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CD4/CD8 Subset Analysis in Antiretroviral-Naïve HIV+ Patients Receiving Lopinavir/ritonavir (Kaletra)

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BACKGROUND

Lopinavir (LPV), an HIV protease inhibitor, co-formulated with ritonavir (r), a cytochrome p450 3A4 inhibitor, has been shown to be safe and effective in reducing viral load (VL) and increasing CD4 cell counts in both antiretroviral-naïve and experienced HIV-infected patients. However, detailed analyses of CD4 and CD8 subsets have not previously been reported.

Thirty-eight ARV-naïve patients were randomized (1:1) to receive d4T+3TC with LPV/r 800/200 mg QD or 400/100 mg BID in study M99-056. As previously reported,[1]

- 74% of QD and 79% of BID patients had VL<50 c/mL at Week 48 (ITT, p=0.71, Figure 1).
- Mean increases in CD4 count from baseline to Week 48 were 235 and 248 cells/mm^3 for the QD and BID groups (Figure 2).
- Genotypic and phenotypic results were available for 4 patients with viral load above 400 copies/mL between Week 24 and Week 48. Consistent with results observed in previous studies of LPV/r in ARV-naïve patients,[2] 0 of 4 patients demonstrated primary or active site mutations in protease,[3] and 2 of 4 patients demonstrated resistance to 3TC (M184V/I mutation).
- Four patients discontinued prior to Week 48, including 2 due to LPV/r-related adverse events. The two premature discontinuations due to LPV/r related adverse events were: one subject in the QD group discontinued due to pruritis, rash, chills, fever, nausea, vomiting, and diarrhea (all probably related to LPV/r), and one patient in the BID group discontinued due to diarrhea and dehydration (both possibly related to LPV/r).
- Nausea (n=3 QD, n=1 BID) and diarrhea (n=1 each QD and BID) were the most common moderate or severe LPV/r-related adverse events.
- Lipid elevations to Grade 3 (total cholesterol >300 mg/dL or triglycerides >750 mg/dL) were infrequent, occurring in 2 patients in each treatment group. With the exception of baseline and Week 24, laboratory determinations were performed without regard to fasting. Fasting total cholesterol/HDL ratio at Week 24 was not significantly changed from baseline (-0.30 in QD and +0.01 in BID treated patients).

Figure 1. Proportion <50 copies/mL (ITT Missing=Failure) at Week 48

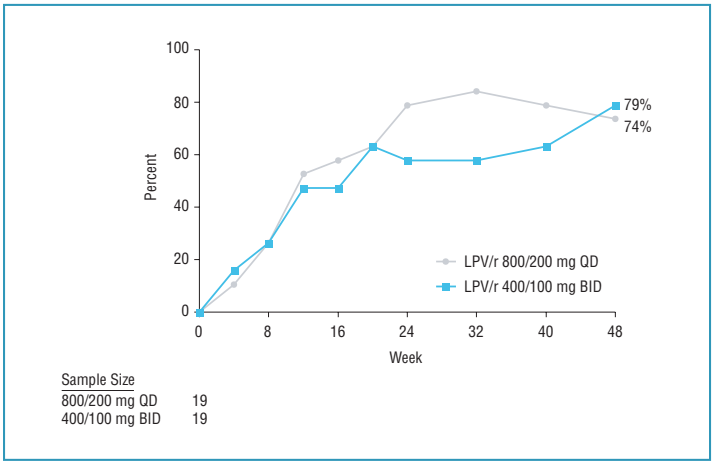
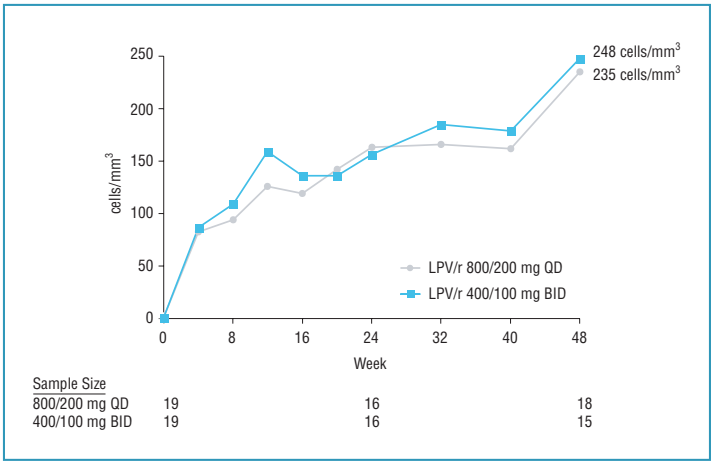


Figure 2. CD4 Cell Count Mean Change from Baseline



METHODS

Entry Criteria

- Antiretroviral-naïve patients
- Plasma HIV RNA level above 50 copies/mL
- No minimum CD4 cell count

Study Design and Analysis

- This study reports CD4 and CD8 subset results from the M99-056 study described in the background.
- Plasma HIV RNA was quantified using the Roche Amplicor HIV-1 Monitor Ultra-sensitive Quantitative PCR assay (LOQ [limit of quantitation] 50 copies/mL) at each visit.
- CD4/CD8 subsets [% activation (CD38+ HLA DR+), naïve cells/mm^3 (62L+ 45RA+), and memory cells/mm^3 (45RO+ 45RA-)] were analyzed by four-color customized flow-cytometry at each visit. Flow-cytometry testing was performed by Covance Central Laboratory.
- Mean changes from baseline to each study visit in immunologic parameters were evaluated using paired *t* tests. The Pearson correlation coefficient and Fisher's exact test were used to evaluate relationships of immunologic and virologic response, respectively, with markers of immune activation.
- Immunologic changes were similar for the QD and BID groups; therefore, groups were combined for analysis.

RESULTS

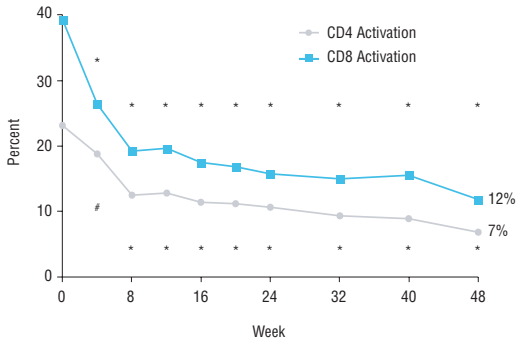
Baseline Characteristics

- 68% of patients were male, 39% Black, 29% Caucasian, 24% Hispanic, 8% Asian/Pacific Islander. Mean age was 39 years.
- Mean baseline HIV RNA was 4.7 $\log_{10}$ copies/mL (range 2.8-5.9), and mean baseline CD4 cell count was 259 cells/mm^3 (range 5-917).

Percent Activated CD4 and CD8 Cells

- Percent activated CD4 and CD8 cells (CD38+ and HLA DR+) decreased significantly from baseline through Week 48 (Figure 3). Changes from baseline were statistically significant at all visits after baseline. Among 33 patients with values at both baseline and Week 48, mean CD4 cell activation decreased from 23% at BL to 7% at Week 48, and mean CD8 cell activation decreased from 39% at BL to 12% at Week 48.

Figure 3. CD4 and CD8 Mean Activation Values over Time

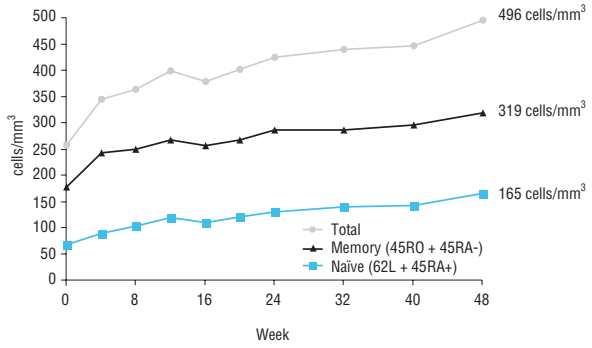


#Statistically significant decrease from baseline ($p<0.05$); *Statistically significant decrease from baseline ($p<0.001$)

CD4/CD8 Total, Naïve, and Memory Cells

- Statistically significant increases from baseline in total, naïve, and memory CD4 cells were observed at all visits after baseline (Figures 4 and 5). Among 33 patients with values at both baseline and Week 48:
  - Total CD4 cells increased a mean of 241 cells/mm^3, from 255 at baseline to 496 at Week 48.
  - Naïve CD4 cells increased a mean of 99 cells/mm^3, from 66 at baseline to 165 at Week 48.
  - Memory CD4 cells increased a mean of 143 cells/mm^3, from 176 at baseline to 319 at Week 48.
- Statistically significant increases from baseline in naïve CD8 cells but not memory CD8 cells were observed at all visits after baseline (Figures 6 and 7). Among 33 patients with values at both baseline and Week 48, naïve CD8 cells increased a mean of 140 cells/mm^3, from 153 at baseline to 293 at Week 48.

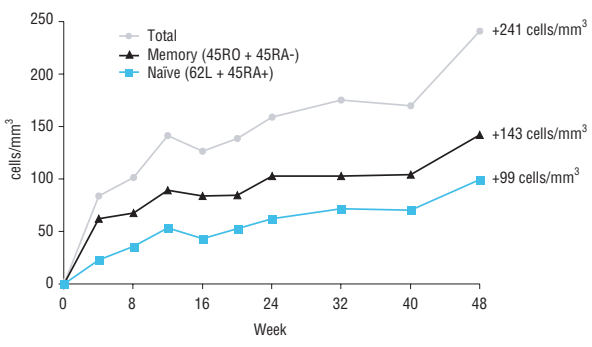
Figure 4. CD4 Cells: Mean Values over Time



Sample Size	38	32	33

Mean increases from baseline for total, memory, and naïve CD4 cells were statistically significant (p<0.001) at all visits.

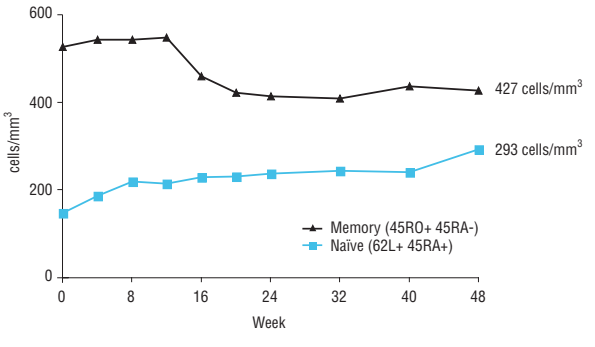
Figure 5. CD4 Cells: Mean Change from Baseline



Sample Size	38	32	33

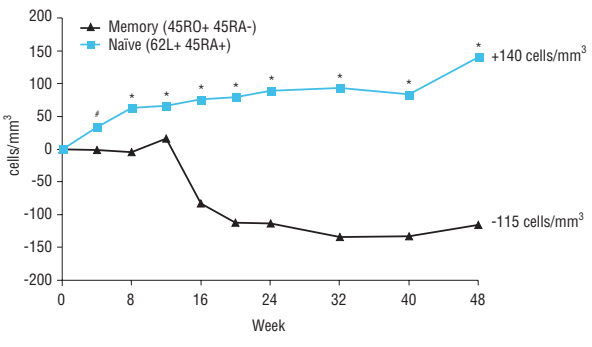
Mean increases from baseline for total, memory, and naïve CD4 cells were statistically significant (p<0.001) at all visits.

Figure 6. CD8 Cells: Mean Values over Time



Sample Size	38	32	33

Figure 7. CD8 Cells: Mean Change from Baseline



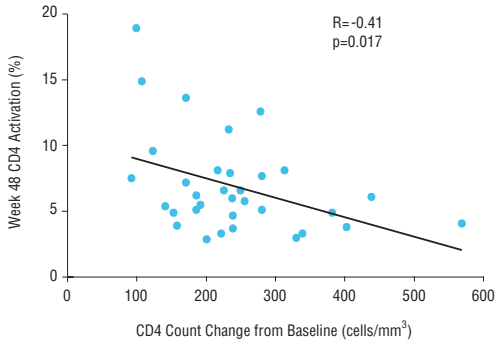
Sample Size	38	32	33

* Statistically significant change from baseline (p<0.001)
\# Statistically significant change from baseline (p<0.05)

Immunologic and Virologic Response vs. Week 48 CD4/CD8 Activation

- The change from baseline to Week 48 in CD4 count was negatively correlated with Week 48 CD4 activation (R=–0.41, R^2=0.17, p=0.017, Figure 8) but was not significantly correlated with Week 48 CD8 activation (R=–0.21, R^2=0.045, p=0.237, Figure 9).
- Patients with viral load (VL) ≥50 and <50 c/mL at Week 48 had similar mean CD4 activation at Week 48 (8.1% [n=5] and 6.7% [n=28], respectively), but patients with VL ≥50 c/mL had significantly higher Week 48 mean CD8 activation (19.1% vs. 10.5%, p=0.01, Figure 10). Notably, all 5 patients with VL ≥50 copies/mL had VL <1000 copies/mL.

Figure 8. CD4 Change from Baseline vs. Week 48 CD4 Activation



RESULTS

Figure 9. CD4 Change from Baseline vs. Week 48 CD8 Activation

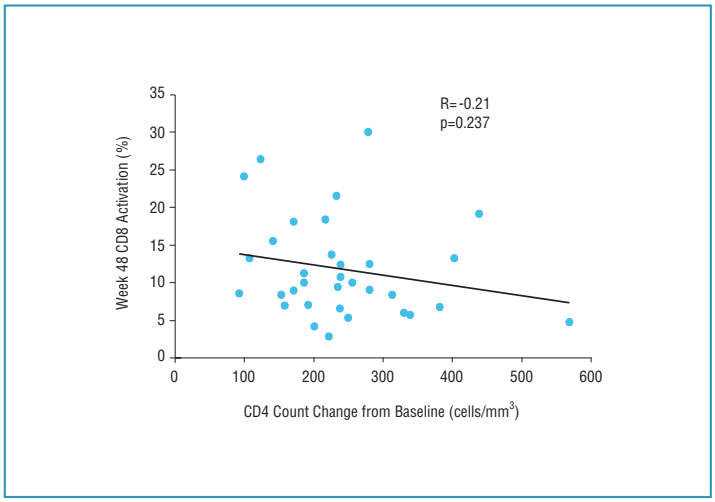
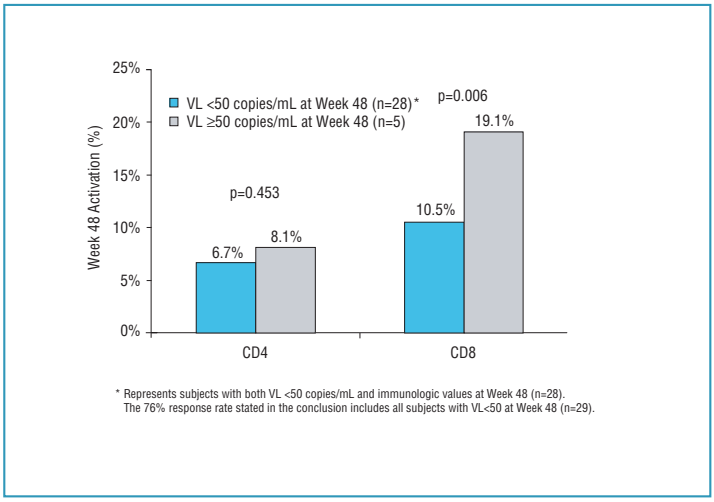


Figure 10. Week 48 Viral Suppression vs. CD4/CD8 Activation



* Represents subjects with both VL <50 copies/mL and immunologic values at Week 48 (n=28). The 76% response rate stated in the conclusion includes all subjects with VL<50 at Week 48 (n=29).

CONCLUSIONS

- Treatment with a regimen based on LPV/r QD or BID resulted in potent viral suppression and substantial immunologic improvements, with 76% of enrolled patients having VL <50 copies/mL at Week 48 and a mean increase in CD4 cell count from baseline to Week 48 of 241 cells/mm^3.
- Naïve and memory CD4 cells increased significantly from baseline through Week 48.
- Naïve CD8 cells increased significantly from baseline through Week 48, while memory CD8 cells trended downward.
- CD4 and CD8 cell activation decreased significantly from baseline through Week 48.
- Change from baseline to Week 48 in CD4 count was negatively correlated with Week 48 CD4 activation but was not significantly correlated with Week 48 CD8 activation.
- Patients with VL ≥50 and <50 copies/mL at Week 48 had similar mean CD4 activation at Week 48 but patients with VL ≥50 copies/mL had higher Week 48 mean CD8 activation.
- The data presented suggest the usefulness of on-therapy markers of immune activation in assessing patient response to antiretroviral therapy.

REFERENCES

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M99-056 Study Patients	
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Rush-Presbyterian St. Luke's Medical Center	*J Mohlman*
Tower Infectious Diseases	*T Clover*
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