Poster #H-165

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Lopinavir/ritonavir (Kaletra) in Antiretroviral-Naïve HIV+ Patients: 4-Year 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 of 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 ≥70 when dosed at 400/100 mg twice a day, 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-naïve and experienced HIV-infected patients. However, few long-term data are available on continued safety and efficacy. The M97-720 study is an ongoing phase II trial of LPV/r in combination with d4T and 3TC in antiretroviral-naïve patients. This was the first trial of LPV/r in HIV-infected patients and hence provides the longest duration of follow-up for patients treated with LPV/r. This poster presents data on antiviral activity, immunologic parameters and safety through 204 weeks (4 years).

METHODS

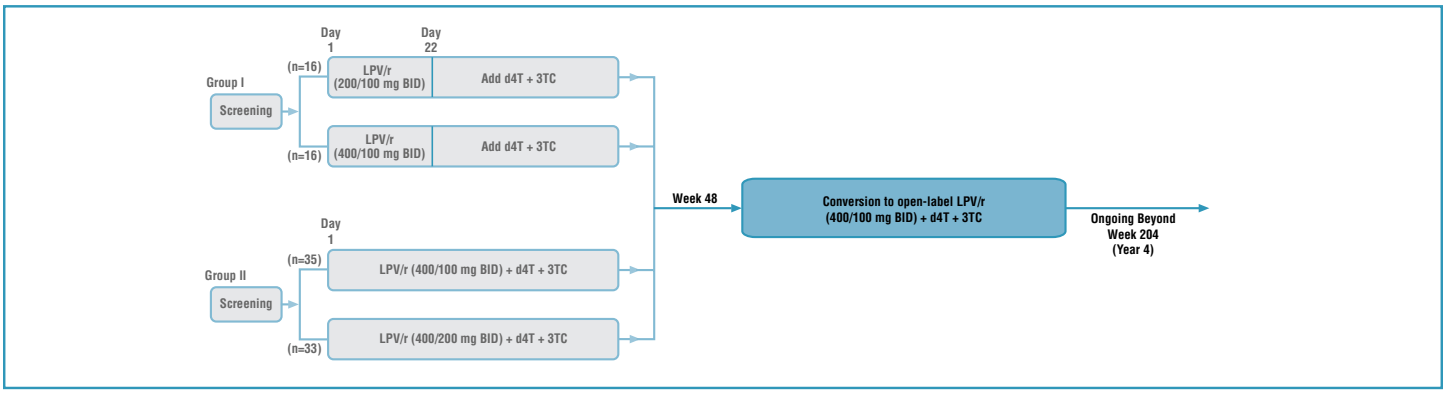
Entry Criteria

- Antiretroviral-naïve patients.
- Plasma HIV RNA ≥5,000 copies/mL with no CD4 cell count restriction.

Study Design and Analysis

- One hundred antiretroviral-naïve patients were randomized to receive one of three dosage levels of LPV/r (200/100 mg BID, 400/100 mg BID or 400/200 mg BID), together with d4T (40 mg BID) and 3TC (150 mg BID) given either after 3 weeks of monotherapy (Group I) or from study entry (Group II) (Figure 1).
- Enrollment into Group II began following an evaluation of preliminary efficacy and safety of LPV/r in Group I.
- After 48 weeks, all patients began conversion to open-label LPV/r 400/100 mg BID dosing.
- Plasma HIV RNA was quantified using Roche Amplicor HIV-1 Monitor™ (lower limit of quantitation [LOQ] 400 copies/mL) and the Roche Amplicor HIV-1 Monitor Ultrasensitive Quantitative PCR, Version 1.0 (LOQ 50 copies/mL).

Figure 1. M97-720 Study Schema



Antiviral Activity

- Proportion of patients HIV RNA below the limit of quantitation (LOQ) was measured using an on-treatment method (missing values and values obtained during treatment interruptions excluded) and an intent-to-treat, noncompleter=failure method (ITT NC=F, missing values considered failure unless the immediately preceding and following values were below the LOQ).
- Time to loss of virologic response was analyzed using a Kaplan-Meier procedure. Loss of virologic response was defined by two consecutive HIV RNA measurements above 400 copies/mL following any value below 400 copies/mL or failure to achieve HIV RNA below 400 copies/mL.
- Patients were considered virologic failures if they met loss of response criteria but achieved viral resuppression without a change in study medication.

Virologic Evaluation

- Samples from patients with sustained HIV RNA rebound to >400 copies/mL while receiving LPV/r during the study were submitted for genotypic and phenotypic analyses. Genotype (GeneSeq™) and phenotype (PhenoSense™) analyses 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) confirmed by phenotypic analyses (≥2.5 fold increase in IC_{50} to LPV relative to wild type HIV). Resistance to 3TC was defined as the presence of an M184V and/or M184I mutation in reverse transcriptase.

Safety

- Cumulative incidence through Week 204 for adverse events and grade 3/4 laboratory values was summarized, as was prevalence at Week 204, defined as the presence of an ongoing adverse event or a grade 3/4 lab measurement obtained at the Week 204 visit.
- All laboratory measurements were obtained without regard to fasting.

RESULTS

Baseline Characteristics

- Ninety-six male and 4 female patients: 65% Caucasian, 29% Black, 6% Hispanic.
- Mean age: 35 years (range 21-59).
- Median Plasma HIV RNA: 4.8 $\log_{10}$ copies/mL (range 3.3-6.3).
- Median CD4 count: 326 cells/mm^3 (range 3-918).

Viral Load Suppression Below the LOQ

- Based on the ITT NC=F analysis through Week 204, 71% of patients had HIV RNA <400 copies/mL (on-treatment analysis: 99%) (Figure 2) and 70% of patients had HIV RNA <50 copies/mL (on-treatment analysis: 97%) (Figure 3).

Figure 2. HIV RNA <400 copies/mL Through Week 204

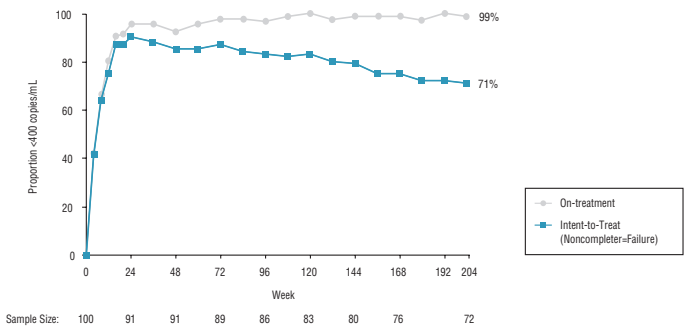
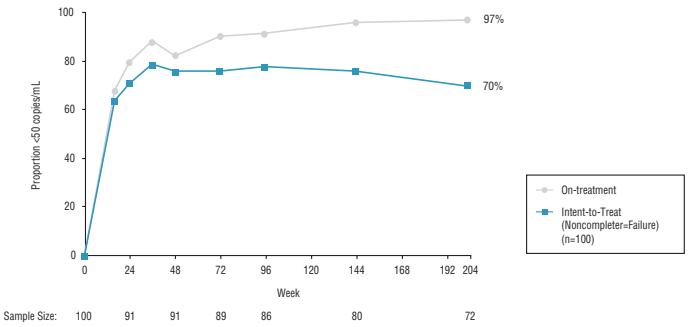


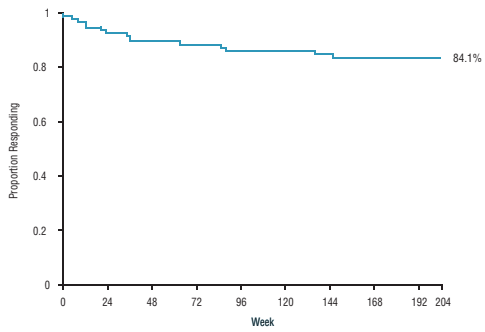
Figure 3. HIV RNA <50 copies/mL Through Week 204



Duration of Virologic Response Analysis

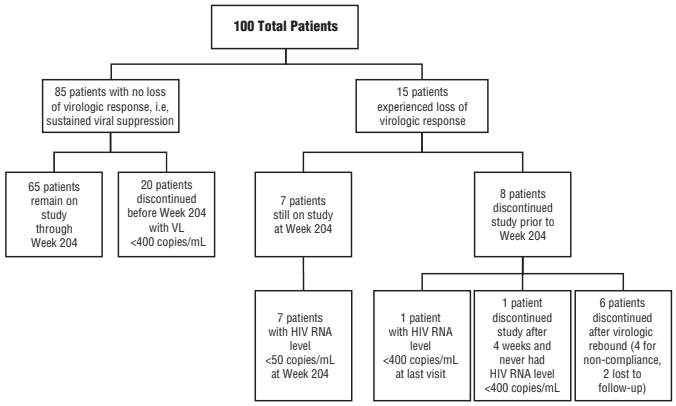
- Through Week 204, the proportion of patients maintaining virologic response was 84.1% by Kaplan-Meier analysis (Figure 4).
- Among the 15 patients with loss of virologic response, 7 remained on study through Week 204 without change in regimen, and all 7 patients had HIV RNA <50 copies/mL at Week 204.

Figure 4. Kaplan-Meier Analysis of Time to Loss of Virologic Response



RESULTS

Figure 5. M97-720: Virologic Disposition Through Week 204

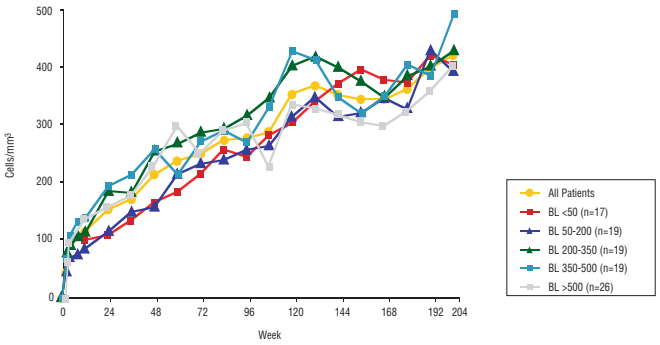


- Through Week 204, genotype was available on 6 patients with sustained HIV RNA rebound to >400 copies/mL while receiving LPV/r. Consistent with results obtained in previous studies of LPV/r in ARV-naïve patients,[2,3] 0 of 6 patients demonstrated protease inhibitor resistance, and 3 of 6 demonstrated 3TC resistance.

CD4 Cell Count Response

- Among subjects with values at both baseline and Week 204, the mean CD4 cell count increased from 281 cells/mm^3 at baseline to 721 cells/mm^3 at Week 204, an increase of 440 cells/mm^3 (Figure 6).
- CD4 cell count response appeared to be consistent regardless of baseline CD4 cell count. Among patients with baseline CD4 cell count <50 cells/mm^3, mean CD4 cell count increased from 23 cells/mm^3 at baseline to 446 cells/mm^3 at Week 204, an increase of 423 cells/mm^3.

Figure 6. CD4 Cell Count (Mean Change from Baseline)



Safety

Table 1. Patient Disposition Through Week 204

Patients enrolled	100
Patients discontinuing at or before Week 204	28
Discontinuations possibly or probably related to study drugs	
AST/ALT increases	2
Diarrhea	1
Arthralgia	1
Liver enlargement with pain and fatty deposits	1
Elevated cholesterol	1
Death[1]	1
Other reasons for discontinuation	
Adverse event/HIV-related event unrelated to study drugs (lymphoma, hyperglycemia in diabetic patient, alcohol detoxification)[2]	3
Personal reasons (left USA, drug addiction, moved out of state,[2] "virologic success")[3]	5
Noncompliance[2]	5
Lost to follow-up	9

[1] Death of unknown cause occurred in a patient ten days following thoracic spinal surgery with perioperative myocardial infarction.
[2] One patient was discontinued due to both noncompliance and alcohol detoxification.
[3] One patient discontinued based on the primary physician's recommendation to temporarily suspend ARV treatment because the patient was "doing so well on present regimen."

Table 2. Most Common Adverse Events* Through Week 204

	Incidence Through Week 204 (n=100)	Prevalence at Week 204 (n=72)
Diarrhea†	28%	3%
Nausea	16%	0%
Abdominal Pain	10%	0%
Abnormal Stool††	8%	1%
Asthenia	8%	0%
Headache	8%	1%
Vomiting	6%	0%

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

RESULTS

Table 3. Most Common Grade 3/4 Laboratory Abnormalities Through Week 204[1]

	Incidence Through Week 204 (n=100)	Prevalence at Week 204 (n=70)[2]
Cholesterol (>300 mg/dL)	22%	1%
Triglycerides (>750 mg/dL)	22%	6%
AST/ALT (>5X ULN)[3]	11%	1%

[1] All laboratory values were obtained without regard to fasting.
[2] Laboratory values were not available at Week 204 for 2 patients. Neither patient had a Grade 3 lipid value at the visits immediately preceding and following Week 204.
[3] Baseline positive hepatitis B surface antigen or hepatitis C virus antibody was associated with 7-fold increased relative risk of developing a Grade 3/4 AST or ALT elevation.

Table 4. Prevalence of Lipid Elevations at Week 204[1,2]

	Prevalence at Week 204 (n=70)[3]	
Total Cholesterol (mg/dL)		
<240	57	(81%)
240-300	12	(17%)
300-400	1	(1%)
>400	0	(0%)
Triglycerides (mg/dL)		
<400	48	(69%)
400-750	18	(26%)
750-1200	3	(4%)
>1200	1	(1%)

[1] All laboratory values were obtained without regard to fasting.
[2] 15 patients were using lipid-lowering agents at Week 204. Of these, 14 (93%) demonstrated total cholesterol reductions of at least one grade level. 11/15 (73%) had triglycerides of grade 0-1 and/or a reduction of one grade level.
[3] Laboratory values were not available at Week 204 for 2 patients. Neither patient had a Grade 3 lipid value at the visits immediately preceding and following Week 204.

CONCLUSIONS

- Through 4 years of follow-up, antiretroviral-naïve patients receiving LPV/r-based therapy exhibited sustained virologic response, with 71% of patients demonstrating HIV RNA <400 copies/mL and 70% demonstrating HIV RNA <50 copies/mL by intent-to-treat (NC=F) analysis. Corresponding on-treatment response rates were 99% and 97%, respectively.
- The proportion of patients maintaining virologic response through Week 204 was 84.1% by Kaplan-Meier analysis.
- Through 204 weeks of follow-up, no protease inhibitor resistance mutations have been observed in subjects with sustained viral load rebound.
- LPV/r was well tolerated, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events (7/100, 7%).

ACKNOWLEDGMENTS

M97-720 Study Subjects
Covance Central Laboratory Services

AIDS Research Consortium of Atlanta	*Dudley R*
Beth Israel Deaconess Medical Center–Harvard	*Fitch H*
Cornell Clinical Trials Unit	*Stroberg T*
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Northwestern University	*Bruce J*
Pacific Oaks Research	*Bautista J*
Rush Presbyterian St. Luke's Medical Center	*Narkiewicz E*
Thomas Street Clinic	*Sepcie B*
University of Colorado	*Canmann S, Putnam B*
University of North Carolina at Chapel Hill	*Marcus C*
PPD Development	*McCarley S, Wheat R*
Abbott Laboratories	*Kempf D, Potthoff A, Real K, Rode R, Sheehan K, Manning L, Yang G*

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