

# Resistance Implications of 96 Weeks of Treatment with Once- (QD) or Twice- (BID) Daily Lopinavir/ritonavir (LPV/r) with Tenofovir DF (TDF) and Emtricitabine (FTC) in Antiretroviral (ARV)-naïve Subjects

PE3.3/1

Daniel E. Cohen, Martin S. King, Christian T. Naylor, Theresa M. Marsh, Barbara A. da Silva, Barry M. Bernstein  
Abbott, Abbott Park, IL USA

12th European AIDS Conference • 11-14 November 2009 • Cologne, Germany

Corresponding author: Daniel Cohen, M.D., Abbott, 200 Abbott Park Rd., Abbott Park, IL 60064-6146 USA;  
Tel: +1-847-938-1494; Fax: +1-847-938-3711; E-mail: daniel.cohen@abbott.com

## Background

- Lopinavir/ritonavir (LPV/r) is a coformulation of the HIV-1 protease inhibitors lopinavir and low-dose ritonavir, which acts as a pharmacokinetic enhancer; LPV/r has been used extensively in both antiretroviral-naïve and antiretroviral-experienced patients, demonstrating durable response to therapy<sup>1-4</sup>
- LPV/r was originally approved in 2000 for twice-daily (BID) dosing at 400/100 mg in both antiretroviral-naïve and treatment-experienced HIV-1-infected patients; LPV/r 800/200 mg administered once daily (QD) was approved for use in treatment-naïve patients in the US in 2005 and the EU in 2009
- Previous findings have demonstrated that resistance develops infrequently in antiretroviral-naïve subjects treated with LPV/r<sup>2,5,6</sup> (Table 1)

**Table 1. Proportion of antiretroviral-naïve subjects with treatment-emergent resistance-associated mutations**

Study	Regimen (N)	Incidence of resistance in subjects with available genotype data, n/N (%)			
		LPV/r resistance	3TC/FTC resistance	TDF resistance	d4T resistance
M97-720 <sup>2</sup>	LPV/r BID + 3TC+d4T through 360 weeks (N=100)	0/19 (0%)	4/19 (21%)	n/a	0/19 (0%)
M98-863 <sup>5</sup>	LPV/r BID + 3TC+d4T through 108 weeks (N=326)	0/51 (0%)	19/51 (37%)	n/a	0/51 (0%)
M02-418 <sup>6</sup>	LPV/r BID + FTC+TDF through 96 weeks (N=75)	0/8 (0%)	1/8 (13%)	0/8 (0%)	n/a
M02-418 <sup>6</sup>	LPV/r QD + FTC+TDF through 96 weeks (N=115)	0/15 (0%)	3/15 (20%)	0/15 (0%)	n/a

- Study M05-730 was a 96-week trial designed to compare the safety and efficacy of QD and BID LPV/r tablets in antiretroviral-naïve subjects<sup>7</sup>

## Objective

To evaluate the emergence of resistance in antiretroviral-naïve subjects treated with QD and BID LPV/r through 96 weeks of treatment

## Methods

- Study M05-730 randomized 664 antiretroviral-naïve subjects with HIV-1 RNA levels >1000 copies/mL to LPV/r QD (N=333) or BID (N=331) with tenofovir DF (TDF) and emtricitabine (FTC) for 96 weeks<sup>7</sup>
- Genotyping analysis was performed for study drug-related resistance for subjects who met either of the following criteria beginning at Week 24:
  - A plasma HIV-1 RNA level >50 copies/mL confirmed by a subsequent HIV-1 RNA level >400 copies/mL
  - A final HIV-1 RNA level ≥50 copies/mL with any prior HIV-1 RNA level ≥400 copies/mL
- Genotypic resistance definitions were based on the IAS-USA panel<sup>8</sup>
  - FTC resistance:
    - K65R or M184V/I mutation in reverse transcriptase
  - TDF resistance:
    - K65R or K70E mutation in reverse transcriptase
  - LPV/r resistance:
    - any of the following protease mutations: I47A/V, G48V, I50V, V82A/F/S/T, I84V, L90M;
    - or ≥3 of the following protease mutations: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M36I, M46I/L, F53L, I54 (any change), A71T/V, G73S
- Phenotypic sensitivity analyses were conducted using the PhenoSense™ assay (Monogram Biosciences, South San Francisco, California)

## Results

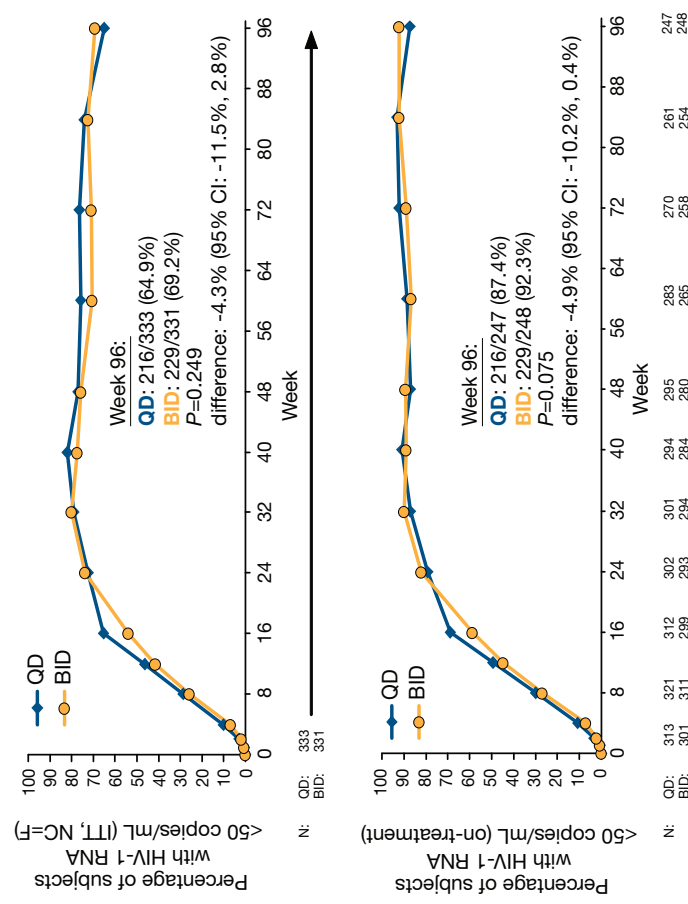
### Subjects

- Baseline demographics were similar between treatment groups<sup>7</sup>
  - However, mean baseline HIV-1 RNA was greater for subjects in the BID dosing group (QD: 4.93 log<sub>10</sub> copies/mL; BID: 5.05 log<sub>10</sub> copies/mL;  $P=0.020$ )
- Through 96 weeks, the proportion of subjects discontinuing the study prematurely was similar for QD-treated subjects (N=77, 23.1%) and subjects in the BID group (N=77, 23.3%), with comparable rates of discontinuation due to adverse or HIV-related events and virologic failure<sup>9</sup>

### Efficacy

- QD and BID dosing of LPV/r resulted in similar efficacy through 96 weeks according to both intent-to-treat, noncompleters=failure analysis and on-treatment analysis (Figure 1)<sup>9</sup>
- Similar efficacy in QD and BID treated subjects was also observed in subsets of subjects when stratified by baseline HIV-1 RNA level or CD4<sup>+</sup> T-cell count<sup>9</sup>

**Figure 1. Antiviral efficacy of QD and BID LPV/r through 96 weeks of treatment in antiretroviral-naïve subjects**



## Results, cont.

### Resistance

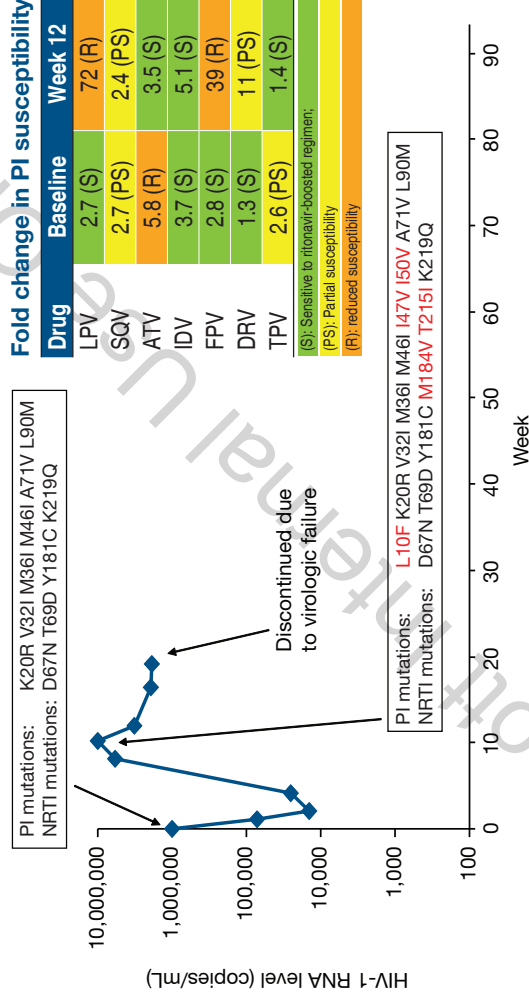
- Genotypic resistance results were available for 51 (25 QD and 26 BID) subjects who met criteria for genotypic testing
- The frequency of treatment-emergent resistance to study drugs was comparable for subjects taking LPV/r QD and BID (Table 2)

**Table 2. Incidence of treatment-emergent study drug resistance during 96 weeks of treatment, n (%)**

	QD (N=25)	BID (N=26)
FTC	4 (16.0%)	6 (23.1%)
TDF	0 (0%)	0 (0%)
LPV	0 (0%)	1 (3.8%)

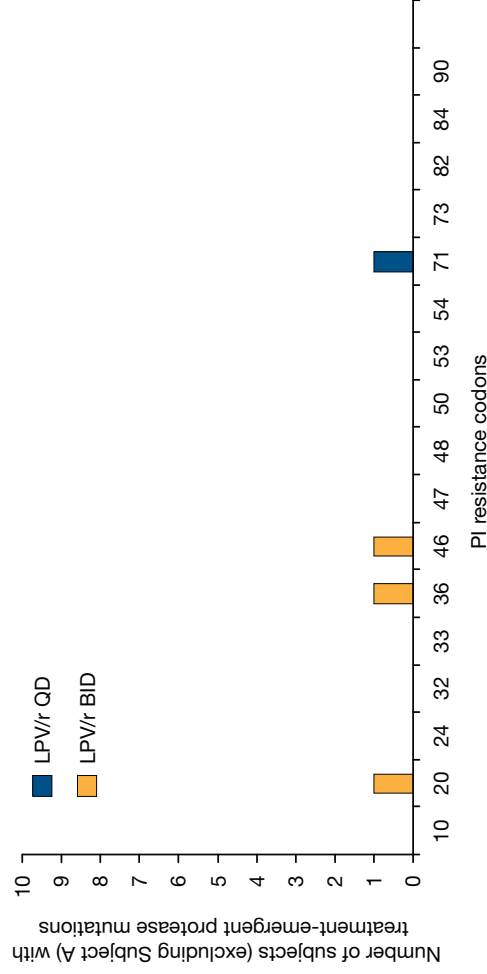
- One BID-dosed subject (“Subject A”) with several protease inhibitor-associated resistance mutations at baseline demonstrated additional resistance mutations after 12 weeks of treatment (Figure 2)
  - Fold change in lopinavir susceptibility (compared to wild type virus) correspondingly increased from 2.7-fold at screening to 72-fold at Week 12, although the subject’s rebound isolate remained sensitive or partially sensitive to most other ritonavir-boosted protease inhibitors, including saquinavir, atazanavir, indinavir, darunavir, and tipranavir.

**Figure 2. Genotypic and phenotypic changes from wild type HIV-1 observed in isolates from subject A**



- Emergence of secondary protease mutations<sup>8</sup> was also uncommon, with no obvious differences in the pattern of new substitutions between QD and BID subjects (Figure 3)

**Figure 3. Number of subjects with treatment-emergent protease mutations\***



\*L10F/I18V, K20M/R, L24I, V32I, L33F, M36I, M46I/L, I47A/V, G48V, I50V, F53L, I54 (any change), A71T/V, G73S, V82A/F/S/T, I84V, L90M.

## Summary

- In this study, antiretroviral-naïve subjects treated with an LPV/r-based antiretroviral regimen demonstrated a low frequency of resistance to FTC; no TDF-associated resistance mutations were detected in any subject
- One subject (BID treatment group) with several protease inhibitor-associated mutations at baseline revealed additional protease and reverse transcriptase resistance mutations after 12 weeks of treatment; the subject's isolate retained sensitivity or partial sensitivity to saquinavir, atazanavir, indinavir, darunavir, and tipranavir
- The pattern and frequency of treatment-emergent resistance mutations was similar to that seen at 48 weeks in Study M05-730 and in previous studies of LPV/r treatment in naïve subjects through 360 weeks<sup>2,5-7</sup>
- The incidence of resistance to study drugs did not differ between QD- and BID-treated subjects

## Conclusions

- No LPV/r QD-treated subject developed evidence of lopinavir resistance over 96 weeks of treatment
- In addition, QD LPV/r was associated with a low risk of FTC or TDF resistance
- These findings are similar to those observed in antiretroviral-naïve subjects receiving BID LPV/r and confirm that QD LPV/r dosing maintains a resistance profile comparable to BID LPV/r dosing

## Acknowledgements

This study is registered with ClinicalTrials.gov (NCT00262522). The authors wish to acknowledge Laura Maroldo, PA (Abbott), for critical review of the poster content, and Elaine M. Smith, PhD (Abbott), for assistance in writing the poster.

## Disclosures

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

## References

1. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of infection. *N Engl J Med*. 2002;346:2039-2046.
2. Murphy R, da Silva BA, Hicks CB, et al. Seven-Year Efficacy of a Lopinavir/Ritonavir-Based Regimen in Antiretroviral-Naïve HIV-1-Infected Patients. *HIV Clin Trials*. 2008;9:1-10.
3. Bongiovanni M, Bini T, Capetti A, et al. Long-term antiretroviral efficacy and safety of lopinavir/ritonavir HAART-experienced subjects: 4 year follow-up study. *AIDS*. 2005;19:1934-1936.
4. Benson CA, Deeks SG, Brun SC, et al. Safety and antiviral activity at 48 weeks of lopinavir/ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human immunodeficiency virus type 1-infected protease inhibitor-experienced patients. *J Infect Dis*. 2002;185:599-607.
5. Kempf DJ, King MS, Bernstein B, et al. Incidence of resistance in a double-blind study comparing lopinavir/ritonavir plus stavudine and lamivudine to nelfinavir plus stavudine and lamivudine. *J Infect Dis*. 2004;189:51-60.
6. Molina JM, Podszadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses*. 2007;23:1505-1514.

7. Gathe J, da Silva BA, Cohen DE, et al. A Once-Daily Lopinavir/Ritonavir-Based Regimen Is Noninferior to Twice-Daily Dosing and Results in Similar Safety and Tolerability in Antiretroviral-Naive Subjects Through 48 Weeks. *J Acquir Immune Defic Syndr*. 2009;50:474-481.
8. Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: 2007. *Top HIV Med*. 2007;15:119-125.
9. Gonzalez-Garcia J, Cohen DE, Johnson M, et al. Comparable safety and efficacy with once-daily (QD) versus twice-daily (BID) dosing of lopinavir/ritonavir (LPV/r) tablets with emtricitabine (FTC) + tenofovir DF (TDF) in antiretroviral (ARV)-naïve, HIV-1-infected subjects: 96 week results of the randomized trial M05-730. Paper presented at: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; 19-22 July, 2009; Cape Town, South Africa.