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CD4+ T-cell Response to Lopinavir/ritonavir-based Therapy in Antiretroviral-naïve HIV-1 Infected Subjects: The Role of Adherence

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Background

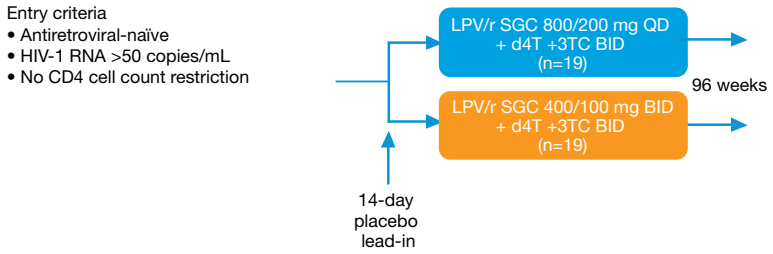
Associations between (medication) adherence and virologic outcomes in HIV treatment have been described but the relationship between adherence and immunologic response is less well defined. In general, virologic responses have been more closely associated with adherence than immunologic responses.

Methods

Two prospective, randomized, 96-week, parallel arm clinical trials compared the safety and efficacy of lopinavir/ritonavir soft-gel capsules administered once- (QD) or twice-daily (BID) in antiretroviral-naïve HIV-1 infected subjects (see Figure 1).

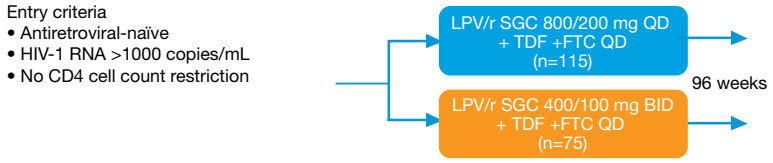
Figure 1. Study Designs for M99-056 and M02-418

M99-056



Eron JJ, et al. Once-Daily versus Twice-Daily Lopinavir/ritonavir in Antiretroviral-Naïve HIV-Positive Patients: A 48-Week Randomized Clinical Trial. *J Infec Dis* 2004:189;265-72.

M02-418



Johnson MA, et al. A Once-Daily Lopinavir/ritonavir-based Regimen Provides Noninferior Antiviral Activity Compared with a Twice-Daily Regimen. *J Acquir Immune Defic Syndr* 2006;43:153-60.

CD4+ T-cell counts were measured every 4 weeks (Baseline to Week 8), every 8 weeks (Week 8 to Week 48) and every 12 weeks (Week 48 to Week 96). For this analysis, time to immunologic response was defined by the first of two consecutive CD4+ T-cell counts at least 100 cells/mm^3 above baseline after initiating lopinavir/ritonavir-based therapy. Sensitivity analyses using alternative definitions of immune response were performed.

MEMS® monitors recorded and stored dosing histories with the lopinavir/ritonavir component of the antiretroviral regimen. Summary adherence statistics were computed for each inter-visit period during participation in the study. Timing adherence, a summary statistic that assesses the number of deviations in dosing intervals that are either too short ("over-dosing") or too long ("under-dosing"), was calculated as:

$$100 \times \left(\frac{\text{number of openings within } \pm 3 \text{ hours around the prescribed interval}}{\text{number of prescribed doses} - 1} \right)$$

Subjects were post-stratified using timing adherence from Baseline to Week 4 into four groups: <80%, 80%–<90%, 90%–<100%, ≥100%.

Results

Of 228 subjects enrolled, 214 (94%) were considered evaluable. Demographic and baseline characteristics were similar for subjects receiving lopinavir/ritonavir QD or lopinavir/ritonavir BID. However, subjects who received lopinavir/ritonavir QD had statistically significantly higher timing adherence from Baseline to Week 4 compared to subjects who received lopinavir/ritonavir BID (see Table 1).

Table 1. Demographics and Baseline Disease Characteristics of Subjects with MEMS Data Available

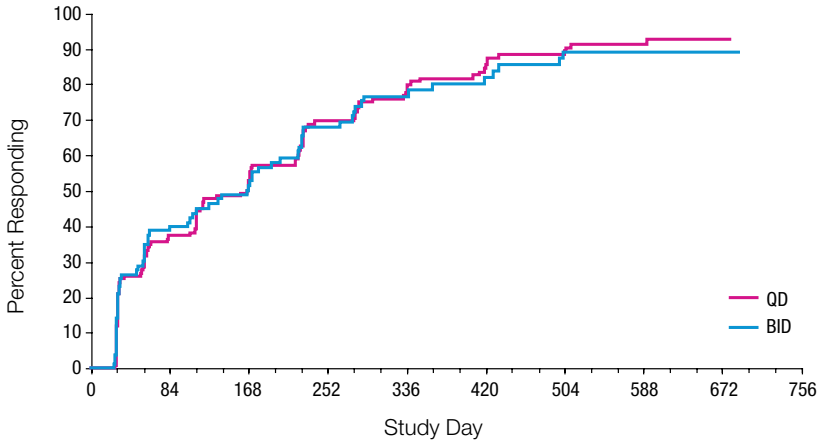
	LPV/r QD (n=127)	LPV/r BID (n=87)	P-value (QD vs. BID)
Study			
M99-056	18 (14.2%)	17 (19.5%)	0.348
M02-418	109 (85.8%)	70 (80.5%)	
Gender			
Male	102 (80.3%)	65 (74.7%)	0.401
Female	25 (19.7%)	22 (25.3%)	
Race@			
White	69 (54.3%)	38 (43.7%)	0.329
Black	35 (27.6%)	34 (39.1%)	
Hispanic	14 (11.0%)	9 (10.3%)	
Asian	8 (6.3%)	5 (5.7%)	
Other	1 (0.8%)	1 (1.1%)	
Age (Years)			
N	127	87	
Mean ± SD	40.0 ± 11.09	37.3 ± 8.84	0.060
Median	39	38	0.116
IQR	32, 47	30, 42	
Time Since HIV-1 Diagnosis (Years)			
N	127	87	
Mean ± SD	2.41 ± 4.157	1.87 ± 3.406	0.320
Median	0.42	0.40	0.604
IQR	0.15, 2.15	0.20, 1.66	
HIV-1 RNA (log_{10} copies/mL)			
N	127	87	
Mean ± QD	4.88 ± 0.730	4.73 ± 0.720	0.156
Median	4.85	4.64	0.293
IQR	4.30, 5.32	4.31, 5.32	
CD4+ T-cell count (cells/mm^3)			
N	127	87	
Mean ± SD	255.2 ± 202.56	237.7 ± 176.59	0.515
Median	211	226	0.782
IQR	106, 378	74, 343	
0–99	30 (23.6%)	24 (27.6%)	
100–199	28 (22.0%)	16 (18.4%)	
200–349	33 (26.0%)	27 (31.0%)	0.709
350–499	25 (19.7%)	12 (13.8%)	
≥500	11 (8.7%)	8 (9.2%)	
Timing Adherence (Baseline – Week 4)			
N	127	87	
Mean ± SD	90.4 ± 18.39	81.1 ± 22.69	0.001
Median	100	90	<0.001
IQR	89, 100	71, 98	
<80%	21 (16.5%)	30 (34.5%)	
80% – <90%	11 (8.7%)	13 (14.9%)	<0.001
90% – <100%	27 (21.3%)	27 (31.0%)	
≥100%	68 (53.5%)	17 (19.5%)	

LPV/r = Lopinavir/ritonavir; IQR = Interquartile range

@ Includes one Native American/Alaskan Native (LPV/r QD) and one Other race (LPV/r BID).

Median time to an immunologic response with an increase in CD4+ T-cell counts at least 100 cells/mm^3 above baseline was similar for subjects receiving lopinavir/ritonavir QD or lopinavir/ritonavir BID (167 days vs. 166 days; p=0.816 [Log-rank test], see Figure 2).

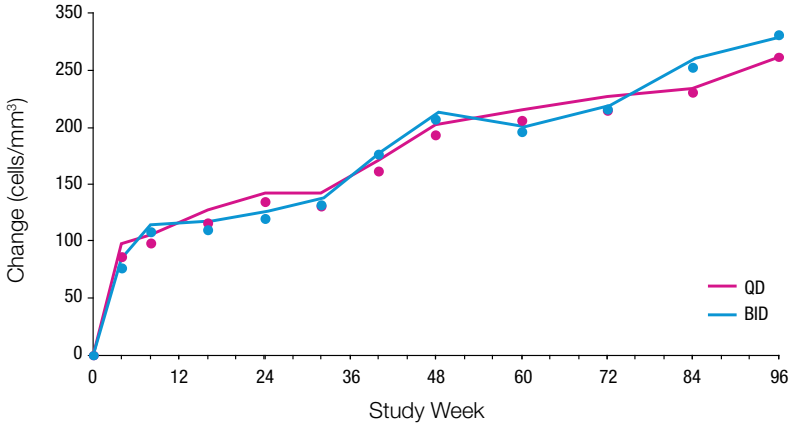
Figure 2. Time to Immunologic Response by Lopinavir/ritonavir Dosing Frequency



There was no apparent difference between lopinavir/ritonavir QD and lopinavir/ritonavir BID with respect to the number of subjects censored from analysis (15.75% vs. 21.84%; p=0.282 [Fisher's exact test]). Censoring refers to those subjects who did not achieve immunologic response prior to premature discontinuation or completion of the study in either M99-056 or M02-418.

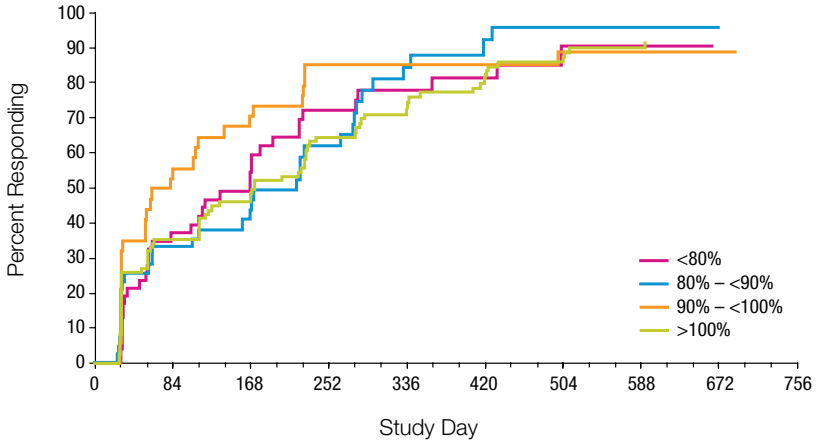
Longitudinal analysis suggests no difference over time in CD4+ T-cell response profiles of subjects receiving lopinavir/ritonavir QD or lopinavir/ritonavir BID (treatment main effect [p=0.952], treatment-by-time interaction effect [p=0.231]; see Figure 3).

Figure 3. Change from Baseline in CD4+ T-cell Count (cells/mm^3) Stratified by Randomized Treatment Assignment



For the four Baseline to Week 4 timing adherence strata, median time to immunologic response was similar (p=0.684 [Log-rank test], see Figure 4).

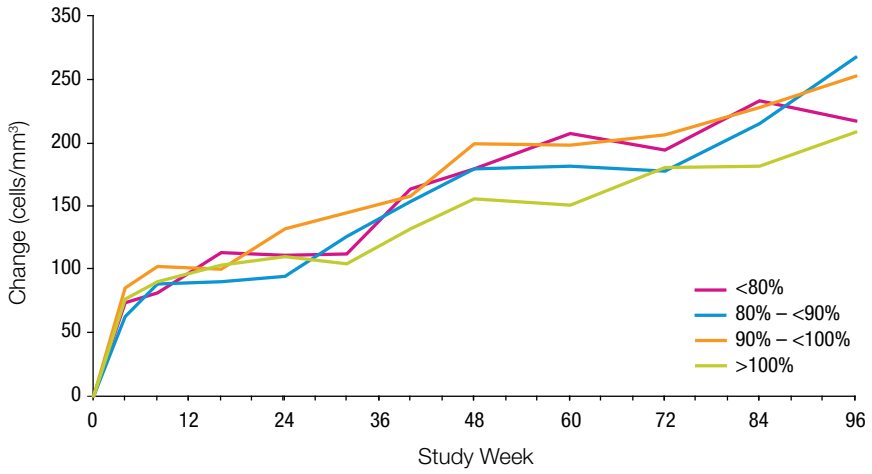
Figure 4. Time to Immunologic Response by Timing Adherence



There was a trend, however, toward more (and earlier) censoring with decreasing timing adherence (p<0.001 [Log-rank test]).

Longitudinal analysis of CD4+ T-cell counts also suggests no difference over time in the response profiles of subjects in the four timing adherence strata (timing adherence strata main effect [p=0.283], timing adherence strata-by-time interaction effect [p=0.207]; see Figure 5).

Figure 5. Change from Baseline in CD4+ T-cell Count (cells/mm^3) Stratified by Timing Adherence (Baseline to Week 96)



Sensitivity analyses using alternative definitions of immunologic response were performed and showed similar results for the time to event analyses.

Immunologic response defined by the first of two consecutive CD4+ T-cell counts at least 50 cells/mm^3 above baseline

Median time to immunologic response was similar for subjects receiving lopinavir/ritonavir QD compared to lopinavir/ritonavir BID (55 days vs. 50 days; p=0.873 [Log-rank test]), and there was no apparent difference between lopinavir/ritonavir QD and lopinavir/ritonavir BID with respect to the number of subjects censored from analysis (8.66% vs. 10.34%; p=0.812 [Fisher's exact test]). Median time to immunologic response was similar for the four Baseline to Week 4 timing adherence strata (p=0.336). However, there was a trend toward more (and earlier) censoring with decreasing timing adherence (p=0.001 [Log-rank test]).

Immunologic response defined by the first of two consecutive CD4+ T-cell counts at least 200 cells/mm^3 above baseline

Median time to immunologic response was similar for subjects receiving lopinavir/ritonavir QD compared to lopinavir/ritonavir BID (500 days vs. 592 days; p=0.292 [Log-rank test]), and there was no apparent difference between lopinavir/ritonavir QD and lopinavir/ritonavir BID with respect to the number of subjects censored from analysis (47.24% vs. 57.47%; p=0.165 [Fisher's exact test]). Median time to immunologic response was similar for the four Baseline to Week 4 timing adherence strata (p=0.337), and there was no apparent difference between timing adherence strata with respect to the number of subjects censored from analysis (p=0.974 [Fisher's exact test]).

Immunologic response defined by the first of two consecutive CD4+ T-cell counts at least 200 cells/mm^3 above baseline for subjects with CD4+ T-cell counts <200 cells/mm^3 at baseline

Of the 214 subjects included in the primary analysis, 98 (45.8%) had baseline CD4+ T-cell counts at or below 200 cells/mm^3. Median time to immunologic response was similar for subjects receiving lopinavir/ritonavir QD compared to lopinavir/ritonavir BID (p=0.176 [Log-rank test]), and there was no apparent difference between lopinavir/ritonavir QD and lopinavir/ritonavir BID with respect to the number of subjects censored from analysis (48.28% vs. 67.50%; p=0.066 [Fisher's exact test]). Median time to immunologic response was similar for the four Baseline to Week 4 timing adherence strata (p=0.623 [Log-rank test]), and there was no apparent difference between timing adherence strata with respect to the number of subjects censored from analysis (p=0.776 [Fisher's exact test]).

Conclusions

Time to immunologic response and CD4+ T-cell count profiles (over time) were not statistically significantly different between subjects receiving lopinavir/ritonavir QD and lopinavir/ritonavir BID. Similarly, time to immunologic response did not appear to differ based on adherence measures (from Baseline to Week 4), though results may be confounded with censoring.

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