Improved Treatment Compliance with Once-Daily (QD) Compared to Twice-Daily (BID) Lopinavir/ritonavir (LPV/r) in HIV-1-Infected, Antiretroviral-Experienced Subjects

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Background

- Lopinavir/ritonavir (LPV/r), a coformulated HIV-1 protease inhibitor (PI), has been approved for use in combination therapy in both antiretroviral-naïve and treatment-experienced HIV-1-infected patients
- Prior studies of antiretroviral-naïve subjects indicated that once-daily (QD) dosing of LPV/r offered similar safety and antiviral activity as twice-daily (BID) administration[1-3], leading to approval for QD administration in antiretroviral-naïve individuals in the US and EU
- Prior analyses also noted that QD dosing resulted in greater treatment compliance than BID administration[1, 4]
- Study M06-802 was designed to test the safety, tolerability, and efficacy of QD compared to BID LPV/r in HIV-1-infected subjects with prior antiretroviral treatment experience, but who were naïve to LPV/r[5]
- QD and BID LPV/r demonstrated therapeutic equivalence through 48 weeks of treatment in antiretroviral-experienced subjects in Study M06-802[5]

Objective

To examine the relationship between LPV/r adherence and virologic response in antiretroviral-experienced subjects

Methods

Study Design

- Study M06-802 was a Phase 3, randomized, open label trial that included antiretroviral-experienced subjects failing their current regimen with plasma HIV-1 RNA >1000 copies/mL[5]
- Subjects received LPV/r tablets QD (800/200 mg, N=300) or BID (400/100 mg, N=299) with at least 2 investigator-selected nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

Adherence

- Adherence was measured by Medication Event Monitoring Systems® (MEMS®; Aardex Ltd., Zug, Switzerland) monitors (bottle caps) through 24 weeks of treatment; results were unblinded and analyzed at study end
- From baseline to Week 4, Week 8, and Week 24, three measures of adherence were calculated:
  - **Taking Compliance [TAC]**, the percentage of prescribed doses taken:

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

  - **Correct Dosing [COD]**, the 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]**, the percentage of doses taken within the prescribed interval:

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

Statistical Analysis

- Mean levels of subjects' adherence to prescribed LPV/r dosing were compared between treatment groups using a one-way analysis of variance
- The efficacy endpoint was loss of virologic response, defined as a failure to achieve confirmed HIV-1 RNA <50 copies/mL or a confirmed HIV-1 RNA rebound ≥50 copies/mL after achieving confirmed virologic suppression <50 copies/mL
- Time to loss of virologic response was summarized with Kaplan-Meier estimates and compared by quartiles of adherence using the log-rank test. Two populations were assessed:
  - All subjects with adherence data
  - Subjects with adherence data who achieved initial virologic suppression <50 copies/mL
- The effects of adherence, LPV/r dosing frequency (i.e., treatment group), and NRTI dosing frequency on the time to loss of virologic response were assessed using a Cox proportional hazards model

Results

Subjects

- Adherence data through 8 weeks were available for 256 subjects in the LPV/r QD dosing group and 265 subjects in the LPV/r BID dosing group. There was no between-group difference in the proportion of subjects with unavailable adherence data. The most frequently reported reason for the absence of adherence data was the loss of the MEMS® monitor.
- For subjects with available adherence data, baseline characteristics were similar between LPV/r treatment groups (Table 1)

Table 1. Baseline Demographics of Subjects with Available Adherence Data

Characteristic	LPV/r QD N=256	LPV/r BID N=265
Gender, n (%)		
Male	169 (66%)	177 (67%)
Female	87 (34%)	88 (33%)
Race, n (%)		
White	135 (53%)	137 (52%)
Black	87 (34%)	85 (32%)
Other	34 (13%)	43 (16%)
Ethnicity, n (%)		
Hispanic	88 (34%)	99 (37%)
Non-Hispanic	168 (66%)	166 (63%)
Age, mean ± SD	40 ± 9.1	41 ± 8.5
Hepatitis status, n (%)		
Hepatitis C positive	49 (16%)	41 (14%)
Hepatitis B positive	14 (4%)	17 (6%)
Plasma HIV-1 RNA (log_{10} copies/mL), mean ± SD	4.21 ± 0.82	4.23 ± 0.81
CD4+ T-cell count, mean ± SD	246 ± 157	269 ± 183

- The dose frequency of background NRTIs was comparable between treatment groups (Table 2)

Table 2. Subjects with Indicated Dose Frequency of NRTI Regimen

NRTI dose frequency, n (%)	LPV/r QD N=256	LPV/r BID N=265	*P* value
Entirely QD	112 (44%)	93 (35%)	0.105
Entirely BID	26 (10%)	36 (14%)	
Mix of QD and BID	118 (46%)	136 (51%)	

Adherence

- Across all measures of treatment compliance, LPV/r QD-dosed subjects had significantly greater mean adherence compared to LPV/r BID-dosed subjects (Table 3)

Table 3. Mean Adherence Rates

Time period	Adherence measure	Mean adherence values		*P* value
		LPV/r QD	LPV/r BID	
Baseline to Week 8 (N=256 QD, N=265 BID)	TAC	89.6%	84.5%	0.009
	COD	84.6%	75.2%	<0.001
	TIC	72.3%	65.5%	0.007
Baseline to Week 24 (N=251 QD, N=255 BID)	TAC	84.4%	78.1%	0.006
	COD	79.6%	68.1%	<0.001
	TIC	65.8%	58.2%	0.004

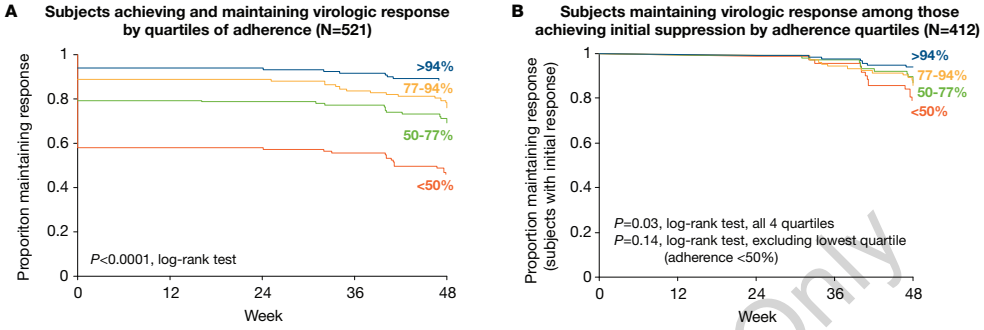
- Adherence measures were highly correlated with one another (R≥0.80, *P*<0.001 for TAC vs. COD, TAC vs. TIC, and COD vs. TIC from baseline to Week 8)

Results

Adherence and Virologic Response

- All adherence measures were strongly correlated with virologic response
  - When treatment groups were combined for analysis, adherence was strongly and broadly associated with achieving and maintaining virologic response through 48 weeks (Figure 1A)
  - Among all subjects who achieved initial viral suppression (HIV-1 RNA <50 copies/mL), only the lowest quartile of adherence was associated with an increased risk of virologic rebound through 48 weeks (Figure 1B)

Figure 1. Relationship Between Timing Compliance From Baseline to Week 8 and Virologic Response Through 48 Weeks (All Subjects)



- However, differences in the relationship between adherence and virologic response were noted when the treatment groups were analyzed individually
  - In the QD LPV/r group, while adherence was associated with the achievement of initial viral suppression (Figure 2A), it was not significantly associated with virologic rebound among subjects achieving initial suppression (Figure 2B)
    - The lowest adherence quartile had a risk of virologic rebound similar to that of the highest adherence quartile
  - In the BID LPV/r group, adherence was again associated with the achievement of initial viral suppression (Figure 3A), but in contrast to the QD-dosed LPV/r group, adherence remained significantly associated with the risk of virologic rebound among those with initial viral suppression (Figure 3B)
    - The two lowest adherence quartiles had a higher risk of virologic rebound than the two highest adherence quartiles
- Sensitivity analyses using other adherence measures (TAC or COD) or measuring adherence through other timepoints (Baseline to Week 4 or Baseline to Week 24) were consistent with these results (data not shown)

Figure 2. Relationship Between Timing Compliance From Baseline to Week 8 and Virologic Response Through 48 Weeks (QD Subjects)

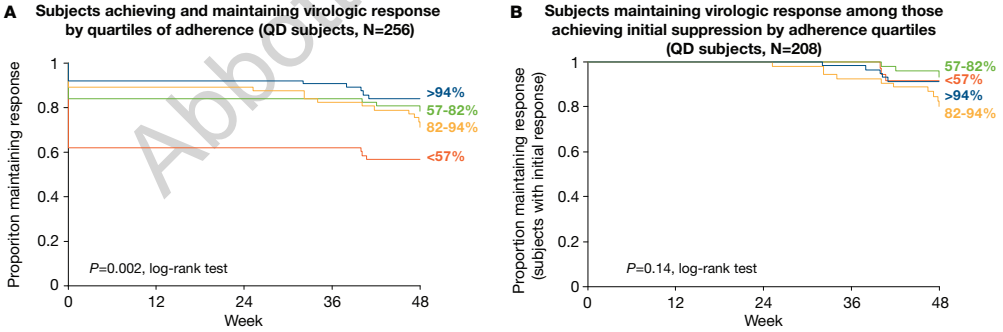
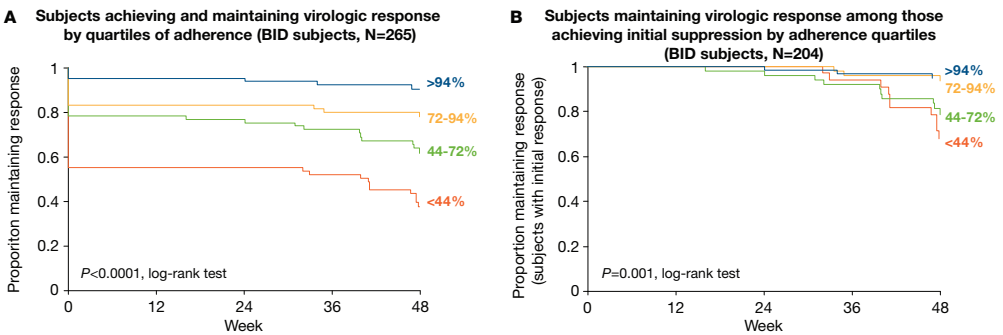


Figure 3. Relationship Between Timing Compliance From Baseline to Week 8 and Virologic Response Through 48 Weeks (BID Subjects)



Results

- LPV/r dosing frequency (QD versus BID) did not affect virologic response, before or after adjustment for adherence (Table 4)
- Dosing frequency of the NRTI regimen was not associated with loss of virologic response, and the effect of treatment group remained nonsignificant after adjustment for NRTI dosing frequency (data not shown)

Table 4. Effect of LPV/r Dose Frequency on Virologic Response

Endpoint	Unadjusted treatment effect HR (95% CI)* *P* value	Adjusted for adherence HR (95% CI)* *P* value
Failure to achieve HIV-1 RNA <50 copies/mL or time to virologic rebound ≥50 copies/mL	1.23 (0.89, 1.70) *P*=0.20	1.07 (0.78, 1.49) *P*=0.67
Time to virologic rebound ≥50 copies/mL among subjects achieving initial virologic response	1.30 (0.73, 2.31) *P*=0.37	1.21 (0.68, 2.16) *P*=0.52

*HR: Hazard Ratio; 95% CI: 95% confidence interval; values >1.0 favor longer duration of response in the QD group.

Summary

- Consistent with prior studies on predictors of antiretroviral adherence[6], mean adherence rates were lower across both LPV/r QD and BID dosing groups in this treatment-experienced population compared to rates previously observed with LPV/r in naïve subjects[1]
  - Treatment-experienced subjects may include individuals with poor adherence to prior antiretroviral regimens, which has been described to predict adherence to the current regimen[6]
- LPV/r dose frequency did not affect virologic outcome despite increased adherence with QD LPV/r administration
- The results suggest that, among subjects achieving virologic suppression, the maintenance of virologic response was less sensitive to reduced adherence with QD-dosed LPV/r than with BID-dosed LPV/r
  - Adherence was not predictive of virologic rebound in subjects achieving virologic response when LPV/r was administered QD; however, the lowest levels of adherence were associated with loss of virologic response in subjects receiving LPV/r BID who initially achieved virologic suppression
  - Further research is necessary to fully understand the relationship between virologic efficacy and adherence, particularly its impact on the maintenance of virologic response in antiretroviral-experienced subjects treated with LPV/r QD and BID

Conclusion

As observed in antiretroviral-naïve subjects, QD administration of LPV/r features increased adherence compared to BID LPV/r dosing in treatment-experienced, HIV-1-infected subjects

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Disclosures

Abbott provided financial support for this study. All authors are employees of Abbott and may hold Abbott stock or options.

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