Poster #220

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Kaletra (Lopinavir/ritonavir) Therapy in Single Protease Inhibitor Experienced Patients: 144-Week Follow-up

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BACKGROUND

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir, which functions as an inhibitor of cytochrome P450 3A. Even at low ritonavir doses, there is a substantial increase in LPV exposure. At a dosage of 400 mg LPV/100 mg ritonavir twice daily (3 co-formulated tablets BID), ritonavir concentrations are below those required for antiviral activity.[1] By contrast, the mean LPV C_{trough}/IC_{50} ratio (Inhibitory Quotient or IQ) for wild-type HIV is ≥75 when dosed at 400/100 mg twice a day, potentially providing a barrier to emergence of viral resistance and activity against resistant virus.

The efficacy and safety of Kaletra (lopinavir/ritonavir, formerly known as ABT-378/r) are currently being studied in HIV-infected patients, both antiretroviral-naïve and PI-experienced. The M97-765 study is an ongoing phase II trial of LPV/r in combination with nevirapine and 2 NRTIs in single PI-experienced, NNRTI-naïve patients. Results through Week 144 are presented here.

METHODS

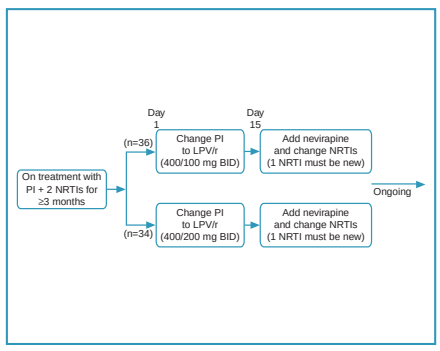
Entry Criteria

- Plasma HIV RNA 10^3–10^5 copies/mL.
- On treatment with 1 PI and 2 NRTIs for ≥3 months at study entry.
- Single PI-experienced (no prior treatment with any PI, other than the current one, for ≥6 weeks, and no prior dual PI therapy).
- Naïve to at least one NRTI, with no prior NNRTI experience.

Study Design and Analysis

- Seventy patients were randomized to receive LPV/r (400/100 mg BID or 400/200 mg BID) in place of their current PI, in combination with their existing NRTIs.
- On study day 15, nevirapine (200 mg QD for 14 days then 200 mg BID) was added and NRTIs were changed to include at least one which was new to the patient (Figure 1).
- Plasma HIV RNA was quantified using Roche Amplicor HIV-1 Monitor ™ (lower limit of quantitation [LLQ] 400 copies/mL) and the Roche Amplicor HIV-1 Monitor Ultrasensitive HIV RNA quantitative PCR, version 1.0 (LLQ 50 copies/mL).

Figure 1. M97-765 Study Schema



RESULTS

Baseline Characteristics

- Sixty-three male and 7 female patients: 66% Caucasian, 24% Black, 7% Hispanic, 3% Asian/Pacific Islander.
- Mean age: 40 years (range 22–66).
- Median plasma HIV RNA: 4.0 $\log_{10}$ copies/mL (range 2.9–5.8).
- Median CD4 count: 349 cells/mm³ (range 72–807).
- Previous PI experience included indinavir (44%), nelfinavir (36%), saquinavir (13%), ritonavir (6%), and amprenavir (1%).
- 3TC was the most common NRTI being used at baseline (87%), followed by d4T (56%) and zidovudine (43%), with a small minority receiving ddI (10%).

Baseline Viral Susceptibility

- Protease inhibitor phenotypic susceptibility data were available for 57/70 baseline viral isolates (VIRCO Antivirogram® method).
- Baseline viruses from 63% of patients (36/57) displayed a ≥4-fold loss in susceptibility to the previous PI, and 32% of patients (18/57) had viruses with ≥4-fold loss in susceptibility to three or more PIs (Table 1).
- Of 56 patients for whom baseline phenotype for all of the drugs in the previous regimen was available, the incidence of ≥4-fold change in IC_{50} to one, two or three previous drugs was 36%, 45%, and 16%, respectively.
- Nineteen percent of patients (11/57) had ≥4-fold reduction in susceptibility to LPV at baseline.

Table 1. Baseline Susceptibility to Previous Protease Inhibitor

		Fold Change in IC_{50} Compared with Wild-Type	
Previous PI	n	Mean	Range
Indinavir	24	7.4	0.4–26
Nelfinavir	21	19.1	0.8–>54
Saquinavir	9	9.5	0.7–32
Ritonavir	3	23.0	7.3–41

Viral Load Response at Week 2

- Viral suppression was rapid with a marked reduction in HIV RNA during the first two weeks of therapy. At Week 2, prior to the addition of nevirapine, 80% (56/70) of patients had a ≥1 $\log_{10}$ copies/mL decrease in HIV RNA or achieved a viral load <400 copies/mL (Figure 2).
- Viral load decline through Week 2 was independent of the IC_{50} of LPV against baseline viral isolates (range 0.7–26-fold) (Figure 3). This initial decline was also independent of prior PI experience.

Figure 2. HIV RNA Mean Change from Baseline

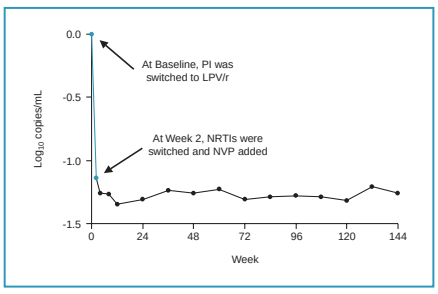
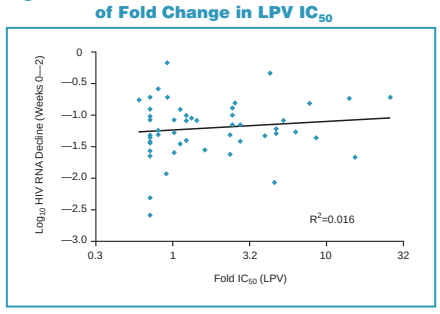


Figure 3. HIV RNA Decline as a Function of Fold Change in LPV IC_{50}



Viral Load Suppression at Week 144

- On-treatment analysis (OT): 83% of patients in the 400/100 mg dose group and 86% of patients in the 400/200 mg dose group had viral load (VL) <400 copies/mL at Week 144 (Figure 4).
- Intent-to-treat analysis (ITT M=F; missing values considered as treatment failure): 53% of patients in the 400/100 mg dose group and 56% of patients in the 400/200 mg dose group had a VL <400 copies/mL at Week 144 (Figure 5).

Figure 4. M97-765 HIV RNA <400 Copies/mL (OT)

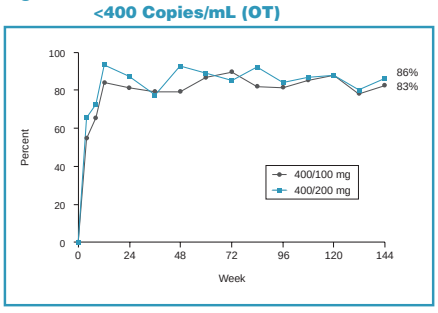


Figure 5. M97-765 HIV RNA <400 Copies/mL (ITT M=F)

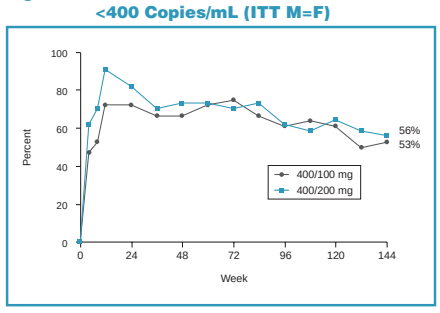


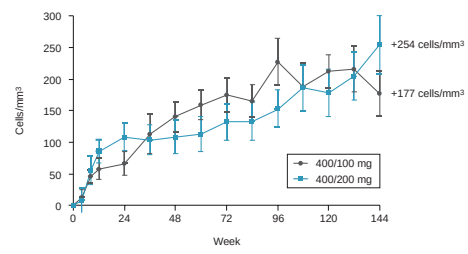
Table 2. Percentage of Patients with Plasma HIV RNA <50 Copies/mL at Week 144

Analysis	400/100 mg (n=36) %	400/200 mg (n=34) %	Overall (n=70) %
On-treatment	73%	78%	76%
Intent-to-treat (M=F)	44%	53%	49%

CD4 Cell Response

- The mean CD4 cell count at Week 144 was 587 cells/mm³, an increase from baseline of 211 cells/mm³ (Figure 6).
- No statistically significant differences between treatment groups were observed at any visit.

Figure 6. M97-765 CD4 Cell Count Mean Change from Baseline



Tolerability

- The most common drug-related adverse events through 144 weeks were diarrhea and asthenia (Table 3).
- Grade 3/4 lipid elevations were generally transient. At Week 144 (or last available observation for patients who discontinued prior to Week 144), 2 patients (one each on 400/100 mg [3%] and 400/200 mg [3%]) had Grade 3 cholesterol and 2 patients (one each on 400/100 mg [3%] and 400/200 mg [3%]) had Grade 3 triglycerides.
- Patients with baseline AST/ALT elevations above the upper limit of normal were at a significantly higher risk of Grade 3/4 AST or ALT elevations on treatment: 50% of those with high BL values had elevations compared to 14% of those without BL elevations (relative risk = 3.7, 95% CI [1.5, 9.0]).
- No cases of symptomatic hepatitis attributed to LPV/r therapy were reported.
- Twenty-two patients discontinued the study through 144 weeks; of these, only six discontinuations were due to adverse events related to study drug (Table 4).

Table 3. Most Common Adverse Events and Laboratory Abnormalities

	400/100 mg (n=36)	400/200 mg (n=34)
Adverse Events*		
Diarrhea+	31%	29%
Asthenia	6%	9%
Weight Loss	0%	12%
Nausea	3%	9%
Laboratory Abnormalities		
Glucose (>250 mg/dL)	3%	6%
Cholesterol (>300 mg/dL)	31%	42%
Triglycerides (>750 mg/dL)	22%	39%
GGT (>5X ULN)	22%	36%
AST/ALT (>5X ULN)	11%	27%
Amylase (>2X ULN)	6%	6%

* Adverse events of at least moderate severity and probable, possible, or unknown relationship to LPV/r are included
\+ >3 loose stools/day

Table 4. Patient Disposition Through Week 144

	400/100 mg	400/200 mg
Patients Enrolled	36	34
Patients Discontinuing before Week 144	12	10
Discontinuations Related to LPV/r (Diarrhea (2), Flatulence, Rash, Asthenia, Depression)	4	2
Other Reasons for Discontinuation		
AE (myocardial infarction on study day 1)	1	0
Death (metastatic lung carcinoma, Rhabdomyolysis with acute renal failure)	0	2
Noncompliance	1	1
Personal Reasons/Other	5	3
Lost to Follow-up	1	2

CONCLUSIONS

- LPV/r plus NVP and NRTIs exhibit a potent and durable antiviral effect through 144 weeks in PI-experienced patients, with VL <400 copies/mL in 84% of patients on treatment (ITT M=F: 54%) and <50 copies/mL in 76% of patients on treatment (ITT M=F: 49%).
- LPV/r was well tolerated with only 6/70 patients discontinuing due to adverse events related to study drug through 144 weeks.
- Viral suppression was achieved and maintained in the majority of patients, despite high-level baseline resistance to prior PIs and NRTIs.
- Antiviral activity was demonstrated during the initial two weeks of the study when the only alteration to the baseline regimen was substitution of the previous PI with LPV/r.
- While significant viral suppression was observed in this study of patients with prior PI and NRTI experience, antiviral activity in antiretroviral-naïve patients receiving LPV/r with d4T and 3TC was higher at a similar timepoint.[1] This suggests that early use of LPV/r may be associated with optimal outcome.

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REFERENCE

1. White AC, Brun S, King M, et al. Lopinavir/ritonavir (Kaletra) in Antiretroviral-Naïve HIV+ Patients: Week 144 Follow-up. 1st IAS Conference on HIV Pathogenesis and Treatment, Buenos Aires, Argentina, July 2001 (Poster 217).