Abstract 7.3/16

9th European AIDS Conference, Warsaw, Poland, 26–29 October 2003

5-Year Results of Lopinavir/ritonavir (LPV/r)-Based Therapy in Antiretroviral-Naïve HIV-Infected Patients

C Hicks[1] , B da Silva[11], KR King[11], J Eron[2], C Benson[3], R Gulick[4], M Glesby[4], M Thompson[5], M Albrecht[6], P Wolfe[7], R Murphy[8], AC White[9], H Kessler[10], M King[11], S Brun[11]

[1]Duke University Medical Center, [2]University of North Carolina at Chapel Hill, [3]University of Colorado, [4]Weill Medical College of Cornell University, [5]AIDS Research Consortium of Atlanta, [6]Harvard University, [7]Pacific Oaks Research, [8]Northwestern University, [9]Baylor College of Medicine, [10]Rush Medical College, [11]Abbott Laboratories, USA

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 252 weeks (5 years).

METHODS

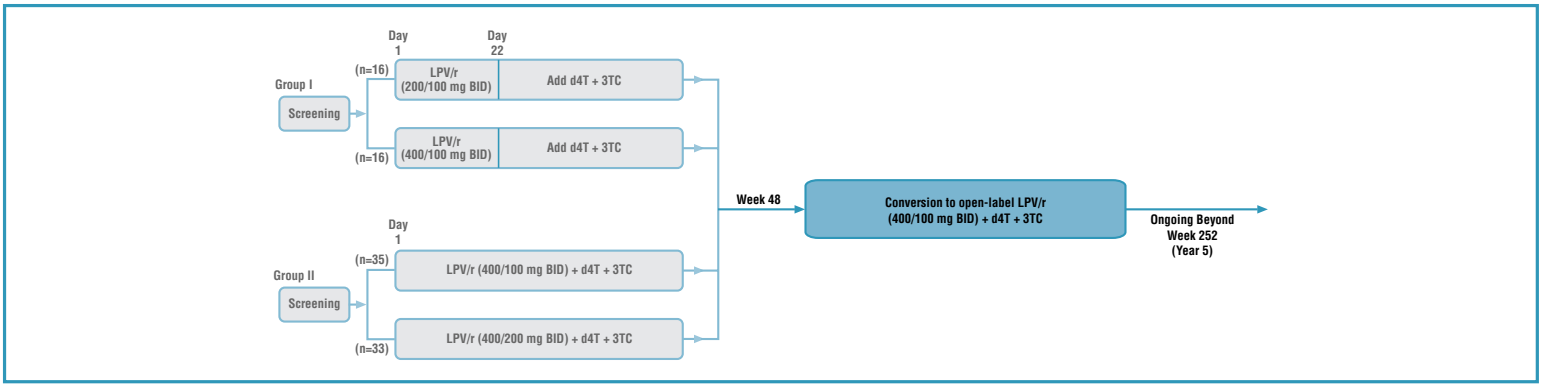
Entry Criteria

- 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.
- CD4+ cell counts were measured by flow cytometry.

Figure 1. M97-720 Study Schema



Efficacy

- 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).
- 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 even if they achieved viral resuppression without a change in study medication.
- Immunologic response was assessed by the mean change in CD4 count from baseline to each study visit.

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 252 for adverse events and grade 3/4 laboratory values was summarized, as was the prevalence at Week 252, defined as the presence of an ongoing adverse event or a grade 3/4 lab measurement obtained at the Week 252 visit.
- All laboratory measurements were obtained without regard to fasting.
- Effects of the use of lipid-lowering agents were assessed by comparing the last lipid value prior to lipid-lowering agent initiation to the minimum and final available lipid values through Week 252.

RESULTS

Antiviral Activity

- Based on the ITT NC=F analysis through Week 252, 67% of patients had HIV RNA <400 copies/mL (on-treatment analysis: 99%) (Figure 2) and 64% of patients had HIV RNA <50 copies/mL (on-treatment analysis: 94%) (Figure 3). The only HIV RNA >400 copies/mL at year 5 occurred during a lengthy treatment interruption. Three patients with HIV RNA between 50 and 400 copies/mL (65, 100 and 274) maintained HIV RNA <400 copies/mL at the following visit (Week 264, ultrasensitive testing not conducted).
- Disposition of subjects meeting loss of virologic response criteria (2 consecutive rebound HIV RNA values above 400 copies/mL) is summarized in Figure 4.

Figure 2. HIV RNA <400 copies/mL Through Week 252

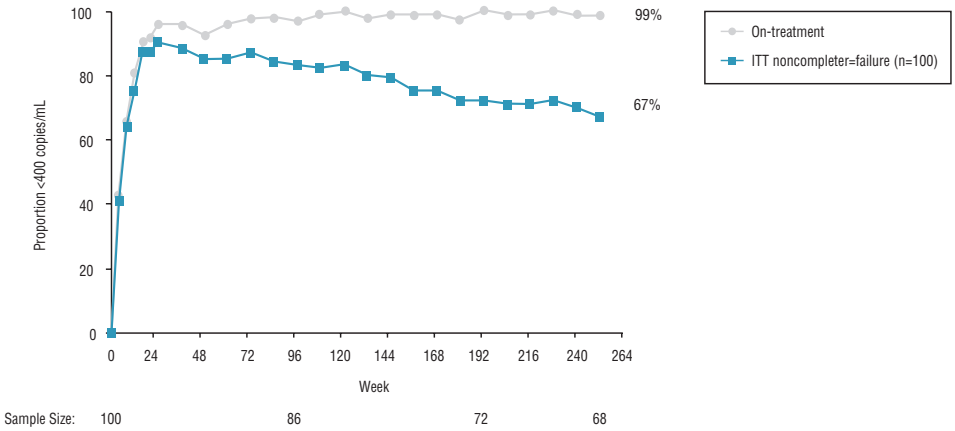


Figure 3. HIV RNA <50 copies/mL Through Week 252

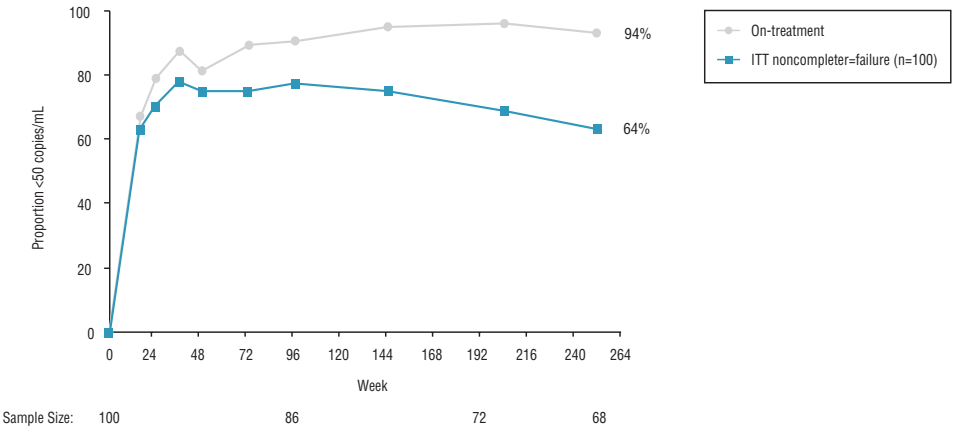
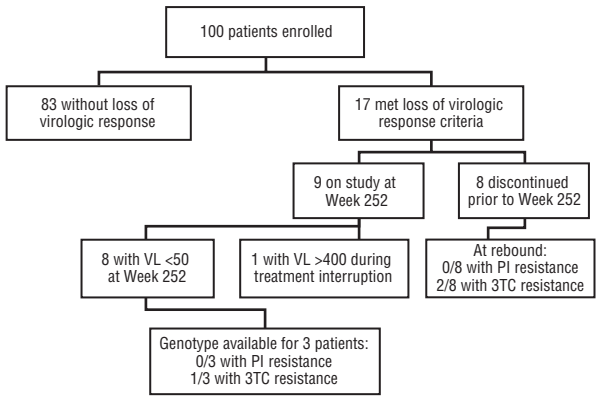


Figure 4. Virologic Disposition Through Week 252

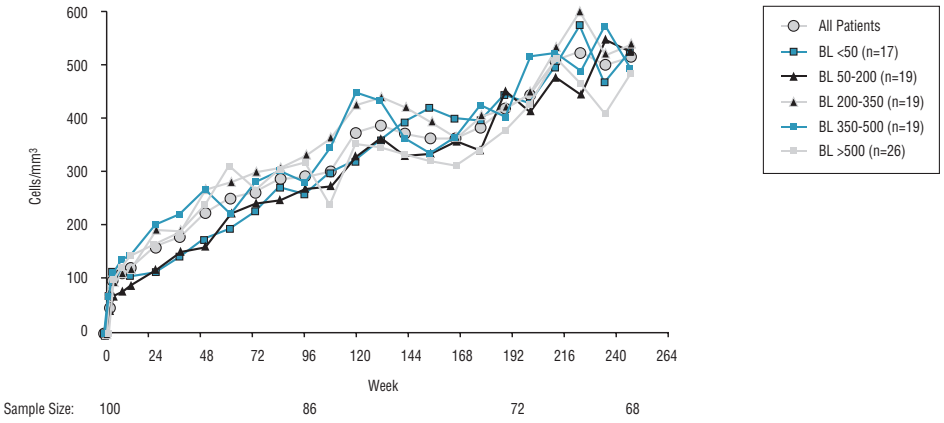


- Through Week 252, genotype was available on 11 patients with confirmed HIV RNA rebound to >400 copies/mL while receiving LPV/r, including all 8 who prematurely discontinued the study. Consistent with results obtained in previous studies of LPV/r in ARV-naïve patients,[2,3] 0 of 11 patients demonstrated protease inhibitor resistance, and 3 of 11 demonstrated 3TC resistance.

CD4 Cell Count Response

- Among subjects with values at both baseline and Week 252, the mean CD4 cell count increased from 281 cells/mm^3 at baseline to 791 cells/mm^3 at Week 252, an increase of 510 cells/mm^3 (Figure 5).
- 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 24 cells/mm^3 at baseline to 543 cells/mm^3 at Week 252, an increase of 519 cells/mm^3.
- Other studies have observed an association between higher age and lower CD4 count increases,[4,5] but no correlation was observed between age and CD4 count increase in this study through Week 252 (r=0.013, p=0.92).

Figure 5. CD4 Cell Count (mean change from baseline)



Safety

Table 1. Patient Disposition Through Week 252

Patients enrolled	100
Discontinuations prior to Week 252	32
Discontinuations probably or possibly related to study drugs	
AST/ALT increases	2
Diarrhea	1
Liver pain, enlargement, fatty deposits	1
Arthralgia	1
Elevated cholesterol	1
Fat redistribution	3
Death[1]	1
Other reasons for discontinuation	
Adverse Event unrelated to study drugs (lymphoma, hyperglycemia in diabetic patient, alcohol detoxification[2])	3
Lost to follow-up	9
Noncompliance	5
Personal/other reasons [moved (3), drug addiction, "virologic success"[3])	5
Patients on study at Week 252	68

[1] Death of unknown cause occurred in a patient 10 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 (occurring in ≥10% of patients) Through Week 252

Moderate/Severe Drug-related AEs	Incidence Through Week 252 (n=100)	Prevalence at Week 252 (n=68)
Diarrhea	28%	0%
Nausea	16%	0%
Lipodystrophy	12%	15%
Abdominal pain	10%	0%

Table 3. Most Common Grade 3/4 Laboratory Abnormalities (occurring in ≥10% of patients) Through Week 252

Grade 3/4 Lab Abnormalities	Incidence Through Week 252 (n=100)	Prevalence at Week 252 (n=68)
Cholesterol (>300 mg/dL)	23%	0%
Triglycerides (>750 mg/dL)	26%	6%
AST/ALT (>5X ULN)	11%	0%

Use of Lipid-lowering Agents

- All lipid measurements were obtained without regard to fasting.
- 23 patients initiated lipid-lowering agents (LLA) at some point during the study. All 23 demonstrated grade 2 or higher total cholesterol (>240 mg/dL) and 19/23 also demonstrated grade 2 or higher triglycerides (>400 mg/dL). All lipid measurements were obtained without regard to fasting.
- 17 of these 23 patients used a statin (11 pravastatin, 9 atorvastatin, including 4 who used both) and 9 used a fibrate (8 fenofibrate), including 3 patients who used both statins and fibrates.
- 21/23 patients (91%) subsequently demonstrated a total cholesterol value ≤240 mg/dL, including 11 (48%) who demonstrated total cholesterol ≤200 mg/dL.
- 17/19 patients (89%) with triglycerides >400 mg/dL who initiated lipid-lowering agents subsequently demonstrated triglycerides ≤400 mg/dL, including 8 (42%) who demonstrated triglycerides ≤250 mg/dL.
- In patients with grade 2 total cholesterol at the time of LLA initiation, the median decrease to the minimum value through Week 252 was 33% and the median decrease to the final value through Week 252 was 21%. Corresponding mean (median) values were 300 (291) mg/dL at the time of LLA initiation and 229 (234) mg/dL at the most recent value through Week 252.
- In patients with grade 2 triglycerides at the time of LLA initiation, the median decrease to the minimum value through Week 252 was 64% and the median decrease to the final value through Week 252 was 38%. Corresponding mean (median) values were 816 (719) mg/dL at the time of LLA initiation and 513 (463) mg/dL at the most recent value through Week 252.
- A summary of final available lipid values through Week 252 by LLA use is presented in Table 4.

Table 4. Summary of Week 252 or Final Lipid Value by Lipid-lowering Agent Use

	Patients Ever Using LLA (n=23)	Patients Never Using LLA (n=77)	All Patients (n=100)
Total Cholesterol (mg/dL)			
<200	17%	49%	42%
200-240	48%	34%	37%
>240-300	35%	14%	21%
>300-400	0%	3%	2%
>400	0%	0%	0%
Triglycerides (mg/dL)			
<250	30%	61%	54%
250-400	30%	18%	25%
>400-750	26%	13%	16%
>750-1200	13%	3%	5%
>1200	0%	0%	0%

Note: All lipid values were obtained without regard to fasting.

CONCLUSIONS

- Through 5 years of follow-up, antiretroviral-naïve patients receiving LPV/r-based therapy exhibited sustained virologic response, with 67% of patients demonstrating HIV RNA <400 copies/mL and 64% demonstrating HIV RNA <50 copies/mL by intent-to-treat (NC=F) analysis. Corresponding on-treatment response rates were 99% and 94%, respectively.
- Through 252 weeks of follow-up, no protease inhibitor resistance mutations have been observed in subjects with sustained viral load rebound.
- LPV/r was generally well tolerated, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events (10/100, 10%).
- Lipid values generally declined with lipid-lowering agent use, as approximately 90% of patients treated with lipid-lowering agents subsequently demonstrated lipid values below grade 2 levels.

ACKNOWLEDGMENTS

M97-720 Study Subjects
Covance Central Laboratory Services

AIDS Research Consortium of Atlanta	*Sanders J*
Beth Israel Deaconess Medical Center–Harvard	*Fitch H*
Cornell Clinical Trials Unit	*Stroberg T*
Duke University Medical Center	*Harmon L*
Northwestern University	*Bruce J*
Pacific Oaks Research	*Sandoval B*
Rush Presbyterian St. Luke's Medical Center	*Fritsche J*
Thomas Street Clinic	*Sepcie B*
University of Colorado	*Canmann S, Putnam B*
University of North Carolina at Chapel Hill	*Marcus C*
PPD Development	*Wheat R, McCarley S, Bullard M*
Abbott Laboratories	*Sheehan K, Yang G, Tokimoto D, King KR*

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, King M, Bauer E, et al. Analysis of the emergence of secondary mutations with or without primary PI resistance in ARV-naïve subjects with detectable viral load on Nelfinavir or Lopinavir/Ritonavir therapy. XI International HIV Drug Resistance Workshop, Seville, Spain, 2002 (Abstract 145).
3. Feinberg J, Bernstein B, King M, et al. Once Daily vs. Twice Daily Kaletra (lopinavir/ritonavir) in Antiretroviral-naïve HIV+ patients: 72-week follow-up. XIV International AIDS Conference, Barcelona, Spain, 2002 (Abstract TUPEB4445).
4. Kalayjian R, Lederman MM, Pollard R, et al. Older Age is Associated with Reduced Naïve T-cell Responses to Antiretroviral Therapy: 48 week Results of ACTG Protocol 5015. 10th Conference on Retroviruses and Opportunistic Infections, Boston, USA, 2003 (abstract 346).
5. Viard J-P, Mocroft A, Chiesi A, et al. Influence of Age on CD4 Cell Recovery in Human Immunodeficiency Virus-Infected Patients Receiving Highly Active Antiretroviral Therapy: Evidence from the EuroSIDA Study. *JID* 2001;183:1290-4.

E0304263D