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Achieving and Maintaining Undetectable HIV-1 RNA: The Role of Adherence

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Background

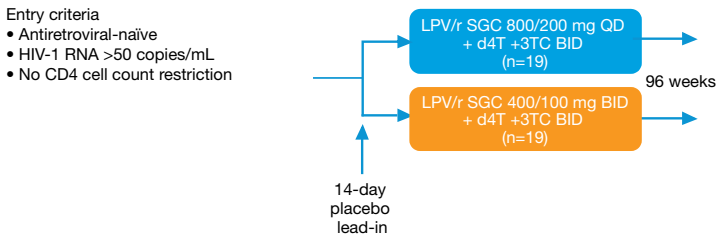
Level of adherence to antiretroviral therapy is an important predictor of success in the treatment of HIV-1 infection, with earlier studies suggesting that 95% adherence was necessary to optimize response.[1] Whether this level of adherence is required for treatment success with current therapy including potent ritonavir-boosted protease inhibitor-based regimens has been questioned.[2] In addition, the degree of adherence needed to achieve plasma HIV-1 RNA (viral load) suppression might differ from that needed to maintain viral load suppression. In this study, we investigate the relationship between the level of adherence required first to achieve and then to maintain viral load suppression.

Methods

M99-056 and M02-418 were similarly designed prospective, randomized, parallel arm, 96-week trials evaluating the safety and efficacy of lopinavir/ritonavir dosed once- (QD) or twice-daily (BID) in antiretroviral-naïve HIV-1 infected subjects (see Figure 1).

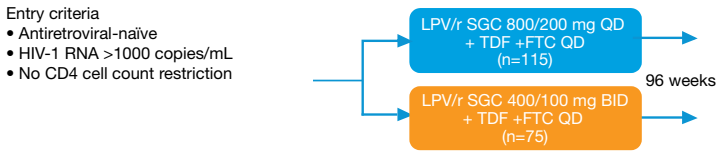
Figure 1. Study Designs for M99-056 and M02-418

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.

The studies differed with respect to sample size and NRTI backbone: M99-056 (n=38) utilized stavudine (d4T) and lamivudine (3TC) dosed BID; M02-418 (n=190) used tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) dosed QD. Plasma HIV-1 RNA was measured every 4 weeks (from Baseline to Week 24), every 8 weeks (from Week 24 to Week 48) and every 12 weeks (from Week 48 to Week 96). For the analysis, viral load suppression was defined by the first of two consecutive viral loads <50 copies/mL after initiating treatment. Loss of viral load suppression, or viral rebound, was defined by at least one viral load ≥50 copies/mL after initial suppression of the viral load. MEMS® monitors were used to compile dosing histories with the lopinavir/ritonavir component of the antiretroviral regimen. Subjects underwent a 5–14 day placebo lead-in period during which instruction on use of MEMS monitors and feedback on adherence were provided. Taking adherence, defined as the percentage of prescribed doses taken, was used to summarize adherence. In evaluating the association between the time to viral load suppression and adherence to lopinavir/ritonavir, taking adherence was estimated from the time the subject initiated study treatment until initial detection of viral load suppression, or the subject's last visit in cases where the subject never achieved viral load suppression. In relating adherence and time to viral rebound, taking adherence was estimated from the subject's dosing history during the 30-day period before a viral rebound was detected, or the subject's last visit in cases where viral load rebound did not occur.

The pattern of the relationships between either time to viral load suppression or time to viral rebound and taking adherence was assessed using Cox proportional hazards models where smoothing splines are used to transform the explanatory variable. As output from this model, the relationships between the log hazard ratio (a relative measure of the rate of viral suppression/rebound events at a certain time) and the taking adherence were plotted. The threshold in taking adherence above which there was no further improvement in the log hazard ratio of virologic suppression/viral rebound was visually identified. The significance of this threshold was further tested using a Log-rank test.

Results

Of 228 subjects enrolled, 214 (94%) were evaluable and 189 (83%) achieved viral load suppression at some point during the 96-week studies. Demographic and baseline characteristics were similar for subjects who received either lopinavir/ritonavir QD or lopinavir/ritonavir BID in these studies (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 ± SD	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	

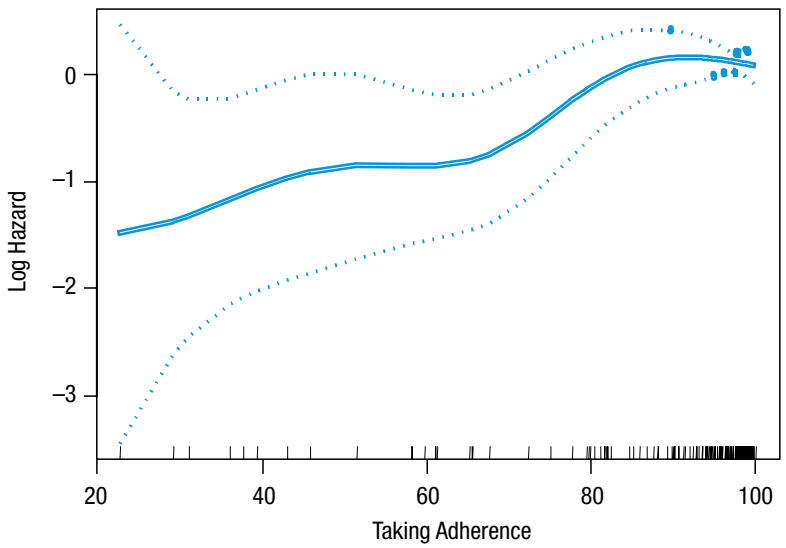
LPV/r = Lopinavir/ritonavir; IQR = Interquartile range

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

Achieving Viral Load Suppression – The Role of Adherence

The relationship between the time to achieve viral load suppression and taking adherence is summarized in Figure 2.

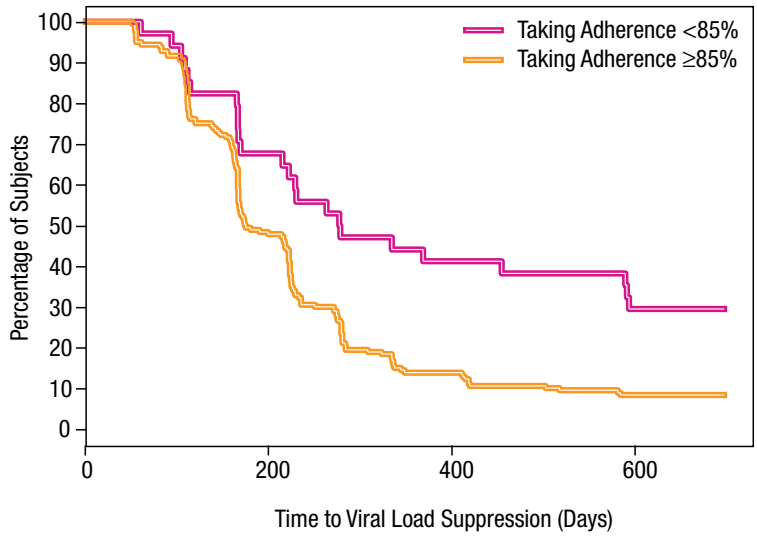
Figure 2. Relationship Between Time to Achieve Viral Load Suppression and Taking Adherence (derived from a Cox proportional hazards model with smoothing splines of taking adherence, and 4 degrees of freedom)



The model suggests a plateau of log hazard ratio near a taking adherence of 85%, indicating the level of taking adherence – the percentage of prescribed doses taken – needed over time to achieve viral load suppression.

Subjects were then stratified post-hoc into two distinct groups using their estimated taking adherence over time (i.e., <85% vs. ≥85%). After stratification, subjects with taking adherence ≥85% were more likely to achieve viral load suppression than those with taking adherence <85% (Log rank test: P=0.001, see Figure 3).

Figure 3. Kaplan-Meier Curves for the Percentage of Subjects Not Yet Achieving Viral Load Suppression Stratified by Taking Adherence Level

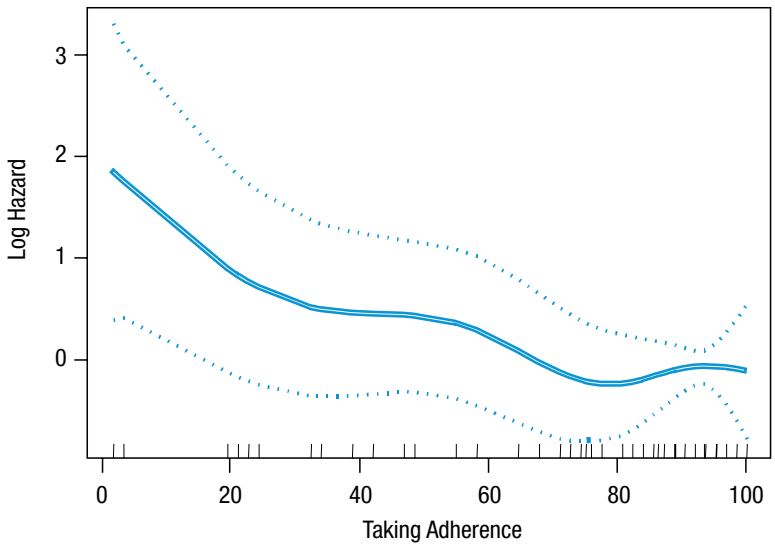


Maintaining Viral Load Suppression – The Role of Adherence

Of the 189 subjects achieving viral load suppression, 65 (34%) subsequently experienced viral rebound with at least one viral load ≥50 copies/mL. Taking adherence was measured during the 30-day period prior to viral rebound (or for 30 days prior to the last visit if failure did not occur). For subjects with missing adherence data around this time, two analyses were performed: 1) patients who experienced a "non-monitored" period of adherence during this time were excluded from the analysis (15 patients); and 2) patients who experienced a non-monitored period during this time were included, but assumed to have taking adherence of zero.

The relationship between the time to viral load rebound (loss of viral load suppression) and taking adherence is shown in Figure 4.

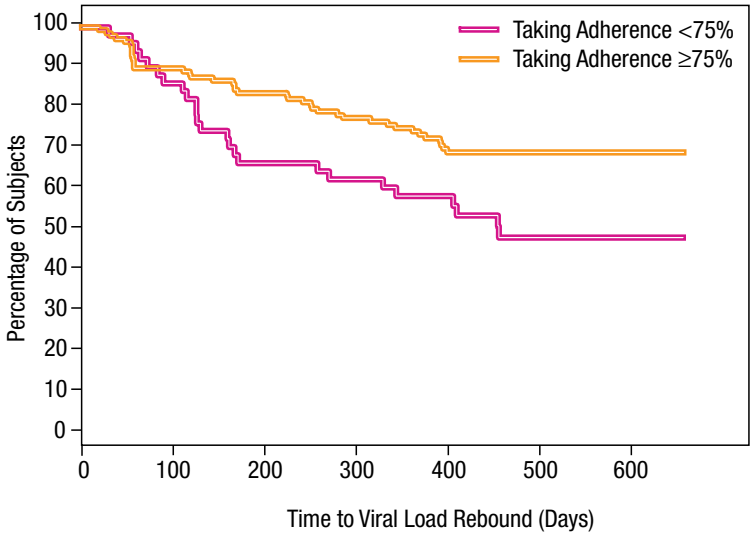
Figure 4. Relationship Between Time to Viral Load Rebound and Taking Adherence in Those Subjects Who Previously Achieved Viral Load Suppression (derived from a Cox proportional hazards model with smoothing splines of taking adherence, and 4 degrees of freedom)



The model suggests a plateau in the log hazard ratio near a taking adherence level of 75%, indicating the level of taking adherence necessary to maintain viral load suppression in those subjects who previously achieved viral load suppression. The shape of the log-hazard function was similar regardless of the assumptions made with respect to taking adherence during non-monitored periods.

The relationship between adherence and viral rebound is shown in Figure 5.

Figure 5. Kaplan-Meier Curves for the Percentage of Subjects Who Previously Achieved Viral Load Suppression and Did Not Experience Viral Load Rebound By Taking Adherence Level



Subjects with taking adherence <75% (see above figure) were more likely to experience at least one viral load ≥50 copies/mL than those with taking adherence ≥75% (Log rank test: P=0.015).

Discussion

Previous adherence research has mainly focused on the percentage of prescribed doses taken to provide explanation for untoward clinical events that arise from patient nonadherence. Unfortunately, the percentage of prescribed doses taken is a one-dimensional expression of dosing history data that excludes the important dimension of time: when doses were missed and the length of sequential omissions of doses (drug holidays). As an example, the clinical impact of missing 8 single doses in the course of a two-month period is probably considerably less than that of an 8-day drug holiday of sequentially missed doses. Yet each of these two patterns of dose omission produces the same percentage of prescribed doses taken. Given the documented diversity of temporal patterns of dosing errors, there is a clear need to understand how these various types of error impact viral load evolution and emergent drug resistance.

Conclusions

For a lopinavir/ritonavir-based regimen, subjects with less than 95% adherence were able to achieve and then maintain viral load suppression. Further, a greater level of taking adherence may be needed to achieve viral load suppression (~85%) than to maintain viral load suppression (~75%) in these subjects. These relationships may differ for other protease inhibitors and other antiretroviral treatment regimens.

References

1. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000 Jul 4;133(1):21–30.

2. Shuter J, Sarlo JA, Kanmaz TJ, et al. HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rates less than 95%. *J Acquir Immune Defic Syndr.* 2007 May 1;45(1):4–8.