TuPeB4445

XIV International AIDS Conference, Barcelona, July 2002

Once-Daily vs. Twice-Daily Kaletra (lopinavir/ritonavir) in Antiretroviral-Naive HIV+ Patients: 72-Week Follow-up

J Feinberg[1]*, B Bernstein[11], M King[11], L Manning[11], R Bertz[11], G Beall[2], J Eron[3], F Carpio-Cedraro[4], H Horowitz[5], D Wheeler[6], H Kessler[7], D Mildvan[8], P Ruane[9], B Yangco[10] and E Sun[11]
[1]University of Cincinnati, [2]Harbor UCLA Medical Center, [3]University of North Carolina at Chapel Hill, [4]AltaMed Health Services, [5]Westchester Medical Center, [6]Infectious Disease Physicians, [7]Rush-Presbyterian-St. Luke's Medical Center, [8]Beth Israel Medical Center, [9]Tower Infectious Disease, [10]Infectious Disease Research Institute, and [11]Abbott Laboratories

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. Lopinavir trough concentrations exceed the protein binding-adjusted IC_{50} of wild-type HIV by ≥75-fold when dosed at 400/100 mg twice a day,[1] potentially providing a barrier to emergence of viral resistance and activity against resistant virus.

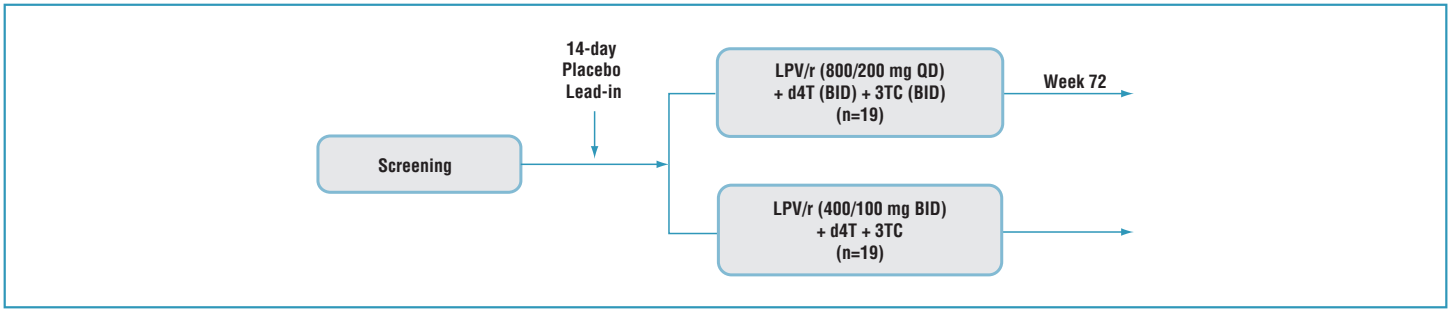
Lopinavir/ritonavir (LPV/r, marketed as Kaletra™) has been studied in both antiretroviral-naive and experienced HIV-infected patients. The M99-056 study is a pilot study of LPV/r 800/200 mg QD or 400/100 mg BID both in combination with d4T (BID) and 3TC (BID) in antiretroviral-naive patients. This poster presents 72-week results on safety, efficacy and pharmacokinetics of these regimens.

METHODS

Entry Criteria

- Antiretroviral-naive patients
- Plasma HIV RNA level above 50 copies/mL
- No minimum CD4 cell count

Figure 1. M99-056 Study Schema



Study Design and Analysis

- Thirty-eight antiretroviral-naive patients were randomized equally to receive LPV/r 800/200 mg QD or 400/100 mg BID. All patients also received d4T (30 mg or 40 mg BID) and 3TC (150 mg BID) (Figure 1).
- Patients started with a 14-day placebo lead-in period during which they were dispensed a supply of placebo capsules and were enrolled in a medication support and monitoring service. This was done to acclimate patients to daily use.
- Steady-state plasma concentrations of LPV were measured throughout a dosing interval at Week 3. Additional LPV trough levels were measured at Weeks 8, 16, 24, and 48.
- Noncompartmental methods used to determine pharmacokinetic (PK) variables. ANOVA performed on log-transformed PK variables; linear mixed effects analysis performed on log-transformed trough concentrations over Weeks 3-48. Median trough and IQ for individual subject calculated as the median trough observations from Weeks 3-48.
- Plasma HIV RNA was quantified using the Roche Amplicor HIV-1 Monitor Ultrasensitive Quantitive PCR assay (LLQ 50 copies mL) at each visit.
- Adherence was measured by the Medication Events Monitoring System (MEMS®, AARDEX, Inc.) caps on the LPV/r bottles.

Virologic Evaluation

- Samples from all patients with HIV RNA >400 copies/mL at Weeks 24-72 while on the assigned regimen were submitted for genotypic and phenotypic analyses. Genotype (GeneSeq™) and phenotype (PhenoSense™) were performed by ViroLogic, Inc.
- Genotypic resistance to LPV was defined as the development of any primary or active site mutation in protease (amino acids 8, 30, 32, 46, 47, 48, 50, 82, 84 and 90) and confirmed by phenotypic analysis.

Demographics

Table 1. Baseline Characteristics

	QD (N=19)	BID (N=19)
Gender (No. patients)		
Male	13	13
Female	6	6
Age (years)		
Mean (range)	42 (25-74)	35 (22-54)
Race (No. patients)		
Caucasian	6	5
Black	6	9
Hispanic	4	5
Asian/Pacific Islander	3	0
Baseline HIV RNA (log_{10} copies/mL)		
Mean/Median	4.6/4.6	4.7/4.7
Range	3.5-5.6	2.8-5.9
CD4 count (cells/μL)		
Mean/Median	265/259	252/269
Range	5-917	6-474

Pharmacokinetic Data

- LPV AUC and C_{max} were similar for the QD and BID regimens.
- Across all patients, LPV C_{trough} did not differ over time from Weeks 3 to 48 (p=0.55).
- Overall median lopinavir C_{trough}/IC_{50} (protein binding-adjusted) was 40 (range 3.6-220) for QD and 84 (range 36-174) for BID regimens.
- Two patients on QD regimen had median LPV C_{trough}/IC_{50} <10.

Figure 2. M99-056 Lopinavir Mean (SD) Concentration-Time Profiles, Week 3

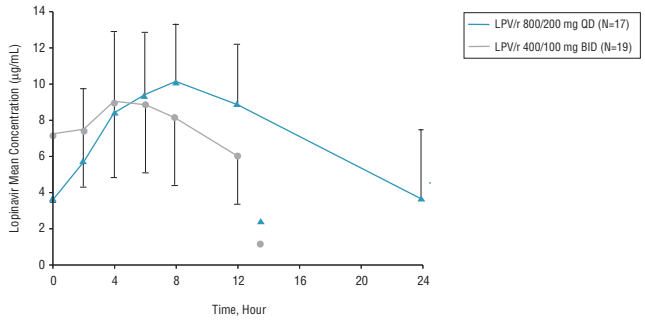
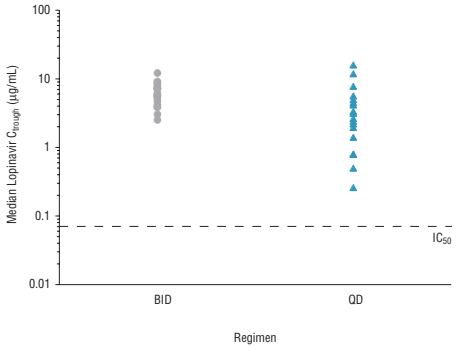


Figure 3. M99-056 Lopinavir Median C Scatter Plot



Inhibitory Quotients for QD Protease Inhibitor Regimens

The inhibitory quotient (IQ, C_{trough}/IC_{50} ratio) is a pharmacodynamic parameter that has been used to estimate the potential *in vivo* activity of protease inhibitors. The IQ has been demonstrated to be associated with virologic response in clinical studies evaluating two different protease inhibitors.[2]

IQ values were calculated based on C_{trough} values derived from published sources (Table 2) and IC_{50} values were measured for wild type HIV in the presence of 50% human serum,[3] a condition that approximates the free fraction of LPV in 100% human serum.[4] The IQ for LPV/r QD regimens compares favorably to the IQ values for other QD protease inhibitor-based regimens.

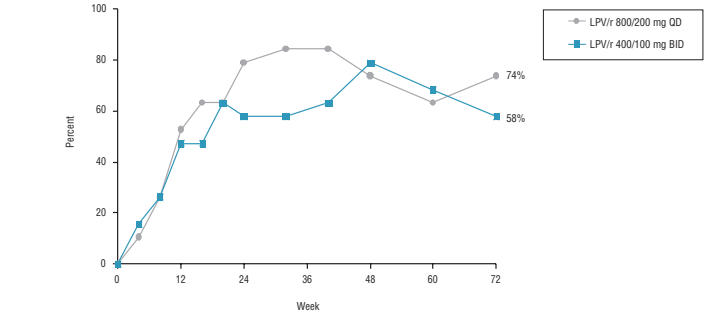
Table 2. Inhibitory Quotients for Protease Inhibitor Regimens

Regimen	N	C_{trough} (µg/mL)	IC_{50} (µg/mL)*	IQ	Reference for C_{trough}
LPV/r 800/200 mg QD	17	Median (range) 2.8 (0.25-15.4)	0.07	40	Bertz, et al. 9th CROI [Abs 126], 2002.
Atazanavir (ATZ) 400 mg QD	20	Mean ± SD 0.25 ± 0.15	0.023	10.9	Sanne, et al. 40th ICAAC [Abs 691], 2000.
APV/RTV 1200/200 mg QD	12	Point Est. (90%CI) 1.2 (0.8-1.7)	0.28	4.2	Agenerase Package Insert, 2002.
SQV/RTV 1600/100 mg QD	15	Mean (range) 0.245 (0.200-0.250)	0.25	1	Mars, et al. 1st IAS [Abs 676], 2001.
LPV/r 400/100 mg BID	19	Median (range) 5.9 (2.5-12.2)	0.07	84	Bertz, et al. 9th CROI [Abs 126], 2002.

All studies conducted in HIV-infected patients.
*Protein binding-adjusted IC_{50} for wt-HIV in 50% human serum using method reported in Molla A, et al. *Virology* 1998;250:255-262.

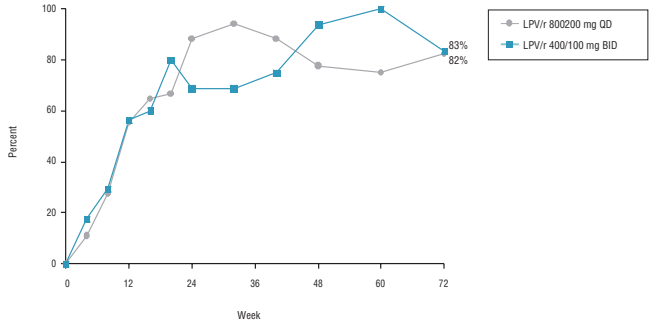
Efficacy

Figure 4. Proportion <50 copies/mL (ITT Noncompleter=Failure) at Week 72



Sample Size	
800/200 mg QD	19
400/100 mg BID	19

Figure 5. Proportion <50 copies/mL (On Treatment) at Week 72



Sample Size		
800/200 mg QD	19	17
400/100 mg BID	19	12

Viral Load Suppression at 72 Weeks

- Intent-to-treat analysis (ITT NC=F) 74% of patients and 58% of patients in the QD and BID groups, respectively, had VL <50 copies/mL at Week 72 (Figure 5). This difference is not statistically significant.
- Of the five patients in both groups with HIV RNA >50 copies/mL at Week 72, two had HIV RNA <100 copies/mL, two had HIV RNA between 100 and 1000 copies/mL, and one patient (whose HIV RNA measurement was performed during a dose interruption) had HIV RNA >1000 copies/mL. Three of these five patients had a subsequent HIV RNA <50 copies/mL without a change in regimen.

CD4 Response at 72 Weeks

- Among patients on study at Week 72, the mean CD4 cell count increases from baseline to Week 72 were 283 and 242 cells/mm^3 for the QD and BID groups, respectively.

Genotype and Phenotype Results

- Genotypic and phenotypic results were available for 5 patients with HIV RNA above 400 copies/mL on the assigned regimen between Week 24 and Week 72. Consistent with results observed in previous studies of LPV/r in ARV-naïve patients,[5] 0 of 5 patients demonstrated resistance to LPV/r. Three of 5 patients developed resistance to lamivudine (M184V/I mutation).

Safety and Tolerability

Table 3. Patient Disposition at Week 72

	QD	BID
Subjects enrolled	19	19
Subjects discontinuing before Week 72	2	6
Study drug-related adverse event	1	2
Withdrew consent	0	1
Noncompliance*	0	1
Site closure	1	2

* Patient discontinued at discretion of Investigator.

- One patient in the QD group prematurely discontinued on Day 4 due to pruritis, rash, chills, fever, nausea, vomiting, and diarrhea, all considered probably related to LPV/r. Two patients in the BID group discontinued due to adverse events. One patient discontinued due to diarrhea and dehydration considered possibly related to LPV/r, and one patient discontinued due to nausea that was considered possibly related to LPV/r, hyperlactemia attributed to d4T, and pedal edema attributed to hypothyroidism.
- The most common study-drug related adverse events of at least moderate severity were diarrhea, nausea and asthenia, while the most common laboratory abnormality was lipid elevations (Table 4). Of note, lipid measurements were made without regard to fasting.
- Lipid elevations to Grade 3 levels were infrequent, occurring in 2 patients in the QD group and 3 patients in the BID group.
- Mean changes from baseline to Week 72 were similar between treatment groups for triglycerides (95 mg/dL for the QD group and 137 mg/dL for the BID group) and total cholesterol (52 mg/dL for the QD group and 50 mg/dL for the BID group).
- Fasting total cholesterol/HDL ratio at Week 24 was not significantly changed from baseline (-0.30 in QD and +0.01 in BID) treated patients.

Table 4. Most Common Adverse Events* and Grade 3/4 Laboratory Abnormalities

Event	LPV/r 800/200 mg QD (N=19)	LPV/r 400/100 mg BID (N=19)
Diarrhea	1	1
Nausea	3	1
Asthenia	0	2
Total Cholesterol (>300 mg/dL)	1	1
Triglycerides (>750 mg/dL)	2	2

* Includes all moderate/severe events of probable or possible relationship to LPV/r and laboratory abnormalities experienced by more than 1 patient.
** Laboratory determinations obtained without regard to fasting.

Adherence

- Dosing history for each patient was obtained using MEMS caps to monitor LPV/r dosing and provided to the clinical study sites.
- Adherence was similar between the treatment groups. The mean percentage of days with the correct number of LPV/r doses taken was 90% for the QD group and 87% for the BID group (p=0.88) at Week 48.

CONCLUSIONS

- Both LPV/r-based regimens exhibited a potent antiviral effect through 72 weeks in antiretroviral-naive patients, with VL<50 copies/mL by intent-to-treat (noncompleter=failure) analysis with 74% and 58% of patients demonstrating VL <50 copies/mL in the QD and BID groups, respectively.
- LPV/r was well tolerated, with only three patients out of 38 discontinuing due to adverse events prior to Week 72.
- Side effects were similar to those seen in other studies of LPV/r in ARV-naive patients.
- Overall median lopinavir C_{trough}/IC_{50} (protein binding-adjusted) was 40 (range 3.6-220) for QD and 84 (range 36-174) for BID regimens.
- A high rate of adherence was observed and was similar for the QD and BID groups, based on MEMS caps data. The tolerability profile and QD dosing of LPV/r may promote patient adherence, a critical factor in achieving long-term viral suppression.

REFERENCES

1. Bertz R, Lam W, Brun S et al. Multiple-dose pharmacokinetics (PK) of LPV/ritonavir (LPV/r) in HIV+ subjects. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, USA, 1999 (abstract 0327).
2. Kempf D, Hsu A, Isaacson J et al. Evaluation of the Inhibitory Quotient as a Pharmacodynamic Predictor of Virologic Response to Protease Inhibitor Therapy. 3rd International Workshop on Clinical Pharmacology of HIV Therapy, The Netherlands, April 2-4, 2001.
3. Molla A et al. *Virology* 1998;250:255-262.
4. Hsu A, Bertz R, Hickman D et al. Protein binding of lopinavir (LPV) and ritonavir (RTV): *in vitro* and *ex vivo* data from HIV infected patients and healthy volunteers. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, IL, February 2001.
5. Bernstein B et al. Comparison of the Emergence of Resistance in a Blinded Phase III Study with Kaletra (lopinavir/ritonavir) or Nelfinavir plus d4T/3TC from Week 24 Through Week 96. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 2001.

ACKNOWLEDGMENTS

M99-056 Study Patients; AltaMed Health Services, M Lopez; Beth Israel Medical Center, G Costantini, A Murshak; Harbor UCLA Medical Center, M Guerrero; Infectious Diseases Physicians, J Gourley; Infectious Diseases Research Institute, K Halkias; Rush-Presbyterian-St. Luke's Medical Center, J Mohlman; Tower Infectious Diseases, T Clover; University of Cincinnati, P Daniel; University of North Carolina at Chapel Hill, D Ragan; Westchester Medical Center, K O'Keefe; Paragon Biomedical, J Ball, E Campbell, N Miyao, N Vidal; Abbott Laboratories, K Real, A Potthoff, R Heuser, K Robinson, C Foit, M Luo, C Locke, Y-L Chiu, X Ye