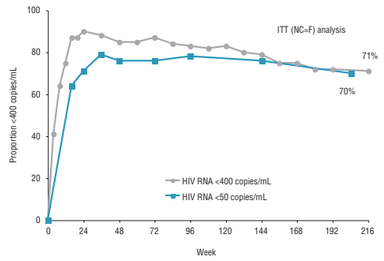
## RESULTS *continued*

### Viral Load Suppression Below the LOQ

- 71% of patients (71/100, ITT NC=F) had HIV RNA <400 copies/mL at Week 216 (on treatment: 99%, 71/72, Figure 6). One patient had HIV RNA = 708 copies/mL at Week 216 following a treatment interruption, with follow-up HIV RNA values <400 copies/mL at Weeks 228, 240, 252, and 264.
- 70% of patients (70/100, ITT NC=F) had HIV RNA <50 copies/mL at Week 204 (on treatment: 97%, 70/72) (Figure 6).

**Figure 6. HIV RNA <400 or <50 copies/mL**




- Genotypic and phenotypic data were obtained for 8 subjects with sustained HIV RNA >400 copies/mL while receiving LPV/r. Consistent with results observed in previous studies of LPV/r,[2,3] no subjects demonstrated resistance in protease, and 2 of 8 demonstrated resistance to lamivudine (defined as M184V/I mutation).

### Safety

**Table 4. Most Common AEs[1] and Laboratory Abnormalities[2] Through Week 216**

| | Incidence Through Week 216 (n=100) | Prevalence at Week 216 (n=72) |
|---|---|---|
| Diarrhea[3] | 27% | 2% |
| Nausea | 16% | 0% |
| Abdominal pain | 10% | 0% |
| Abnormal stools[4] | 8% | 1% |
| Asthenia | 8% | 1% |
| Headache | 8% | 1% |
| Vomiting | 6% | 0% |
| Cholesterol (>300 mg/dL) | 22% | 1% |
| Triglycerides (>750 mg/dL) | 22% | 4% |
| AST/ALT (>5X ULN)[5] | 11% | 0% |

[1] Moderate and Severe AEs of probably, possible, or unknown relationship to LPV/r.
[2] All laboratory values were obtained without regard to fasting.
[3] >3 loose stools/day
[4] <3 loose stools/day
[5] 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.

## CONCLUSIONS

- Through 4 years of follow-up, antiretroviral-naïve patients receiving LPV/r-based therapy demonstrated sustained and significant CD4 cell count increases. Mean CD4 cell count was 793 cells/mm$^3$ at Week 216, a mean increase from baseline of 500 cells/mm$^3$.
- 82% of patients on study at Week 216 had CD4 above 500 cells/mm$^3$. Increased CD4 activation was observed in patients with the lowest Week 216 CD4 counts.
- Patients also 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.
- Through 216 weeks of follow-up, no protease inhibitor resistance mutations have been observed.
- LPV/r was well tolerated, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events (7/100, 7%).

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## ACKNOWLEDGMENTS


| | |
|---|---|
| M97-720 Study Subjects | |
| Covance Central Laboratory Services | |
| AIDS Research Consortium of Atlanta | *J Sanders* |
| Beth Israel Deaconess Medical Center – Harvard | *H Fitch* |
| Cornell Clinical Trials Unit | *T Stroberg* |
| Duke University Medical Center | *L Harmon* |
| Northwestern University | *J Bruce* |
| Pacific Oaks Research | *B Sandoval* |
| Rush Presbyterian St. Luke's Medical Center | *J Fritsche* |
| Thomas Street Clinic | *B Sepcie* |
| University of Colorado | *S Canmann, B Putnam* |
| University of North Carolina at Chapel Hill | *C Marcus* |
| PPD Development | *R Wheat, S McCarley, M Bullard* |
| Abbott Laboratories | *K Sheehan, G Yang, D Tokimoto* |

E0303727J



Abstract #568

Second IAS Conference on HIV Pathogenesis and Treatment, Paris, France, 13-16 July 2003


# CD4 Cell Increases Through More Than 4 Years in Antiretroviral-Naïve HIV+ Patients Treated with Lopinavir/ritonavir-Based Therapy


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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 ≥75 when dosed at 400/100 mg twice a day, potentially providing a barrier to emergence of viral resistance and activity against HIV with reduced susceptibility to other PIs.

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 open label extension of a phase II double-blind 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 CD4 cell count changes, antiviral efficacy, and safety through 216 weeks.

## METHODS

### Entry Criteria

- Antiretroviral-naïve patients.
- Plasma HIV RNA ≥5,000 copies/mL with no CD4 cell count restriction.
- Patients who had a positive hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV) antibodies test at screening were excluded from enrollment in Group I, and up to 20% of the patients in Group II were allowed to enroll with a positive HBsAg or anti-HCV antibodies test at screening.

### 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 LPV/r (Group I, n=32) or from study entry (Group II, n=68) (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).
- CD4+ cell counts 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).

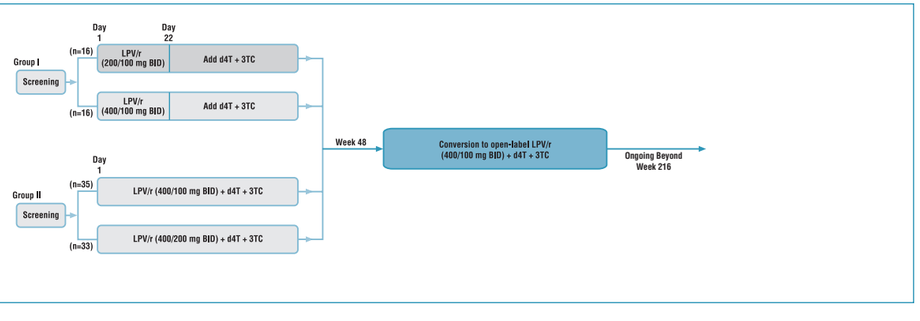
### Virologic Evaluation

- 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 216 for adverse events and grade 3/4 laboratory values was summarized, as was prevalence at Week 216, defined as the presence of an ongoing adverse event or a grade 3/4 lab measurement obtained at the Week 216 visit.
- All laboratory measurements were obtained without regard to fasting.

**Figure 1. M97-720 Study Schema**



## RESULTS

### Baseline Characteristics

- Ninety-six male and 4 female patients: 65% Caucasian, 29% Black, 6% Hispanic.
- Median age: 34 (range 21-59).
- Median Plasma HIV RNA: 4.8 $\log_{10}$ copies/mL (range 3.3-6.3).
- The median CD4 count was 326 cells/mm$^3$ (range 3-918) for all patients and 254 cells/mm$^3$ (range 3-918) for the 72 patients who remained on study for at least 4 years (216 weeks). Baseline CD4 cell count was not available for one patient.

### Table 1. Patient Disposition at Week 216

| | |
|---|---|
| **Patients enrolled** | **100** |
| **Patients discontinuing at or before Week 216** | **28** |
| Discontinuations possibly/probably related to study drugs | |
| AST/ALT increases | 2 |
| Diarrhea | 1 |
| Liver pain with enlargement and fatty deposits | 1 |
| Arthralgia | 1 |
| Elevated cholesterol | 1 |
| Death[1] | 1 |
| Other reasons for discontinuation | |
| Adverse event/HIV-related event (lymphoma, hyperglycemia in diabetic patient, alcohol detoxification)[2] | 3 |
| Personal or other reasons (left USA, drug addiction, moved out of state [2], "virologic success"[3]) | 5 |
| Noncompliance[2] | 4 |
| Lost to follow-up | 9 |

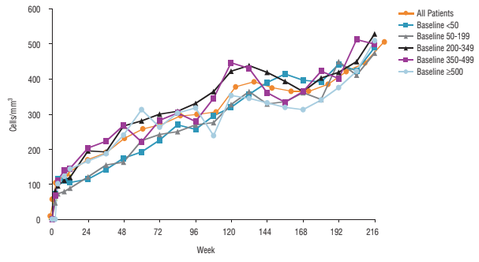
[1] Death of unknown cause occurred in a patient 10 days following thoracic spinal surgery with perioperative myocardial infarction.
[2] One patient discontinued due to both alcohol detoxification and noncompliance.
[3] One patient discontinued due to primary physician recommendation to suspend treatment since patient was "doing so well on present regimen."

### Immunologic Responses Through Week 216

CD4 Cell Count Response

- Among patients with values at both baseline and Week 216, mean (median) CD4 cell count was 793 (738) cells/mm$^3$ at Week 216, a mean (median) increase of 500 (455) cells/mm$^3$ (Figure 2).
- Increases were consistent regardless of baseline CD4 count (Table 2).
- All 72 subjects on study at Week 216 had CD4 cell count increases of at least 99 cells/mm$^3$ (IQR: 322-630, range 99-1657).

### Figure 2. CD4 Cell Count Mean Change from Baseline by Baseline CD4 Count




### Table 2. CD4 Cell Count Increase at Week 216 by Baseline CD4 Cell Count

| Baseline CD4 Cell Count (cells/mm$^3$) | Mean CD4 Cell Count Increase from Baseline to Week 216 (cells/mm$^3$) |
|---|---|
| <50 (n=16) | 489 |
| 50-199 (n=13) | 473 |
| 200-349 (n=15) | 528 |
| 350-499 (n=12) | 498 |
| ≥500 (n=16) | 508 |

- 82% of patients on study at Week 216 had CD4 cell counts >500 cells/mm$^3$. Of the 13 patients with CD4 cell counts <500 cells/mm$^3$ at Week 216, 9 had CD4 cell counts <50 cells/mm$^3$ at baseline (Table 3).
- Of the 28 patients who discontinued at or before Week 216, 71% had CD4 cell counts >500 cells/mm$^3$.

### Table 3. CD4 Count by Baseline CD4 Category

| | Week 216 CD4 Count (cells/mm$^3$) | | | | |
|---|---|---|---|---|---|
| **Baseline CD4 Count (cells/mm$^3$)** | **0-99** | **100-199** | **200-349** | **350-500** | **≥500** |
| <50 (n=16) | – | 2* | 2 | 5 | 7 |
| 50-199 (n=13) | – | – | 1 | 3 | 9 |
| 200-349 (n=15) | – | – | – | – | 15 |
| 350-499 (n=12) | – | – | – | – | 12 |
| ≥500 (n=16) | – | – | – | – | 16 |
| **Total (n=72)** | **0** | **2** | **3** | **8** | **59** |

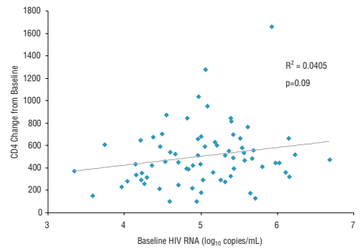
* The two subjects with CD4 cell count <200 at Week 216 had baseline CD4 cell counts of 3 and 11 cells/mm$^3$. At Week 216, their CD4 cell counts were 101 and 187 cells/mm$^3$, respectively.

## RESULTS *continued*

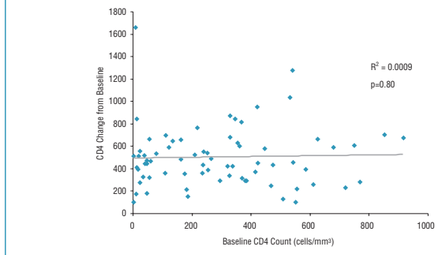
### Effect of Baseline CD4 and Viral Load on CD4 Cell Count Change from Baseline

- The magnitude of CD4 cell count increase was not significantly correlated with baseline CD4 cell count or baseline viral load (Figures 3a and 3b).

### Figure 3a. Effect of Baseline Viral Load on CD4 Count Change from Baseline



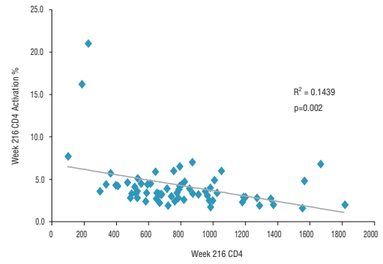

### Figure 3b. Effect of Baseline CD4 Count on CD4 Change from Baseline




### Relationship Between T Cell Activation and Week 216 CD4 Cell Count

- Consistent with a recent report by Hunt. et al.,[4] patients with the lowest CD4 cell counts at Week 216 (101, 187, and 226 cells/mm$^3$) had the highest T cell activation values (CD38+ HLA- DR+) at the same timepoint (Figure 4).
- However, without these 3 patients, no significant correlation was observed between CD4 activation and Week 216 CD4 cell count ($R^2$=0.037, p=0.13).

### Figure 4. Correlation of Activation and CD4 Cell Count at Week 216




### CD4 Cell Count Change by Time Period

- For patients on Study at Week 216, increases in CD4 cell count were largest during the first 48 weeks of study. An increase of 141 cells/mm$^3$ was observed during the fourth year of study (between Weeks 156-216) following annual increases of 56 and 72 cells/mm$^3$ during the second and third years of study (Weeks 48-156) (Figure 5).

### Figure 5. CD4 Count Change by Time Period