

The Steady-State Pharmacokinetics of Efavirenz and Lopinavir/Ritonavir in HIV-Infected Persons Requiring Hemodialysis: AIDS Clinical Trials Group Study A5177

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ABSTRACT (UPDATED)

BACKGROUND: EFV and LPV/RTV primarily undergo hepatic metabolism. It has been assumed that renal failure does not influence their PK. However, renal failure has affected the disposition of other drugs undergoing extensive hepatic metabolism. The objectives of this study were to estimate the PK of these agents in renal failure and compare to those with normal renal function.

METHODS: A prospective, observational study of the steady-state PK of HIV-infected subjects requiring hemodialysis receiving either one 600mg tablet daily of EFV (N=13) or three 133.33mg capsules twice daily of LPV/RTV (N=13) was conducted. Subjects were excluded if other CYP450 inhibitors/inducers were prescribed. C_{trough}, C_{max}, and AUC (24 and 12 hours for EFV and LPV/RTV, respectively, on non-dialysis days) were compared to HIV-infected historical controls with normal renal function using the bioequivalence method of calculating the geometric mean ratio (GMR) and associated 90% confidence interval (CI). Inhibitory quotients (IQ) for LPV were estimated by dividing C_{trough} by 0.07µg/mL (wildtype IC50).

RESULTS: Median age and percentage of men were 47 years and 92%, respectively, in both groups. Blacks represented 100% and 92% of the EFV and LPV/RTV groups, respectively. The median CD4 cell counts were 360 and 271 for the EFV and LPV/RTV groups, respectively. All results are presented as geometric means (95% CI; %CV).

	C _{trough} (µg/mL)	C _{max} (µg/mL)	AUC(µg·h/mL)
EFV	2.23 (1.19, 4.18; 99%)	5.04 (3.48, 7.29; 72%)	71.4 (43.1, 118.3; 93%)
LPV	3.76 (2.63, 5.38; 42%)	8.45 (6.41, 11.15; 52%)	69.5 (55.5, 87.0; 37%)
RTV	0.14 (0.09, 0.21; 55%)	0.58 (0.44, 0.76; 41%)	3.73 (2.91, 4.80; 37%)

Mean AUCs for EFV, LPV, and RTV of 58.1, 92.6, and 4.6µg·h/mL, respectively, were used as historical controls. The AUC GMR (90% CI) for EFV, LPV, and RTV were 132.2% (88.8, 196.9), 80.8% (67.3, 97.1), and 91.5% (73.9, 113.3), respectively. The median (range) C_{trough} and IQ for LPV were 4.27µg/mL (0.86-6.70) and 61 (12-96), respectively.

CONCLUSIONS: Using no-effect boundaries of 50-200%, the AUCs of EFV and LPV/RTV appear bioequivalent between HIV-infected subjects requiring hemodialysis and those with normal renal function. Despite lower PK, LPV IQs remained high. Dose adjustments for EFV and LPV/RTV in HIV-infected patients requiring hemodialysis may not be necessary. Further studies are needed to explain the large variability in EFV PK in this population.

INTRODUCTION

- Prevalence of HIV-infected patients with ESRD and requiring hemodialysis is increasing
- Non-nucleoside reverse transcriptase inhibitors and protease inhibitors are commonly used in this population
- Because these classes of ARVs are primarily metabolized by the liver, it has been assumed that renal failure would not affect their pharmacokinetics
- Other drugs that are hepatically metabolized have been shown to be influenced by renal impairment
- Prospectively obtained data in large cohorts are lacking

METHODS

• Prospective, multicenter, observational, intensive steady-state pharmacokinetic studies of HIV-infected patients requiring hemodialysis and already receiving one 600mg tablet daily of efavirenz (EFV) or three 133.33mg capsules of lopinavir/ritonavir (LPV/RTV) twice daily as part of the regimen for 30 days prior to study entry

• Subjects eligible if from 18-65 years of age; no significant liver, biliary, or pancreatic abnormalities; Hgb > 8.0mg/dL; no DAIDS Grade ≥ 2 nausea, vomiting, diarrhea, or abdominal pain for 7 days prior to entry; no other CYP450 inhibitors or inducers other than EFV or LPV/RTV for 30 days prior to entry

• EFV and LPV/RTV subjects underwent 24-hour and 12-hour PK evaluations on non-dialysis days in GCRCs of their home institutions

• Observed EFV dose administered at 7pm; LPV/RTV administered at 8am; standardized moderate-fat meals provided

• EFV levels were measured using ultraviolet high performance liquid chromatography with a lower limit of quantification of 25ng/mL; LPV and RTV levels were measured using liquid chromatography-tandem-mass spectrometry with lower limits of detection of 50ng/mL and 25ng/mL, respectively.

• C_{trough}, C_{max}, and AUC of EFV and LPV/RTV in hemodialysis subjects then compared to HIV-infected historical control^{1,2} with normal renal function receiving the same formulations of drug using the bioequivalence method of calculating geometric mean ratios (GMR) with 90% confidence intervals

RESULTS

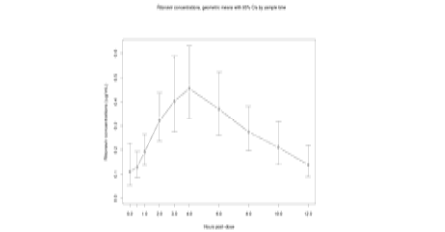
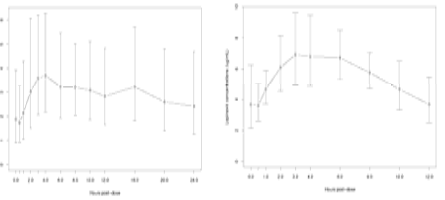
	Subject Characteristics	
	EFV (N=13)	LPV/RTV (N=13)
Median age (years)	47	47
Male (%)	92	92
Black (%)	100	92
Hepatitis B Ag Pos (%)	8	31
Hepatitis C Ab Pos (%)	62	15*
Median CD4 (cells/µL)	360	271
VL (% undetectable)	62	33

*N=12

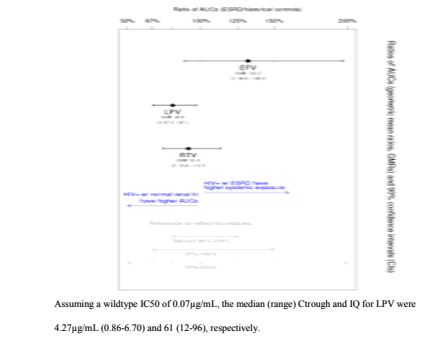
RESULTS

Pharmacokinetic Parameters*	EFV	LPV	RTV
	C _{min} (µg/mL)	2.23 (1.19, 4.18; 99)	3.76 (2.63, 5.38; 42)
C _{max} (µg/mL)	5.04 (3.48, 7.29; 72)	8.45 (6.41, 11.15; 52)	0.58 (0.44, 0.76; 41)
AUC (µg·h/mL)	71.38 (43.08, 118.27; 93)	69.48 (55.52, 86.95; 37)	3.73 (2.91, 4.80; 37)
C _{ss} (µg/mL)	2.97 (1.79, 4.93)	5.79 (4.63, 7.25)	0.31 (0.24, 0.40)
CL (L/h)	8.41 (5.07, 13.93)	5.76 (4.60, 7.20)	26.79 (20.85, 34.41)
Median T _{max} (h)	4.0	3.0	3.0
Median T _{1/2} (h)	13.69**	8.38***	4.61***

*All results are geometric means (95% CI; %CV) unless stated otherwise
N=11; *N=12
†Efavirenz concentrations, geometric means with 95% CI by sample time
‡Lopinavir concentrations, geometric means with 95% CI by sample time



RESULTS



CONCLUSIONS

- Using no-effect boundaries of 50-200%, AUCs of EFV and LPV/RTV appear bioequivalent between hemodialysis and normal renal function
- Large variabilities in EFV PK (pharmacogenomic evaluations pending)
- Modestly lower LPV PK in hemodialysis (protein-binding evaluations pending), but LPV IQs remain high
- Dose adjustments do not appear necessary for those requiring hemodialysis
- Further study of once daily dosing of LPV/RTV tablets in hemodialysis is warranted

REFERENCES

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2. Sandoz package insert. Wilmington (DE): Dooport Pharmaceuticals, 2002.

