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Once-Daily and Twice-Daily Lopinavir/ritonavir-Based Regimens Provide Similar Virologic Response Through 48 Weeks: Results of a Meta-Analysis

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Abstract P17

Background

Combination therapy regimens based on lopinavir/ritonavir (LPV/r) 800/200 mg dosed once daily (QD) have been investigated and compared to twice-daily (BID) dosing of LPV/r (400/100 mg BID) in several studies of antiretroviral-naïve subjects. While most studies found no difference in virologic response between QD and BID LPV/r-based regimens, some recent analyses have concluded that there were significant differences in response rates favoring the BID regimen, particularly among subjects with high baseline viral loads.

To synthesize these apparently inconsistent results, we conducted meta-analyses to compare, across studies, virologic response between QD and BID LPV/r-based regimens.

Methods

- We conducted searches of PubMed, clinicaltrials.gov, and recent HIV scientific conferences to identify clinical trials that included both once-daily and twice-daily lopinavir/ritonavir-based regimens in antiretroviral-naïve subjects.
- Virologic response was assessed, based on available published data, via two complementary definitions:
  - HIV-1 RNA <50 copies/mL at week 48, based on an intent-to-treat analysis in which subjects who did not complete 48 weeks of treatment were considered failures.
  - Time to virologic failure, defined as 2 plasma HIV-1 RNA values ≥200 copies/mL after 2 values <200 copies/mL, or 2 consecutive plasma HIV-1 RNA values ≥200 copies/mL after week 24, or HIV-1 RNA ≥200 copies/mL at week 48.
- Random effects meta-analysis models were used to synthesize results across studies.
  - For the endpoint of HIV-1 RNA <50 copies/mL at week 48, the differences in response rates (QD minus BID) and corresponding 95% confidence intervals were assessed for each study.
  - For the endpoint of time to virologic failure, hazard ratios and corresponding 95% confidence intervals were calculated from individual subject data based on the Cox proportional hazards model. In cases where individual subject-level data were not available, hazard ratios were calculated based on Kaplan-Meier estimates and confidence intervals were calculated by simulation. Sensitivity analyses confirmed the robustness of the simulation method.
- Analyses were conducted for all subjects and for the subset of subjects with baseline plasma HIV-1 RNA ≥100,000 copies/mL.

Results

Summary of individual studies

- Five studies with more than 1,500 antiretroviral-naïve subjects receiving either LPV/r QD or BID (Table 1).

Table 1. Studies Included in the Analysis

Study	N (QD)	N (BID)	Randomized*	Data Available for HIV-1 RNA <50 at Week 48	Data Available for Time to Confirmed Rebound ≥200 Copies/mL
Study 056	19 (5)	19 (7)	Yes	X	X
Study 418	115 (53)	75 (20)	Yes	X	X
A5073	161 (82)	159 (82)	Yes		X
ARTEMIS	52 (18)	267 (92)	No	X	
Study 730	333 (159)	331 (193)	Yes	X	X
Total	680 (317)	851 (394)			

* Value in parentheses represents number with baseline HIV-1 RNA ≥100,000 copies/mL

** Assignment to QD or BID dosing schedule was randomized

- Summary of individual study results:
  - Studies 056 (Eron 2004), 418 (Johnson 2006) and 730 (Gathe 2008) demonstrated relatively similar virologic responses between QD and BID regimens, and Studies 418 and 730 achieved pre-specified criteria for demonstrating non-inferiority of QD compared to BID.
  - Study A5073 (Mildvan 2007) demonstrated no significant difference between QD and BID in the overall study, but in the subgroup with baseline HIV-1 RNA ≥100,000 copies/mL, a significant difference in favor of the BID regimen was observed.
  - ARTEMIS (Clumeck 2007) results numerically favored the BID group both among all subjects and in the subset with baseline HIV-1 RNA ≥100,000 copies/mL, although the difference between QD and BID was not statistically significant.

HIV-1 RNA <50 copies/mL at Week 48

- The meta-analysis of the difference in response rates indicated no difference between QD-treated and BID-treated subjects (Figure 1).
- Similarly, when the analysis was restricted to subjects with a baseline plasma HIV-1 RNA level ≥100,000 copies/mL, no difference in response rates was observed (Figure 2).
- None of the 4 individual studies identified a significant difference between QD and BID groups in the week 48 response rate, either among all subjects or in those with higher baseline HIV-1 RNA levels.

Figure 1. Meta-Analysis of Effect of Dosing Frequency on ITT Percentage with HIV-1 RNA <50 Copies/mL at Week 48

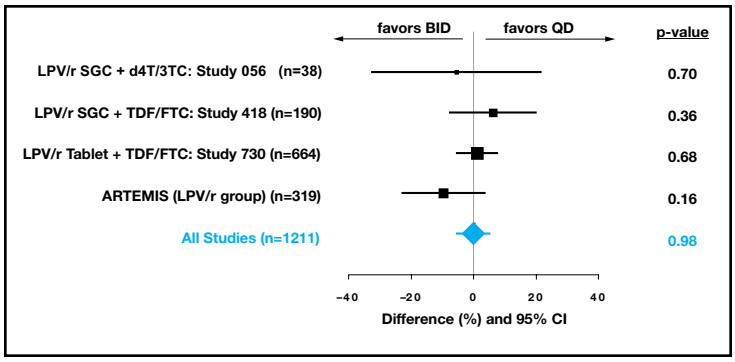
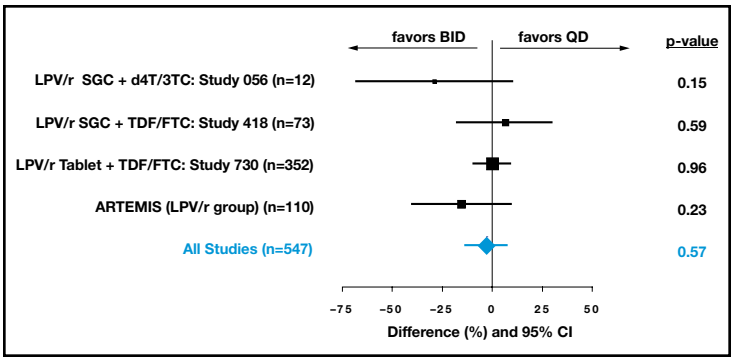


Figure 2. HIV-1 RNA <50 Copies/mL at Week 48: Subjects with Baseline HIV-1 RNA ≥100,000 Copies/mL



Time to virologic failure

- In the analysis of all subjects, no individual study demonstrated a significant difference between the QD and BID groups. Correspondingly, the meta-analysis of all subjects indicated no difference between groups (Figure 3).
- In the analysis of subjects with baseline plasma HIV-1 RNA ≥100,000 copies/mL, one of the 4 studies demonstrated a significant difference favoring the BID group. However, in the meta-analysis, the risk of virologic failure was similar between groups (Figure 4).

Figure 3: Meta-Analysis of Effect of Dosing Frequency on Time to Confirmed Virologic Rebound ≥200 Copies/mL

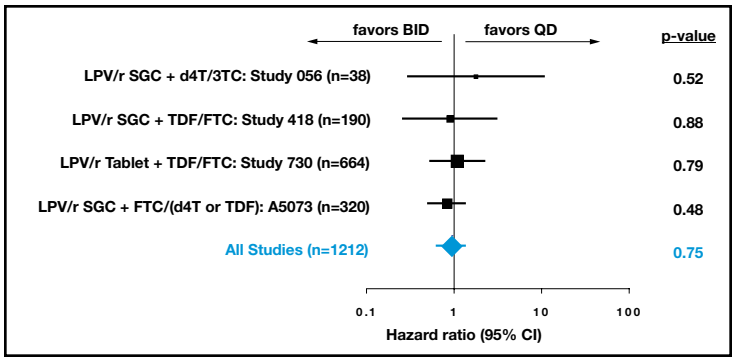
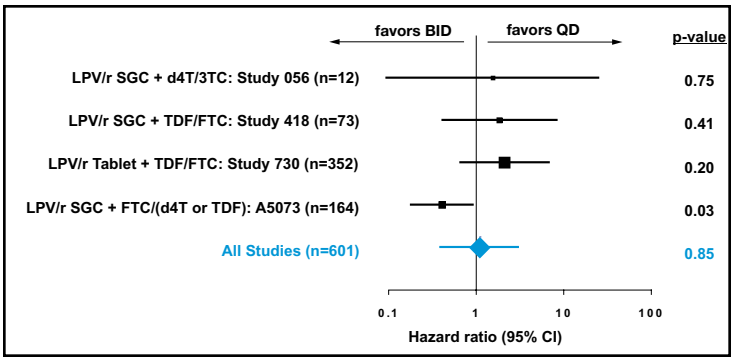


Figure 4: Confirmed Virologic Rebound ≥200 Copies/mL: Subjects with Baseline HIV-1 RNA ≥100,000 Copies/mL



Discussion

- We conducted 4 meta-analyses comparing virologic response through 48 weeks for QD and BID LPV/r-based regimens. Observed differences between QD and BID groups were not statistically significant, and were numerically quite small, suggesting nearly identical response profiles for the different dosing schedules.
- In only 1 of 16 analyses from individual studies was a statistically significant difference observed. In Study A5073, in subjects with screening plasma HIV-1 RNA ≥100,000 copies/mL, the BID group had a significantly longer time to virologic failure than the QD group (Mildvan 2007). However, in the QD group, Kaplan-Meier response rates at week 48 were similar between subjects with higher vs. lower (≥100,000 vs. <100,000 copies/mL) screening viral loads (76% vs. 80%, respectively). In contrast, in the BID group, the response rate was much higher in those with higher baseline viral loads (89% vs. 72%, respectively). The better response in subjects with higher baseline viral load is somewhat unexpected, as response rates in subjects with higher pre-treatment viral loads are typically similar to or worse than those in subjects with lower pre-treatment viral loads. As such, this result from Study A5073 may not be representative of results expected in general practice.
- For the non-randomized comparison in the ARTEMIS study, the abstract of Clumeck, et al. concluded that subjects using LPV/r QD have lower rates of suppression than those using it BID (Clumeck 2007). However, as shown in our analysis, differences between these groups were not statistically significant, either among all subjects or the subset with baseline plasma HIV-1 RNA ≥100,000 copies/mL.

Conclusions

- Based on 4 meta-analyses assessing 2 different virologic endpoints, no difference in virologic response through 48 weeks was observed between QD and BID LPV/r-based regimens.
- Results were independent of baseline viral load, as outcomes were similar between QD and BID both
  in the group of all subjects combined, and in the subgroup with baseline plasma HIV-1 RNA ≥100,000 copies/mL.

References

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