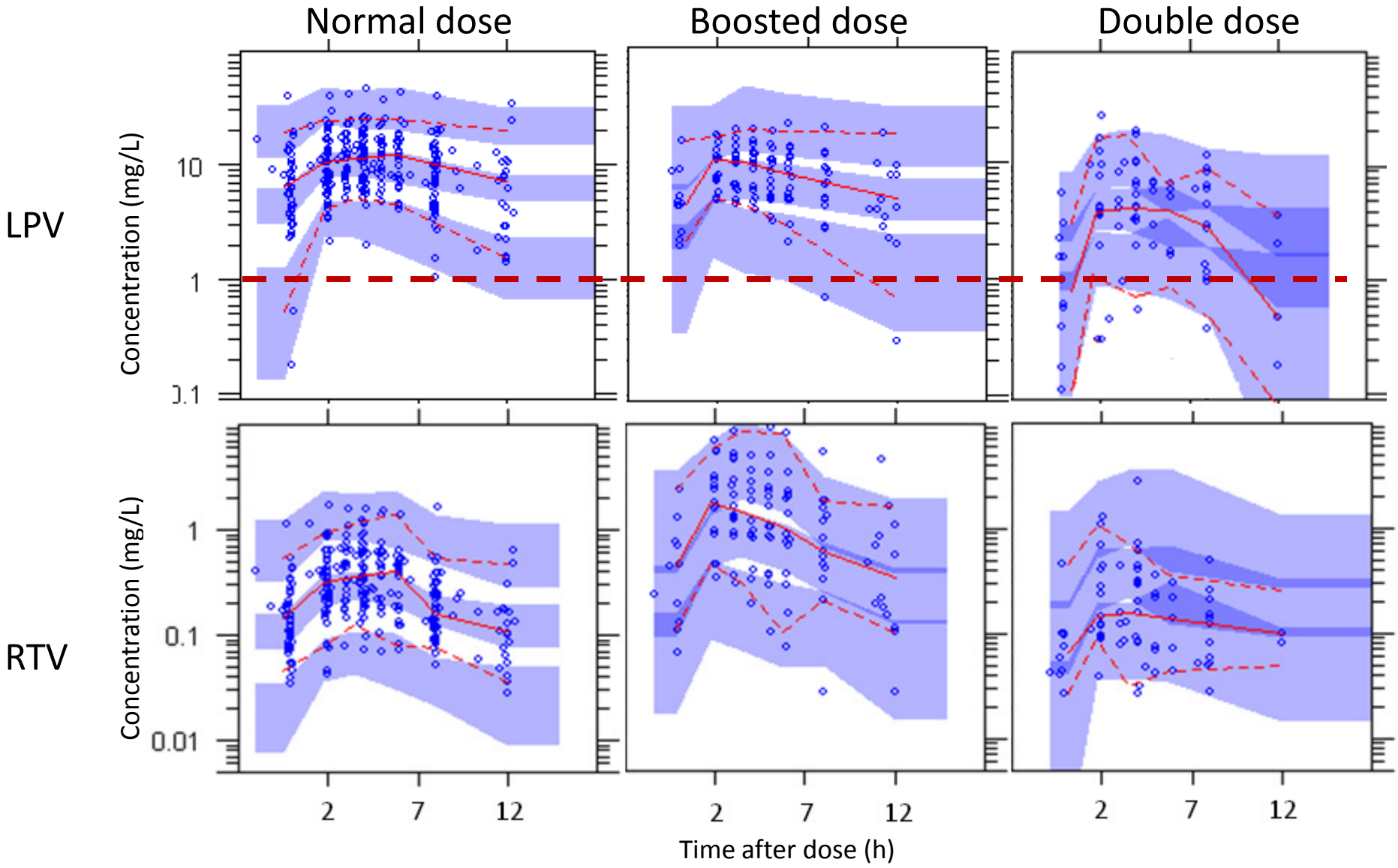
LPV Parameters		Typical value	RSE* (%)
CL/F (L/h)		4.27	11.6
V/F (L)		11.7	11.4
Ka (h^{-1})		0.744	22.4
F	boosted dose	44.7%	10.7
	double dose	21%	19.0
IIV V		56.6%	33.4
IOV Ka		76.2%	49.9
IOV F1		51.8%	32.1
Emax		0.9(fix)	
EC50 (mg/L)		0.0497	23.0

RTV Parameters		Typical value	RSE* (%)
CL/F (L/h)	no TB and after TB	12.7	9.8
	with TB treatment	19	12.7
V/F (L)		105	11.9
Ka (h^{-1})		2.31	40.3
MTT (h)		1.28	17.3
IIV CL		72.8%	14.9
IOV CL		41.6%	30.1
IIV V		43.3%	25
IOV MTT		31.1%	26.3
IOV KA		98.1%	36.3

ΔOFV = -95.459

*results from 250 bootstrap

Model evaluation (5%, 50%, 95% percentile of dataset)



Simulation for dose optimization during TB treatment

Target: **95%** of patients with **C_{min}>1 mg/L**

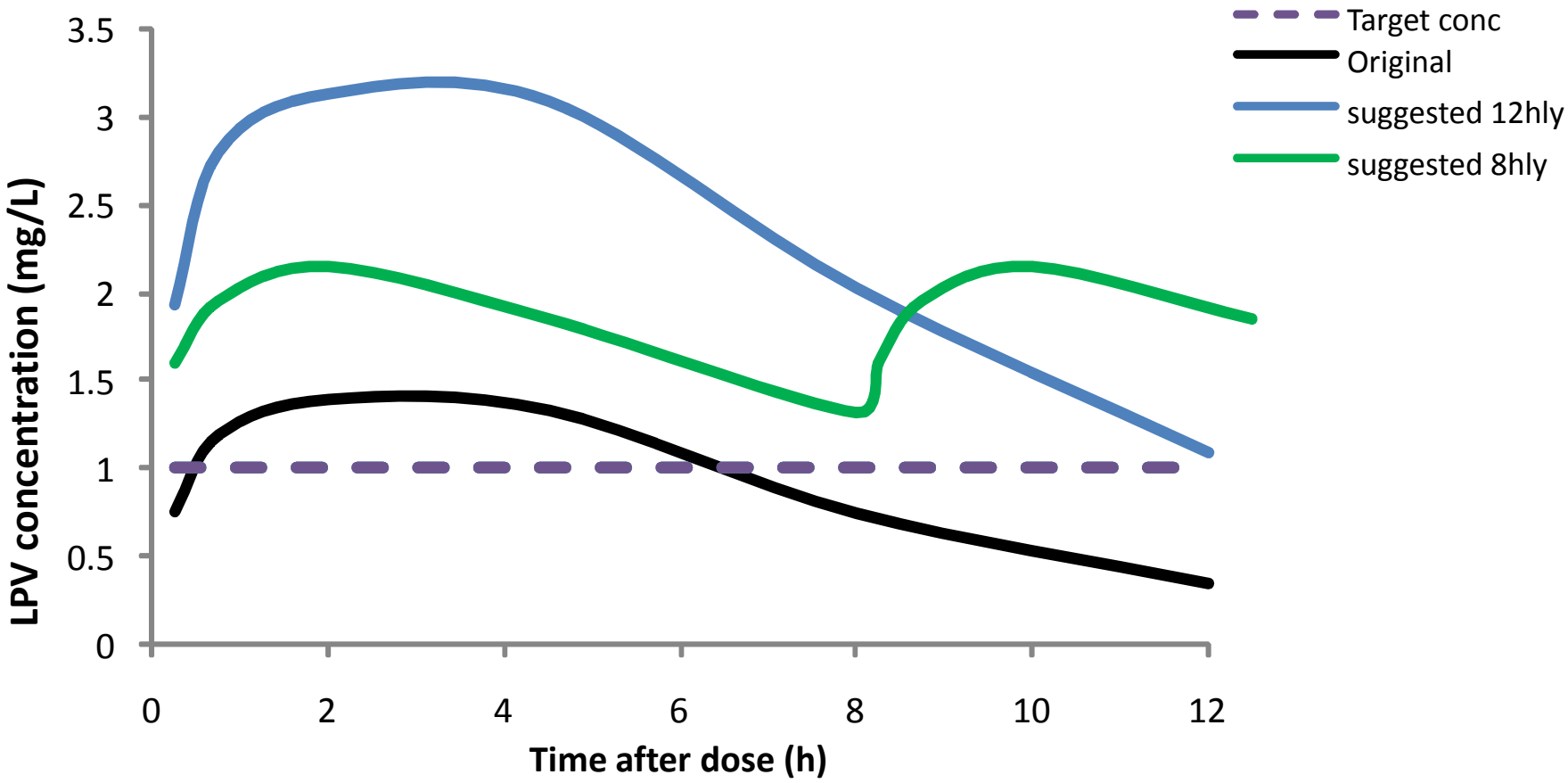
Current median dose (median body weight = 8.7 kg) :

Normal ratio (4:1) 23 mg/kg

Boosted ratio (1:1) 14 mg/kg

Body weight	LPV:RTV=4:1		LPV:RTV=1:1
	12 hrly LPV dose (mg/kg)	**8 hrly** LPV dose (mg/kg)	**12 hrly** LPV dose (mg/kg)
4-6 kg	65	30	20
6-8 kg	50	25	17
8-12 kg	40	22	15
12-18 kg	35	18	12

5% of LPV concentrations in different doses with RIF (LPV:RTV=4:1)



Summary

- During RIF-based antitubercular treatment the relative oral bioavailability of LPV
  - was reduced by 79% with LPV/RTV = 8:2.
  - was approximately doubled with LPV/RTV = 4:4
- The effect of RTV concentrations on LPV CL/F was best described with a sigmoidal Emax model.
- Smaller children receiving RIF-based antitubercular treatment require higher mg/kg doses of LPV/RTV (in 4:1 or 1:1 ratio) than larger children.

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