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Immunologic Reconstitution Through 6 Years in Antiretroviral-Naïve Subjects Treated with Lopinavir/ritonavir (LPV/r)

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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 capsules 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 type 1 (HIV-1) is >70 when lopinavir/ritonavir is dosed at 400/100 mg twice a day[1], potentially serving as a barrier to the emergence of drug resistance and providing activity against drug resistant virus.

Lopinavir/ritonavir (LPV/r, marketed as Kaletra®) has been studied in both antiretroviral-naïve and -experienced HIV-1-infected subjects. The M97-720 study is a phase II trial of LPV/r in combination with stavudine (d4T) and lamivudine (3TC) in antiretroviral-naïve, HIV-1-infected subjects. This was the first trial of LPV/r in HIV-1-infected subjects and hence provides the longest duration of follow-up for subjects treated with LPV/r. Long-term data on immune reconstitution from controlled studies of antiretroviral therapy are limited. This poster presents data on antiviral activity and immunologic parameters through 6 years (312 weeks) of therapy.

METHODS

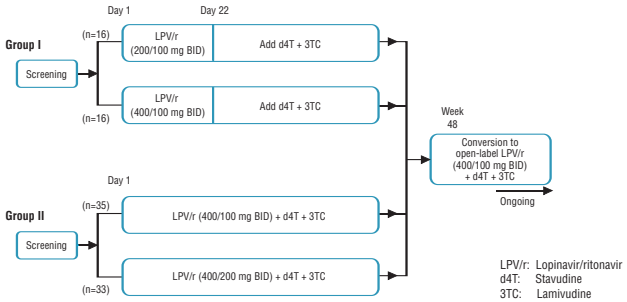
Entry Criteria

- Antiretroviral-naïve subjects with confirmed HIV-1 infection.
- Plasma HIV-1 RNA ≥5,000 copies/mL with no CD4 cell count restriction.
- Exclusion criteria included ALT or AST >2.5x Upper Limit Normal (ULN) and creatinine >1.5x ULN.

Study Design and Analysis

- One hundred antiretroviral-naïve, HIV-1-infected subjects 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 subjects converted to open-label LPV/r 400/100 mg BID dosing.
- Subjects were evaluated every 2–4 weeks for the first 24 weeks and every 12 weeks thereafter.

Figure 1. M97-720: Study Design



Efficacy

- Proportion of subjects with HIV-1 RNA <50 copies/mL through year 6 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 <50 copies/mL).
- Immunology analyses were performed through week 312 for all subjects (n=63) who remained on study through this time period.
- CD4 and CD8 cell counts, B cells (CD19+), NK cells (CD16+ CD56+), and total T cells (CD3+) were obtained at each study visit using multi-parameter flow cytometry. At the year 6 visit, naïve (CD45RA+ CD62L) and memory (CD45RO+ CD45RA–) CD4 cells and activation markers (HLA DR+ CD38+) were also determined using multi-parameter flow cytometry.
- Mean changes from baseline to each visit and/or mean values over time were assessed for CD4 cell counts, CD8 cell counts, and CD4/CD8 ratio by strata of baseline CD4 counts.
- Immunologic values at baseline and year 6 (week 312) were compared to laboratory normal ranges for CD4, CD8, B, NK, and T cells to assess normalization of these parameters.
- Since baseline measures of activation markers for CD4 and CD8 and memory and naïve CD4 cells were not obtained in Study 720, values from week 312 were compared with historical control values from a set of 38 HIV-1-infected, antiretroviral-naïve subjects (with comparable HIV-1 RNA levels and CD4 cell counts, Study M99-056), to assess changes from baseline.

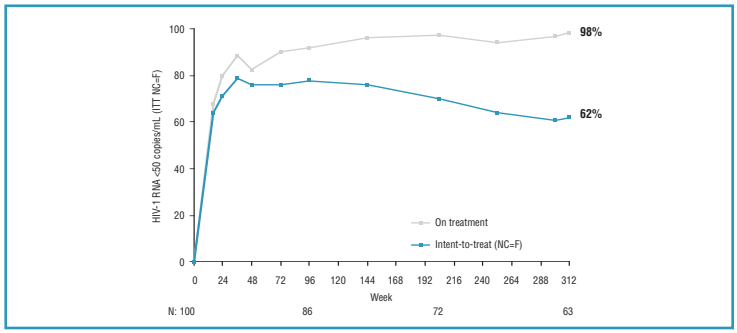
Baseline Characteristics

- Ninety-six male and 4 female subjects: 65% White, 29% Black, 6% Hispanic.
- Mean age: 35 years (range 21–59).
- Among all 100 subjects enrolled, the median baseline HIV-1 RNA and CD4 cell count were 4.8 $\log_{10}$ copies/mL and 326 cells/mm^3, respectively.
- Through 6 years, 37 subjects (37%) prematurely discontinued the study (adverse events, 15%; loss to follow-up, 9%; nonadherence, 4%; death, 1%; other/personal reasons, 8%).
- Among 63 subjects who remained on the study for 6 years, the median baseline HIV-1 RNA and CD4 cell count were 5.1 $\log_{10}$ copies/mL and 245 cells/mm^3, respectively.

Virologic Response

- After 312 weeks of treatment, 62/63 ongoing subjects (on treatment, 98%) had HIV-1 RNA <50 copies/mL, with a corresponding intent-to-treat response rate of 62% (Figure 2).

Figure 2. Study 720: HIV-1 RNA <50 copies/mL



Immunologic Response

CD4 cell count response appeared to be consistent regardless of baseline CD4 cell count (Figures 3a–b). The number of subjects remaining on study at selected timepoints is shown by baseline CD4 stratum in Table 1.

Table 1. Subjects on Study by Baseline CD4 and Visit

Baseline CD4 cells/mm^3	Baseline	Week 96	Week 204	Week 312
<50	17	17	16	15
50–199	19	17	12	12
200–349	19	16	15	12
350–499	19	17	13	11
500 or more	26	19	16	13
Total	**100**	**86**	**72**	**63**

Among subjects with values at both baseline and week 312, the mean CD4 cell count increased from 280 cells/mm^3 to 808 cells/mm^3, an increase of 528 cells/mm^3 (Figures 3a–b).

Figure 3a. Study 720: Mean Change in CD4 Cell Count

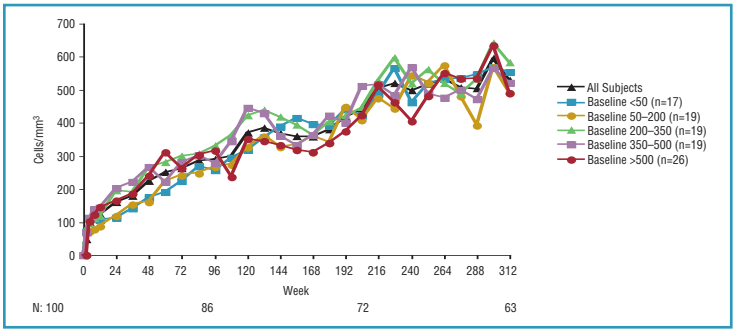
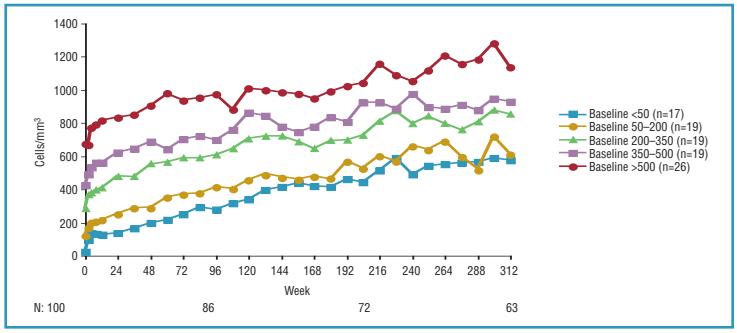


Figure 3b. Study 720: Mean CD4 Cell Count



- Among subjects still on study at year 6, the largest rate of increase in CD4 cell counts occurred early in the study, from weeks 0–12 and weeks 12–48. However, increases were also observed in other time periods (years 1–2, years 2–4, and years 4–6) (Figure 4a).
- Although 39/63 subjects had baseline CD4 counts <350 cells/mm^3, only 3 of these subjects had CD4 count <350 cells/mm^3 at year 6 (Figure 4b).

Figure 4a. Study 720: CD4 Cell Count Change by Time Period

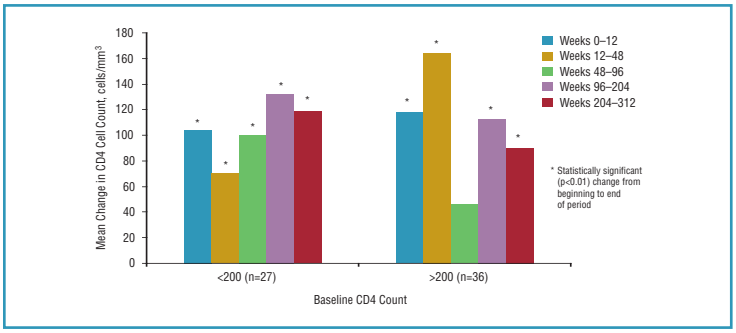
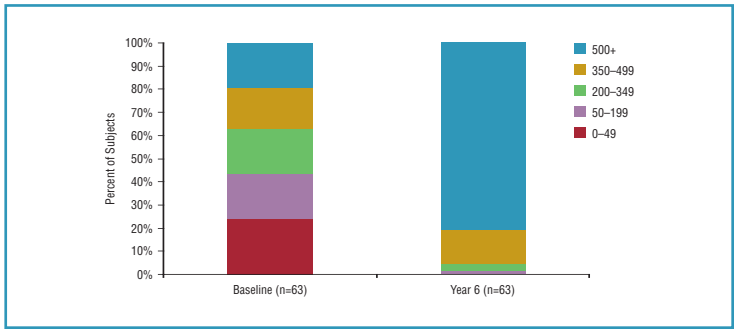


Figure 4b. Study 720: Year 6 vs. Baseline CD4 Cell Count



- Increases from baseline in CD8 cell count were observed in subjects with baseline CD4 cell count <200 cells/mm³, but not among those with higher baseline CD4 cell counts (Figures 5a–b). Mean CD8 values at year 6 were similar across strata of baseline CD4 counts.
- Statistically significant increases in B and NK cells were also observed. Mean B cell counts increased from 139 to 343 cells/mm³ from baseline to year 6 (p<0.001), while mean NK cell counts increased from 141 to 238 cells/mm³ (p<0.001). Increases were generally consistent across strata of baseline CD4 counts.

Figure 5a. Study 720: Mean Change in CD8 Cell Count by Baseline CD4 Stratum

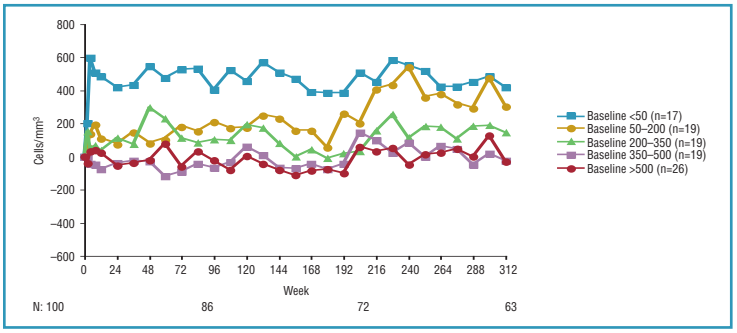
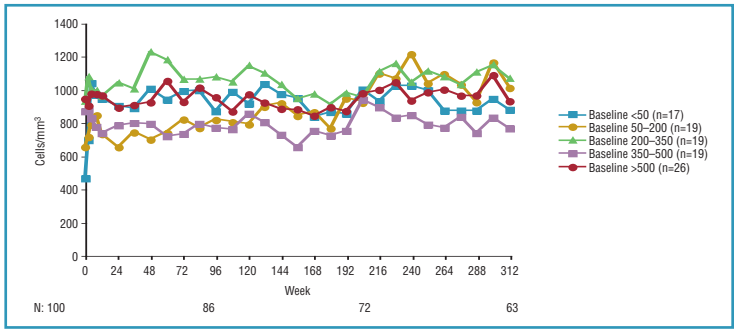


Figure 5b. Study 720: Mean CD8 Cell Count by Baseline CD4 Stratum



- Across all CD4 strata, CD4:CD8 ratio increased significantly from baseline over time (Figure 6).
- Assessment of immunologic values relative to laboratory normal ranges (Figure 7) indicated that most of the immunologic changes occurred in CD4 cells. Laboratory normal ranges in cells/mm³ were as follows: CD4 (320–2350), CD8 (180–1540), T cells (620–3510), B cells (55–985), NK cells (50–1325).

Figure 6. Study 720: Mean CD4/CD8 Ratio

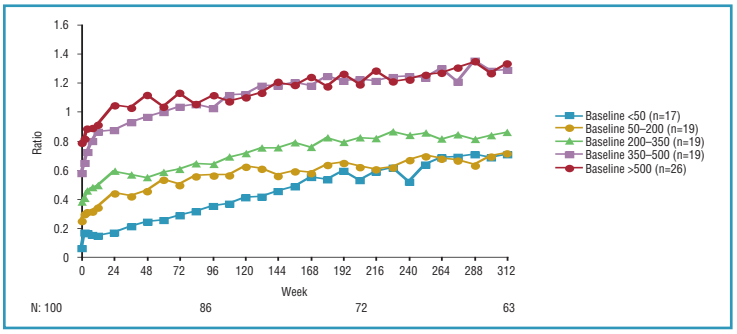
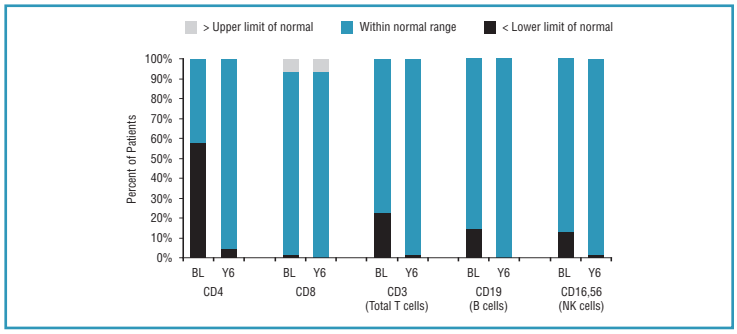


Figure 7. Study 720: Immunologic Values Relative to Laboratory Normal Ranges



- Activation markers and naïve and memory cells were not assessed at baseline. However, comparison with historical control data from 38 antiretroviral-naïve, HIV-1-infected subjects (with baseline HIV-1 RNA and CD4 count values comparable to those in Study 720) suggests that values observed in Study 720 at year 6 likely represent substantial changes from baseline values (Figures 8a–b).
- Median values at year 6 were 3.4% CD4 activation, 5.8% CD8 activation, 223 naïve CD4 cells/mm³ and 458 memory CD4 cells/mm³.
- Mean changes from baseline to year 6 in CD4 cell count were not significantly different among subjects with year 6 CD8 activation >10% (+455 cells/mm³, n=16), compared to those with year 6 CD8 activation <10% (+554 cells/mm³, n=47, p=0.25).

Figure 8a. Study 720: Activation Markers at Year 6

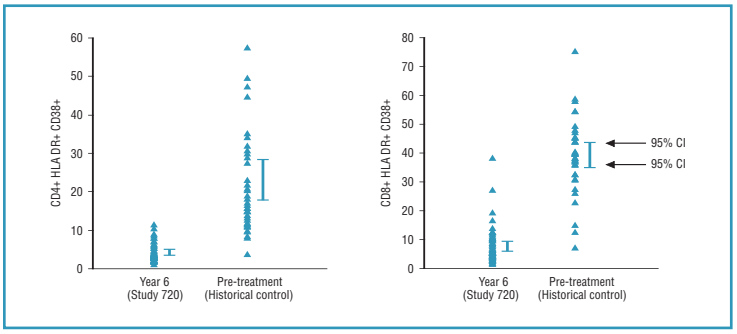
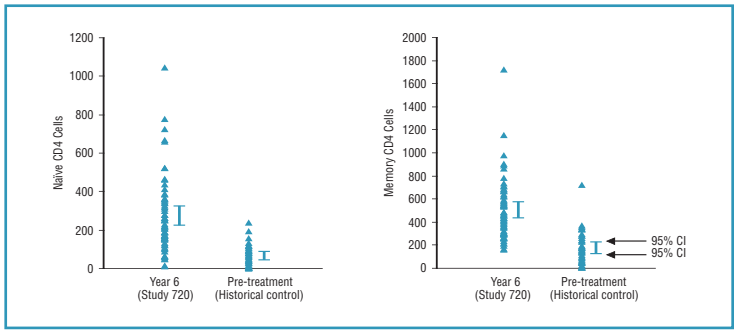


Figure 8b. Study 720: Naïve and Memory CD4 Cells at Year 6



DISCUSSION

- Through 6 years of follow-up, antiretroviral-naïve subjects receiving LPV/r-based therapy exhibited sustained HIV-1 suppression combined with significant increases in CD4 cell counts. 62% of subjects demonstrated HIV-1 RNA <50 copies/mL at week 312 by intent-to-treat analysis, representing 98% of those still on study. A mean increase in CD4 cell count of 528 cells/mm^3 at week 312 was also observed.
- There is evidence of continued immune reconstitution in subjects receiving LPV/r-based therapy with baseline CD4 counts <200 cells/mm^3 (mean CD4 increases between years 4–6 of 118 cells/mm^3), through 6 years. This is in contrast to several studies that evaluated various HAART regimens for up to 7 years of therapy. In these studies, a plateau of the CD4 cell count was noted after 3–4 years of HAART therapy.[2,3,4]
- Among subjects treated for 6 years with LPV/r-based therapy, 81% had CD4 cell counts >500 cells/mm^3 compared to 21% at baseline. Similarly, 95% had CD4 cell counts >350 cells/mm^3 compared to 38% at baseline, indicating a significant immunologic response in subjects receiving LPV/r-based therapy through 6 years.
- Increases in baseline CD8 cell counts were observed mainly in those with baseline CD4 cell counts <200 cells/mm^3; at year 6, mean CD8 values were similar across baseline CD4 strata.
- The CD4/CD8 ratio increased from 0.45 to 0.96 for the cohort of subjects who remained on study through 6 years. Previously, an inverse correlation of the CD4/CD8 ratio with HIV-1 proviral reservoir[5] has been observed.
- Although most subjects had baseline B and NK cell counts within the laboratory normal ranges, significant mean increases in B and NK cell values were observed across all strata of baseline CD4 counts, and subjects with baseline counts below the normal range generally had values within the normal range at year 6. These increases may be an important part of humoral (B cell) and innate (NK cell) immune responses, and they suggest a possible role for functional studies of B and NK cells.
- One of the most significant immunologic findings of this study was the normalization of both CD4 (median value of 3.4%) and CD8 (median value of 5.8%) activation (HLA-DR+CD38+) at year 6. This finding provides further evidence for ongoing immune reconstitution in this cohort of subjects treated with a LPV/r-based regimen and suggests implications for functional immune responses. CD4 increases through 6 years were comparable in subjects with CD8 activation above or below 10%.

CONCLUSIONS

- This study represents the longest follow-up evaluations of immune reconstitution in antiretroviral-naïve, HIV-1-infected subjects on a specific protease inhibitor-based regimen.
- This study provides clear evidence that immune reconstitution continues through 6 years in subjects who are virologically suppressed and receiving a LPV/r-based antiretroviral regimen.

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M97-720 Study Subjects
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