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Effect of lopinavir (LPV) and ritonavir (RTV) dose adjustments on the pharmacokinetic (PK) interaction between LPV/RTV and tipranavir (TPV)

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BACKGROUND

- PK data in HIV+ adults show that co-administration of standard doses of tipranavir (TPV) and lopinavir/ritonavir (LPV/RTV), i.e. TPV 500 mg/LPV 400 mg/RTV 200 mg twice daily, reduces the C_{min}, C_{max}, and AUC of LPV by 40-60%, while TPV and RTV levels are unchanged[1].
- It is currently not recommended to administer these drugs together; however, the combination is potentially useful in the salvage therapy situation.
- Dose adjustment strategies are required which could overcome this negative drug-drug interaction.

OBJECTIVES

- To study the effects of LPV and RTV dose adjustments, when co-administered with TPV, on:
  - Pharmacokinetic parameters of LPV
  - Pharmacokinetic parameters of RTV and TPV
- To study the short-term safety of these combinations

METHODS

Eligibility Criteria

- HIV+ adults
- on stable regimens including LPV 400mg/RTV 100mg twice daily (BID) for at least 4 wks
- no other PIs or NNRTIs
- AST/ALT < 5x upper limit of normal
- Total bilirubin < 3.5x upper limit of normal

Drug regimens

- Open label trial
- From Day 1 to Day 14:
- Group A (n=7) - added TPV 500mg and RTV 200mg twice daily
  - total LPV 400mg/ RTV 300mg twice daily
- Group B (n=6) - added TPV 500mg, LPV 133mg/ RTV 33mg plus RTV 100mg all twice daily
  - total LPV 533mg/RTV 233mg twice daily

Safety assessments

- Screening was performed within 14 days of Day 1
- The following were performed at screening and Day 14
  - medical assessment
  - hematology; and chemistry, including liver enzymes and bilirubin
  - CD4 cell count and fraction; plasma viral load

PHARMACOKINETIC (PK) METHODS

- Blood samples were drawn at pre-dose trough (C_{trough}) on Day 1 and Day 14
- Full 12-hour sampling was also done on Day 14
- Plasma was separated and frozen for later analysis
- Plasma PI concentrations were determined by HPLC-MS/MS
- Paired PK data were compared using Wilcoxon signed rank sum tests

RESULTS

Table 1: Baseline Characteristics (N = 12**)

Gender, n	Male, 12
Age*	50 years (37-64)
Weight*	77 kg (59-102)
Ethnic origin, n	Caucasian, 10 Hispanic, 1 Aboriginal, 1
CD4 cell count*	395 /mm^3 (230-870)
CD4 cell fraction*	20% (11-43)
Viral load (copies/mL)*	<50 (<50 - 2510)
Time on LPV/RTV*	33 months (11-60)

* Median (range)
**1 patient in Group A discontinued study meds due to grade 3 nausea and vomiting; he did not complete the study and therefore is included only in the adverse event analysis

Table 2: Concomitant Antiretrovirals

Agent	N
lamivudine (3TC)	10
tenofovir DF (TDF)	10
didanosine	3
zidovudine	3
abacavir	2
stavudine	1
enfuvirtide (T20)	1

The most common regimen with LPV/RTV was TDF/3TC (n=5)

Table 3: Clinical Adverse Events (Grade 2-3)

	Group A (n=7) (LPV 400/RTV 300)	Group B (n=6) (LPV 533/RTV 233)
diarrhea	2	2
nausea	2*	1
vomiting	1*	0
fatigue	2	1
irritability	0	1
headache	0	1
Worsening peripheral neuropathy	1	0
Shoulder/knee pain	1	0
No adverse event	2/7 (29%)	4/6 (67%)

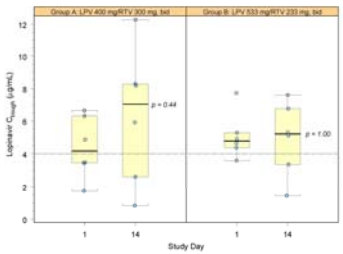
*1 patient in Group A discontinued study meds due to grade 3 nausea and vomiting

Table 4: Laboratory Adverse Events at Day 14 (all Grade 1)

	Group A (n=6) (LPV 400/RTV 300)	Group B (n=6) (LPV 533/RTV 233)
AST	2	0
ALT	1	0
Bilirubin	0	2

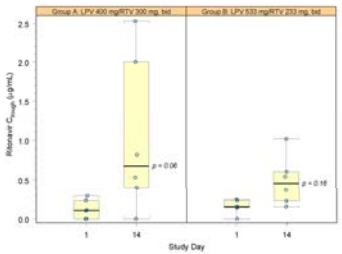
No clinically significant changes in plasma viral load, CD4 cell count or fraction were observed.

Figure 1: Lopinavir C_{trough} (µg/mL)



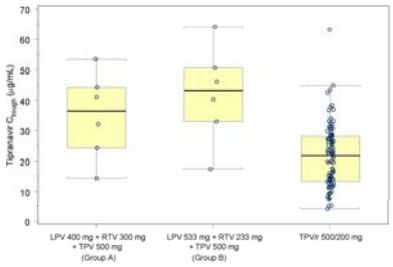
The dotted line indicates the target trough level for LPV in treatment-experienced patients, 4.0 µg/mL (www.hivpharmacology.com)

Figure 2: Ritonavir C_{trough} (µg/mL)



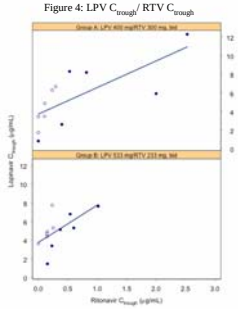
The box plots identify the median (line at middle of the box) and Interquartile range (top and bottom limit for each box). The whiskers are drawn to the nearest value not beyond a standard span (1.5 x interquartile range) from the quartiles; points beyond this value (outliers) are shown individually.

Figure 3: Tipranavir C_{trough} (µg/mL)



Comparison of steady-state plasma TPV trough concentrations for patients receiving LPV/RTV to historical plasma TPV trough concentrations (historical TPV concentrations represent the NONMEM individual predicted concentrations for 106 HIV+ male patients[2])

Figure 4: LPV C_{trough}/ RTV C_{trough}



Open circles = Day 1 concentrations
Closed circles = Day 14 concentrations

CONCLUSIONS

- Regimens including TPV with adjusted doses of LPV/RTV were generally safe and well-tolerated over 14 days, particularly TPV 500mg/ LPV 533mg/RTV 233mg BID (Group B)
- LPV trough concentrations on Day 14 were not statistically different from those observed with LPV 400mg/RTV 100 mg BID without TPV on Day 1, although inter-patient variability on Day 14 is substantial
- Increased RTV plasma concentrations were generally associated with increased LPV levels
- TPV levels were somewhat higher than historical controls for TPV 500mg/RTV 200mg BID (without LPV)
- Therapeutic drug monitoring should be encouraged in view of the substantial inter-patient variability in LPV trough concentrations seen on Day 14

REFERENCES

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2. Yong CL, Sabo JP, Oksala CG et al. Population pharmacokinetic (PK) assessment of systemic steady-state tipranavir (TPV) concentrations for adults administered tipranavir/ritonavir 500/200 mg BID. 12th Conference on Retroviruses and Opportunistic Infections, Boston, MA. 22-25 February, 2005. Abstract 654.

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