

**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/mm³ 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/mm³ (mean CD4 increases between years 4–6 of 118 cells/mm³), 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.

- Among subjects treated for 6 years with LPV/r-based therapy, 81% had CD4 cell counts >500 cells/mm³ compared to 21% at baseline. Similarly, 95% had CD4 cell counts >350 cells/mm³ 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/mm³; 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 load 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 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.

**REFERENCES**


Assessment of immunologic values relative to laboratory normal ranges (Figure 7) indicated that most of the immunologic changes occurred in CD4 cells. Median values at year 6 were 3.4% CD4 activation, 5.8% CD8 activation, 223 naïve CD4 cells/mm$^3$, respectively. Although 39/63 subjects had baseline CD4 counts <350 cells/mm$^3$ and 326 cells/mm$^3$, respectively. Increases from baseline in CD8 cell count were observed in subjects with baseline CD4 cell count <200 cells/mm$^3$ (p<0.001). Increases were generally consistent across strata of baseline CD4 counts.

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/mm$^3$ and 458 memory CD4 cells/mm$^3$. 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/mm$^3$, n=16), compared to those with year 6 CD8 activation <10% (+554 cells/mm$^3$, n=47, p<0.05).

Among subjects with values at both baseline and week 312, the mean CD4 cell count increased from 280 cells/mm$^3$ to 858 cells/mm$^3$, an increase of 578 cells/mm$^3$ (Figures 3a–b).

Among subjects still on study at year 6, the largest rate of increase in CD4 cells 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).
RESULTS

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 log₁₀ copies/mL and 526 cells/mm³, 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 log₁₀ copies/mL and 245 cells/mm³, 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).

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

<table>
<thead>
<tr>
<th>Baseline CD4 cells/mm³</th>
<th>Baseline</th>
<th>Week 26</th>
<th>Week 36</th>
<th>Week 72</th>
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<td>600–899</td>
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<td>20</td>
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<tr>
<td>Total</td>
<td>100</td>
<td>86</td>
<td>72</td>
<td>63</td>
</tr>
</tbody>
</table>

Among subjects with values at both baseline and week 312, the median CD4 cell count increased from 280 cells/mm³ to 528 cells/mm³, an increase of 245 cells/mm³ (Figures 3a–b).

- Increases from baseline in CD4 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.

- 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 (300–500), CD8 (150–300), T cells (600–1000), B cells (50–980), NK cells (50–1300).

- Activation markers and naive 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 cell 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–6).
- 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).
**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/mm³ at week 312 was also observed.

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**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.

**REFERENCES**


**ACKNOWLEDGMENTS**

**METHODS**

**M97-720 Study Subjects**

Converse Central Laboratories Services
AIDS Research Consortium of Atlanta, R Duley
Baylor College of Medicine, Thomas Street Clinic, S Gupta
Beth Israel Deaconess Medical Center, Harvard, R Pitch
Cornell Clinical Trials Unit, T Stroberg
Duke University Medical Center, L Harmon
Northwestern University, J Bruce, J Shore
Pacific Oaks Research, A Simmons
Rush–Presbyterian-St. Luke's Medical Center, J Fritsch
University of Colorado, G Blaker, B Poham
University of North Carolina at Chapel Hill, C Mercue
PFDR Development, R Wheat, J Gelgeman
Abbott Laboratories, K Sheahan, O Yang

**ENTRY CRITERIA**

- Antiretroviral-naïve subjects with confirmed HIV-1 infection.
- Plasma HIV-1 RNA <50 copies/mL with no CD4 cell count restriction.
- Exclusion criteria included ALT or AST >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 dose levels of LPV (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 2 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 NO-F; missing values considered failure unless the immediately preceding and following values were <50 copies/mL).
- Immunologic analyses were performed through week 312 for all subjects (n=69) who remained on study through this time period.
- CD4 and CD4 cell counts, B cells (CD19+), NK cells (CD16+ CD56+) and total CD cells (CD3+) were obtained at each study visit using multi-parameter flow cytometry. At the year 6 visit, naive (CD4DRAD+ CD45RA-) 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, CD4 cell counts, and CD4% 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 naive 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.