Abtract P91

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Adherence in Combination with Lopinavir Inhibitory Quotient (IQ) and Number of Active Antiretrovirals (ARVs) Predicts Virologic Response in Highly ARV-Experienced Patients Receiving High-Dose Lopinavir/ritonavir (LPV/r)

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INTRODUCTION

- Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with low-dose ritonavir (r) which enhances LPV pharmacokinetics.
- At the LPV/r clinical dose of 400/100 mg BID, LPV mean C_{trough} exceeds protein-binding adjusted IC_{50} for *wild-type (wt)* HIV by >75-fold (inhibitory quotient [IQ] or C_{trough}/IC_{50} =75).
- LPV concentrations achieved with the clinical dose have resulted in significant antiviral efficacy and durable response, particularly in patients without previous ARV experience.
- High-level drug resistance is likely in patients previously failing multiple ARV regimens. (Bertz R, et al., 11th CROI, 2004, Presentation 134)
- The relationship between LPV IQ and antiviral response was previously demonstrated in a study of multiple PI-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naïve patients. (Hsu A, et al., AAC 2003;47(1):350-9)
- Recent results show that the number of active nucleoside reverse transcriptase inhibitors (NRTIs) and LPV IQ C_{trough} are significant predictors of antiviral response in multiple PI- and NNRTI-experienced patients. (Bertz R, et al., 11th CROI, 2004, Presentation 134)
  - Higher doses of LPV/r may provide LPV concentrations sufficient to overcome certain degrees of reduced LPV phenotypic susceptibility, resulting in a significant treatment effect

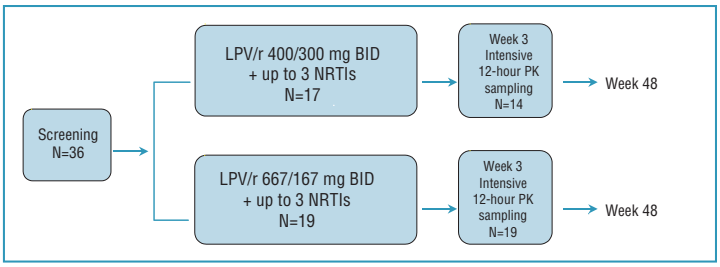
OBJECTIVE

- To assess whether adherence further predicts viral response in patients receiving high-dose LPV/r.

STUDY DESIGN

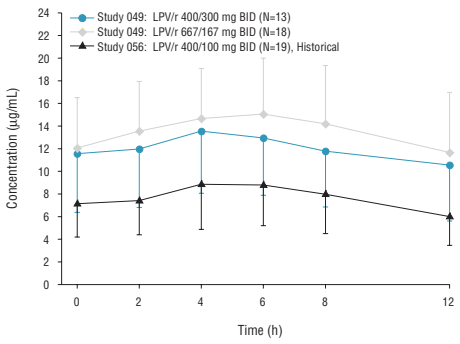
- Open-label, multi-center study in HIV-infected subjects (N=36):
  - Prior ARV treatment with ≥1 PI, ≥1 NNRTI, and ≥1 NRTI
  - HIV RNA >1000 copies/mL
- 3 subjects discontinued prior to PK assessment.
- Concurrent NRTIs: didanosine (N=21), lamivudine (N=15), stavudine (N=15), abacavir (N=13), tenofovir (N=10) and zidovudine (N=8).
- Patient adherence to the LPV/r component of the ARV regimen was monitored using Medication Event Monitoring System (MEMS®, Aardex Ltd.) technology. In particular, each MEMS (bottle cap) opening was taken to indicate the date and time of LPV/r intake.

Figure 1. Study 049 Design



PHARMACOKINETIC RESULTS

Figure 2. Steady-State Lopinavir Mean (SD) Concentration-Time Profiles



Parameter	400/300 mg BID	667/167 mg BID	400/100 mg BID
T_{max} (h)	4.6 ± 3.2	5.0 ± 3.1	4.4 ± 2.4
C_{max} (µg/mL)	14.5 ± 5.5	16.2 ± 4.5	9.8 ± 3.7
C_{trough} (µg/mL)	11.6 ± 5.2	12.0 ± 4.5	7.1 ± 2.9
AUC_{12} (µg•h/mL)	145 ± 59	164 ± 54	93 ± 37

Note: 2 subjects taking efavirenz were excluded from the PK comparison

Flexner C, et al., Poster# 843, 2nd IAS Conf, Paris, July 2003

PHARMACOKINETIC/ PHARMACODYNAMIC RESULTS

Study 049: PK/PD Analysis Methods

- Patient population
  - All patients with post-baseline HIV RNA, PK and MEMS data (N=33)
- Endpoints and analysis
  - Average HIV RNA change from baseline through 48 weeks ("AAUCMB," "TAD" or "DAVG" analysis) – linear regression with forward stepwise selection
  - Viral load was modeled as a function of the time internal exposure (i.e., estimated LPV concentration) fell below the IC_{50} for each inter-visit period. The following HIV RNA categories were used to model the probability of viral load improvement (decrease in viral load from one category to the next) or deterioration (increase in viral load from one category to the next): 0 – <50, 50 – <400, 400 – <2000, ≥2000 copies/mL (see Figure 3 [Vrijens B, et al., Population Approach Group Europe, Verona, Italy, 2003])

    Note: The '[' symbol used on the left side of a mathematical expression is equivalent to the '≥' symbol, while the '[' symbol used on the right side of a mathematical expression is equivalent to the '<' symbol.
- Independent variables
  - Baseline characteristics: age, gender, race, weight, body mass index (BMI), CD4 count, HIV RNA, time since diagnosis
  - Previous and concurrent ARV use: treatment group; no. of previous NRTIs, NNRTIs, and PIs; concurrent tenofovir use
  - Viral susceptibility: LPV fold change from *wt*-IC_{50} (phenotype), genotype (no. of LPV mutations as defined by either the LPV mutation score [Kempf DJ, et al., *J. Virol.* 2001;75(16):7462-9] or the ATU Mutation Set [Isaacson J, et al., 9th CROI, 2002, Poster 559-T]), no. of active NRTIs
  - Pharmacokinetic: LPV C_{min}, C_{trough}, C_{max}, AUC
  - Lopinavir Inhibitory Quotient: (LPV IQ = C_{trough}/ HIV IC_{50})

  Note: PK parameters and LPV phenotype were log-transformed for the analyses.
- Patient compliance based on MEMS data
  - Taking Compliance (TAC), defined as the percentage of prescribed doses taken
  - Correct Dosing (COD), defined as the percentage of days with correct number of doses taken
  - Timing Compliance (TICF), defined as the percentage of doses taken within ±3 hours of the prescribed dosing intervals

Figure 3. Viral Load Categories Used to Model the Probability of Improvement or Deterioration

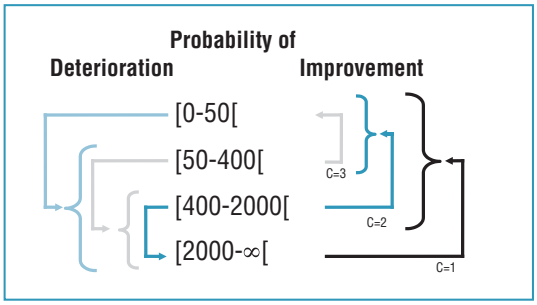


Table 1. Study 049: Selected Baseline Characteristics and PK Parameters

Variable	Median (Min-Max) N=33	Variable	Median (Min-Max) N=33
Age (yrs)	42 (25-57)	Previous PIs	4 (1-5)
Weight (kg)	69 (56-171)	Time since diagnosis (yrs)	8.3 (3-15)
BMI (kg/m^2)	24 (18-48)	No. of active NRTIs	1 (0-3)
CD4 count ($cells/mm^3$)	91 (2-679)	LPV C_{trough} (µg/mL)	11.4 (2.5-21.9)
HIV RNA (log_{10} copies/mL)	4.7 (3.1-5.9)	LPV C_{min} (µg/mL)	9.2 (1.8-17.0)
LPV fold *wt*-IC_{50} (phenotype)	4.5 (0.6-273)	LPV C_{max} (µg/mL)	15.5 (5.5-23.1)
No. of LPV mutations (LPV score)	5 (0-8)	LPV AUC_{12} (µg•h/mL)	146 (41-255)
No. of LPV mutations (ATU set)	3 (0-7)	LPV IQ (C_{trough})	26 (0.7-438)

Study 049: Disposition Through 48 Weeks

- No apparent differences in antiviral activity (667/167 mg BID *vs.* 400/300 mg BID) (Podzamczer D, et al., XV International AIDS Conference, Poster TuPeB4555)
  - Overall, 21/36 (58%) achieved HIV RNA <400 copies/mL
  - 83% demonstrated decreases in HIV RNA of at least 1.0 log_{10} copies/mL from baseline
- Trend toward better tolerability for 667/167 mg BID compared to 400/300 mg BID
  - Lower drug-related diarrhea (11% *vs.* 24%) and vomiting (0% *vs.* 12%) of at least moderate severity
  - Lower grade 3/4 triglycerides (>750 mg/dL): 26% *vs.* 65%

Study 049: PK/PD Analysis Summary of Response Variables

- Average HIV RNA change from baseline through 48 weeks
  - Mean (SD) average change was –1.39 (1.09) log_{10} copies/mL, with a range of –3.47 to +0.41 log_{10} copies/mL
- Proportion achieving HIV RNA <400 copies/mL
  - 21/33 (64%) achieved HIV RNA <400 copies/mL at least once
  - 16/33 (48%) also achieved HIV RNA <50 copies/mL

Summary Measures of Patient Compliance

- Traditional summary measures of "average" patient compliance are summarized for Baseline – Week 12, Baseline – Week 24, and Baseline – Week 48. Mean compliance appears to be highest during the initial period after LPV/r initiation (Baseline – Week 12) and subsequently decreases over time (see Table 2). This relationship may partly explain why compliance measurements do not appear to predict HIV RNA changes from baseline during the initial period after LPV/r initiation but significantly predict changes in HIV RNA during later time periods (see Table 3).

Table 2. Summary of Patient Compliance Through Week 48 Using MEMS Data (N=33)

	Mean ± SD (Minimum – Maximum)		
Variable	**Baseline – Week 12**	**Baseline – Week 24**	**Baseline – Week 48**
TAC (Taking Compliance)	90.5 ± 14.9 (43.1 – 101.4)	89.2 ± 14.4 (44.8 – 101.4)	87.7 ± 15.4 (47.1 – 101.4)
COD (Correct Dosing)	82.5 ± 23.7 (11.7 – 100)	80.9 ± 22.4 (13.6 – 100)	79.0 ± 23.3 (17.9 – 100)
TICF (Timing Compliance)	76.7 ± 25.1 (8.3 – 100)	73.5 ± 25.7 (8.7 – 100)	71.4 ± 26.5 (11.0 – 98.6)

Note: In the event that a patient did not complete at least one of the specified visits (i.e., Week 12, Week 24, Week 48), her/his compliance information was computed through the last available visit.

Table 3. Statistically Significant Effects on Average HIV RNA Change from Baseline

	P-value (Multiple Regression)		
Variable	**Week 12**	**Week 24**	**Week 48**
Active NRTIs (genotype)	ns	0.013	0.003
LPV IQ	0.01	0.003	0.0006
Age	ns	ns	0.055
Gender	ns	ns	0.023
TAC (taking compliance)	ns	0.037	0.041

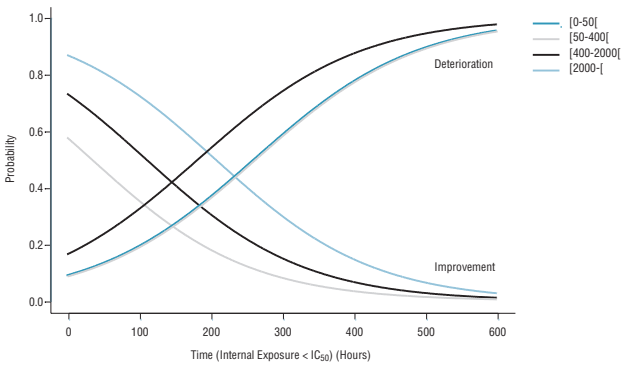
Nonsignificant variables: treatment regimen, race, weight, BMI, baseline CD4 count, baseline HIV RNA, no. previous NRTIs/NNRTIs/PIs, time since diagnosis, tenofovir use, LPV fold *wt*-IC_{50} (phenotype), no. LPV mutations (LPV score), no. LPV mutations (ATU set), active NRTIs (phenotype), LPV C_{min}, LPV C_{trough}, LPV C_{max}, LPV AUC, COD and TICF.

Note: Potential gender differences should be interpreted with caution as the analysis represents data from 28 males and only 5 females.

RESULTS

- Plasma LPV concentrations for each patient were best fitted incorporating MEMS data using a one-compartment model with first-order absorption and first-order elimination. Viral load improvement or deterioration was modeled as function of the "projected" concentrations, phenotypic resistance (for PI- and NNRTI-experienced patients), and adherence as collected by MEMS.

Figure 4. M99-056 (ARV-Naïve Patients)*



* Vrijens et al., Population Approach Group Europe, Verona Italy, June 2003

Figure 5. M99-049 (ARV-Experienced Patients; Assuming LPV Phenotype = 4.0)

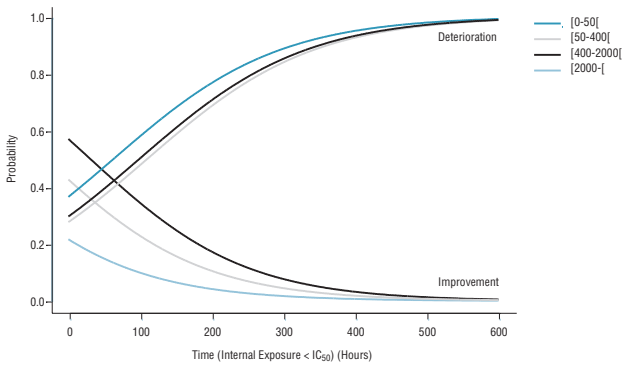


Figure 6. M99-049 (ARV-Experienced Patients; Assuming LPV Phenotype = 10.0)

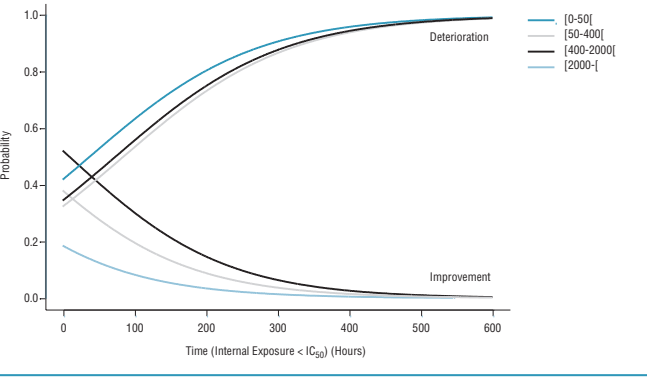
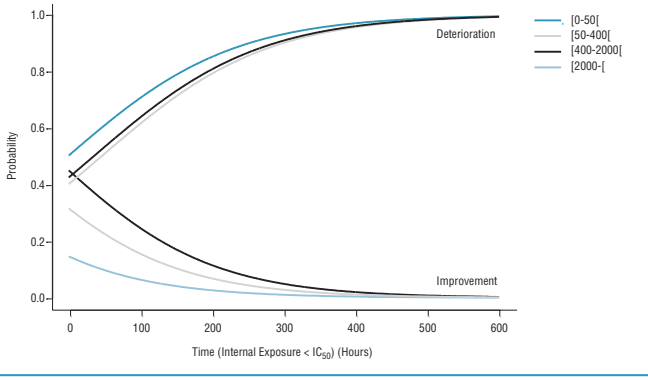


Figure 7. M99-049 (ARV-Experienced Patients; Assuming LPV Phenotype = 40.0)



RESULTS *continued*

- Cross-study comparison of the PK/PD/adherence relationship suggests:
  - ARV-naïve patients have a greater probability of viral load improvement than PI- and NNRTI-experienced patients with progressively higher phenotypic resistance to LPV; however, the probability of improvement diminishes and the probability of deterioration increases with decreasing adherence in all cases.
  - The probability of improvement is greatest in the "higher" viral load categories for ARV-naïve patients and progressively declines with lower viral load, perhaps a reflection of robust first- and second-stage declines in viral load after initiation of ARV therapy (see Figure 4).
  - The probability of improvement is greatest in the "lower" viral load categories in PI- and NNRTI-experienced patients, perhaps suggesting that other factors may be of greater importance in decreasing viral load in this patient population (e.g., addition of "active" agents or medication from a "new" drug class).
  - Baseline viral load may play an increased role in the probability of improvement or deterioration in the face of reduced phenotypic susceptibility to LPV. In particular, for a given level of adherence (or the time internal exposure is less than the IC_{50}), the predicted probability of improvement is lower and the predicted probability of deterioration is higher in patients with progressively reduced phenotypic susceptibility to LPV (see Figures 5-7).

CONCLUSIONS

- LPV IQ, number of active NRTIs co-administered, and adherence (% of prescribed doses taken) were significant predictors of virologic response in multiple regression analyses.
- The use of individual patient adherence profiles collected over time may allow for better prediction of viral load improvement or deterioration compared to more traditional measures of "overall" (average) compliance computed for defined periods of time (e.g., Baseline - Week 12, Baseline - Week 24, and Baseline - Week 48).
- The probability of virologic improvement (i.e., decrease in viral load category from one study visit to the next) increases and the probability of virologic deterioration decreases with increasing adherence (which in turn is a reflection of less time with internal exposure $<IC_{50}$); however, the probability of virologic improvement diminishes and the probability of virologic deterioration increases with decreasing phenotypic susceptibility and decreasing adherence.

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