Poster H-522

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Differences in Treatment Compliance Between Lopinavir/ritonavir (LPV/r) Given Once (QD) Versus Twice (BID) Daily Do Not Affect Virologic or Immunologic Outcomes

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BACKGROUND

Simplified highly active antiretroviral therapy (HAART) regimens may promote adherence and improve outcomes in HIV-1 infected patients. Studies have previously compared QD vs. BID dosing, but the relationship of dosing regimen to adherence and virologic outcome is not well understood. These relationships may differ for different drugs.

METHODS

M02-418 was a randomized, open-label, multicenter, parallel arm study comparing the safety, tolerability, antiviral efficacy and pharmacokinetics of LPV/r soft-gel capsules, administered QD (800/200 mg) or BID (400/100 mg), with tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg (both QD) in antiretroviral-naive, HIV-1 infected subjects. For the purpose of this study, subjects were considered antiretroviral-naive if they had received less than 7 days of prior antiretroviral therapy. In addition, subjects were required to have plasma HIV-1 RNA >1,000 copies/mL at screening; however, there was no CD4+ T-cell count restriction.

Patient safety was assessed throughout the conduct of this study. Blood collection for evaluation of virology (plasma HIV-1 RNA), immunology (CD4+ T-cell count), clinical chemistry and hematology parameters was conducted at baseline, weeks 4, 8, 16 and 24, every 8 weeks thereafter until week 48, and every 12 weeks thereafter until week 96. In addition, treatment compliance was assessed through the use of MEMS® monitors, which electronically recorded and stored LPV/r bottle openings for subjects enrolled in this study.

Three treatment compliance measures were computed during each inter-visit period using electronically captured dosing events:

(1) Taking compliance (TAC): The percentage of prescribed doses taken

Taking compliance is calculated as:

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

If the output from the MEMS monitor for a BID regimen shows 86 openings, and there were 100 prescribed doses (corresponding to a monitored period of 50 days), the percentage of prescribed doses taken, or taking compliance, is 86% [(86/100) X 100].

This measure reflects the average dose received over a given period and hence also the total dose over that period. It accounts for periods of time without drug intake and double dosing. However, it fails to distinguish between a patient who takes their medication regularly and a patient who balances periods of under-dosing with periods of over-dosing, and it captures no information about the timing of drug intake.

(2) Correct dosing compliance (CD): The percentage of days with the correct number of doses taken

Correct dosing compliance is calculated as:

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

If the output from the MEMS monitor for a BID regimen shows 86 openings, but there were exactly 2 openings on only 40 of the 50 monitored days, the percentage of days with the correct number of doses taken, or correct dosing compliance, is 80% [(40/50) X 100].

This statistic captures some measure of the closeness to “correct compliance”. However, it gives no information concerning the timing of dose intake, and it does not distinguish between days of over-dosing and days of under-dosing and thus may not capture deviations most relevant to the drug action.

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

We introduce a measure based on both the periods of “over-dosing” (interval too short) and periods of “under-dosing” (interval too long). This measure looks at the number of deviations that exceed a crucial or meaningful threshold of dosing intervals that are either too short or too long. In this case, timing compliance is calculated as:

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

If the prescribed dosing interval is 12 hours (BID regimen), the number of doses with inter-dose intervals between 9 and 15 hours are calculated. Hence, if the output from a MEMS monitor for a BID regimen shows 86 openings, but only 38 of these openings were within an inter-dose interval of 9–15 hours, and there were 100 openings prescribed (corresponding to a monitored period of 50 days), the % of doses taken within prescribed intervals, or timing compliance, is 38% [38/(100 – 1) X 100].

The three compliance statistics previously defined were computed for each inter-visit period during a given subject's participation in the study. For the purpose of these computations, the inter-visit periods were defined as: baseline to week 4, and weeks 4–8, 8–16, 16–24, 24–32, 32–40, 40–48, 48–60, 60–72, 72–84 and 84–96. A longitudinal mixed effects model was used to evaluate potential changes in treatment compliance over time. In particular, the model incorporated effects for treatment (QD vs. BID), time (defined by the last week for each inter-visit period), treatment-by-time interaction and individual patient (to allow for estimation of intra-patient variability). Akaike's information criterion (AIC) was used to select the variance-covariance matrix used in the "final" model for each compliance measure.

RESULTS

Demographic and baseline disease characteristics were similar between treatment arms as indicated in Table 1.

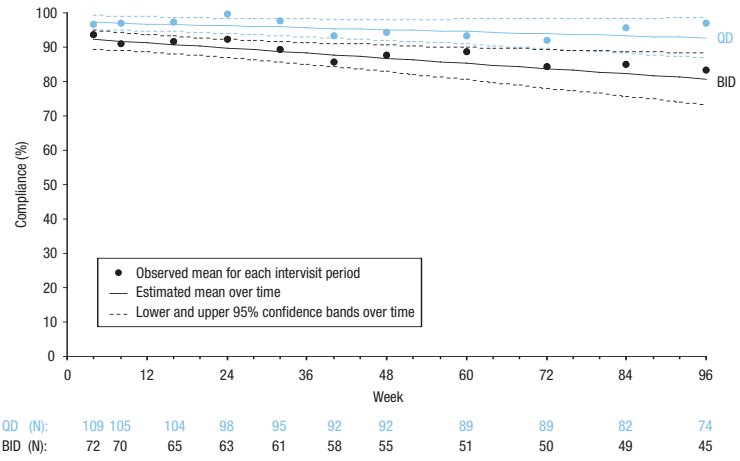
Table 1. Demographics and Baseline Disease Characteristics

	LPV/r 800/200 QD (N=115)	LPV/r 400/100 BID (N=75)	P-value
Gender			0.310
Male	93 (81%)	56 (75%)	
Female	22 (19%)	19 (25%)	
Race/Ethnicity			0.405
Black	31 (27%)	27 (36%)	
White	65 (57%)	38 (51%)	
Other	19 (17%)	10 (13%)	
Age (years)			
Mean ± SD	39.2 ± 11.1	37.7 ± 9.0	0.332
Range	19 – 75	19 – 75	
Time Since HIV Diagnosis (years)			
Mean ± SD	2.4 ± 4.0	2.0 ± 3.5	0.544
Range	0.1 – 18.5	0.1 – 16.7	
Plasma HIV-1 RNA (log_{10} copies/mL)			
Mean ± SD	4.88 ± 0.75	4.72 ± 0.68	0.999
Range	3.48 – 6.44	2.60 – 6.18	
CD4+ T-cell count (cells/mm^3)			
Mean ± SD	266 ± 211	250 ± 198	0.999
Range	3 – 965	5 – 1006	

The study population had relatively advanced HIV disease, as approximately 45% of subjects had baseline CD4+ T-cell count below 200 cells/mm^3 and 38% had baseline plasma HIV-1 RNA above 100,000 copies/mL.

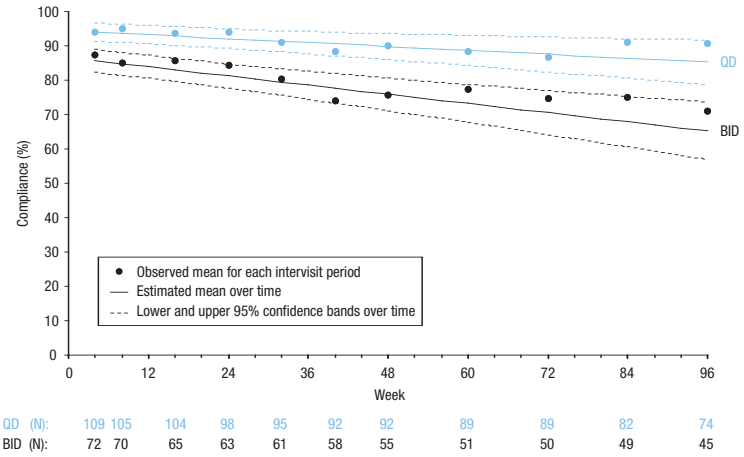
After initiation of LPV/r-based antiretroviral therapy, the estimated mean taking compliance ranged from 97.2% (baseline to week 4) to 92.8% (weeks 84–96) for LPV/r QD. In contrast, the estimated mean taking compliance for LPV/r BID ranged from 92.2% (baseline to week 4) to 80.8% (weeks 84–96). Although the taking compliance profiles for LPV/r QD and LPV/r BID were significantly different (p=0.0130), it should be noted that the magnitude of the difference appeared to remain constant over time (i.e., treatment-by-time interaction p-value=0.175). See Figure 1 for additional details.

Figure 1. Longitudinal Assessment of Taking Compliance



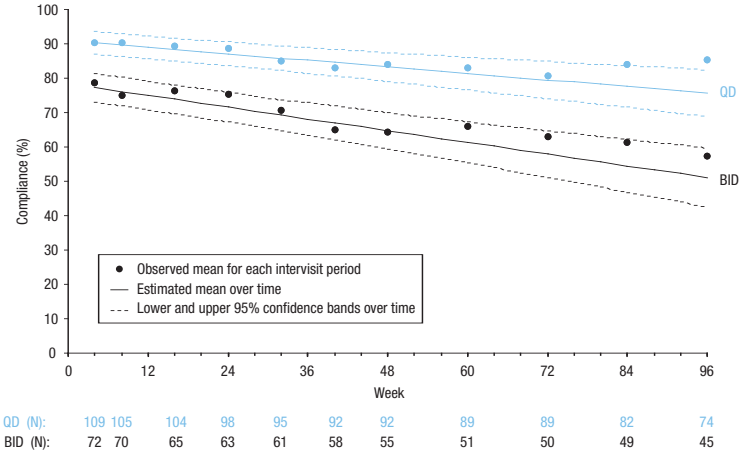
The estimated mean correct dosing compliance ranged from 94.0% (baseline to week 4) to 85.2% (weeks 84–96) for LPV/r QD. In contrast, the estimated mean correct dosing compliance for LPV/r BID ranged from 85.6% (baseline to week 4) to 65.3% (weeks 84–96). This difference between the correct dosing compliance profiles for LPV/r QD and LPV/r BID was statistically significant ($p<0.001$). Further, the treatment-by-time interaction effect was significant ($p=0.027$) suggesting that correct dosing compliance for LPV/r BID decreased at a faster rate over time than for LPV/r QD. See Figure 2 for additional details.

Figure 2. Longitudinal Assessment of Correct Dosing Compliance



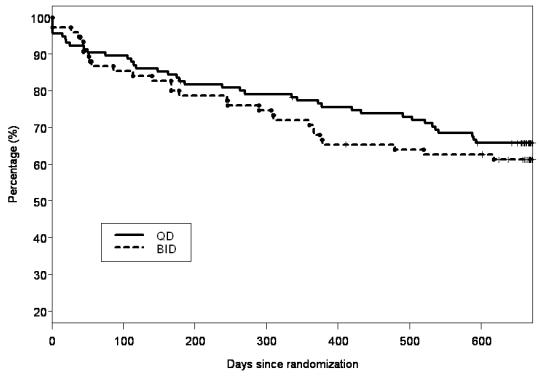
The estimated mean timing compliance ranged from 90.3% (baseline to week 4) to 75.7% (weeks 84–96) for LPV/r QD. In contrast, the estimated mean timing compliance for LPV/r BID ranged from 77.3% (baseline to week 4) to 51.0% (weeks 84–96). This difference between the timing compliance profiles for LPV/r QD and LPV/r BID was statistically significant ($p<0.001$). Further, the treatment-by-time interaction effect was significant ($p=0.033$) suggesting that timing compliance for LPV/r BID decreased at a faster rate over time than for LPV/r QD. See Figure 3 for additional details.

Figure 3. Longitudinal Assessment of Timing Compliance



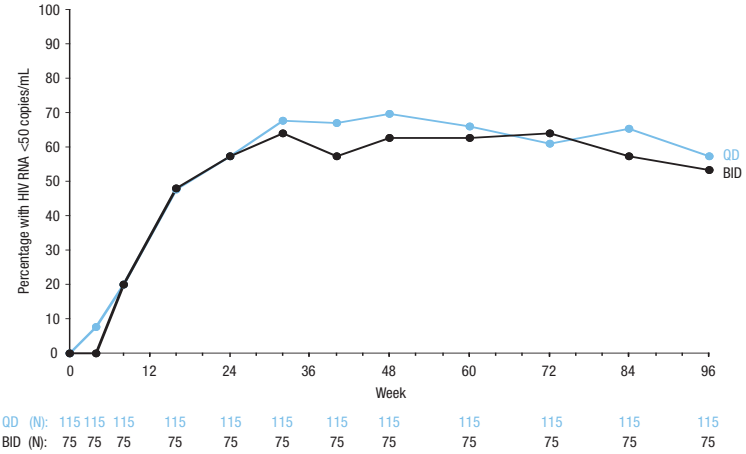
There was no significant difference between the LPV/r QD and LPV/r BID arms with respect to persistence, which was defined by the percentage of patients who remained on LPV/r-based study therapy through week 96 (64.3% vs. 58.7%; $p=0.475$). See Figure 4 for additional details.

Figure 4. Kaplan-Meier Estimates of the Percentage of Subjects Remaining on LPV/r-Based Study Therapy Through Week 96 (Persistence)



A statistically significant difference was detected between the LPV/r QD and LPV/r BID arms at week 4 with respect to the percentage of subjects with plasma HIV-1 RNA below 50 copies/mL (p=0.013). However, after week 4 no statistically significant differences were noted between the two LPV/r treatment arms (p≥0.179). See Figure 5 for additional details.

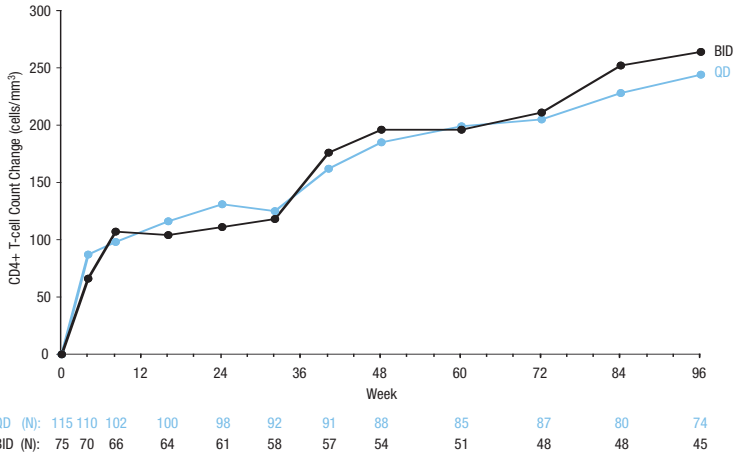
Figure 5. Percentage of Subjects with Plasma HIV-1 RNA <50 copies/mL Over Time (Intent-to-Treat: Noncompleter=Failure)



The frequency and pattern of drug resistance were similar in the LPV/r QD and BID arms. No subjects demonstrated resistance to LPV or TDF through 96 weeks. Four subjects [3 (2.6%) QD, 1 (1.3%) BID] demonstrated resistance to FTC.

Statistically significant increases in CD4+ T-cell counts were observed in both the LPV/r QD and LPV/r BID arms at each time point beginning at week 4 (p<0.001). However, no statistically significant differences were detected at any time point between the LPV/r QD and LPV/r BID arms with respect to mean CD4+ T-cell count increases (p≥0.216). See Figure 6 for additional details.

Figure 6. Change from Baseline in CD4+ T-cell Count Over Time (On-Treatment)



DISCUSSION/CONCLUSION

- In this study population, treatment compliance was found to be higher for HIV-1 infected subjects receiving LPV/r QD compared to LPV/r BID.
  - Consistent differences over time, ranging from 5.0% (baseline to week 4) to 12.0% (weeks 84–96), were noted with respect to mean taking compliance, favoring LPV/r QD over LPV/r BID.
  - Increasing differences over time were noted with respect to both mean correct dosing compliance and mean timing compliance, favoring LPV/r QD over LPV/r BID in each instance.
- Despite differences in treatment compliance, subjects who received either LPV/r QD or LPV/r BID had comparable virologic efficacy, rates of resistance and immunologic improvement through at least 96 weeks of treatment.
  - The magnitude of the difference in treatment compliance observed in this study between LPV/r QD and LPV/r BID did not appear to impact clinical outcomes.
  - Results observed in this study may be specific to LPV/r, and may not reflect the relationships that could occur with other drugs.
- Results from the current analysis are consistent with previous work by Vrijens et al.[1] Analyses evaluating the pharmacokinetic/pharmacodynamic/adherence relationship with LPV/r are ongoing.

REFERENCE

1. Vrijens B, Comté L, Tousset E, Urquhart J. Once-daily versus twice-daily regimens: Which is best for HIV infected patients? Sixth International Workshop on Clinical Pharmacology of HIV Therapy, Quebec City, Quebec, Canada, April 28–30, 2005.