Poster #536

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Assessment of the Multiple Dose Pharmacokinetic Interaction of Lopinavir/ritonavir with Nelfinavir

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ABSTRACT

Background: The HIV PIs nelfinavir (NFV) and lopinavir/ritonavir (LPV/r) are substrates for and inhibitors of CYP3A, as well as metabolic inducers. The purpose was to assess the effects of coadministration of LPV/r and NFV on pharmacokinetic parameters of LPV, ritonavir (RTV), NFV and the hydroxy-t-butylamide metabolite of NFV (M8).

Methods: This was a multiple-dose, sequential, open-label, single-center, non-fasting, drug interaction study. Fourteen healthy subjects were enrolled and 13 subjects completed the study; one subject prematurely discontinued for personal reasons. Each subject received LPV/r 400/100 mg BID for 21 days. NFV, 1000 mg BID, was coadministered with LPV/r starting with the evening dose of day 11 through the morning of day 21. NFV, 1250 mg BID, was administered alone from the evening of day 21 to 35. Plasma samples were collected pre-dose and up to 12 hours after the morning dose on days 11, 21 and 35. Concentrations of LPV, RTV, NFV and M8 were determined using LC/MS/MS and analyzed by noncompartmental methods. Parameter estimates were compared by paired t-test.

Results: The effect of coadministration of NFV with LPV/r can be seen below:

	C_{trough} (µg/mL)+				AUC_{12} (µg•h/mL)+			
Regimen	**LPV**	**RTV**	**NFV**	**M8**	**LPV**	**RTV**	**NFV**	**M8**
LPV/r or 1250 mg NFV alone	7.1	0.2	1.1	0.2	95.9	5.3	24.2	6.4
LPV/r with 1000 mg NFV	4.8*	0.2	1.3	1.2*	70.0*	4.1*	25.8	22.3*

* p<0.05 compared to LPV/r or NFV alone.
+ Geometric mean.

LPV C_{max}, AUC_{12} and C_{trough} were significantly decreased during NFV coadministration by 21, 27 and 33%, respectively. LPV median (range) ratio of C_{trough} to IC_{50} for *wt*-HIV (IQ) was reduced from 105 (55 to 235) to 76 (30 to 136) during NFV; similar decreases in RTV concentrations were noted. Coadministration with LPV/r resulted in similar NFV IQ of 2.3 (0.7 to 7.3) alone and 2.2 (1.2 to 15.9) during LPV/r and increased AUC of M8 by 3-fold despite a 20% reduction in the NFV dose. Safety profiles were not altered with concomitant administration.

Conclusions: NFV decreases the bioavailability of both LPV and RTV, while LPV/r increases the dose-normalized bioavailability of NFV and M8. The dose of LPV/r may need to be increased when coadministered with nelfinavir, particularly in HIV patients with extensive protease inhibitor experience or reduced viral susceptibility to LPV. Concentrations of nelfinavir are similar when dosed at 1000 mg BID with LPV/r compared to NFV 1250 mg BID alone.

INTRODUCTION

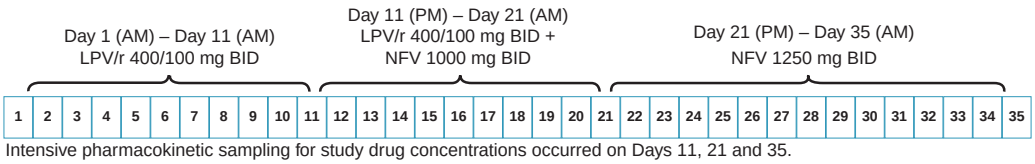
- Lopinavir/ritonavir (LPV/r, Kaletra®) and nelfinavir (NFV, Viracept®) are HIV-protease inhibitors (PIs) approved worldwide for treatment of HIV in combination with other antiretroviral agents.
- Adult clinical dose of LPV/r is 400/100 mg BID; NFV dose is 1250 mg BID.
- At clinical concentrations, LPV/r and NFV inhibit CYP3A-mediated metabolism and are also metabolic inducers.
- The multiple-dose pharmacokinetic interaction between NFV and LPV/r has not previously been assessed.

OBJECTIVE

- To assess
  - The effect of LPV/r on the pharmacokinetics of NFV after multiple dosing.
  - The effect of NFV on the pharmacokinetics of LPV/r after multiple dosing.

STUDY DESIGN

- Multiple-dose, sequential, open-label, single-center, non-fasting drug interaction study.
- Healthy male and female subjects (N=14) were enrolled.
- Subjects received a standardized diet consisting of approximately 30% calories from fat.
- 13 subjects completed; 1 subject discontinued on Day 3 due to personal reasons.



Intensive pharmacokinetic sampling for study drug concentrations occurred on Days 11, 21 and 35.

Table 1. Demographics

	Included in Pharmacokinetic Analysis
N	13
Age (yrs)+	34 (23-53)
Weight (kg)+	80 (60-101)
Height (cm)+	173 (148-190)
Gender	7 Male, 6 Female
Race	10 Caucasian, 3 Black

+ Presented as mean (range).

METHODS

- Within a dosing interval, plasma samples were collected pre-dose and at 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose on Days 11, 21 and 35.
- NFV, hydroxy-t-butylamide metabolite of NFV (M8), LPV and ritonavir (RTV) concentrations were measured by LC/MS/MS.
  - NFV and M8 limit of quantitation (LOQ) = 20.0 ng/mL
  - LPV LOQ = 5.0 ng/mL
  - RTV LOQ = 1.0 ng/mL
- Noncompartmental methods were used to calculate pharmacokinetic parameters.
- Half-life ($t_{1/2}$) within a dosing interval was estimated using concentrations from C_{max} through 12 hours.
- Inhibitory quotient (IQ) calculated as C_{trough}/IC_{50}: based on protein-binding corrected *wt*-HIV IC_{50} of 0.07 µg/mL for LPV and 0.52 µg/mL for NFV [Molla A, Vasavanonda S, Kumar G, et al. *Virology* 1998; 250:255-262.]
- Effect of NFV on LPV/r and effect of LPV/r on NFV were assessed using paired t-tests on log-transformed pharmacokinetic data.
- Point estimates and 90% confidence intervals (CI) for the bioavailability of the combination regimen relative to NFV or LPV/r alone were obtained for log-transformed C_{max}, C_{min}, C_{trough} and AUC_{12}.
  - When calculating bioavailability, NFV concentrations were not dose-normalized.

LOPINAVIR/RITONAVIR PHARMACOKINETIC RESULTS

Figure 1. Lopinavir Steady-State Mean (SD) Concentration-Time Profile

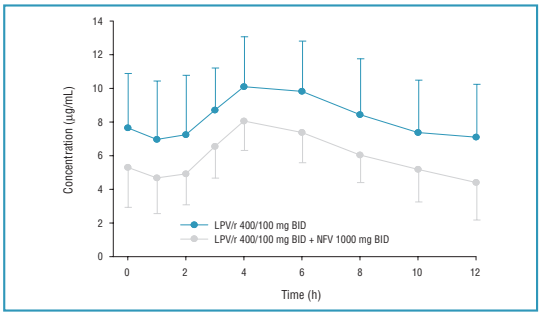


Figure 2. Lopinavir C_{trough} Relative to Protein Binding-Corrected IC_{50}

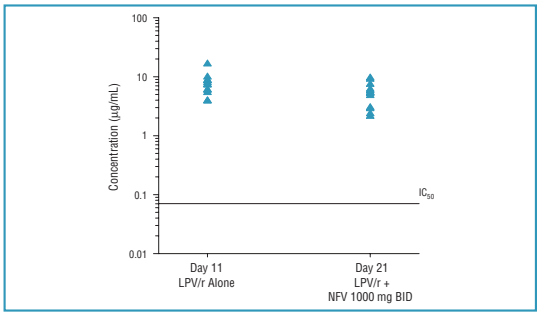
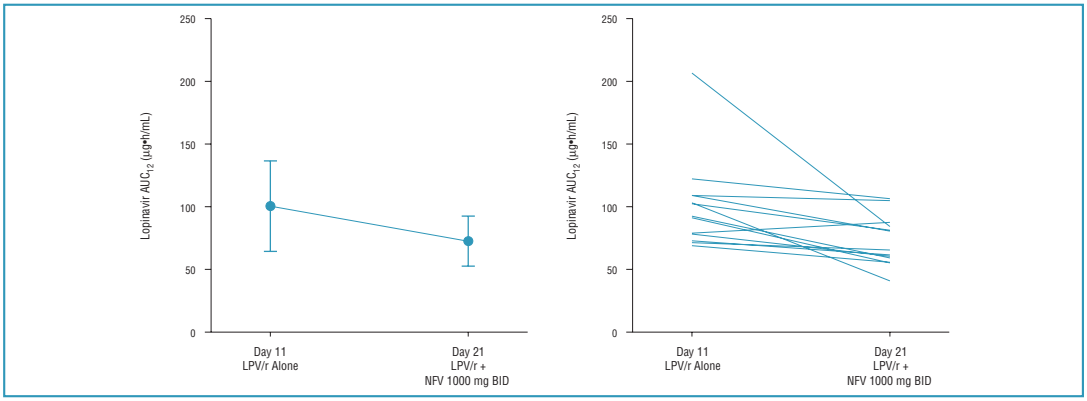


Table 2. Lopinavir Mean ± SD PK Estimates

Parameter	LPV/r 400/100 mg BID + NFV 1000 mg BID Mean ± SD	LPV/r 400/100 mg BID Alone Mean ± SD
T_{max} (h)	4.5 ± 1.1	5.2 ± 2.5
C_{max} (µg/mL)	8.53 ± 1.62*	10.87 ± 2.74
C_{min} (µg/mL)	3.94 ± 1.97*	6.15 ± 2.88
C_{trough} (µg/mL)	5.30 ± 2.37*	7.66 ± 3.22
AUC_{12} (µg•h/mL)	72.5 ± 20.0*	100.3 ± 35.6
IQ (C_{trough}/IC_{50})[a,c]	76.4 (30.3-135.8)	104.9 (55.3-234.8)
$t_{1/2}$ (h)[b]	6.63 ± 3.26	9.27 ± 4.01

[a] IQ presented as median (range); based on protein binding-corrected *wt*-HIV IC_{50}=0.07 µg/mL.
[b] Peak to trough $t_{1/2}$ presented as harmonic mean and pseudostandard deviation.
[c] Not tested statistically.
* Significantly different from LPV/r alone (p<0.05, paired t-test).

Figure 3. Mean (SD) and Individual Lopinavir AUC_{12}



LOPINAVIR/RITONAVIR PHARMACOKINETIC RESULTS cont.

Figure 4. Mean (SD) and Individual Lopinavir C_{min}

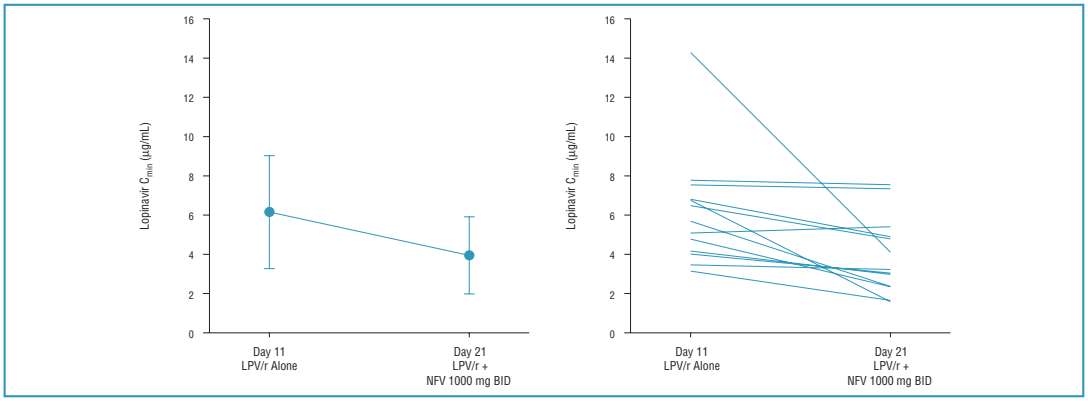


Table 3. Bioavailability of Lopinavir During Nelfinavir Coadministration Relative to LPV/r Alone

		Central Values*		Relative Bioavailability	
(N=13)	Parameter	Combined	Alone	Point Estimate+	90% CI
Combined vs. Alone	AUC_{12}	70.0	95.9	0.730	0.627-0.849
	C_{max}	8.4	10.6	0.790	0.704-0.887
	C_{min}	3.5	5.7	0.619	0.488-0.784
	C_{trough}	4.8	7.1	0.671	0.523-0.861

* Antilogarithm of the least squares means for logarithms.
+ Antilogarithm of the mean of the paired differences for logarithms.

Table 4. Ritonavir Mean ± SD PK Estimates

	LPV/r 400/100 mg BID + NFV 1000 mg BID	LPV/r 400/100 mg BID Alone
Parameter	Mean ± SD	Mean ± SD
T_{max} (h)	4.2 ± 0.9	4.8 ± 2.3
C_{max} (µg/mL)	0.86 ± 0.26*	1.14 ± 0.49
C_{min} (µg/mL)	0.12 ± 0.05	0.17 ± 0.09
C_{trough} (µg/mL)	0.21 ± 0.12	0.28 ± 0.15
AUC_{12} (µg•h/mL)	4.17 ± 0.99*	5.48 ± 1.37
$t_{1/2}$ (h)[a]	3.13 ± 0.38*	3.62 ± 0.99

[a] Peak to trough $t_{1/2}$ presented as harmonic mean and pseudostandard deviation.
* Significantly different from LPV/r alone ($p<0.05$, paired t-test).

NELFINAVIR AND M8 METABOLITE PHARMACOKINETIC RESULTS

Figure 5. Nelfinavir Steady-State Mean (SD) Concentration-Time Profile

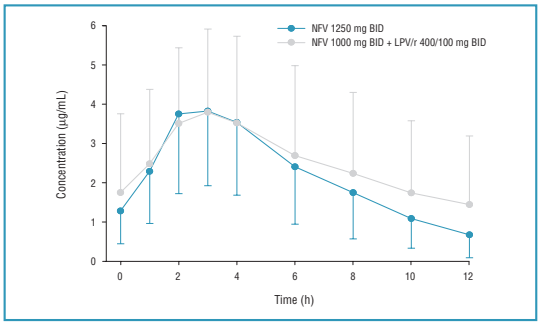


Figure 6. Nelfinavir C_{trough} Relative to Protein Binding-Corrected IC_{50}

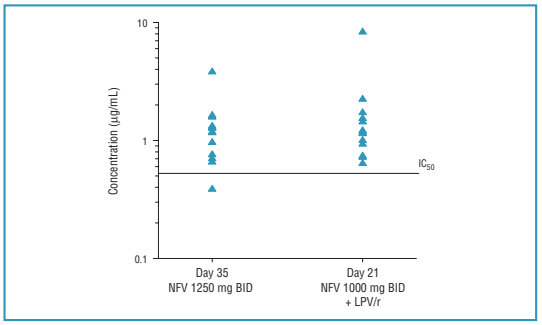


Table 5. Nelfinavir Mean ± SD PK Estimates

	NFV 1000 mg BID + LPV/r 400/100 mg BID	NFV 1250 mg BID Alone
Parameter	Mean ± SD	Mean ± SD
T_{max} (h)	2.9 ± 0.6	2.8 ± 0.9
C_{max} (µg/mL)	3.91 ± 2.23	4.18 ± 2.10
C_{min} (µg/mL)	1.43 ± 1.75*	0.67 ± 0.59
C_{trough} (µg/mL)	1.75 ± 2.01	1.28 ± 0.84
AUC_{12} (µg•h/mL)	30.7 ± 24.1	30.3 ± 17.8
IQ (C_{trough}/IC_{50})[a,c]	2.2 (1.2-15.9)	2.3 (0.7-7.3)
$t_{1/2}$ (h)[b]	5.22 ± 1.43*	3.37 ± 0.59

[a] IQ presented as median (range); based on protein binding-corrected *wt*-HIV IC_{50}=0.52 µg/mL.
[b] Peak to trough $t_{1/2}$ presented as harmonic mean and pseudostandard deviation.
[c] Not tested statistically.
* Significantly different from 1250 mg NFV alone ($p<0.05$, paired t-test).

NELFINAVIR AND M8 METABOLITE PHARMACOKINETIC RESULTS cont.

Table 6. Bioavailability of Nelfinavir During LPV/r Coadministration Relative to NFV Alone

		Central Values*		Relative Bioavailability	
(N=13)	Parameter	Combined	Alone	Point Estimate+	90% CI
Combined vs. Alone	AUC_{12}	25.8	24.2	1.065	0.951-1.193
	C_{max}	3.5	3.7	0.927	0.815-1.054
	C_{min}	1.0	0.6	1.863	1.565-2.217
	C_{trough}	1.3	1.1	1.191	0.987-1.437

* Antilogarithm of the least squares means for logarithms.
+ Antilogarithm of the mean of the paired differences for logarithms.

Figure 7. M8 Steady-State Mean (SD) Concentration-Time Profile

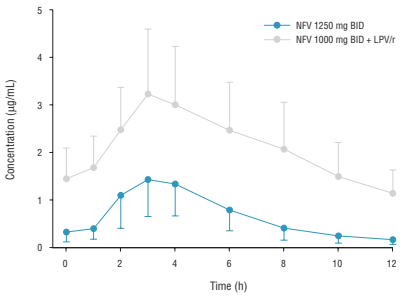


Table 7. M8 Metabolite Mean ± SD PK Estimates

	NFV 1000 mg BID + LPV/r 400/100 mg BID	NFV 1250 mg BID Alone
Parameter	Mean ± SD	Mean ± SD
T_{max} (h)	3.5 ± 1.0	3.3 ± 0.6
C_{max} (µg/mL)	3.34 ± 1.43*	1.54 ± 0.75
C_{min} (µg/mL)	1.13 ± 0.50*	0.16 ± 0.09
C_{trough} (µg/mL)	1.45 ± 0.65*	0.32 ± 0.21
AUC_{12} (µg•h/mL)	25.8 ± 10.4*	8.13 ± 4.13
$t_{1/2}$ (h)[a]	5.61 ± 1.06*	2.60 ± 0.33

[a] Peak to trough $t_{1/2}$ presented as harmonic mean and pseudostandard deviation.
* Significantly different from 1250 mg NFV alone ($p<0.05$, paired t-test).

SAFETY RESULTS

- The most frequently reported treatment-emergent adverse events during the study were diarrhea, headache, nausea, abdominal pain and anorexia.
- No serious adverse events or discontinuations due to adverse events occurred during the study.
- No new safety concerns were identified as a result of 10 days of concurrent administration of NFV and LPV/r.

DISCUSSION AND CONCLUSIONS

Lopinavir

- LPV/r 400/100 mg BID coadministered with NFV 1000 mg BID produced a lower LPV AUC_{12}, C_{max} and C_{min} compared to LPV/r alone; the median ratio of C_{trough} to IC_{50} for *wt*-HIV (IQ) was decreased from 105 to 76 in the presence of NFV.
- The dose of LPV/r may need to be increased when coadministered with NFV, particularly in HIV patients with extensive PI-experience or reduced viral susceptibility to LPV.

Nelfinavir

- NFV 1000 mg BID in combination with LPV/r 400/100 mg BID produced a similar AUC_{12} and C_{max} and higher C_{min} compared to that produced by NFV 1250 mg BID alone; the NFV median IQ was similar despite a 20% lower NFV dose.
- LPV/r also substantially increased concentrations of the active M8 metabolite of NFV; M8 C_{max}, AUC_{12} and C_{min} were increased by 2.4-, 3.5- and 7.5-fold, respectively.