Adherence with Lopinavir/ritonavir (LPV/r) Tablet and Soft-Gel Capsule (SGC)-Based Antiretroviral Regimens and Predictors of Early Treatment Compliance

R Rode PhD, T Marsh, C Naylor, D Cohen MD, T Podsadecki MD

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Corresponding Author: Richard Rode, PhD., Abbott Laboratories, 100 Abbott Park Road, Dept. R436, Bldg. AP9A-2, Abbott Park, IL 60064 P170

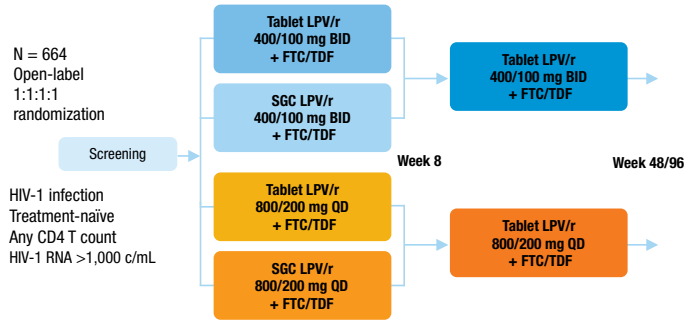
Background

- Simplified antiretroviral (ARV) regimens may promote adherence and improve outcomes in HIV-1 infected patients.
- Clinical studies have previously demonstrated greater adherence with LPV/r soft gel capsules (SGC) when dosed once-daily (QD) compared to twice-daily (BID).[1]
- Previous studies have shown patient preference for the LPV/r tablet over the SGC primarily related to convenience (lack of refrigeration, reduction in pill count and dosing without regard to meals).[2,3]
- The objectives of the current analysis are to compare adherence when LPV/r tablets and LPV/r SGC are dosed QD and BID and to assess predictors of early adherence.

Methods

- M05-730 is an ongoing Phase 3, open-label, randomized, multicenter, multi-country study designed to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of LPV/r tablets dosed QD or BID through 48 and 96 weeks in combination with once daily tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in ARV-naïve HIV-1 infected subjects.
  - 664 ARV-naïve HIV-1-infected subjects were randomized 1:1:1:1 to LPV/r QD SGC, BID SGC, QD tablet, or BID tablet for 8 weeks. At Week 8, subjects taking LPV/r SGC were switched to the LPV/r tablet formulation while maintaining their QD or BID dosing schedule (Figure 1).

Figure 1. Study Design for Study M05-730[2]



MEMS® Monitoring

- Electronic monitoring (Medication Event Monitoring System [MEMS®]; AARDEX) allowed for computation of 3 LPV/r compliance measures through Week 12: taking (TAC; prescribed doses taken), correct dosing (COD; days with correct number of doses taken) and timing (TIC; doses taken within ± 3 hours of prescribed interval) compliance.

Compliance Parameters Measured Using MEMS®*

Taking compliance (TAC) = Percentage of prescribed doses taken

$$\frac{\text{number of openings}}{\text{number of prescribed doses}} \times 100$$

Correct dosing compliance (COD) = Percentage of days with the correct number of doses taken

$$\frac{\text{number of days with openings as prescribed}}{\text{number of monitored days}} \times 100$$

Timing compliance (TIC) = Percentage of doses taken within prescribed intervals

$$\frac{\text{number of openings within } \pm 3 \text{ hours of the prescribed dosing interval}}{\text{number of prescribed doses} - 1} \times 100$$

* MEMS® monitors electronically recorded and stored the date/time of LPV/r bottle openings

Statistical Methods

- Demographic and baseline characteristics were evaluated using a one-way analysis of variance (ANOVA) for continuous measurements and Fisher's exact test for discrete measurements.
- Longitudinal mixed-effects models were used to examine the potential association between treatment compliance (through Week 12) and demographic/baseline characteristics. Given that compliance was measured at equal intervals during the first 12 weeks (i.e., Baseline – Week 4, Week 4 – Week 8, and Week 8 to Week 12), a first-order autoregressive [AR(1)] variance-covariance structure was used.
- Percentages of subjects with plasma HIV-1 RNA levels below 50 copies/mL were evaluated using Fisher's exact test. For the purpose of these analyses, an "Intent-to-Treat (ITT): Non-completer = Failure" assessment was used.
- CD4+ T-cell count changes from baseline were evaluated over time using a mixed-effects model with baseline CD4+ T-cell count as a covariate and assuming an unstructured variance-covariance matrix.

Results

Baseline Demographics

- Of the 664 subjects enrolled, 606 (91%) have MEMS® compliance data available and were included in this analysis.
- Demographic and baseline characteristics were similar between treatment arms (Table 1).

Table 1. Summary of Demographic and Baseline Characteristics by Treatment Arm

Characteristic	LPV/r QD		LPV/r BID		P-value
	Tablet	Soft-Gel Capsule	Tablet	Soft-Gel Capsule	
Sex					0.508
Male	126 (80%)	126 (83%)	117 (78%)	111 (76%)	
Female	32 (20%)	26 (17%)	33 (22%)	35 (24%)	
Age (yr)					0.369
N	158	152	150	146	
Mean (SD)	38.9 (9.81)	38.4 (9.82)	38.3 (9.69)	40.1 (10.11)	
Median	38.0	38.0	37.0	39.5	
Minimum – Maximum	22 – 69	20 – 65	21 – 71	21 – 68	
Race/Ethnicity[#]					0.820
White	127 (80.4%)	116 (76.3%)	113 (75.3%)	107 (73.3%)	
Black	22 (13.9%)	27 (17.8%)	26 (17.3%)	26 (17.8%)	
Asian	4 (2.5%)	4 (2.6%)	4 (2.7%)	8 (5.5%)	
Hispanic	1 (0.6%)	2 (1.3%)	4 (2.7%)	2 (1.4%)	
Native American	2 (1.3%)	2 (1.3%)	1 (0.7%)	1 (0.7%)	
Mixed	1 (0.6%)	1 (0.7%)	2 (1.3%)	1 (0.7%)	
Other	1 (0.6%)	0	0	1 (0.7%)	
Height (cm)					0.100
N	156	149	150	143	
Mean (SD)	174.6 (8.90)	175.1 (9.90)	172.7 (9.22)	173.2 (9.66)	
Median	175.0	175.0	173.5	175.0	
Minimum – Maximum	155 – 201	150 – 213	152 – 191	148 – 193	
Weight (kg)					0.295
N	158	150	150	145	
Mean (SD)	74.3 (16.72)	75.1 (18.76)	71.7 (13.55)	73.8 (14.69)	
Median	72.5	73.5	72.0	73.0	
Minimum – Maximum	41 – 171	37 – 159	44 – 139	33 - 132	
Tobacco Use[@]					0.996
User	64 (40.5%)	62 (40.8%)	63 (42.0%)	64 (43.8%)	
Ex-User	27 (17.1%)	23 (15.1%)	24 (16.0%)	23 (15.8%)	
Non-User	65 (41.1%)	66 (43.4%)	63 (42.0%)	59 (40.4%)	
Not Reported	2 (1.3%)	1 (0.7%)	0	0	
Alcohol Use[@]					0.090
Drinker	84 (53.2%)	87 (57.2%)	98 (65.3%)	85 (58.2%)	
Ex-Drinker	9 (5.7%)	13 (8.6%)	11 (7.3%)	18 (12.3%)	
Non-Drinker	63 (39.9%)	51 (33.6%)	40 (26.7%)	43 (29.5%)	
Not Reported	2 (1.3%)	1 (0.7%)	1 (0.7%)	0	
Hepatitis C Status					
Hepatitis C Reactive	14 (8.9%)	22 (14.5%)	15 (10.1%)	23 (15.8%)	0.195
HIV/AIDS Risk Factors					
Homo/Bisexual Male	99 (62.7%)	77 (50.7%)	83 (55.3%)	78 (53.4%)	0.172
IV Drug User	9 (5.7%)	19 (12.5%)	13 (8.7%)	12 (8.2%)	0.216
Sex Partner HIV+	31 (19.6%)	34 (22.4%)	34 (22.7%)	38 (26.0%)	0.623
Sex Partner IVDU	2 (1.3%)	1 (0.7%)	3 (2.0%)	1 (0.7%)	0.734
Transfusion Recip	1 (0.6%)	2 (1.3%)	0	3 (2.1%)	0.257
Other	8 (5.1%)	10 (6.6%)	9 (6.0%)	10 (6.8%)	0.921
Unknown	18 (11.4%)	20 (13.2%)	16 (10.7%)	13 (8.9%)	0.705
Time Since HIV-1 Diagnosis (yr)					0.049
N	158	152	150	146	
Mean (SD)	2.26 (3.254)	3.30 (4.772)	2.90 (3.947)	2.22 (3.690)	
Median	0.82	1.30	1.42	0.75	
Minimum – Maximum	0.04 – 18.14	0.05 – 26.65	0.04 – 21.27	0.06 – 19.26	
HIV-1 RNA (log_{10} copies/mL)					0.131
N	158	152	149	146	
Mean (SD)	4.93 (0.615)	4.95 (0.659)	5.07 (0.640)	5.06 (0.619)	
Median	5.02	4.96	5.21	5.14	
Minimum – Maximum	3.37 – 6.28	3.20 – 6.66	2.49 – 6.49	3.56 – 6.98	

Results continued

Table 1 (continued)

Characteristic	LPV/r QD		LPV/r BID		P-value
	Tablet	Soft-Gel Capsule	Tablet	Soft-Gel Capsule	
CD4+ T-lymphocyte Count (cells/mm^3)					0.509
N	158	151	150	146	
Mean (SD)	206.8 (122.51)	224.3 (125.87)	223.6 (135.19)	208.5 (144.03)	
Median	205.0	217.0	210.3	210.3	
Minimum – Maximum	20 – 575	20 – 665	20 – 651	20 - 775	
CD8+ T-lymphocyte Count (cells/mm^3)					0.915
N	158	151	150	146	
Mean (SD)	909.8 (563.64)	927.6 (607.94)	907.6 (615.86)	956.1 (819.37)	
Median	777.3	752.0	779.3	783.0	
Minimum – Maximum	113 – 2754	70 – 4873	35 – 4809	141 - 6907	

[#]Fisher's exact test performed after combining subjects from the following race/ethnicity categories: Asian, Hispanic, Native American/Alaskan Native, Mixed, and Other.
[@]Fisher's exact test performed after excluding subjects whose information was "Not Reported."

Compliance by treatment arm is shown in Figures 2a–2c.

Figure 2a. Estimated Taking Compliance by LPV/r Formulation and Dosing Frequency

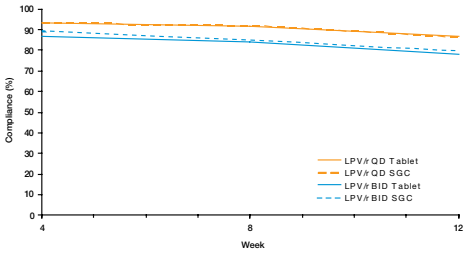


Figure 2b. Estimated Correct Dosing Compliance by LPV/r Formulation and Dosing Frequency

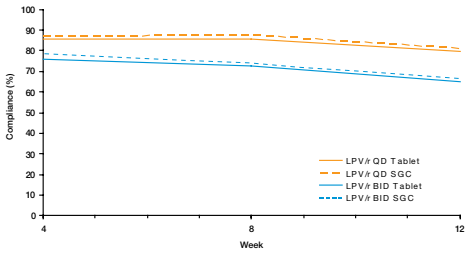
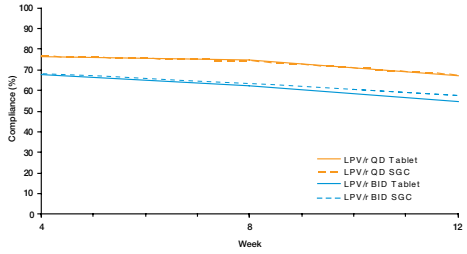


Figure 2c. Estimated Timing Compliance by LPV/r Formulation and Dosing Frequency



- Adherence to LPV/r dosed QD was statistically significantly greater than BID (p <0.001).
- Adherence declined significantly over time (p <0.001), but between-arm differences remained consistent over 12 weeks (p ≥0.353).
- Adherence was similar for subjects taking LPV/r tablets compared to SGC.

Demographic and baseline characteristics significantly associated with early compliance are shown in Table 2.

Table 2. Factors Found to be Significantly Associated with Compliance in Longitudinal Analyses (p≤0.20)

Factor	Taking Compliance	Correct Dosing Compliance	Timing Compliance
Sex	0.003	<0.001	<0.001
Age	0.138	0.030	<0.001
Race	0.098	0.007	0.003
Tobacco Use		0.143	
Homo/Bisexual Male	0.052	0.002	0.018
Sex Partner HIV+	0.080		0.089
HIV-1 RNA	0.104		0.148
CD4+ T-cell Strata	0.129		
CD8+ T-cell Count	0.049		
CD4+ T-cell Strata: 1) <100 cells/mm^3; 2) 100 – <200 cells/mm^3; 3) 200 – <300 cells/mm^3; and 4) ≥300 cells/mm^3			

- Sex, age, race, tobacco use, HIV/AIDS risk factors, HIV-1 RNA, and CD4+ and CD8+ T-cell count were significantly associated with early compliance (p≤0.20).
- The strongest associations were for TIC and sex (M>F), age (older>younger) and race (white>non-white) (p≤0.003) (Table 2; Figures 3a-3c).

Figure 3a. Estimated Timing Compliance by Gender and LPV/r Dosing Frequency

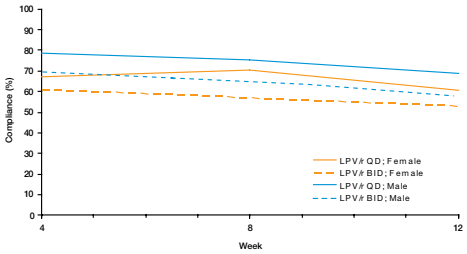


Figure 3b. Estimated Timing Compliance by Age and LPV/r Dosing Frequency

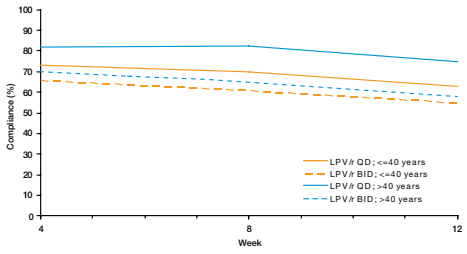
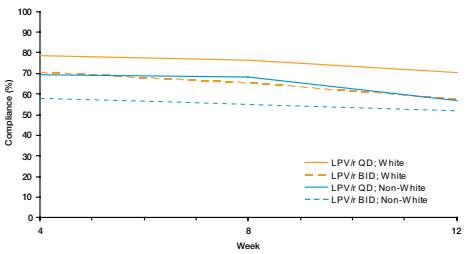


Figure 3c. Estimated Timing Compliance by Race and LPV/r Dosing Frequency



Results continued

Week 48 clinical outcomes did not differ for subjects receiving LPV/r QD or BID. Given the statistically significant association between treatment compliance and sex, age, and race, subgroup analyses were conducted to evaluate potential differences in virologic response to LPV/r-based antiretroviral therapy (Figures 4a-4c).

Figure 4a. Percentage of Subjects with HIV-1 RNA <50 copies/mL by Gender (ITT: Non-completer = Failure)

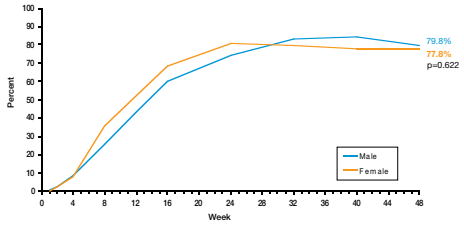


Figure 4b. Percentage of Subjects with HIV-1 RNA <50 copies/mL by Age (ITT: Non-completer = Failure)

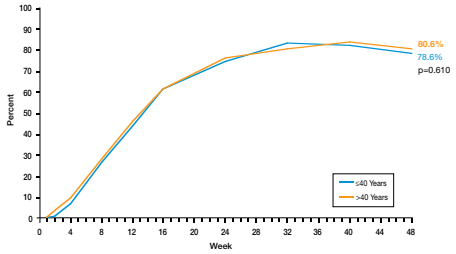
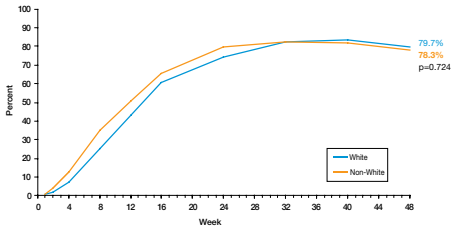


Figure 4c. Percentage of Subjects with HIV-1 RNA <50 copies/mL by Race (ITT: Non-completer = Failure)



- Based on results from these analyses, the percentages of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 did not appear to differ by sex (p=0.622), age (p=0.610) or race (p=0.724).

CD4+ T-cell counts significantly increased over time (p<0.001), with between-strata differences remaining consistent over 12 weeks (p≥0.262). Given the statistically significant association between treatment compliance and sex, age, and race, subgroup analyses were conducted to evaluate potential differences in immunologic response to LPV/r-based antiretroviral therapy (Figures 5a-5c).

Figure 5a. Longitudinal Analysis of CD4+ T-cell Count Changes from Baseline by Gender

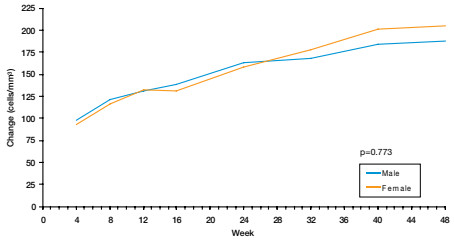


Figure 5b. Longitudinal Analysis of CD4+ T-cell Count Changes from Baseline by Age

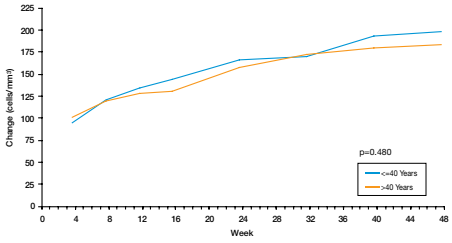
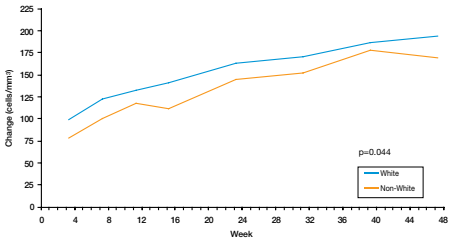


Figure 5c. Longitudinal Analysis of CD4+ T-cell Count Changes from Baseline by Race



- No significant between-strata differences were detected with respect to gender (male vs. female; p=0.773) and age (≤40 years vs. >40 years; p=0.480). However, a significant between-strata difference was detected with respect to race (white vs. non-white; p=0.044). In particular, the overall difference (mean ± SEM) between the two strata was 19.6 ± 9.67 cells/mm^3, with whites tending to have higher mean CD4+ T-cell count changes than non-whites. Of note, however, whites also had higher baseline mean CD4+ T-cell counts than non-whites (222.5 ± 6.11 vs. 193.9 ± 10.99 cells/mm^3; p=0.023).

Conclusions

- During the first 12 weeks of randomized therapy, LPV/r QD dosing resulted in higher levels of adherence than BID dosing.
- In the setting of this clinical trial, adherence to LPV/r tablets and SGC was similar. Of note, because MEMS caps were used, subjects were required to dose LPV/r from the original container which could have impacted potential differences in adherence related to the convenience of the LPV/r tablet.
- Sex, age and race were predictors of early adherence.
- Differences in early adherence at 12 weeks do not appear to predict clinical outcomes at 48 weeks.
- The significant between-strata difference observed in CD4+ T-cell increases when comparing whites to non-whites was consistent over time and may, in part, reflect the baseline CD4+ T-cell count difference between whites and non-whites observed in this study.

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