STEADY-STATE PHARMACOKINETICS (PK) AND TOLERABILITY OF INDINAVIR (IDV) WHEN CO-ADMINISTERED WITH LOPINAVIR/RITONAVIR (LPV/r) IN EXPERIENCED SUBJECTS

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Purpose

- **To characterize the tolerability and PK profile of IDV and LPV when co-administered in ARV-experienced patients.**

Methods

- **A 12-hour PK profile was obtained from HIV-positive patients taking IDV 800 mg bid and LPV/r 400/100 mg bid for at least 2 weeks.**
- **Blood was drawn immediately prior to observed PI administration, and then at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10 and 12 hours afterwards.**
- **IDV and LPV plasma concentrations were measured by a sensitive and selective LC/MS/MS assay. The LLD was 25 ng/mL for both drugs.**
- **PK parameters were compared with data from the Kaletra monograph and historical data from subjects receiving IDV/RTV 800/100 mg bid alone.**

Results

- **5 subjects (4 M, 1 F) were included in the analysis. Median time on IDV & LPV/r at sampling was 3 months (range 1.5-8). No patients were on concurrent NNRTI or other 3A4 modulating drugs.**
- **All subjects had normal renal function. One subject with concomitant hepatitis C had baseline AST and ALT twice the ULN, while the rest had normal baseline LFTs.**

Table 1: Baseline Characteristics

Demographics:	**Median**	**(range)**
age	47 y	(31 - 59)
viral Load log/mL	4.76	(2.89-6.00)
CD_4 cells/uL	110	(10 – 607)
triglycerides mmol/L	2.32	(0.91-3.69)
cholesterol mmol/L	4.42	(3.89-5.43)
Prior medication history at baseline:		
# prior ARVs	9.5	(5-12)
# prior PIs	3.0	(11/21)

Table 2 – Median (Range) Indinavir and Lopinavir PK Parameters

	Cmin (µg/mL)	**Cmax (µg/mL)**	**$AUC_{[0-12]}$ (µg.hr/mL)**
Indinavir:			
• with LPV	0.61 (0.05-1.91)	7.58 (5.35-9.25)	51.84 (29.63-64.45)
• *800/100 mg rtv BID*[1]	*0.99 (0.58-1.4)*	*8.70 (7.5-10)*	*44.0 (29.8-58.2)*
Lopinavir:			
• with IDV	2.90 (0.55-4.40)	6.30 (4.85-8.49)	67.91 (43.64-78.67)
• *alone*[2]	*5.50 ± 4.40*	*9.60 ± 4.4*	*82.80 ± 44.50*

[1]van Heeswijk et al. AIDS 1999;13:F95–99. [2]Kaletra Product Monograph, 2002.

Results (con't)

- **Observed IDV PK parameters were comparable to previously published data in HIV subjects taking IDV 800/rtv 100 mg BID alone. Observed LPV PK parameters were slightly lower than expected.**
- **At a median 11 months follow-up (range 5.5-21), no patient had discontinued therapy or undergone dose adjustment due to IDV- related side effects. There were no cases of nephrolithiasis. One subject had significant lipid elevations (TG +13.35, TC +8.23) which responded to atorvastatin.**

Conclusion

- **This PK study provides evidence against the occurrence of a clinically significant interaction between IDV 800 mg and LPV/r 400/100 mg BID.**
- **A larger sample size is needed to determine whether changes in LPV PK parameters are significant.**
- **Discontinuation of treatment associated with IDV-specific toxicities was not observed.**

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