Population Pharmacokinetics of Lopinavir/Ritonavir in Combination with Rifampicin-based Antitubercular Treatment in HIV-infected Patients

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Background and Objectives

Background: Tuberculosis patients with HIV infection often require lopinavir/ritonavir (co-formulated in 4:1 ratio; LPV/r)-based antiretroviral treatment with rifampicin-based antituberculosis treatment. Rifampicin, a key component of antitubercular treatment, profoundly reduces lopinavir concentrations. Among adults, increasing the amount of LPV/r has been shown to overcome this effect.

Objectives: To develop an integrated population pharmacokinetic model accounting for the drug-drug interactions between lopinavir, ritonavir and rifampicin, and to evaluate optimal dose of LPV/r when co-administered with rifampicin.

Methods

Steady state pharmacokinetics of lopinavir and ritonavir were evaluated in a cohort of **21 HIV-infected South African adults**. The study design (Figure 1) was previously reported by Decloedt. et al. **Four sequential dose regimens** were used and intensive pharmacokinetic sampling was performed at the end of each period. Patients took a meal before the evening dose, but fasted for 10 h for the morning dose. A population pharmacokinetic analysis was conducted using **NONMEM 7**.

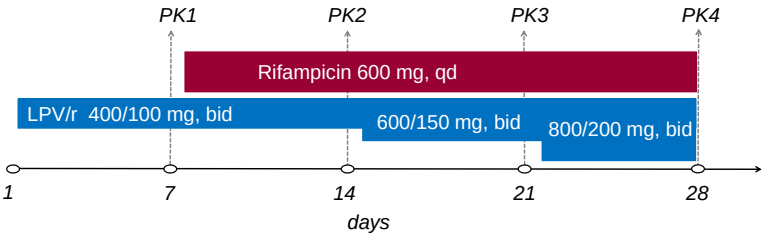

Figure 1. Study design.

Results

- **Lopinavir** was described by one-compartment with first order absorption model
- **Ritonavir** was described by two-compartment with transit absorption model
- **Allometric scaling** of oral clearance by fat free mass (FFM) and of volume of distribution by body weight (BW), for both drugs
- **Dynamic inhibition** of ritonavir concentrations on the oral clearance of lopinavir was modeled as an E_{max} model (Figure 2 and 3)
- **Rifampicin treatment**
  - reduces the bioavailability 20.2% for lopinavir and 45.0% for ritonavir
  - increases the oral clearance 71.0% for lopinavir and 36.0% for ritonavir
- **Diurnal variation was investigated**

  For the evening dose (with meal and not fasted) and night profile:
  - the bioavailability increased by 42.0% for lopinavir and 45.0% for ritonavir
  - the oral clearance of both drugs decreased by 32.7%

Conclusions

- A population pharmacokinetic model was developed to simultaneously capture the drug-drug interactions between lopinavir, ritonavir and rifampicin.
- The model can be used to simulate alternative dosage regimens when lopinavir/ritonavir is co-administered with rifampicin.
- Doubling the dose of LPV/r is required in most patients to maintain lopinavir concentrations > 1 mg/L during rifampicin-based antitubercular treatment.
- The higher morning trough concentrations were explained by both higher bioavailability with the evening meal and lower clearance overnight, possibly due to reduced hepatic blood flow. However, more evidence is needed to confirm this.

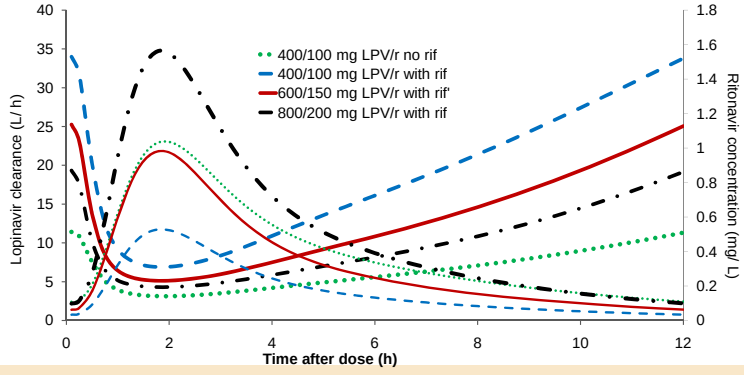

Figure 2. The influence of ritonavir concentrations on the clearance of lopinavir.

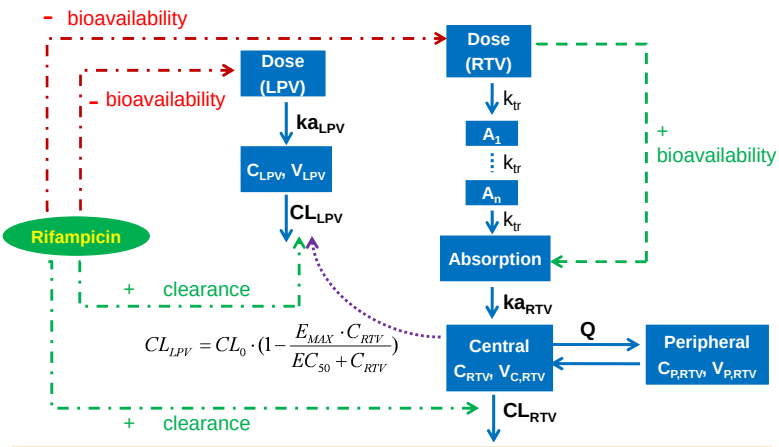

Figure 3. *Structure of the final integrated lopinavir-ritonavir model.*

Table 1. *Estimates for typical values, Inter-individual (IIV), and inter-occasional variability (IOV) for the LPV-RTV integrated population PK model. For CL, Q, V, and V_2, the values refer to a typical 40 kg FFM and 65 kg BW subject.*

Parameter	Estimates	IIV (%)	IOV (%)
Lopinavir			
CL/F (L/h)	37.9	20.2	11.8
RIF effect on CL	+ 71.0%		
V/F (L)	54.7		27.2
k_a (h^{-1})	0.991		94.2
Rel. bioavailability when on RIF	79.8%		21.9
Proportional error (%)	12.7		17.1
Evening/Night effect	+42.0% Bioavailability		-32.7% CL/F
Ritonavir			
Central CL/F (L/h)	19.2	21.5	20.4
RIF effect on CL	+ 36.0%		
Central V/F (L)	22.6	10.2	
k_a (h^{-1})	3.28		
Rel. bioavailability when on RIF	55.0%	36.7	30.3
Bioavailability for 1 mg RTV dose	+ 0.81%		
Peripheral clearance Q/F (L/h)	31.0		
Peripheral volume V_2/F (L)	56.6		
Number of transit cmpts NN	2.03		
Mean Transit Time MTT (h)	1.44		27.9
Proportional error (%)	18.8		
Evening/Night effect	+45.0% Bioavailability		-32.7% CL/F
Inhibition model			
E_{max}	0.953		
EC_{50} (mg/L)	0.0351		

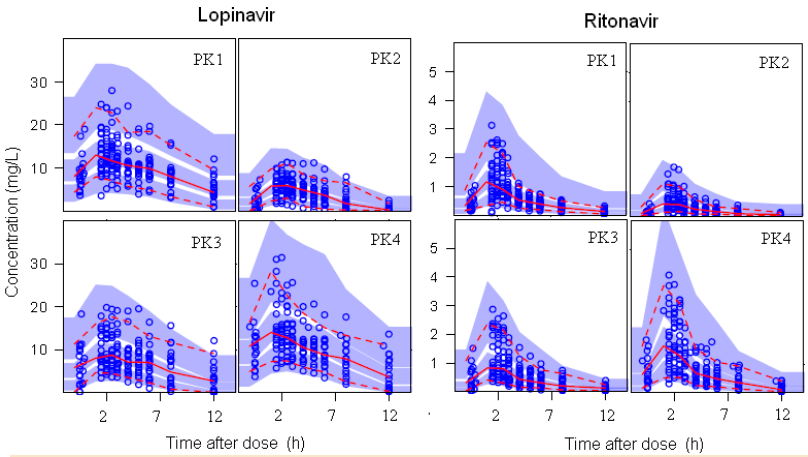

Figure 4. *A visual predictive check (VPC) stratified by PK occasion. The red lines are the median, 5th and 95th percentiles of the observed data respectively. The shaded areas are the 95% confidence intervals for percentiles of simulated data. Blue circles represent the raw data.*

Acknowledgments

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