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

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Background

- Medication persistence is a metric capturing the time from initiation to discontinuation of a prescribed therapy.
- The reasons for premature discontinuation of prescribed therapy in clinical trials are often summarized.
- However, demographic and baseline characteristics of those who do or do not discontinue therapy are infrequently evaluated in an attempt to better understand risk factors for discontinuation and to maximize time on therapy (persistence).
- 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.

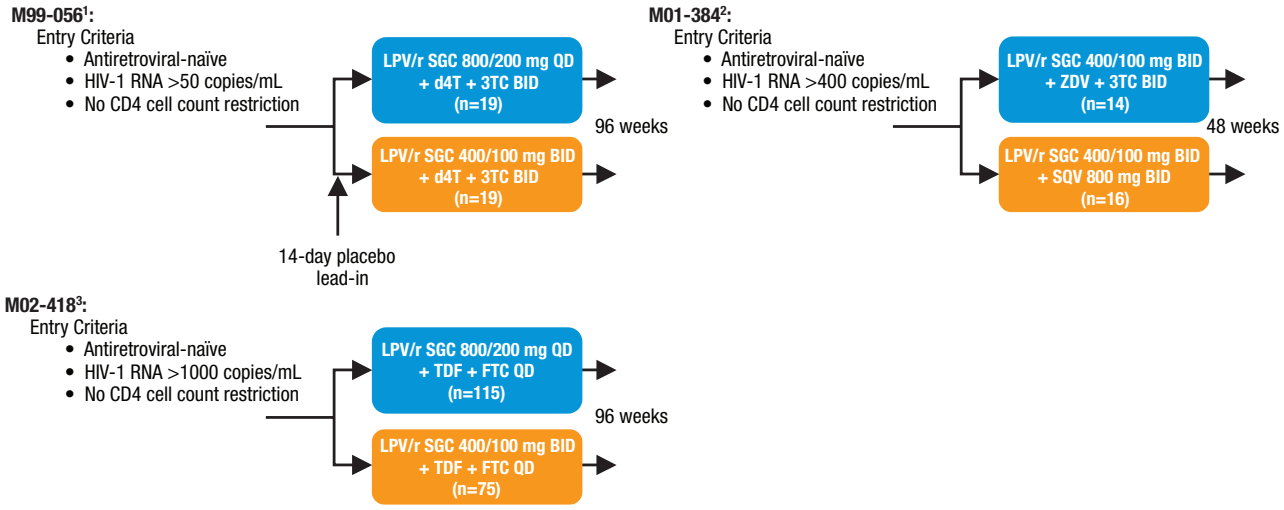
Objective

- The purpose of this analysis was to identify demographic and baseline characteristics of HIV-1 infected subjects from three similarly designed clinical trials who prematurely discontinued prescribed therapy with LPV/r 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

- Abbott studies M99-056[1], M01-384[2] and M02-418[3] were prospective, randomized, parallel arm, 48- to 96-week trials evaluating the safety and efficacy of LPV/r in combination with nucleoside reverse transcriptase inhibitors (NRTIs) in antiretroviral-naïve HIV-1 infected subjects.
- The three studies differed with respect to sample size, LPV/r dosing and NRTI backbone: M99-056 (n=38), LPV/r QD vs. BID, both with d4T+3TC dosed BID; M01-384 (n=30), LPV/r BID, with either SQV dosed BID (no NRTI) or AZT+3TC dosed BID; and M02-418 (n=190), LPV/r QD vs. BID, both with TDF+FTC dosed QD.
- MEMS® monitors recorded LPV/r dosing histories only. Time to premature discontinuation was evaluated using survival trees (GUIDE) to identify risk factors for premature discontinuation and to partition patients into groups with similar persistence outcomes.
- The following demographic and baseline characteristics were considered in the analysis of persistence with LPV/r: study, sex, race, age, height (in vs. cm), weight (lb vs. kg), tobacco use, alcohol use, hepatitis B status, hepatitis C status, HIV risk factors (homo/bisexual male vs. IV drug user), time since HIV-1 diagnosis, baseline HIV-1 RNA level, and baseline CD4+ T-lymphocyte count.
- Taking (TAC), correct dosing (COD), and timing (TIC) compliance during the first four weeks of study therapy were also considered in the analysis of persistence with LPV/r.

Figure 1. Study Design



Results

- Of 253 subjects enrolled, 246 have MEMS data available for the first four weeks of study therapy. Of these, 51 (21%) subsequently discontinued study therapy during the first 48 weeks of follow-up.

Table 1. Summary of Demographic and Baseline Characteristics

Characteristic	M99-056	M02-418	M01-384	Overall
LPV/r Dosing Regimen				
800/200 QD	18 (51.4%)	109 (60.2%)		127 (51.6%)
400/100 BID	17 (48.6%)	72 (39.8%)	14 (46.7%)	103 (41.9%)
400/100 BID + SQV			16 (53.3%)	16 (6.5%)
Sex				
Male	26 (74.3%)	142 (78.5%)	30 (100.0%)	198 (80.5%)
Female	9 (25.7%)	39 (21.5%)		48 (19.5%)
Race/Ethnicity				
White	11 (31.4%)	98 (54.1%)	14 (46.7%)	123 (50.0%)
Black	13 (37.1%)	56 (30.9%)	9 (30.0%)	78 (31.7%)
Hispanic	9 (25.7%)	14 (7.7%)	2 (6.7%)	25 (10.2%)
Asian	2 (5.7%)	11 (6.1%)	2 (6.7%)	15 (6.1%)
Native American/Alaska Native		1 (0.6%)	1 (3.3%)	2 (0.8%)
Mixed			1 (3.3%)	1 (0.4%)
Other		1 (0.6%)	1 (3.3%)	2 (0.8%)
Age (Years)				
N	35	181	30	246
Mean (SD)	37.9 (10.70)	39.1 (10.24)	40.8 (11.32)	39.2 (10.42)
Range	22–74	19–75	21–64	19–75
Height (in)				
N	35	173	27	235
Mean (SD)	67.7 (4.25)	68.0 (3.73)	68.7 (2.47)	68.0 (3.69)
Range	60–76	59–79	63–73	59–79
Weight (lb)				
N	35	181	30	246
Mean (SD)	170.0 (46.64)	161.5 (31.69)	168.8 (29.89)	163.6 (34.03)
Range	102–289	99–270	115–282	99–289
Tobacco Use				
Non-User	17 (48.6%)	74 (40.9%)	14 (46.7%)	105 (42.7%)
User	8 (22.9%)	74 (40.9%)	7 (23.3%)	89 (36.2%)
Ex-User	10 (28.6%)	31 (17.1%)	9 (30.0%)	50 (20.3%)
Not Reported		2 (1.1%)		2 (0.8%)
Alcohol Use				
Non-Drinker	7 (20.0%)	60 (33.1%)	6 (20.0%)	73 (29.7%)
Drinker	17 (48.6%)	101 (55.8%)	18 (60.0%)	136 (55.3%)
Ex-Drinker	11 (31.4%)	18 (9.9%)	6 (20.0%)	35 (14.2%)
Not Reported		2 (1.1%)		2 (0.8%)
Hepatitis B Positive	1 (2.9%)	13 (7.2%)	4 (13.3%)	18 (7.3%)
Hepatitis C Positive		21 (11.7%)	5 (16.7%)	26 (10.6%)
HIV/AIDS Risk Group				
Homo/Bisexual Male	17 (48.6%)	84 (46.4%)	22 (73.3%)	123 (50.0%)
IV Drug User	2 (5.7%)	14 (7.7%)	5 (16.7%)	21 (8.5%)
Sex Partner HIV Positive	9 (25.7%)	72 (39.8%)	9 (30.0%)	90 (36.6%)
Sex Partner IV Drug User	1 (2.9%)	1 (0.6%)	1 (3.3%)	3 (1.2%)
Transfusion Recipient		1 (0.6%)	2 (6.7%)	3 (1.2%)
Other	4 (11.4%)	11 (6.1%)	1 (3.3%)	16 (6.5%)
Unknown	8 (22.9%)	17 (9.4%)	2 (6.7%)	27 (11.0%)
Time Since HIV-1 Diagnosis (Years)				
N	35	181	30	246
Mean (SD)	1.63 (3.764)	2.34 (3.890)	2.98 (4.990)	2.32 (4.019)
Range	0.07–14.28	0.07–18.47	0.14–17.29	0.07–18.47
HIV-1 RNA (log_{10} copies/mL)				
N	35	181	30	246
Mean (SD)	4.71 (0.693)	4.84 (0.732)	5.11 (0.592)	4.85 (0.716)
Range	2.83–5.88	1.70–6.44	3.69–6.21	1.70–6.44
CD4+ T-Lymphocytes (cells/mm^3)				
N	35	181	30	246
Mean (SD)	255.8 (196.13)	246.1 (191.26)	223.0 (188.70)	244.7 (191.06)
Range	5–917	3–965	3–687	3–965
Taking Compliance (Baseline – Week 4)				
N	35	181	30	246
Mean (SD)	98.94 (5.385)	95.37 (15.194)	97.55 (5.707)	96.14 (13.390)

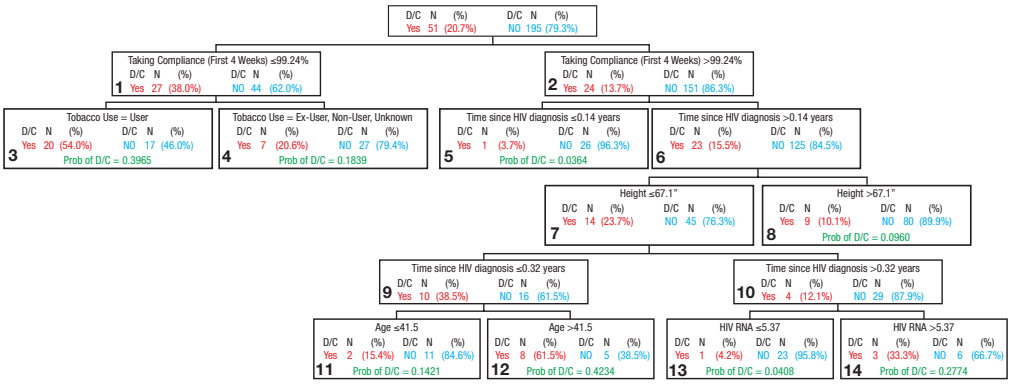
Results continued

Characteristic	M99-056	M02-418	M01-384	Overall
Range	77.42–110.53	0.00–106.25	70.37–101.92	0.00–110.53
Correct Dosing Compliance (Baseline – Week 4)				
N	35	181	30	246
Mean (SD)	92.62 (13.053)	91.37 (18.097)	94.62 (9.716)	91.94 (16.632)
Range	38.71–100.00	0.00–100.00	55.56–100.00	0.00–100.00
Timing Compliance (Baseline – Week 4)				
N	35	181	30	246
Mean (SD)	89.98 (12.682)	85.72 (21.952)	82.35 (17.173)	85.92 (20.377)
Range	50.00–100.00	0.00–100.00	37.70–100.00	0.00–100.00

SQV = saquinavir; SD = standard deviation

- Treatment duration (mean ± standard deviation) for subjects who discontinued LPV/r was 184.5 ± 114.71 days.
- Subjects with taking compliance (TAC) during the first four weeks (TAC_{0-4}) >99.24% and time since HIV diagnosis ≤0.14 years had the lowest probability of discontinuation (Prob=0.04). In contrast, the highest probability of discontinuation (Prob=0.42) was observed in subjects who were greater than 41.5 years of age, at most 67.1 inches tall, with TAC_{0-4} >99.24% and time since HIV diagnosis between 0.14 and 0.32 years.

Figure 2. Survival Tree of Persistence



- Persistence on LPV/r-based therapy is summarized in the following Kaplan-Meier plots. Log-rank P-values for comparison of the stratification groups formed by the conditional splits from the survival tree and represented in Figures 3–9 are <0.001 (Nodes 1 vs. 2), 0.006 (Nodes 3 vs. 4), 0.104 (Nodes 5 vs. 6), 0.022 (Nodes 7 vs. 8), 0.016 (Nodes 9 vs. 10), 0.015 (Nodes 11 vs. 12), and 0.016 (Nodes 13 vs. 14), respectively.

Figure 3. Persistence with LPV/r-Based Therapy Stratified by Taking Compliance During the First Four Weeks

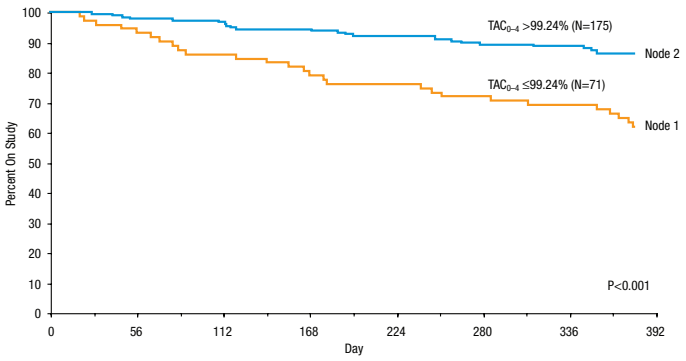


Figure 4. Persistence with LPV/r-Based Therapy Stratified by Tobacco Use

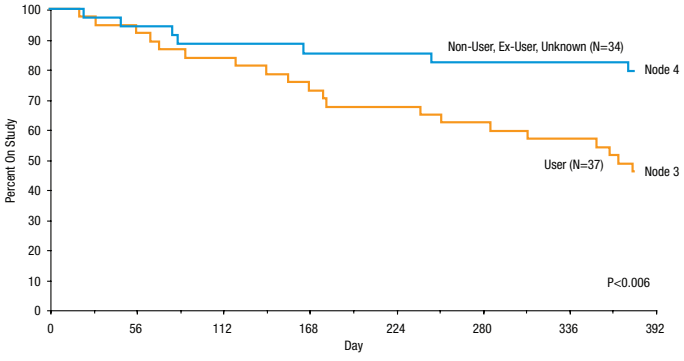


Figure 5. Persistence with LPV/r-Based Therapy Stratified by Time Since HIV-1 Diagnosis

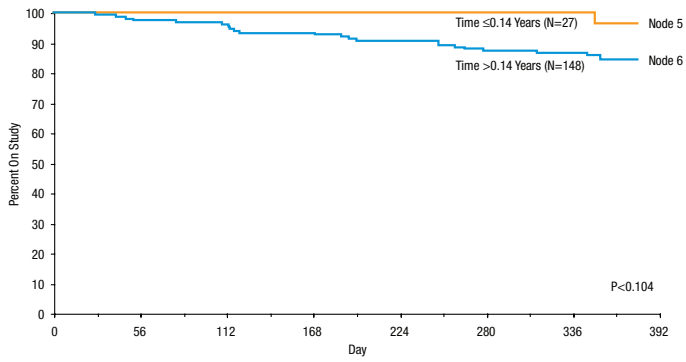
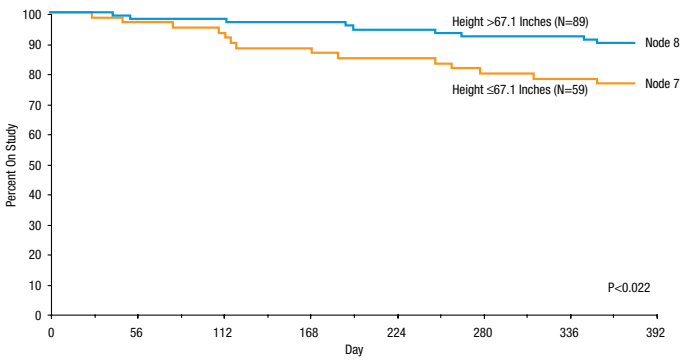


Figure 6. Persistence with LPV/r-Based Therapy Stratified by Subject Height



Results continued

Figure 7. Persistence with LPV/r-Based Therapy Stratified by Time Since HIV-1 Diagnosis

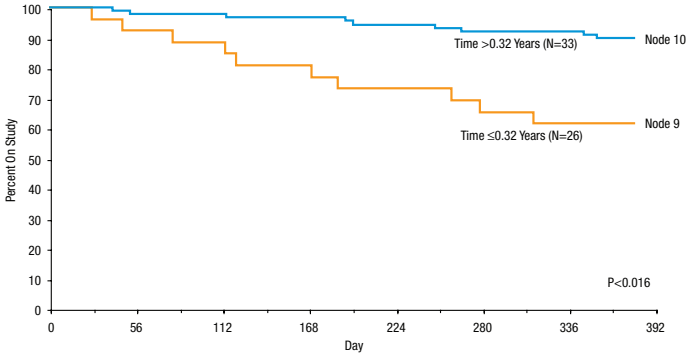


Figure 8. Persistence with LPV/r-Based Therapy Stratified by Subject Age

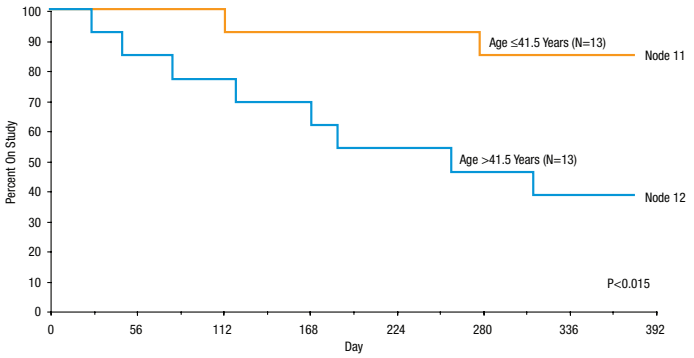
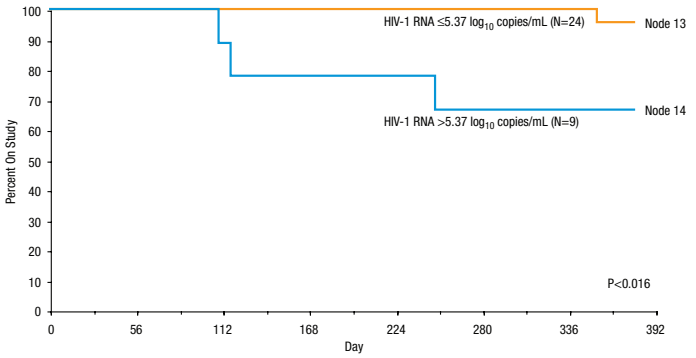


Figure 9. Persistence with LPV/r-Based Therapy Stratified by HIV-1 RNA



Discussion/Conclusions

Taking compliance during the first four weeks of therapy, tobacco use, time since HIV-1 diagnosis, height, age and baseline HIV-1 RNA level were found to be statistically significant predictors of the time to premature discontinuation.

Results are similar to those from a previous analysis of persistence (yes vs. no) in which timing compliance during the first four weeks of therapy, tobacco use, time since HIV-1 diagnosis, height and alcohol use were found to be statistically significant predictors of persistence.[4]

Demographic and baseline disease characteristics, as well as treatment compliance during the first four weeks of therapy, may aid identification of subjects at greater risk for discontinuation of LPV/r, and may offer intervention targets to support medication persistence. Associations with height require further evaluation.

References

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