Trough Lopinavir Concentrations <1 µg/mL Are Not Associated with Virologic Failure in Antiretroviral-Naïve Patients Receiving a Lopinavir/ritonavir-Based 3-Drug Regimen

Yi-Lin Chiu, Cheri Enders Klein, Jianling Li, Linda Fredrick, Barbara da Silva, Barry Bernstein

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Introduction

- The clinical utility of therapeutic drug monitoring (TDM) for lopinavir/ritonavir (LPV/r) is uncertain.
- The 1 µg/mL threshold has been used in several PK studies and suggests that lopinavir (LPV) trough concentrations <1 µg/mL may be associated with viral load rebound.[1]

Objectives

- To evaluate the clinical utility of a C_{trough} cutoff point for TDM as well as other potential cutoff values in antiretroviral-naïve subjects from 5 prospective clinical trials.
- To assess the relationship between LPV exposure and virologic response in treatment-naïve patients from a large data set with multiple time points.

Study Population

- 856 HIV-1 infected, antiretroviral-naïve subjects from 5 studies were included in this analysis; each had LPV trough concentrations and viral load data measured simultaneously. The number of subjects, LPV/r doses received and the background NRTI agents for each study are summarized in Table 1.

Table 1. Studies Included in this Analysis

Study	LPV/r subjects enrolled	Number of subjects with LPV trough concentrations	LPV/r doses (mg)	NRTIs
720	100	46	200/100, 400/100, or 400/200 BID*	d4T+3TC
863	326	178	400/100 BID	d4T+3TC
056	38	35	400/100 BID or 800/200 QD	d4T+3TC
418	190	156	400/100 BID or 800/200 QD	TDF+3TC
730	664	441	400/100 BID or 800/200 QD	TDF+3TC

* Converted to open-label 400/100 mg BID after Week 48

Each study included multiple study visits per subject from study days 3–728 with on average 3–4 study visits plus a baseline visit per subject. Subjects' demographics at baseline are shown in Table 2.

Table 2. Baseline Demographics

Continuous Variables	Mean	SD	Min	Max
Age (yrs)	39	9.7	19	75
Weight (kg)	74	15.2	33	171
Plasma HIV-1 RNA (log_{10} copies/mL)	4.94	0.70	1.72	6.98
CD4+ T-cell count (cells/mm^3)	241	179	2	1086

Categorical Variables	N (%)
Gender	168 females (20%), 688 males (80%)
Race	184 black (21.5%), 612 white (71.5%), 60 other (7%)

Plasma HIV-1 RNA levels declined over time following the initiation of LPV/r therapy, as depicted in Figure 1. LPV trough levels reached steady state in 7 days and remained stable throughout the study. Therefore, for the analysis at Week 48, the mean concentration for each subject averaged across visits was used to correlate with the virologic response. The LPV trough concentrations and the overall trend line were plotted in Figure 2. The average LPV trough concentrations were 5.42 µg/mL for all subjects.

Study Population continued

Figure 1. Plasma HIV-1 RNA Levels During the Study

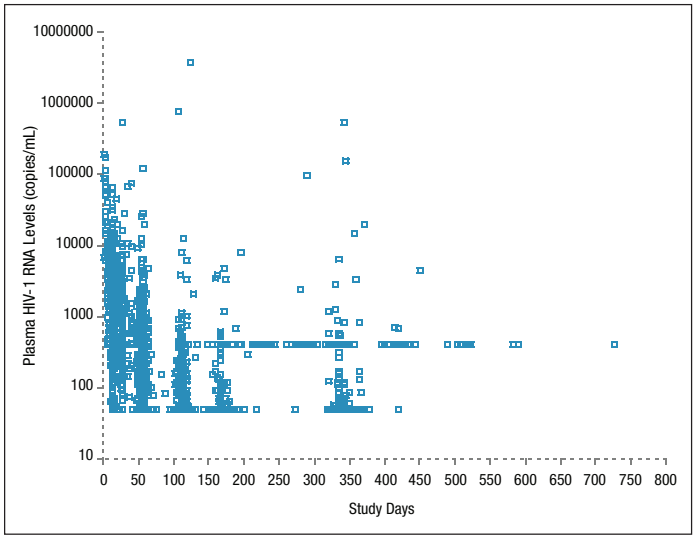
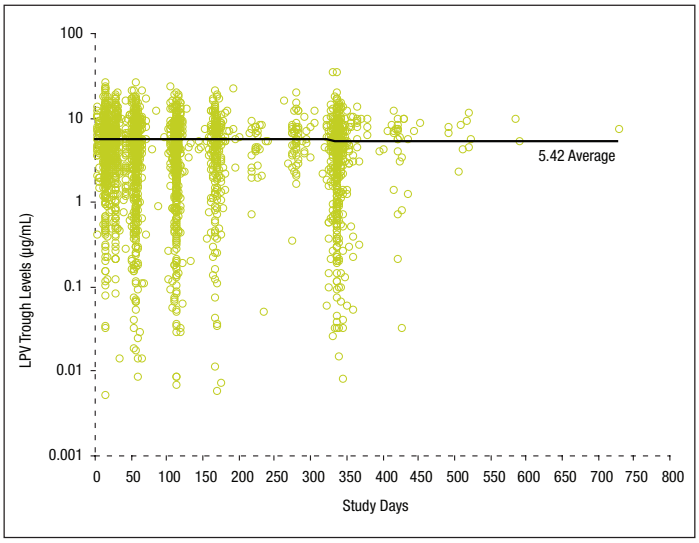


Figure 2. Lopinavir Trough Levels During the Study



Methods

- Potential TDM cutoff values assessed in this analysis ranged from 0.1 µg/mL to 1 µg/mL in 0.1 µg/mL increments. The IC50 WT for lopinavir = 0.07 mcg/mL.
- Virologic response (<50 copies/mL or otherwise) was compared between subjects with lopinavir trough concentrations below vs. above a cutoff value, utilizing Fisher's exact test, provided that there were at least 5 subjects per category.
- Exposure-virologic response models were performed to explore the relationship between virologic suppression (HIV-1 RNA <50 copies/mL) and the C_{trough} cutoff value. Baseline plasma HIV-1 RNA, CD4+ T-cell count, body weight, age, gender, race and study were included as covariates.

Results

At Week 48, the suppression rates were similar between subjects with concentration below or above various cutoff values (P>0.48). Table 3 shows the proportion of subjects with virologic failure and suppression for various levels of LPV trough concentrations. Additional cutoffs below 0.5 µg/mL were not displayed/analyzed due to small number of subjects (<5).

Table 3. Suppression Rates by LPV Trough Concentration

N (%)	<0.5 µg/mL	<0.6 µg/mL	<0.7 µg/mL	<0.8 µg/mL	<0.9 µg/mL	<1.0 µg/mL	≥1.0 µg/mL
Failure (≥50 copies/mL)	5 (18%)	7 (21%)	8 (20%)	9 (20%)	9 (18%)	11 (19%)	128 (16%)
Suppression (<50 copies/mL)	23 (82%)	27 (79%)	32 (80%)	37 (80%)	41 (82%)	48 (81%)	669 (84%)

At Week 48, average LPV trough concentration did not predict viral response (detectable, or <50 copies/mL). For the exposure-virologic response modeling for Week 48, the P-values for all the predictors (covariates) and the slopes (for continuous variables) are presented in Table 4.

Table 4. Predictive Factors for Viral Response

Predictors	Slope	P-value
LPV average trough concentration	0.003	0.98
Study	N/A	0.34
Body weight	–0.002	0.72
Age	0.039	0.70
Gender	N/A	0.95
Race	N/A	0.44

Results continued

The observed individual virologic responses (either suppression as 100%, or 0% as failure) at Week 48 are plotted against the LPV trough concentrations using the "+" symbol. The model predicted virologic response and the corresponding 95% confidence interval for the population are in blue lines (Figures 3 and 4). Figure 3 shows the LPV trough concentration axis in the linear scale. Since the low concentration values are of interest, Figure 4 shows the data with the LPV trough concentration axis in the log scale. In both Figures 3 and 4, there is no correlation between LPV trough concentration and the antiviral activity because the slope is essentially flat.

Figure 3. Observed and the Predicted (95% Confidence Interval) Virologic Response Versus Lopinavir Trough Concentration

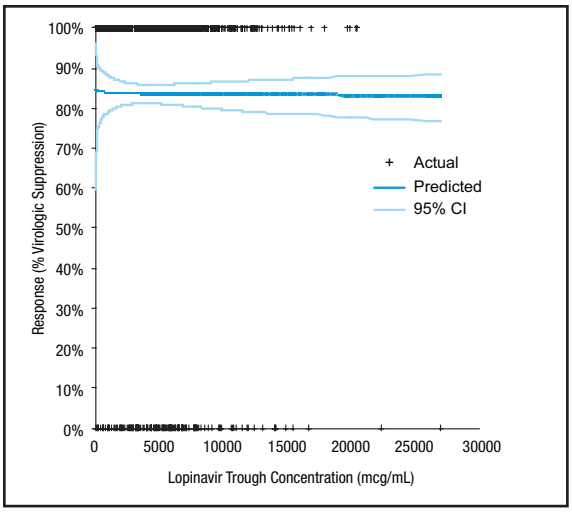
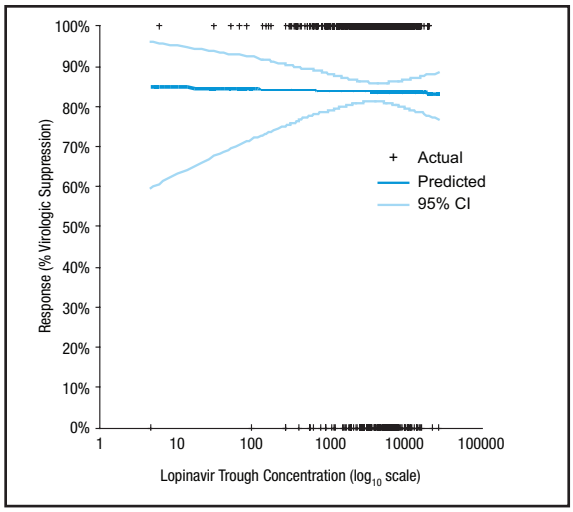


Figure 4. Observed and the Predicted (95% Confidence Interval) Virologic Response Versus Lopinavir Trough Concentration on the Log_{10} Scale



- Similar results were obtained when subjects who received lopinavir/ritonavir QD were evaluated separately.
- Additional exposure-response models were performed utilizing data from all visits and adjusting for covariates. There was no significant association between lopinavir trough concentration and plasma HIV-1 RNA levels obtained at the same visit, regardless of whether plasma HIV-1 RNA was treated as a categorical (detectable versus undetectable, P=0.67) or continuous (log-transformed level, P=0.42) variable.

Conclusions

In these 856 antiretroviral-naïve subjects treated with lopinavir/ritonavir plus 2 NRTIs:

- Investigation of potential cutoff values did not identify a lopinavir trough concentration correlated with virologic response.
- Trough lopinavir concentrations did not predict the level of plasma HIV-1 RNA at the same visit nor virologic outcome at Week 48 in this meta-analysis of 5 clinical studies.
- These data question the clinical utility of therapeutic drug monitoring to optimize virologic response of lopinavir/ritonavir in patients on an initial antiretroviral drug regimen.

Reference

1. Ananworanich J., Kosalaraksa P., Hill A., Siangphoe U., Bergshoeff A., Pancharoen C., Engchanil C., Ruxrungtham K., Burger D. and the HIV-NAT 017 Study Team. Pharmacokinetics and 24-Week Efficacy/Safety of Dual Boosted Saquinavir/Lopinavir/Ritonavir in Nucleoside-Pretreated Children. *The Pediatric Infectious Disease Journal.* Volume 24, Number 10, October 2005.

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