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Three-Year Immunologic Responses In Antiretroviral-Naive HIV+ Patients Treated with Lopinavir/ritonavir (Kaletra) Based Therapy

A. Landay[1]*, S. Brun[11], M. King[11], K. Garren[11], R. Murphy[2], C. Hicks[3], J. Eron[4], R. Gulick[5], M. Glesby[5], R. Stryker[6], M. Thompson[7], C. White[8], C. Benson[9], M. Albrecht[10], H. Kessler[1], and E. Sun[11] for the M97-720 Study Group; [1]Rush Medical College, [2]Northwestern, [3]Duke, [4]U.N. Carolina, [5]Cornell, [6]Pacific Oaks Res., [7]AIDS Res. Consortium of Atlanta, [8]Baylor, [9]U. Colorado, [10]Harvard, 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. 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 ≥75 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-naive 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 double-blind trial of LPV/r in combination with d4T and 3TC in antiretroviral-naive 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 156 weeks.

METHODS

Entry Criteria

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

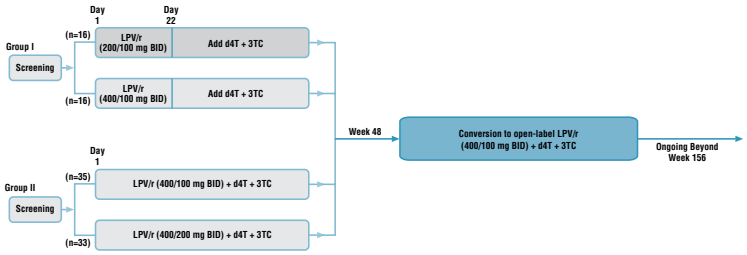
Study Design and Analysis

- 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 [LLQ] 400 copies/mL) and the Roche Amplicor HIV-1 Monitor Ultrasensitive Quantitative PCR, Version 1.0 (LLQ 50 copies/mL).
- T lymphocyte subpopulations (CD4+, CD8+), B lymphocytes (CD19+), and NK cells (CD16+CD56+) were measured by flow cytometry.

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.

Figure 1. M97-720 Study Schema



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). Baseline CD4 count was not available for one patient.

Table 1. Patient Disposition at Week 156

Patients enrolled	**100**
Patients discontinuing at or before Week 156	**23**
Discontinuations possibly or probably related to study drugs	
AST/ALT increases[1]	2
Diarrhea	1
Arthralgia	1
Death[2]	1
Other reasons for discontinuation	
Adverse event/HIV-related event unrelated to study drugs (lymphoma, hyperglycemia in diabetic patient, alcohol detoxification)	3
Personal reasons (left USA, drug addiction, moved out of state [2])	4
Noncompliance	4
Lost to follow-up	7

[1] Includes one patient with chronic hepatitis B infection at Baseline and another patient with Grade 2 elevations (2-5 times upper limit of normal), both asymptomatic.
[2] Death of unknown cause occurred in a patient ten days following thoracic spinal surgery with perioperative myocardial infarction.

Viral Load Suppression Below the LOQ

- Based on the ITT NC=F analysis, 75% of patients had HIV RNA <400 copies/mL at Week 156 (on-treatment analysis: 99%) (Figure 2).
- Based on the ITT NC=F analysis, 76% of patients had HIV RNA <50 copies/mL at Week 144 (on-treatment analysis: 96%) (Figure 3).

Figure 2. HIV RNA <400 copies/mL Through Week 156

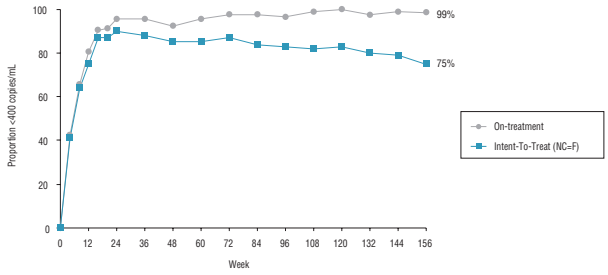
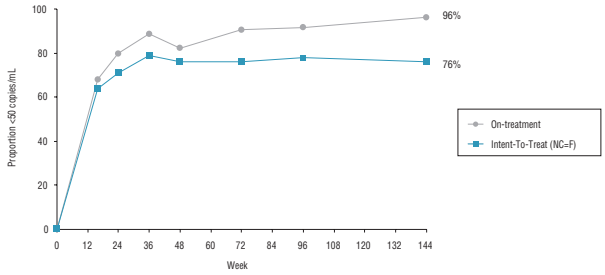


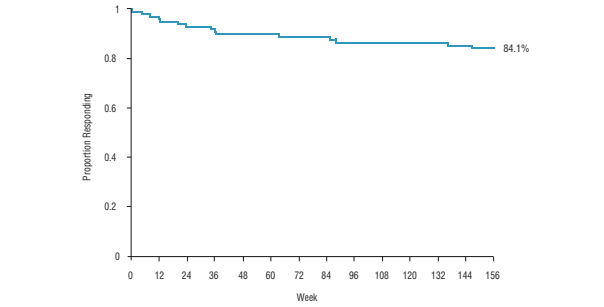
Figure 3. HIV RNA <50 copies/mL Through Week 144



Time to Loss of Virologic Response

- Through Week 156, the Kaplan-Meier estimate of the proportion of patients maintaining virologic response was 84.1% (Figure 4).
- 8/15 patients (53%) who experienced loss of virologic response through Week 156 demonstrated resuppression of HIV RNA levels to <400 copies/mL at Week 156 or latest available study visit without change in ARV regimen.
- Genotypic and phenotypic data were obtained for 6 subjects with sustained viral load rebound to >400 copies/mL while receiving LPV/r. Consistent with results observed in previous studies of LPV/r in ARV-naïve patients,[2,3] 0 of 6 subjects demonstrated resistance in protease, and 3 of 6 demonstrated resistance to lamivudine (M184V/I mutation).

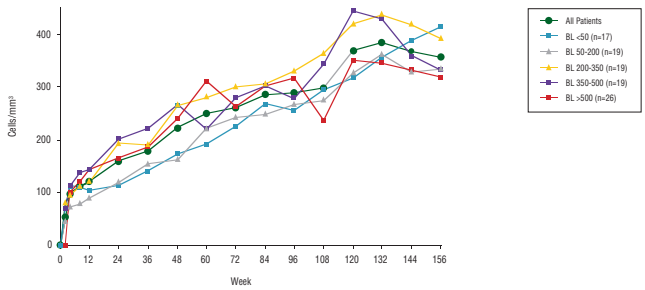
Figure 4. Kaplan-Meier Analysis of Time to Loss of Virologic Response



Immunologic Responses Through Week 156

- **CD4 Cell Count Response**
  - Among subjects with values at both baseline and Week 156, the mean CD4 cell count increased from 298 cells/mm³ to 654 cells/mm³, an increase of 356 cells/mm³ (Figure 5).
  - CD4 cell count response appeared to be consistent regardless of baseline CD4 cell count.

Figure 5. CD4 Cell Count (Mean Change from Baseline)



  - 36% of patients had baseline CD4 count <200 cells/mm³, while only 5% were still <200 cells/mm³ at Week 156 (LOCF). Similarly, 56% of patients had baseline CD4 count <350 cells/mm³ compared to only 14% at Week 156(LOCF) (Table 2).
  - 5 patients had Week 156 or LOCF CD4 value <200 cells/mm³.
    - 2 of the 5 were prematurely discontinued during the first year due to noncompliance. Both patients started and ended with CD4 counts between 100 and 150 cells/mm³.
    - The other 3 patients remained on study for at least 144-156 weeks. Baseline values ranged from 2-11 cells/mm³; final values ranged from 159-192 cells/mm³.
  - Among 79 patients with CD4 values at Weeks 144-156, only 8 had an increase from baseline of <100 cells/mm³, including 2 with a decrease from baseline. These 8 patients had a median baseline CD4 count of 626 cells/mm³ (range 415-1086 cells/mm³), and all 8 remained above 500 cells/mm³ at the final value.

Table 2. CD4 Count (cells/mm³) by Baseline Strata

Baseline CD4 Count (cells/mm³)	N	Week 156 or LOCF CD4 Count (% patients) 0-99	100-199	200-349	350-499	500+	Median
0-49	17	0 (0%)	3 (18%)	4 (24%)	7 (42%)	3 (18%)	391
50-199	19	0 (0%)	2 (11%)	4 (21%)	7 (37%)	6 (32%)	389
200-349	19	0 (0%)	0 (0%)	0 (0%)	4 (21%)	15 (79%)	564
350-499	18	0 (0%)	0 (0%)	1 (6%)	2 (11%)	15 (83%)	643
500+	26	0 (0%)	0 (0%)	0 (0%)	0 (0%)	26 (100%)	905
Overall	99	0 (0%)	5 (5%)	9 (9%)	20 (20%)	65 (66%)	596

- **CD4 Cell Count Change by Time Period Within Baseline CD4 Stratum**
  - Increases in CD4 cell count tended to be relatively consistent over time in subjects initiating therapy with CD4 counts <350 cells/mm³. CD4 cell count increases were of greatest magnitude during the first 48 weeks of therapy for subjects with baseline CD4 count >350 cells/mm³ (Figure 6).
- **Effects of Baseline Immunologic Parameters and Viral Load on CD4 Cell Count Change from Baseline**
  - Among patients with values at Weeks 144-156, univariate analysis of CD4 cell count change from baseline showed no statistically significant association with baseline CD3, CD4, CD8, CD19, CD16+CD56+.
  - A marginally significant effect (p=0.08) of baseline HIV RNA on CD4 count change from baseline was observed, with larger changes in CD4 in patients with higher baseline HIV RNA (Figure 7).

Figure 6. CD4 Count Change by Time Period Within Baseline CD4 Stratum

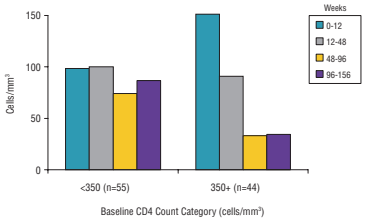
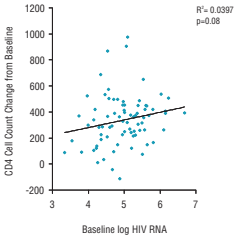
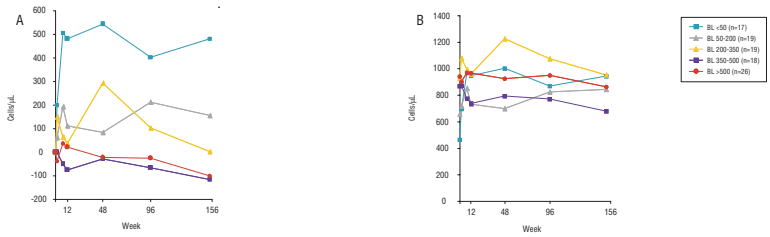


Figure 7. Association of Baseline HIV RNA with CD4 Count Change from Baseline



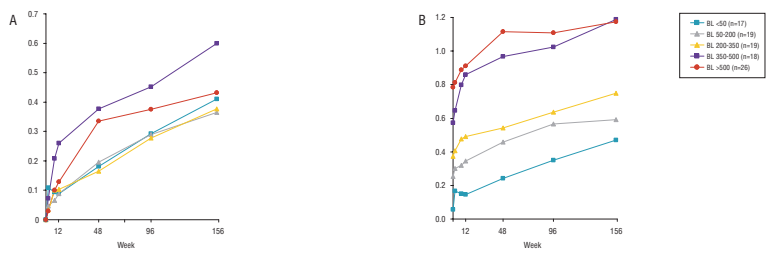
- **CD8 Cell Count Response**
  - CD8 cell count increases were of greatest magnitude during the first 48 weeks of therapy for subjects with baseline CD4 count <350 cells/mm³ (Figure 8).

Figure 8. CD8 Count Mean Change from Baseline (A) and Mean Values over Time (B)



- Across all baseline CD4 count strata, mean CD4/CD8 ratio increased significantly from baseline (0.4 to 0.85) (Figure 9).

Figure 9. CD4/CD8 Ratio Mean Change from Baseline (A) and Mean Values over Time (B)



- **Responses for Other Lymphocyte Subsets**
  - Mean B lymphocyte (CD19+) counts tended to increase across all baseline CD4 strata (Figure 10).
  - Mean NK cell (CD16+CD56+) counts tended to have larger increases from baseline in subjects with lower baseline CD4 values (Figure 11).

Figure 10. B Lymphocyte (CD19+) Count Mean Change from Baseline (A) and Mean Values over Time (B)

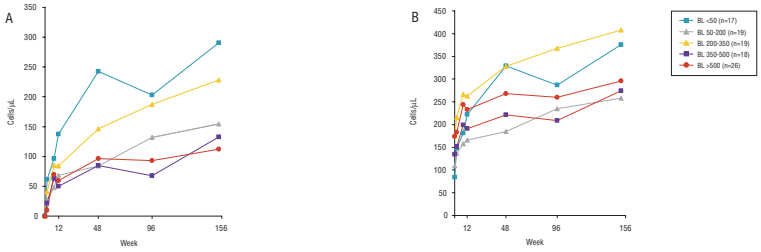
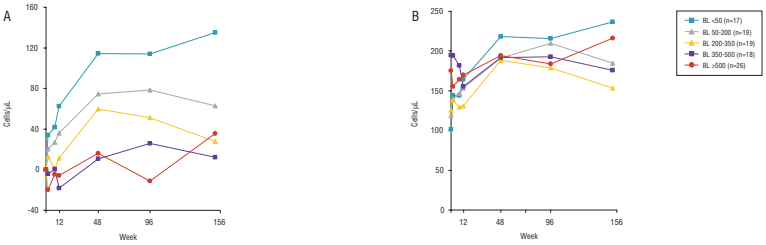


Figure 11. NK Cell (CD16+CD56+) Count Mean Change from Baseline (A) and Mean Values over Time (B)



CONCLUSIONS

- LPV/r-based therapy exhibits sustained virologic response over long-term follow-up in antiretroviral-naive patients, with 75% (on treatment: 99%) and 76% (on treatment: 96%) of patients demonstrating HIV RNA <400 copies/mL through 156 weeks or <50 copies/mL through 144 weeks, respectively, by ITT NC=F analysis.
- No protease resistance mutations have been observed in subjects with sustained viral load rebound through 156 weeks.
- A significant and sustained impact on CD4 T cell increases through 156 weeks was observed in all baseline CD4 cell count strata (0-49, 50-199, 200-349, 350-499, >500 cells/mm^3). These data demonstrate that clinically relevant CD4 increases can occur even in the most advanced patients (baseline CD4 <50), but further functional studies are necessary to determine long-term (>5-10 years) outcomes.
- While kinetic changes of CD4 cell count are consistent across baseline CD4 strata, CD8 T cell responses vary by initial CD4 strata. The subjects with lowest baseline CD4 counts show a rapid early CD8 rise. This finding most likely relects high viral load in more advanced HIV disease (low CD4 count) leading to upregulation of cell adhesion molecules and cell trapping in lymphoid tissue.[4] With initiation of therapy, viral load is reduced, likely leading to reduced expression of cell adhesion molecules and release of CD8 cells into the periphery.
- Both B lymphocyte (CD19+) and NK cell (CD16+CD56+) populations were increased at all CD4 strata following therapy. These quantitative increases may be an important component of functional reconstitution of humoral and innate immune responses.
- LPV/r was well tolerated, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events (5/100, 5%).

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ACKNOWLEDGMENTS

M97-720 Study Subjects

Covance Central Laboratory Services

AIDS Research Consortium of Atlanta — *Sullivan M*

Beth Israel Deaconess Medical Center — *Fitch H*

Cornell Clinical Trials Unit — *Stroberg T*

Duke University Medical Center — *Giner J, Harmon L*

Northwestern University — *Bruce J*

Pacific Oaks Research — *Perry B, Walker S*

Rush Presbyterian St. Luke's Medical Center — *Narkiewicz E*

Thomas Street Clinic — *Sepcie B*

University of Colorado — *Canmann S, Putnam B, Ray MG*

University of North Carolina at Chapel Hill — *Ngo L*

PPD Development — *McCarley S, Nicks B, Wheat R*

Abbott Laboratories — *Kempf D, Potthoff A, Real K, Rode R, Sheehan K, Yang G*