



# Pharmacokinetic Model of Capravirine, a Novel Non-Nucleoside Reverse Transcriptase Inhibitor, Co-Administered with Kaletra in Healthy and HIV-Infected Subjects

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## Background

- Capravirine (CPV, AG1549), a non-nucleoside reverse transcriptase inhibitor (NNRTI), exhibits potent in-vitro activity against NNRTI-resistant HIV isolates, including those with the K103N mutation.
- In March 2003 a randomized, double-blind study started in patients who have failed multiple regimens. Patients receive either CPV 200, 400, 700 mg BID or placebo with a background therapy of Kaletra (KLT), which is a combination of the protease inhibitor (PI) lopinavir (LPV) and low-dose ritonavir (RTV), and at least two nucleoside reverse transcriptase inhibitors (NRTIs).
- CPV is metabolized primarily by CYP3A4, which is inhibited by RTV.

## Objectives

- To characterize the pharmacokinetics of CPV in combination with KLT, which contains the potent CYP3A4 inhibitor RTV.
- To provide insight into selecting CPV doses for Phase 2 studies, including the recently started study with KLT.

## Methods

**Data**  
PK data from a published study of KLT and two Phase 1 studies of CPV were used to develop the model:  
Study 1. KLT in HIV-infected ARV-naïve patients at 3 or 4 and 24 weeks (n=21) (Murphy et al. 2001).  
Study 2. CPV 1400 mg BID alone, CPV 700 mg with RTV 100 mg BID, CPV 700 mg with KLT 400/100 mg BID, and KLT 400/100 mg BID alone, in healthy volunteers over 24-34 days (n=23).  
Study 3. CPV 200, 400, and 700 mg with KLT 400/100 and 533/133 mg BID, and KLT 400/100 mg BID alone, in healthy volunteers over 34 days (n=39).  
Trough and serial blood samples were obtained to determine plasma concentrations of each of the drugs.

### Exploratory Data Analysis—Effects of KLT on CPV

- RTV decreases CPV clearance, presumably due to RTV's CYP3A4 inhibition (Figure 1).
- LPV in the presence of RTV decreases CPV concentrations, relative to the previous case (Figure 1).
- Increasing KLT from 400/100 mg to 533/133 mg has a minimal effect on CPV concentrations (Figure 2).

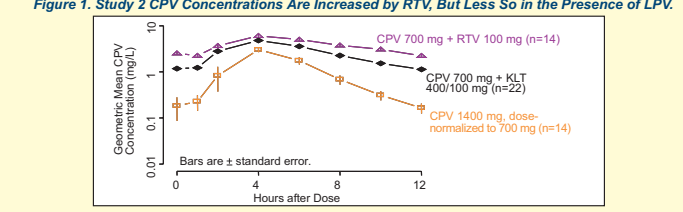


Figure 1. Study 2 CPV Concentrations are Increased by RTV, But Less So in the Presence of LPV.

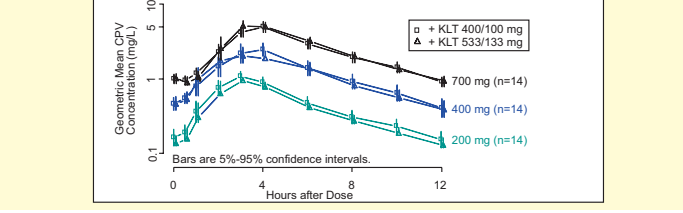


Figure 2. Study 3 CPV Concentrations are Not Significantly Lowered when KLT is Increased From the Standard 400/100 mg Dose.

### Exploratory Data Analysis—Effects of CPV on KLT

- CPV decreases concentrations of both LPV and RTV (Figures 3 and 4).
- LPV does not affect RTV pharmacokinetics significantly.

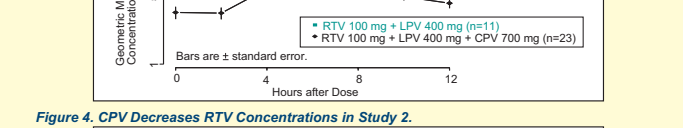


Figure 3. CPV Decreases LPV Concentrations in Study 2.

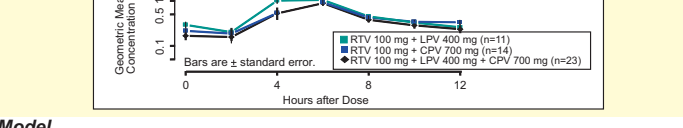
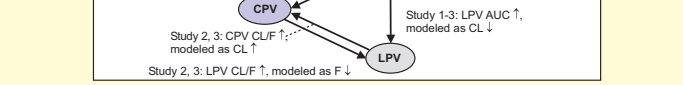


Figure 4. CPV Decreases RTV Concentrations in Study 2.

### Model

- Based on these observations, clearance and bioavailability interactions among CPV and the two components of KLT were modeled (Figure 5).
- Clearance interactions were modeled as concentration-dependent effects on metabolic enzymes.
- Bioavailability interactions were modeled as dose-dependent absorption.

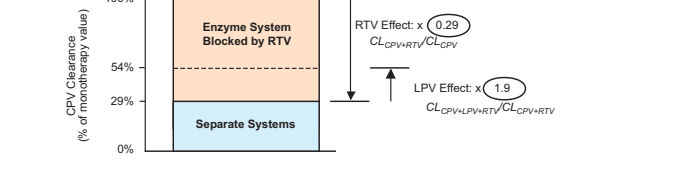
### Figure 5. Interactions Among CPV and the Components of KLT were Modeled as Either Clearance (CL) or Bioavailability (F) Effects, Based on the Shapes of the Concentration vs. Time Curves.



**Fitting**  
• Population PK models with one compartment, lagged first-order absorption, and first-order or second-order elimination were derived for CPV as monotherapy and RTV dosed as KLT, using the first-order approximation method in the NONMEM nonlinear estimation package.  
• Based on these, additional interactions were incorporated for LPV + RTV, CPV + RTV, and CPV + LPV (Figure 7).  
– Better fits for CPV in the presence of RTV were obtained by assuming that multiple enzyme systems metabolize CPV, only one of which is blocked by RTV (Figure 6).  
• Monte Carlo simulations of patients with this model provided distributions which were checked against study data (Figure 8).

## Methods (cont.)

Figure 6. CPV is Hypothesized to be Metabolized by Multiple Enzyme Systems, Only One of Which is Blocked by RTV.



**Comparisons with IC50s**  
CPV IC50s in clinical isolates from NNRTI-experienced patients were found to be approximately lognormal with a very high coefficient of variation (~900%). Therefore 90th percentile as well as median IC50s were used. IC50s were adjusted for protein binding.

Figure 7. The Three-Drug PK Model Includes Interaction Factors for the 5 Arrows in Figure 5.

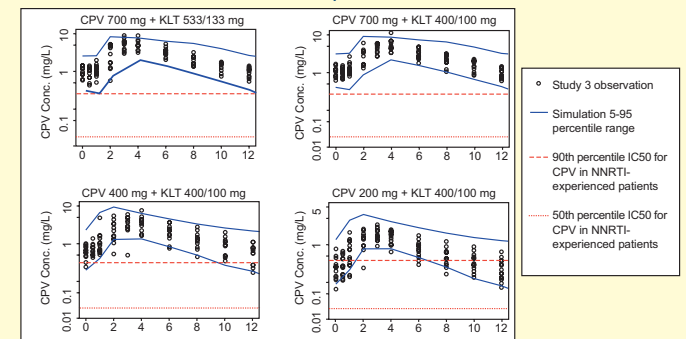
Drug	Parameter (Units)	Estimate	Inter-Indiv. Variability	Symbol
CPV	Oral Clearance (L/h)	105	26%	CL <sub>C</sub>
	Volume (L)	295	11%	V <sub>C</sub>
	Absorption Rate Constant (1/h)	2.1	194%	k <sub>aC</sub>
	Absorption rate multiplier (no units)	2.1	(fixed)	f <sub>k<sub>aC</sub></sub>
	Absorption Lag for 700mg CPV (h)	1.9	(fixed)	
	Absorption Lag for <700mg CPV (h)	0.93	(fixed)	
	RTV effect on CPV clearance (no units)	0.71	(fixed)	f <sub>CL</sub>
	LPV EC50 for "inhibition" of CPV CL (µg/mL)	12	(fixed)	C50 <sub>LC</sub>
	Abs <sub>C</sub> = -k <sub>aC</sub> Abs <sub>C</sub> (lagged), C <sub>C</sub> = A <sub>C</sub> / V <sub>C</sub>			
	A <sub>C</sub> ' = f <sub>k<sub>aC</sub></sub> k <sub>aC</sub> Abs <sub>C</sub> - (1 - f <sub>CL</sub> C50 <sub>LC</sub> / (C50 <sub>LC</sub> + C <sub>C</sub> )) CL <sub>C</sub> C <sub>C</sub>			
LPV	Oral Clearance (L/h)	5.3	27%	CL <sub>L</sub>
	Volume (L)	54	17%	V <sub>L</sub>
	Absorption Rate Constant (1/h)	0.93	44%	k <sub>aL</sub>
	Absorption Lag (h)	1.8	19%	
	CPV ED50 for "inhibition" of LPV Ka (mg)	1020	(fixed)	D50 <sub>CL</sub>
	RTV EC50 for "inhibition" of LPV CL (µg/mL)	1.4	(fixed)	C50 <sub>RL</sub>
	Abs <sub>L</sub> = -k <sub>aL</sub> Abs <sub>L</sub> (lagged), C <sub>L</sub> = A <sub>L</sub> / V <sub>L</sub> , A <sub>L</sub> ' = [D50 <sub>CL</sub> / (D50 <sub>CL</sub> + Dose <sub>C</sub> )] k <sub>aL</sub> Abs <sub>L</sub> - [C50 <sub>RL</sub> / (C50 <sub>RL</sub> + C <sub>R</sub> )] CL <sub>L</sub> C <sub>L</sub>			
RTV	Oral Clearance (L/h)	24	41%	CL <sub>R</sub>
	Central Volume (L)	91	53%	V <sub>R</sub>
	Distribution Clearance (L/h)	18	18%	CL <sub>2R</sub>
	Peripheral Volume (L)	888	13%	V <sub>2R</sub>
	Absorption Rate Constant (1/h)	0.54	(fixed)	k <sub>aR</sub>
	Absorption Lag (h)	2.0	(fixed)	
	CPV ED50 for "inhibition" of RTV Ka (mg)	1510	(fixed)	D50 <sub>CR</sub>
Abs <sub>R</sub> = -k <sub>aR</sub> Abs <sub>R</sub> (lagged), C <sub>R</sub> = A <sub>R</sub> / V <sub>R</sub> , C <sub>2R</sub> = A <sub>2R</sub> / V <sub>2R</sub> , A <sub>R</sub> ' = [D50 <sub>CR</sub> / (D50 <sub>CR</sub> + Dose <sub>C</sub> )] k <sub>aR</sub> Abs <sub>R</sub> - CL <sub>R</sub> C <sub>R</sub> - CL <sub>2R</sub> (C <sub>R</sub> - C <sub>2R</sub> ), A <sub>2R</sub> ' = CL <sub>2R</sub> (C <sub>R</sub> - C <sub>2R</sub> )				

**Notes:** Drug interaction parameters are in *italics*. Symbols use subscripts C = CPV, L = LPV, R = RTV. In equations, ' = time derivative, A = Amount, C = concentration, abs = absorption, default compartment is plasma. Estimates are maximum likelihood from NONMEM V, ADVAN6 subroutine, first-order method with post-hoc estimation of individual parameters. All parameters were modeled as lognormal or fixed. Covariances among CL, V, and k<sub>a</sub> parameters were included (estimates not shown). Inter-individual variability is expressed as the lognormal coefficient of variation or sqrt(e<sup>σ<sup>2</sup></sup>-1) (= σ for small σ) where σ is the underlying normal's standard deviation.

## Results

- Monte Carlo simulation with the model gave distributions that matched the study data well (Figure 8).
- The apparent clearance (CL/F) of CPV was decreased by 71% in the presence of RTV and 46% in the presence of KLT.
- CPV increased the CL/F of both LPV and RTV when dosed as KLT, in a dose-dependent manner. The estimated model parameters D50<sub>CL</sub> and D50<sub>CR</sub> correspond to increases of 69% and 46% respectively at 700 mg CPV. CPV effect is much less at lower doses.
- Modeling suggested that CPV affected LPV absorption not systemic clearance, and most of CPV's overall effect on LPV is direct not through RTV.

Figure 8. Simulations are Consistent with Study 3 Observations and Suggest that CPV Concentrations are Sufficient for NNRTI-Experienced Patients.



Note: LPV concentrations exceed IC50s in all cases.

## Conclusions

- Comparisons of CPV plasma concentrations and the IC50s in NNRTI-experienced patients suggest that all 3 doses of CPV administered in combination with KLT may provide effective concentrations.
- The current Phase 2 study includes 200, 400, and 700 mg doses of CPV in combination with KLT to identify a dose response.
- An extra capsule (133/33 mg) of KLT BID is required when CPV is dosed at 700 mg BID, due to CPV's inductive effect upon the CL of LPV, similar to the effect of other NNRTIs.
- The population PK model allows alternative regimens, e.g., with higher or lower CPV doses, to be simulated quickly to support future trial designs.

## References

- Hsu A. et al. 1997. Multiple-dose pharmacokinetics of zalcitabine in human immunodeficiency virus-infected subjects. *Antimicrobial Agents and Chemotherapy* May 1997; 39:905
- Murphy R.L. et al. 2001. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48 week results. *AIDS* 15:1-9