Figure 6. Duration of Virologic Response by Baseline HIV RNA Level

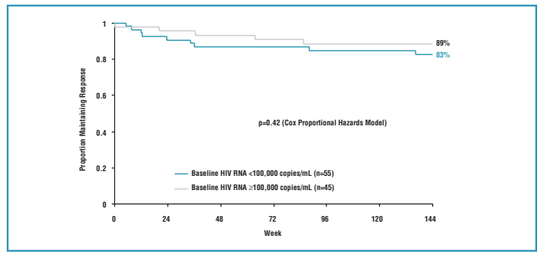

Figure 7. Duration of Virologic Response by Baseline CD4 Cell Count

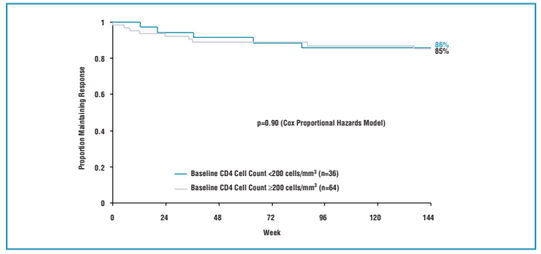

Table 5. Proportion of Patients with HIV RNA <50 copies/mL at Week 144 by Baseline VL and CD4 Cell Count

	BL HIV RNA <100,000 copies/mL (N=55)	BL HIV RNA ≥100,000 copies/mL (N=45)	p-value
On Treatment	40/40 (100%)	36/39 (92%)	0.12
Intent-to-Treat (NC=F)	40/55 (73%)	36/45 (80%)	0.48
	BL CD4 Cell Count <200 cells/mm³ (N=36)	**BL CD4 Cell Count ≥200 cells/mm³ (N=64)**	**p-value**
On Treatment	30/32 (94%)	46/47 (98%)	0.56
Intent-to-Treat (NC=F)	30/36 (83%)	46/64 (72%)	0.23

DISCUSSION/CONCLUSIONS

- LPV/r-based therapy exhibits sustained virologic response through 144 weeks in antiretroviral-naive patients, with 79% (on treatment: 99%) and 76% (on treatment: 96%) of patients demonstrating HIV RNA <400 copies/mL or <50 copies/mL, respectively, by ITT NC=F analysis.
- LPV/r was well tolerated, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events (5/100, 5%).
- Achieving and/or sustaining HIV RNA ≤3 copies/mL through the first 72 weeks of LPV/r therapy does not appear to predict risk of virologic failure at either <50 or <400 copies/mL through an additional 72 weeks of follow-up.
- Intermittent viremia >3 copies/mL may be due to assay variability, variation in adherence patterns, or other physiologic factors such as the presence of subacute intercurrent illness. The inability to suppress viral load to ≤3 copies/mL may be due to the aforementioned factors as well as the potential impact of the size of the reservoir of latently infected cells or the status of the immune system.
- These observations may differ depending on the potency, tolerability and genetic barrier of the antiretroviral regimen being evaluated.
- Among patients with high BL VL (>100,000 copies/mL) or low BL CD4 count (<200 cells/mm³), the time to loss of virologic response through Week 144 was similar to that for patients with less advanced disease.
- A longer duration of follow-up is necessary to determine whether any of these virologic or immunologic factors will eventually have an impact on the duration of virologic response.

ACKNOWLEDGMENTS

M97-720 Study Subjects	
Covance Central Laboratory Services	
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Northwestern University	*Murphy R, Bruce J*
Pacific Oaks Research	*Stryker R, Perry B, Walker S*
Rush Presbyterian St. Luke's Medical Center	*Kessler H, Narkiewicz E*
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University of North Carolina at Chapel Hill	*Eron J, Marcus C, Ngo L*
PPD Development	*McCarley S, Nicks B, Wheat R*
Abbott Laboratories	*Kempf D, Potthoff A, Rode R, Sheehan K, Yang G*

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*Amplicor HIV-1 Monitor is a trademark of Roche Molecular Diagnostics

Poster #1927

41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, December 2001

Failure to Achieve HIV RNA ≤3 copies/mL Does Not Predict Loss of Virologic Response to Kaletra (lopinavir/ritonavir) Therapy Through 3 Years

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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 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}/EC_{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 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.

Investigators have observed that in patients who have achieved virologic suppression on antiretroviral therapy, transient viremia ("blips") above 50 copies/mL is not uncommon but does not systematically increase the risk of virologic rebound during 72-84 weeks of follow-up.[2,3,4] The objective of this presentation is to evaluate if the inability to achieve or consistently maintain HIV RNA ≤3 copies/mL during the first 72 weeks of LPV/r based therapy was predictive of subsequent loss of virologic response through 144 weeks of follow-up.

METHODS

Entry Criteria

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

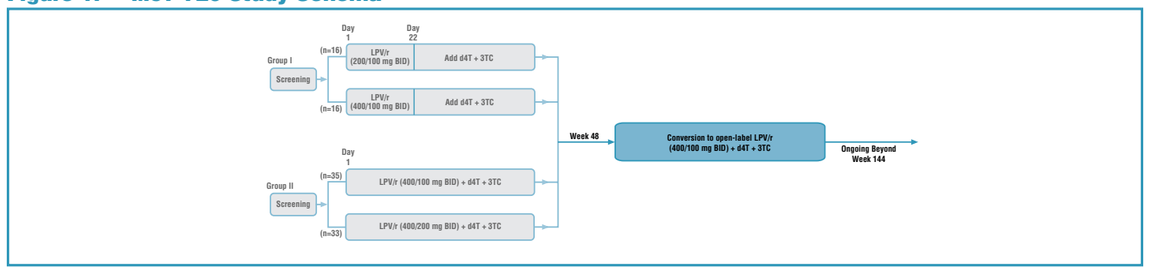
Study Design and Analysis

- 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 LPV/r 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). Samples from patients with HIV RNA <50 copies/mL at Weeks 24, 48 or 72 were analyzed using an experimental modification of the standard Roche Amplicor HIV RNA previously described by Perrin et al. This modified assay allows for a limit of quantitation of ≤3 copies/mL.[5]

Antiviral Activity

- Proportion with HIV RNA below the LLQ (on treatment) at each visit: Patients who discontinued prior to the visit, patients with missing values, and values obtained during a treatment interruption of at least 3 days were excluded from the analysis.
- Proportion with HIV RNA below the LLQ (intent-to-treat [noncompleter=failure]) (ITT NC=F) at each visit: Patients who discontinued prior to the visit were considered non-responders (HIV RNA > LLQ). Patients with missing values at a visit were considered non-responders unless HIV RNA was below the LLQ at the immediately preceding and immediately following visits.
- Duration of virologic response was defined as the time from study initiation to the time of loss of virologic response (two consecutive HIV RNA measurements above 400 copies/mL following any measurement below 400 copies/mL). If the final measurement for a patient was above 400 copies/mL (and the patient had not previously demonstrated a loss of response), the time of loss of response was defined to be the time of the last measurement. Subjects who had never experienced a loss of response were considered censored at the time of their final measurement, including subjects who prematurely discontinued prior to demonstrating a loss of response. Subjects who never achieved an HIV RNA level below 400 copies/mL were considered to have had a loss of response at Day 1.

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).

Overview of Antiviral Efficacy and Safety/Tolerability at Week 144

- Based on the ITT NC=F analysis, 79% of patients had HIV RNA <400 copies/mL at Week 144 (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 144

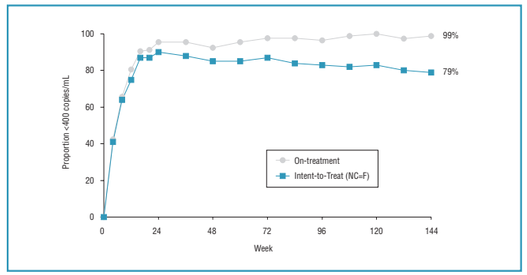


Figure 3. HIV RNA <50 copies/mL Through Week 144

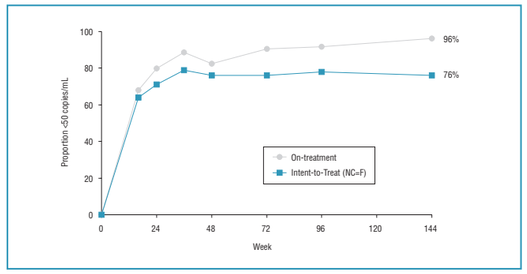


Table 1. Week 144 Safety Summary

Most Common Adverse Events* and Grade 3/4 Laboratory Abnormalities	All Patients (n=100)
Diarrhea+	25%
Nausea	15%
Abdominal Pain	8%
Abnormal Stools++	8%
Asthenia	8%
Headache	8%
Vomiting	5%
Cholesterol (>300 mg/dL)	17%
Triglycerides (>750 mg/dL)	16%
AST/ALT (>5X ULN)	10%

* 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.

Table 2. Patient Disposition at Week 144

Patients enrolled	**100**
Patients discontinuing at or before Week 144	**20**
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)	3
Noncompliance	4
Lost to follow-up	5

[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.

Proportion of Patients with HIV RNA ≤3 copies/mL Through 72 Weeks

- Four patients discontinued prior to Week 24 and were not tested with the ≤3 copies/mL assay
- 56% (54/96) of patients on treatment demonstrated a viral load ≤3 copies/mL for at least one visit (Table 3).
- 72% (38/53) of patients with Baseline (BL) HIV RNA <100,000 copies/mL achieved a viral load ≤3 copies/mL for at least one visit compared to only 37% (16/43) of those with BL HIV RNA >100,000 copies/mL (Table 3).
- 67% (41/61) of patients with BL CD4 cell count ≥200 cells/mm^3 achieved a viral load ≤3 copies/mL for at least one visit compared to only 37% (13/35) of those with BL CD4 cell counts <200 cells/mm^3 (Table 3).

Table 3. Proportion of Patients with HIV RNA ≤3 copies/mL Through 72 Weeks

	At Least One HIV RNA Level ≤3 copies/mL at Weeks 24, 48, 72	Multiple HIV RNA Levels ≤3 copies/mL at Weeks 24, 48, 72
Overall	54/96 (56%)	32/96 (33%)
BL HIV RNA Level <100,000	38/53 (72%)	28/53 (53%)
BL HIV RNA Level >100,000	16/43 (37%)	4/43 (9%)
BL CD4 Cell Count ≥200	41/61 (67%)	24/61 (39%)
BL CD4 Cell Count <200	13/35 (37%)	8/35 (23%)

Duration of Virologic Response (<400 copies/mL) Through 144 Weeks Based on ≤3 copies/mL Results During the First 72 Weeks of Therapy

- No greater risk of loss of virologic response through Week 144 was observed in patients who did not achieve HIV RNA ≤3 copies/mL during the first 72 weeks of therapy compared to those who did experience viral load suppression to this level (Figure 4).
- The risk of loss of virologic response through Week 144 was similar in patients who maintained HIV RNA ≤3 copies/mL on more than one occasion compared to patients who achieved this level of viral suppression at 0-1 evaluations during the first 72 weeks of therapy (Figure 5).

Figure 4. Duration of Virologic Response Comparing Patients Who Did or Did Not Achieve HIV RNA ≤3 copies/mL

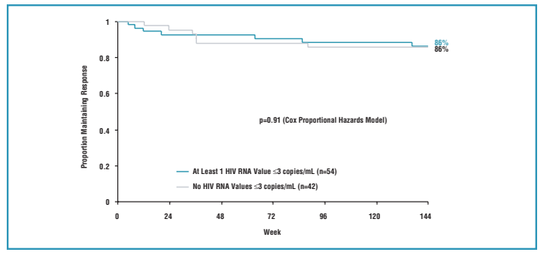
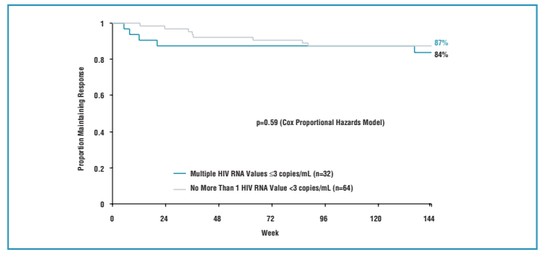


Figure 5. Duration of Virologic Response Comparing Patients Who Did or Did Not Achieve Multiple HIV RNA Values ≤3 copies/mL



Virologic Suppression to <50 copies/mL at Week 144 Based on HIV RNA ≤3 copies/mL Results During the First 72 Weeks of Therapy

- Failure to achieve HIV RNA ≤3 copies/mL during the first 72 weeks did not predict a significantly lower response rate (<50 copies/mL) at Week 144, nor did failure to achieve multiple HIV RNA values ≤3 copies/mL (Table 4).

Table 4. Proportion of Patients with HIV RNA <50 copies/mL at Week 144 by Achievement of HIV RNA ≤3 copies/mL

	At Least One HIV RNA Level ≤3 copies/mL at Weeks 24, 48, 72 (N=54)	No HIV RNA Level ≤3 copies/mL at Weeks 24, 48, 72 (N=42)	p-value
On Treatment	45/46 (98%)	31/33 (94%)	0.57
Intent-to-Treat (NC=F)	45/54 (83%)	31/42 (74%)	0.31
	Multiple HIV RNA Levels ≤3 copies/mL at Weeks 24, 48, 72 (N=32)	**0 or 1 HIV RNA Level ≤3 copies/mL at Weeks 24, 48, 72 (N=64)**	**p-value**
On Treatment	27/27 (100%)	49/52 (94%)	0.55
Intent-to-Treat (NC=F)	27/32 (84%)	49/64 (77%)	0.44

Virologic Response at Week 144 Stratified by Baseline HIV RNA and CD4 Cell Count

- Since patients with baseline HIV RNA <100,000 copies/mL or CD4 count >200 cells/mm^3 tended to be more likely to achieve and maintain HIV RNA ≤3 copies/mL, an evaluation of virologic response through Week 144 stratified by baseline HIV RNA and CD4 count was performed.
- Among patients with high HIV RNA (>100,000 copies/mL) or low CD4 count (<200 cells/mm^3) at baseline, duration of virologic response (<400 copies/mL) and the proportion of patients with HIV RNA <50 copies/mL at Week 144 were comparable to patients with lower baseline HIV RNA or higher CD4 cell count, respectively (Figures 6 and 7; Table 5).