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Failure to Achieve HIV RNA ≤3 copies/mL by Week 72 Is Not Associated with Loss of Virologic Response Through 4 Years of 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 LPV/100 mg ritonavir twice daily (3 co-formulated capsules 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 ≥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-naive and experienced HIV-infected patients. However, few long-term data are available on continued safety and efficacy. Study 720 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 medians of 12 to 19 months of follow-up.[2-5]

The objective of this presentation is to evaluate whether 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 4 years (204 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 [LOQ] 400 copies/mL) and the Roche Amplicor HIV-1 Monitor Ultrasensitive Quantitative PCR, Version 1.0 (LOQ 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 assay previously described by Yerly et al. This modified assay allows for a limit of quantitation of ≤3 copies/mL.[5]

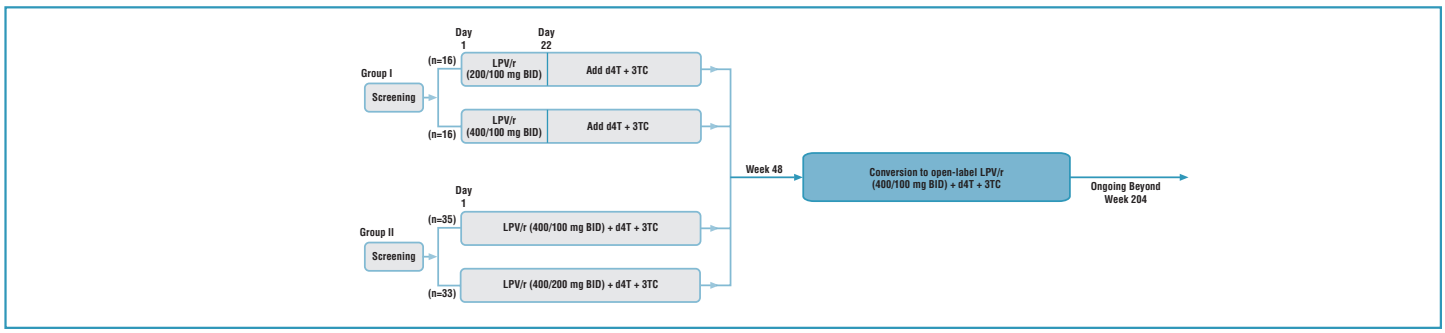
Antiviral Activity

- 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.
- Proportion of patients with HIV RNA below the limit of quantitation (LOQ) was measured using 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).
- Patients were compared by number of HIV RNA values ≤3 copies/mL from 24-72 weeks: 0 vs. 1-3 values ≤3 copies/mL and 0-1 vs. 2-3 values ≤3 copies/mL. Four patients who discontinued prior to Week 24 were excluded from the analyses.
- Patients were also compared by baseline HIV RNA level (above or below 100,000 copies/mL) and baseline CD4 cell count (above or below 200 cells/mm^3).

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.

Figure 1. Study 720 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 204

- Based on the ITT NC=F analysis through Week 204, 71% and 70% of patients had HIV RNA <400 copies/mL (on-treatment analysis 99%) or <50 copies/mL (on-treatment analysis 97%) at Week 204 (Figure 2).
- Mean increase from baseline to Week 204 in CD4 cell count was +440 cells/mm^3 (Figure 3).
- 15 patients met loss of virologic response criteria.
  - 7/15 remained on study through 204 weeks, and 7/7 had HIV RNA <50 at Week 204.
  - 8/15 patients discontinued. 1 patient discontinued at Week 4 without achieving HIV RNA <400 copies/mL, 1 patient discontinued with HIV RNA resuppressed <400 copies/mL at final visit, and 6 patients discontinued after rebound (2 lost to follow-up, 4 due to noncompliance).
- Genotype was available on 10 patients, including all 8 who discontinued after loss of virologic response. Isolates from 0/10 patients demonstrated resistance in protease, and 3/10 demonstrated 3TC resistance.
- 28 patients discontinued prior to Week 204, including 7 due to adverse events probably or possibly related to LPV/r (Table 1). Diarrhea and nausea were the most common adverse events, and lipid elevations were the most common laboratory abnormalities (Table 2).

Figure 2. Study 720: Undetectable HIV RNA Through Year 4 Intent-to-treat (noncompleter=failure)

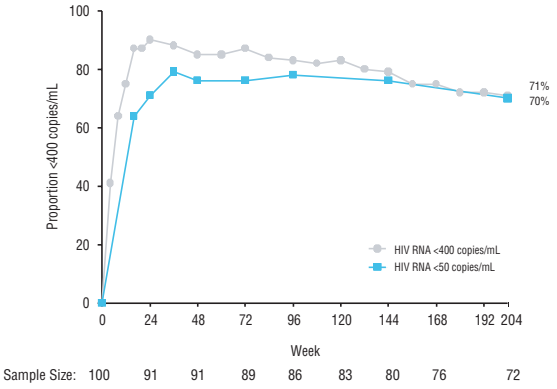


Figure 3. Study 720: CD4 Cell Count Mean Change from Baseline by Baseline CD4 Count

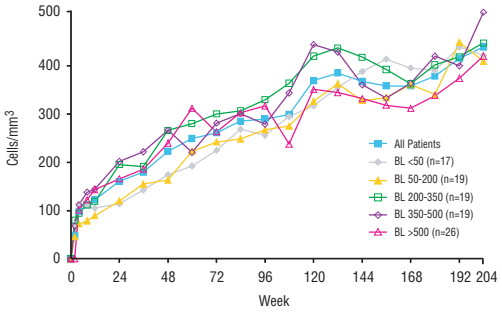


Table 1. Study 720: Patient Disposition Through Week 204

Patients enrolled	100
Patients discontinuing at or before Week 204	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
Other (moved [2 pts], drug addiction, withdrew consent, "virologic success")[3]	5
Noncompliance[2]	5
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."

Table 2. Study 720: Most Common AEs1 and Grade 3/4 Laboratory Abnormalities Through Week 204

	Incidence Through Week 204 (n=100)	Prevalence at Week 204 (n=72)[2]
Diarrhea[3]	28%	3%
Nausea	16%	0%
Abdominal pain	10%	0%
Cholesterol (>300 mg/dL)	22%	1%
Triglycerides (>750 mg/dL)	22%	6%
AST/ALT (>5X ULN)[3]	11%	1%

[1] Moderate and severe AEs of probable, possible, or unknown relationship to LPV/r.

[2] n=70 for laboratory measurements. Laboratory values obtained without regard to fasting. 81% and 69% of patients had Grade0-1 total cholesterol (<240 mg/dL) or triglycerides (<400 mg/dL) at Week 204.

[3] ≥3 loose stools/day.

RESULTS

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).
- Patients with lower baseline viral load (VL) and higher baseline CD4 count were more likely to achieve VL ≤3 copies/mL (Table 3).

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

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

Virologic Response Through Week 204 Based on ≤3 copies/mL Results Through Week 72

- Patients who never achieved VL ≤3 copies/mL at Weeks 24-72 were no more likely to experience virologic failure through 4 years of treatment than patients who achieved at least one VL ≤3 copies/mL (Figure 4).
- Patients who achieved 0 or 1 VL value ≤3 copies/mL at Weeks 24-72 were no more likely to experience virologic failure through 4 years of treatment than patients who achieved multiple VL values ≤3 copies/mL (Figure 5).
- Likewise, in the analysis of the proportion of patients with VL <50 copies/mL at Week 204, patients with 0 vs. 1-3 VL values ≤3 copies/mL at Weeks 24-72 had comparable response rates (69% vs. 76%, respectively, p=0.49), as did patients with 0-1 vs. 2-3 VL values ≤3 copies/mL (75% vs. 69%, respectively, p=0.63) (Figure 6).

Figure 4. Time to Loss of Virologic Response: 0 Values vs. 1-3 Values ≤3 copies/mL

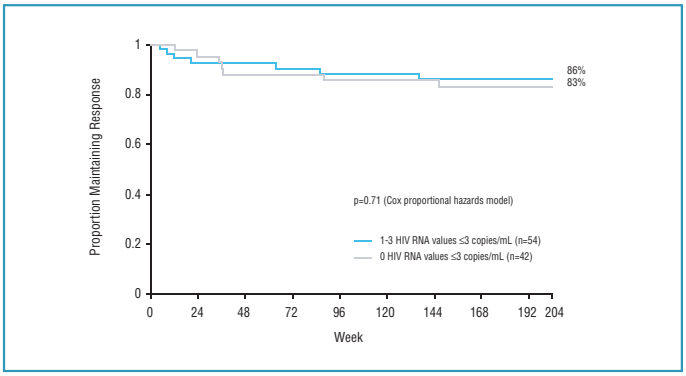


Figure 5. Time to Loss of Virologic Response: 0-1 Values vs. 2-3 Values ≤3 copies/mL

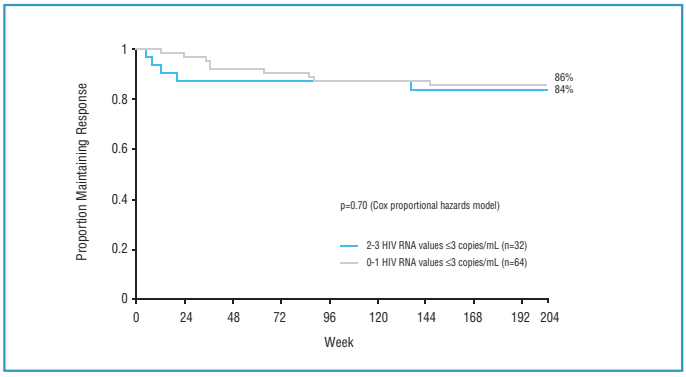
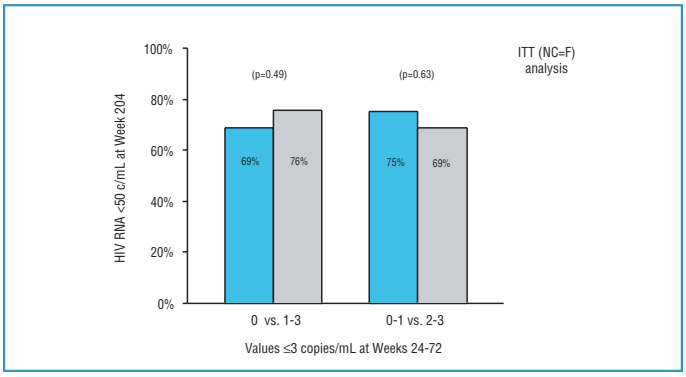


Figure 6. HIV RNA <50 copies/mL at Week 204 vs. HIV RNA ≤3 copies/mL at Weeks 24-72



RESULTS

Virologic Response Through Week 204 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 204 stratified by baseline HIV RNA and CD4 count was performed.
- Patients with high baseline HIV RNA (>100,000 copies/mL) or low baseline CD4 cell count (<200 cells/mm^3) were not more likely to demonstrate loss of virologic response through Week 204 (Figures 7 and 8) or HIV RNA <50 copies/mL at Week 204 (Figure 9). In fact, response rates tended to be higher in patients with more advanced HIV.

Figure 7. Time to Loss of Virologic Response by Baseline HIV RNA Level

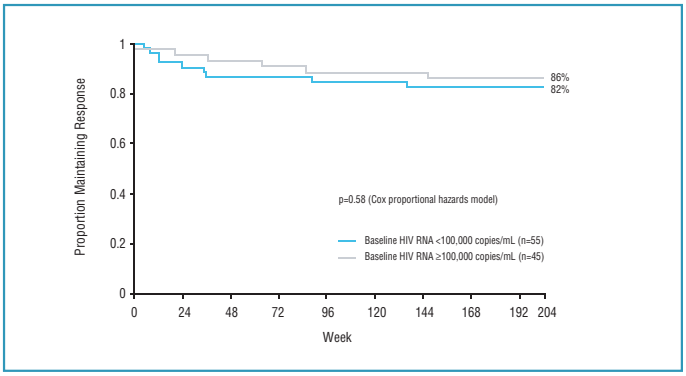


Figure 8. Time to Loss of Virologic Response by Baseline CD4 Cell Count

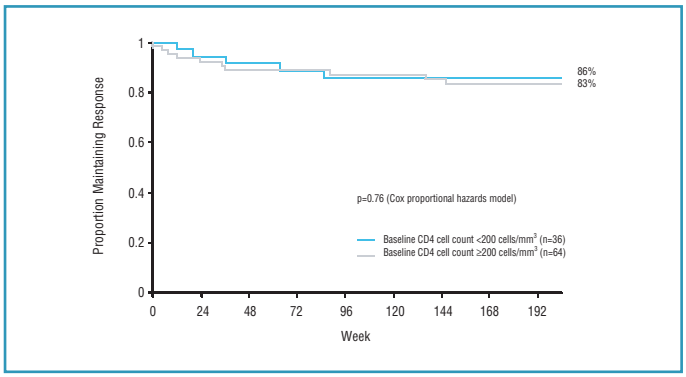
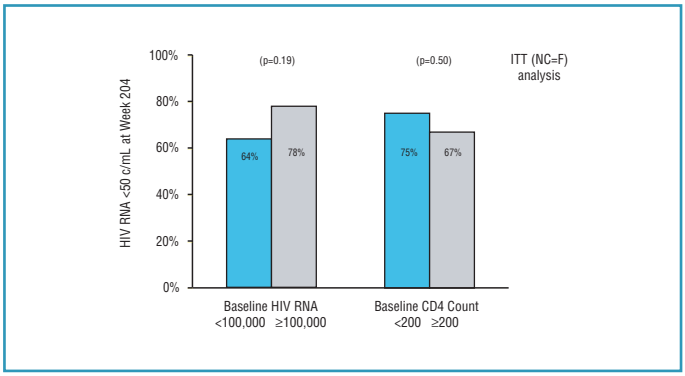


Figure 9. HIV RNA <50 copies/mL at Week 204 vs. Baseline HIV RNA and CD4 Count



DISCUSSION/CONCLUSIONS

- Through 4 years of follow-up, antiretroviral-naïve patients receiving LPV/r-based therapy exhibited sustained virologic response, with 71% and 70% of patients demonstrating HIV RNA <400 copies/mL or <50 copies/mL, respectively (ITT noncompleter=failure). LPV/r was well tolerated, as indicated by the low (7%) rate of study drug-related discontinuations.
- Achieving and/or sustaining HIV RNA ≤3 copies/mL through the first 1.5 years of LPV/r therapy does not appear to predict risk of virologic failure at either <50 or <400 copies/mL through an additional 2.5 years 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/mm^3), virologic response through Week 204 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.

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