The steady state pharmacokinetics (PK) of lopinavir/ritonavir (LPV/r) 533/133 mg *b.i.d* plus nevirapine (NVP) (200 mg *b.i.d*) in adult HIV-1 infected individuals (The NRTI sparing study)

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BACKGROUND

- Interest in NRTI sparing regimens to treat antiretroviral naive patients has increased due to concern over the long term side effects associated with NRTI treatment. NRTIs inhibit the enzyme mitochondrial DNA polymerase gamma and diminish host mitochondrial DNA soon after initiating therapy. This mitochondrial depletion appears to underlie many adverse effects attributed to NRTI use, including peripheral neuropathy, liver dysfunction and lipoatrophy. An NRTI sparing approach may prevent these adverse reactions, improve adherence to treatment and preserve the NRTI class for the future.
- The combination of LPV/r and NVP offers a regimen with a low pill burden and a high genetic barrier to resistance[1].
- However, studies performed in HIV-1 infected adult and paediatric patients revealed a significant decrease in LPV trough concentrations with co-administration of NVP[2,3,4]. This interaction is based on the common metabolism of all three drugs by CYP3A and could be explained by induction of CYP3A by NVP[5,6].
- Consequently, a 33% increase of LPV/r dosage to 533/133 mg (4 capsules *b.i.d*) from the standard dose of 400/100 mg (3 capsules *b.i.d*) is recommended in combination with NVP[5].

OBJECTIVE

- To assess the influence of NVP (200 mg *b.i.d*). on LPV/r (533/133 mg *b.i.d*) pharmacokinetics throughout the 12 hour dosing interval, in order to optimise dosing regimens.

METHODS

Patients

- 15 HIV-1 infected adults (Table 1), naive to NNRTI and PI treatment, received LPV/r (533/133 mg *b.i.d*) and NVP (200 mg *q.d* for 2 weeks followed by NVP 200 mg *b.i.d*).

Table 1. Patient baseline characteristics (n=15)

	LPV/r (533/133 mg *b.i.d*) + NVP (200 mg *b.i.d*) (n = 20)
Male [n (%)]	13 (87)
Age, yr, mean (SD)	40 (8.6)
BMI, kg/m^2, mean (SD)	25.1 (6.6)
AIDS [n (%)]	5 (33.3)
HIV-1 viral load, copies/ml, mean (range)	282292 (41650-1000000)
CD4 count, cells/mm^3, mean (range)	208 (8-427)

PK Sampling

- Blood samples were collected pre-dose (0h) and 1, 2, 4, 6, 8, 12 hour post-dose.
- LPV and RTV plasma concentrations were determined by HPLC-MS/MS and NVP concentrations by HPLC-UV.

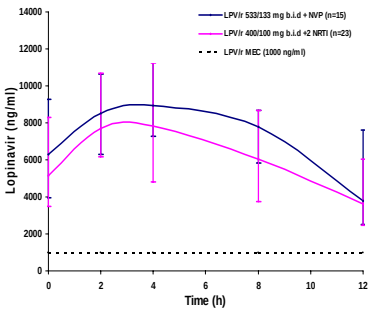
Data Analysis

- The results were compared with data from a cohort of patients (n=23), analysed in our laboratory, who received LPV/r at the standard dose of 400/100 mg *b.i.d* plus 2 NRTI.

RESULTS

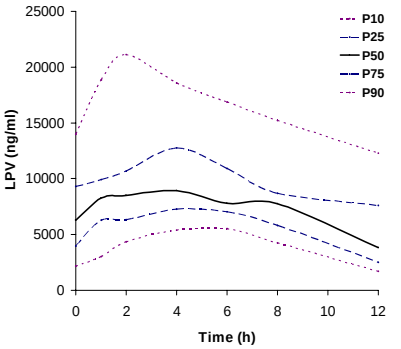
- Following an increase in the LPV/r dosage, the median (IQR) LPV C_{trough} was 3805 ng/ml (2510-7613), which was not significantly different from the C_{trough} for LPV at the standard dose of 400/100 mg *b.i.d* + 2 NRTI [3604 ng/ml (2447-6040) (P=0.637, 95% confidence interval (CI) -1277 to 2531) *Mann Whitney U Test*].
- No statistically significant difference was observed in LPV exposure, expressed as median LPV AUC_{0-12}, at the standard dose of LPV/r (400/100 mg *b.i.d*) versus the higher dose (533/133 mg *b.i.d*) [79087 ng.h/ml (56730-108040) versus 85588 ng.h/ml (70190-111347) (P=0.3286, CI -40550 to 11740) *Mann Whitney U test*] (Figure 1).

Figure 1. Median (IQR) LPV PK profiles for LPV/r 533/133 mg *b.i.d* + NVP (n=15) vs. LPV/r 400/100 mg *b.i.d* + 2 NRTI (n=23). Dotted line indicates previously reported LPV MEC (1000 ng/ml) for treatment naïve patients with wild type HIV-1.



- Inter-subject variability (CV%) in LPV C_{trough} was high for both regimens, and increased from 73% to 77% when NVP was co-administered with LPV/r.
- 14 (93%) patients maintained LPV trough levels above the previously reported minimum effective concentration (MEC) for treatment naive patients with wild-type HIV-1 (1000 ng/ml)[7].

Figure 2. Median LPV concentrations over 12-hour dosing interval including the 10th, 25th, 75th and 90th percentiles (n=15).



- Calculated population percentiles (Figure 2) complied with data from industry[8], with exception of the 90th percentile.
- Fundamentally, patients within the 10th percentile had LPV C_{trough} above the recommended MEC for treatment naïve patients. Percentiles below 10% were deemed unreliable for the purpose of this study, due to the limited data set.

CONCLUSIONS

- Although there are limitations in comparing PK parameters from different patient groups; all analytical data were processed through the same laboratory.
- The study shows that an increase in LPV/r dosage to 533/133 mg (4 capsules *b.i.d*) is appropriate when used in combination with NVP. However, given the high inter subject variability in LPV trough concentrations the use of TDM is recommended.
- We await data for the new tablet formulation of LPV/r in the presence of NVP.

REFERENCES

1. Negredo E. *et al. J Aquir Immune Defic Syndr*, 2005, 38: 47-52.
2. Solas C. *et al. Br J Clin Pharmacol*, 2003, 57: 436-440.
3. Hsu A. et al. 5th International Congress on Drug Therapy in HIV, Glasgow, Abstract P92, 2000.
4. Bertz et al, XIVth International AIDS Conference, Barcelona, 2002.
5. Cvetkovic RS. *et al. Drugs*, 2003, 63(8): 769-902.
6. Smith PF. *et al. Clin Pharmacokinet*, 2001, 40(12): 893-905.
7. Kappelhoff. *et al. Clin Pharmacokinet*, 2004, 43(13): 845-853.
8. Kaletra capsules-prescribing information- Abbott Laboratories, 2006.