Predictors of Persistence With Lopinavir/ritonavir (LPV/r) Soft-Gelatin Capsule-Based Antiretroviral Regimens

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45th Annual Meeting of the Infectious Diseases Society of America (IDSA), 4–7 October 2007, San Diego, CA, USA

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Poster #954

Background

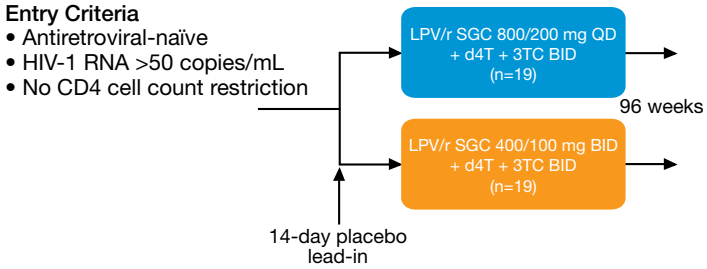
Medication persistence is a metric capturing the time from initiation to discontinuation of a prescribed therapy. Though the reasons for premature discontinuation of prescribed therapy in clinical trials are often summarized, determinants of persistence have not been well defined in HIV-1 infected subjects. Lack of persistence may complicate clinical management, resulting in the need for additional follow-up care, changes to the antiretroviral treatment regimen and additional diagnostic testing. The purpose of this study was to identify demographic and baseline characteristics of HIV-1 infected subjects from two similarly designed clinical trials who prematurely discontinued prescribed therapy with lopinavir/ritonavir in an attempt to better understand risk factors for discontinuation and to maximize persistence. Better understanding of predictors of persistence may allow for the development of targeted interventions to improve or enhance adherence.

Methods

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

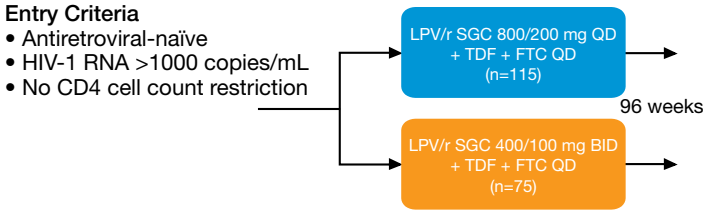
Figure 1. Study Designs for M99-056 and M02-418

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:



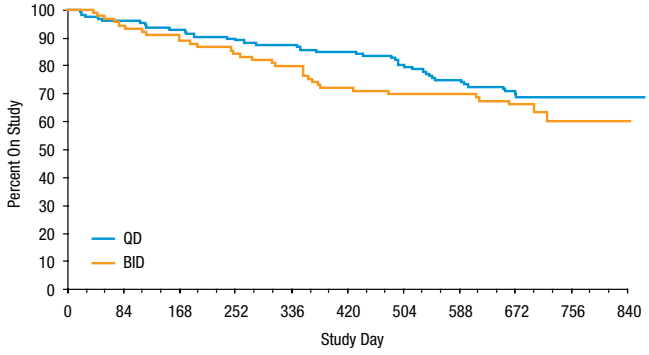
Johnson MA, et al. A Once-Daily Lopinavir/ritonavir-based Regimen Provides Noninferior Antiviral Activity Compared with a Twice-Daily Regimen. *J Acquir Immune Defic Syndr* 2006:43;153–60.

The studies differed with respect to sample size and NRTI backbone: M99-056 (n=38) utilized stavudine and lamivudine dosed twice daily; M02-418 (n=190) used tenofovir disoproxil fumarate and emtricitabine dosed once daily. MEMS® monitors recorded and stored dosing histories with the lopinavir/ritonavir component of the regimen only. Subjects underwent a 5-14 day placebo lead-in period during which instruction on use of MEMS monitors and feedback on adherence were provided. Classification tree methodology (CART®) was used to evaluate premature discontinuations as a function of demographic and baseline characteristics. In particular, the Gini index was used to evaluate all possible binary (recursive) partitions, with discrete variables automatically evaluated using all possible two-way splits (groupings) and continuous variables evaluated at cut-points along the spectrum. Surrogate splitting rules were used in the event that demographic or baseline characteristics were associated with missing data. For the purpose of this analysis: study; lopinavir/ritonavir dosing frequency; gender; race/ethnicity; tobacco use; alcohol use; individual HIV risk factors; hepatitis B surface antigen status; and hepatitis C antibody status were considered discrete variables, while age; height; weight; time since diagnosis; baseline HIV-1 RNA level; and baseline CD4+ T-cell count were considered continuous variables.

Results

216 subjects had MEMS data available and were included in the analysis. Of these, 74 (34%) prematurely discontinued treatment with lopinavir/ritonavir. Figure 2 shows Kaplan-Meier curves of subject persistence with prescribed therapy in the combined analysis by lopinavir/ritonavir dosing frequency.

Figure 2. Persistence with Prescribed Therapy by Lopinavir/ritonavir Dosing Frequency (Combined Analysis)



Persistence did not differ by lopinavir/ritonavir dosing frequency (p=0.5706; Log-Rank test).

Demographic and baseline characteristics for the subjects included in the analysis are shown in Table 1.

Results continued

Table 1. Summary of Demographic/Baseline Characteristics for Subjects Who Did or Did Not Prematurely Discontinue Study Therapy

	Prematurely Discontinued		Period of Premature Discontinuation			
	Yes	**No**	**Days 1–168**	**Days 169–336**	**Days 337+**	**Never DC'd**
Study	P=0.5601		P=0.4293			
M99-056	10 (28.6%)	25 (71.4%)	1 (2.9%)	1 (2.9%)	8 (22.9%)	25 (71.4%)
M02-418	64 (35.4%)	117 (64.6%)	17 (9.4%)	15 (8.3%)	32 (17.7%)	117 (64.6%)
Lopinavir/ritonavir Dosing Frequency	P=0.6652		P=0.4303			
Once daily	42 (33.1%)	85 (66.9%)	9 (7.1%)	7 (5.5%)	26 (20.5%)	85 (66.9%)
Twice daily	32 (36.0%)	57 (64.0%)	9 (10.1%)	9 (10.1%)	14 (15.7%)	57 (64.0%)
Gender	P=0.4910		P=0.3343			
Male	60 (35.7%)	108 (64.3%)	14 (8.3%)	11 (6.6%)	35 (20.8%)	108 (64.3%)
Female	14 (29.2%)	34 (70.8%)	4 (8.3%)	5 (10.4%)	5 (10.4%)	34 (70.8%)
Race/Ethnicity	P=0.2189		P = N/A (Insufficient Memory)			
White	35 (32.1%)	74 (67.9%)	6 (5.5%)	9 (8.3%)	20 (18.3%)	74 (67.9%)
Black	25 (36.2%)	44 (63.8%)	6 (8.7%)	5 (7.2%)	14 (20.3%)	44 (63.8%)
Hispanic	12 (52.2%)	11 (47.8%)	4 (17.4%)	2 (8.7%)	6 (26.1%)	11 (47.8%)
Asian	2 (15.4%)	11 (84.6%)	2 (15.4%)	0 (0.0%)	0 (0.0%)	11 (84.6%)
American Indian/Alaska Native	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Other	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Age (Years)	P=0.4439 (0.5078)		P=0.3542 (0.4581)			
N	74	142	18	16	40	142
Mean ± SD	39.7 ± 10.79	38.5 ± 10.04	43.1 ± 12.33	38.9 ± 10.00	38.4 ± 10.30	38.5 ± 10.04
Median	40	38	42.5	41.5	38.0	38.0
IQR	(31, 46)	(31, 44)	(33.0, 51.0)	(30.5, 43.0)	(31.0, 43.5)	(31.0, 44.0)
Time Since Diagnosis (Yrs)	P=0.6315 (0.7213)		P=0.7735 (0.4965)			
N	74	142	18	16	40	142
Mean ± SD	2.05 ± 3.429	2.32 ± 4.091	2.76 ± 4.002	1.57 ± 2.324	1.92 ± 3.550	2.32 ± 4.091
Median	0.52	0.39	1.63	0.28	0.48	0.39
IQR	(0.17, 2.10)	(0.18, 1.76)	(0.28, 3.89)	(0.19, 1.99)	(0.15, 1.27)	(0.18, 1.76)
HIV-1 RNA (log_{10} copies/mL)	P=0.7636 (0.9817)		P=0.7591 (0.9829)			
N	74	142	18	16	40	142
Mean ± SD	4.80 ± 0.798	4.83 ± 0.688	4.88 ± 0.720	4.64 ± 1.104	4.82 ± 0.694	4.83 ± 0.688
Median	4.77	4.78	4.70	4.71	4.82	4.78
IQR	(4.38, 5.43)	(4.31, 5.43)	(4.45, 5.43)	(4.02, 5.55)	(4.39, 5.43)	(4.31, 5.43)
CD4+ T-cell Count (cells/mm^3)	P=0.6545 (0.5486)		P=0.7406 (0.5256)			
N	74	142	18	16	40	142
Mean ± SD	255.8 ± 190.43	243.5 ± 192.78	221.6 ± 177.83	289.2 ± 166.50	257.8 ± 205.99	243.5 ± 192.78
Median	224	210	162	267	224	210
IQR	(95, 378)	(100, 343)	(79, 368)	(173, 439)	(89, 376)	(100, 343)
Taking Compliance (Lead-in Period) @	P=0.0807 (0.0639)		P=0.2795 (0.2862)			
N	64	117	17	15	32	117
Mean ± SD	94.9 ± 23.63	101.3 ± 23.10	91.2 ± 29.98	94.0 ± 19.93	97.3 ± 21.85	101.3 ± 23.10
Median	100	100	100	100	100	100
IQR	(80, 105)	(100, 120)	(80, 110)	(90, 100)	(80, 110)	(100, 120)
Correct Dosing Compliance (Lead-in Period) @	P=0.0597 (0.0791)		P=0.2526 (0.2744)			
N	64	117	17	15	32	117
Mean ± SD	74.8 ± 27.74	82.0 ± 22.45	72.9 ± 30.77	72.0 ± 28.08	77.0 ± 26.61	82.0 ± 22.45
Median	80	80	80	80	80	80
IQR	(60, 100)	(80, 100)	(60, 100)	(60, 80)	(70, 100)	(80, 100)
Timing Compliance (Lead-in Period) @	P=0.0838 (0.0611)		P=0.2503 (0.2473)			
N	64	117	17	15	32	117

Results continued

	Prematurely Discontinued		Period of Premature Discontinuation			
	Yes	No	Days 1–168	Days 169–336	Days 337+	Never DC'd
Mean ± SD	72.8 ± 34.57	81.2 ± 29.05	67.2 ± 41.04	70.7 ± 34.00	76.7 ± 31.65	81.2 ± 29.05
Median	89	100	89	78	89	100
IQR	(50, 100)	(67, 100)	(25, 100)	(56, 100)	(53, 100)	(67, 100)
History of Tobacco Use	P=0.0388		P=0.3179			
Non-User	24 (26.4%)	67 (73.6%)	7 (7.7%)	5 (5.5%)	12 (13.2%)	67 (73.6%)
Ex-User	12 (29.3%)	29 (70.7%)	3 (7.3%)	2 (4.9%)	7 (17.1%)	29 (70.7%)
User	37 (45.1%)	45 (54.9%)	8 (9.8%)	9 (11.0%)	20 (24.4%)	45 (54.9%)
Unknown	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)
History of Alcohol Use	P=0.0207		P=0.0446			
Non-Drinker	15 (22.4%)	52 (77.6%)	1 (1.5%)	5 (7.5%)	9 (13.4%)	52 (77.6%)
Ex-Drinker	15 (51.7%)	14 (48.3%)	6 (20.7%)	2 (6.9%)	7 (24.1%)	14 (48.3%)
Drinker	43 (36.4%)	75 (63.6%)	11 (9.3%)	9 (7.6%)	23 (19.5%)	75 (63.6%)
Unknown	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)
Risk Factor: Homo/Bisexual Male	P>0.9999		P=0.5632			
No	39 (33.9%)	76 (66.1%)	11 (9.6%)	10 (8.7%)	18 (15.7%)	76 (66.1%)
Yes	35 (34.7%)	66 (65.3%)	7 (6.9%)	6 (5.9%)	22 (21.8%)	66 (65.3%)
Risk Ractor: IV Drug User	P=0.5859		P=0.4985			
No	70 (35.0%)	130 (65.0%)	16 (8.0%)	15 (7.5%)	39 (19.5%)	130 (65.0%)
Yes	4 (25.0%)	12 (75.0%)	2 (12.5%)	1 (6.3%)	1 (6.3%)	12 (75.0%)
Risk Factor: Sex Partner HIV Positive	P=0.4608		P=0.8733			
No	49 (36.3%)	86 (63.7%)	12 (8.9%)	10 (7.4%)	27 (20.0%)	86 (63.7%)
Yes	25 (30.9%)	56 (69.1%)	6 (7.4%)	6 (7.4%)	13 (16.0%)	56 (69.1%)
Risk Factor: Sex Partner IV Drug User	P>0.9999		P=0.5689			
No	73 (34.1%)	141 (65.9%)	18 (8.4%)	16 (7.5%)	39 (18.2%)	141 (65.9%)
Yes	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)
Risk Factor: Transfusion Recipient	P>0.9999		P>0.9999			
No	74 (34.4%)	141 (65.6%)	18 (8.4%)	16 (7.4%)	40 (18.6%)	141 (65.6%)
Yes	0 (0.0%)	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
Risk Factor: Unknown	P=0.1227		P=0.4692			
No	69 (36.1%)	122 (63.9%)	16 (8.4%)	15 (7.9%)	38 (19.9%)	122 (63.9%)
Yes	5 (20.0%)	20 (80.0%)	2 (8.0%)	1 (4.0%)	2 (8.0%)	20 (80.0%)
Risk Factor: Other	P=0.1560		P=0.1088			
No	66 (32.8%)	135 (67.2%)	16 (8.0%)	13 (6.5%)	37 (18.4%)	135 (67.2%)
Yes	8 (53.3%)	7 (46.7%)	2 (13.3%)	3 (20.0%)	3 (20.0%)	7 (46.7%)
Hepatitis B Surface Antigen	P>0.9999		P=0.9587			
Negative	69 (34.3%)	132 (65.7%)	17 (8.5%)	15 (7.5%)	37 (18.4%)	132 (65.7%)
Positive	5 (35.7%)	9 (64.3%)	1 (7.1%)	1 (7.1%)	3 (21.4%)	9 (64.3%)
Hepatitis C Virus	P=0.8096		P=0.8124			
Negative	66 (34.0%)	128 (66.0%)	16 (8.2%)	15 (7.7%)	35 (18.0%)	128 (66.0%)
Positive	8 (38.1%)	13 (61.9%)	2 (9.5%)	1 (4.8%)	5 (23.8%)	13 (61.9%)
Height (cm)	P=0.9408 (0.9981)		P=0.0674 (0.0736)			
N	72	136	18	15	39	136
Mean ± SD	172.5 ± 10.28	172.6 ± 9.40	168.9 ± 9.93	169.5 ± 11.65	175.3 ± 9.27	172.6 ± 9.40
Median	172.7	172.7	169.0	167.6	175.3	172.7
IQR	166.2 – 180.3	166.0 – 179.0	163.0 – 172.7	157.5 – 180.3	170.2 – 182.0	166.0 – 179.0
Weight (kg)	P=0.9700 (0.8043)		P=0.9700 (0.9653)			
N	74	142	18	16	40	142
Mean ± SD	73.8 ± 16.53	73.9 ± 15.28	71.4 ± 13.25	72.3 ± 17.26	75.5 ± 17.71	73.9 ± 15.28
Median	71.3	71.9	72.3	71.5	70.3	71.9
IQR	63.5 – 81.2	63.5 – 82.1	62.6 – 81.2	60.9 – 80.5	64.0 – 80.6	63.5 – 82.1

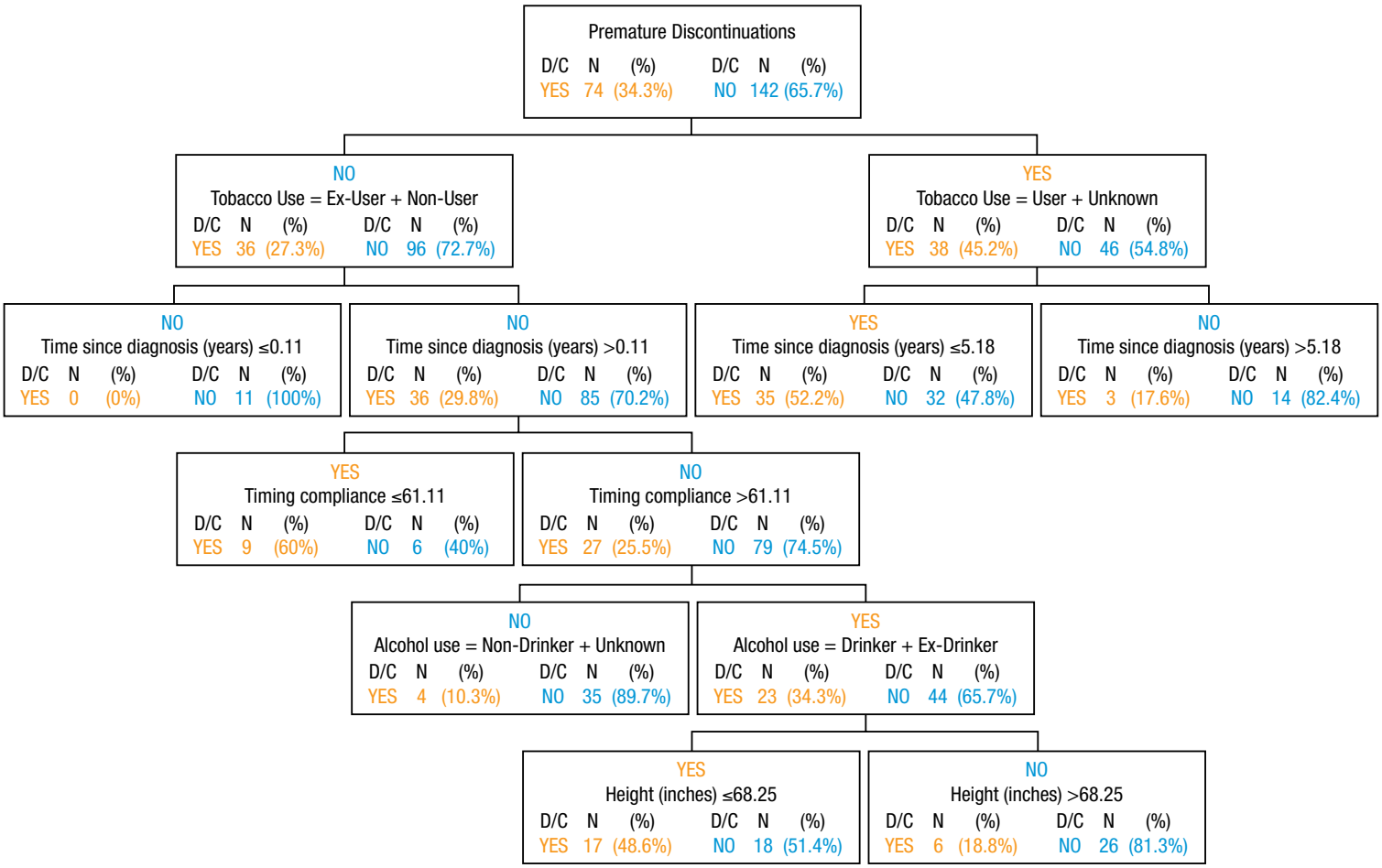
Note: Discrete variables were evaluated using Fisher's exact test, while continuous variables were evaluated using both a one-way analysis of variance (ANOVA) model and the Kruskal-Wallis test (p-values within parentheses). @ = M02-418 only

Results continued

In univariate analyses, study assignment, lopinavir/ritonavir dosing frequency, gender, race, age, height, weight, baseline HIV-1 RNA and CD4+ T-cell count, risk factors for HIV infection, hepatitis B or C co-infection status and lead-in compliance parameters did not differ between subjects who did or did not discontinue lopinavir/ritonavir (p≥0.060). Non-users of tobacco were less likely to discontinue lopinavir/ritonavir (p=0.039), as were non-drinkers of alcohol (p=0.021).

The classification tree (Figure 3) included tobacco use (Ex-User + Non-User *vs.* User + Unknown, categories were grouped together by CART® as they provided the best split), time since HIV-1 diagnosis (≤0.11 yrs *vs.* >0.11 yrs; ≤5.18 yrs *vs.* >5.18 yrs), lead-in timing compliance (≤61.11% *vs.* >61.11%), alcohol use (Non-Drinker + Unknown *vs.* Drinker + Ex-Drinker) and height (≤68.25" *vs.* >68.25"). Area under the ROC curve was 0.763.

Figure 3. Classification Tree of Premature Discontinuations as a Function of Demographic and Baseline Characteristics



Conditional analysis conducted at each split from the classification tree presented in Figure 3 suggests that tobacco use (Ex-User + Non-User *vs.* User + Unknown; p=0.008), time since diagnosis ([a] ≤0.11 years *vs.* >0.11 years; p=0.035 and [b] ≤5.18 years *vs.* >5.18 years; p=0.014), lead-in timing compliance (≤61.11% *vs.* >61.11%; p=0.013), alcohol use (Non-Drinker + Unknown *vs.* Drinker + Ex-Drinker; p=0.006), and height (≤68.25 inches *vs.* >68.25 inches; p=0.019) are associated with premature discontinuation of subjects who received lopinavir/ritonavir-based antiretroviral therapy.

Conclusions

- Tobacco and alcohol use, time since HIV-1 diagnosis and timing compliance during a pre-treatment lead-in period may aid identification of subjects at greater risk for discontinuation of lopinavir/ritonavir soft-gelatin capsules, and may be targets for interventions to support medication persistence. Further research is needed to verify these results.

Acknowledgements

The authors would like to acknowledge the contributions made by the study subjects and investigators who participated in these studies. In addition, we would like to acknowledge Renee Heuser, Kevin Niemi and Karen Wikstrom for their role in collecting and analyzing the data.