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Trough Lopinavir Concentrations Do Not Predict Virologic Response to Lopinavir/ritonavir-Based Three-Drug Regimens in Antiretroviral-Naïve Patients

Yi-Lin Chiu, PhD[1]; Martin S King, PhD[1]; Jianling Li, MS[1]; Cheri E Klein, PhD[1]; and George J Hanna, MD[1]
[1]Abbott Laboratories, Abbott Park, United States

Background and Objective

- The clinical utility of therapeutic drug monitoring (TDM) for lopinavir/ritonavir (LPV/r) is uncertain.
- A study in children suggested that lopinavir (LPV) trough concentrations <1 µg/mL may be associated with viral load rebound.‡
- Lack of an association between trough lopinavir concentrations and virologic response at Week 48 of therapy was previously observed in one lopinavir/ritonavir clinical trial.§
- The aim of the current analysis was to assess the relationship between LPV exposure and virologic response in a large data set with multiple time points from 4 prospective clinical trials.

Description of Data

- 447 HIV-infected, antiretroviral-naïve subjects from 4 studies with LPV trough concentration and viral load data measured simultaneously.

Table 1. Summary of Studies

Study	Enrolled	With LPV Trough Concentrations	LPV/r Doses (mg)	NRTIs
720	100	46	200/100, 400/100, or 400/200 BID*	d4T+3TC
863	326	186	400/100 BID	d4T+3TC
56	38	35	400/100 BID or 800/200 QD	d4T+3TC
418	190	180	400/100 BID or 800/200 QD	TDF+3TC

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

- Multiple visits per patient from study days 3–728
- Averaged 3–4 visits plus baseline data per subject

Table 2. Baseline Demographics

	Mean	SD	Min	Max
Age (yrs)	38	9.7	19	75
Weight (kg)	74	15.3	42	136
Plasma HIV-1 RNA (copies/mL, $\log_{10}$ scale)	4.86	0.74	1.70	6.78
CD4+ T-cell count	269	213.1	2	1086
		N (%)		
Gender	87 Females (19%), 360 Males (81%)			
Race	125 Black (28%), 296 White (66%), 26 Other (6%)			

Figure 1. Plasma HIV-1 RNA Levels (copies/mL)

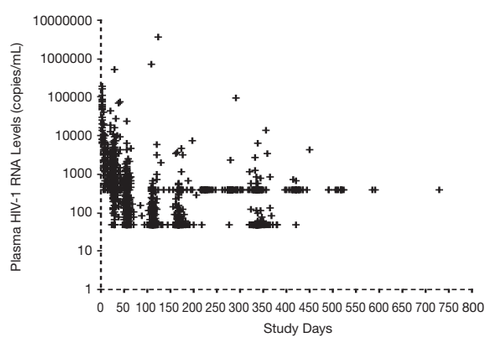
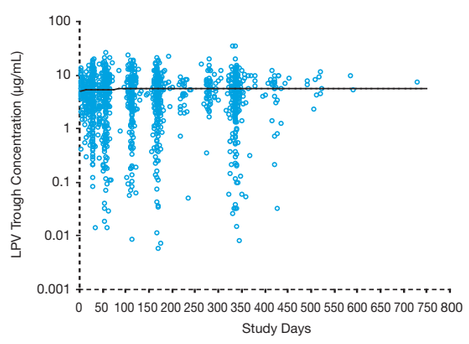


Figure 2. LPV Trough Concentrations



Statistical Methods

- Model 1: Logistic regression to compare the average trough concentrations for responders vs. non-responders at Week 48 by IIT, dropouts=censored analysis
- Model 2: Evaluate the association between LPV trough concentration and virologic response using longitudinal logistic regression model
- Model 3: Mixed effects model to analyze log-transformed HIV-1 RNA levels

For each model, baseline plasma HIV-1 RNA, CD4+ T-cell count, body weight, age, gender, race and study were included as covariates.

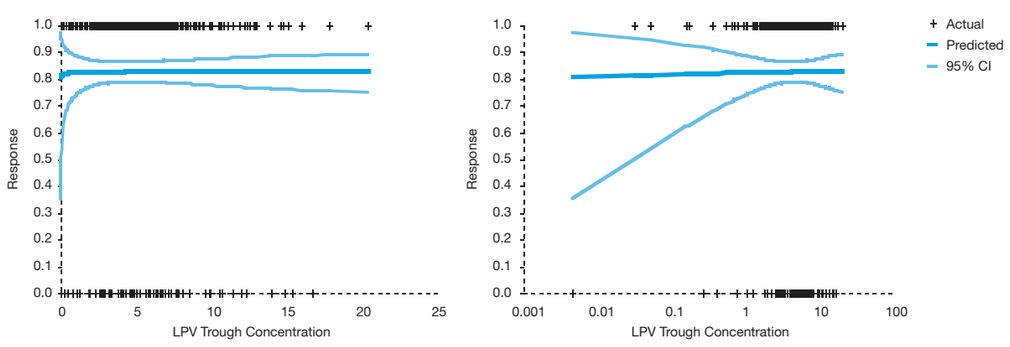
Result 1

Model 1: Average LPV trough concentration does not predict viral response (detectable, or undetectable if ≤50 copies/mL) at Week 48.

Table 3. Logistic Regression of Virologic Response at Week 48

Predictor	Slope	P-Value
LPV average trough concentration	–0.005	0.975
Study		0.845
Baseline plasma HIV-1 RNA	–0.596	<0.001
Baseline CD4+ T-cell count	–0.00003	0.969
Body weight	–0.008	0.746
Age	–0.018	0.202
Gender		0.737
Race		0.379

Figure 3. LPV Average Trough Concentration vs. Actual and Predicted Virologic Response and 95% Confidence Interval at Week 48 (Model 1)



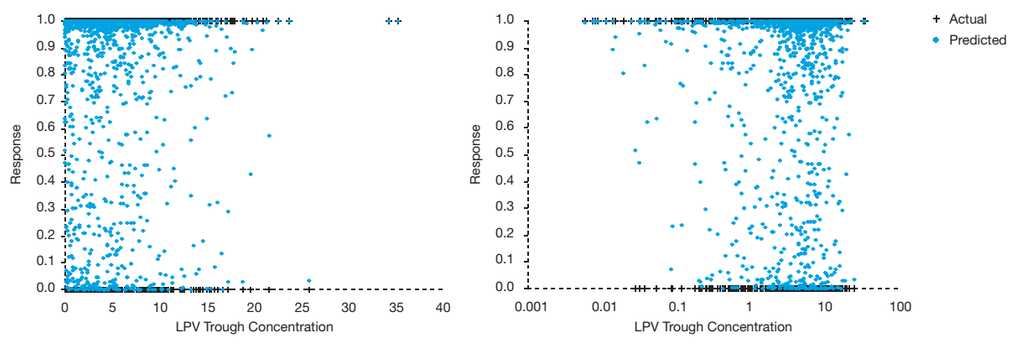
Result 2

Model 2: LPV trough concentration does not predict virologic suppression at the same time point.

Table 4. Longitudinal Logistic Regression for Virologic Suppression

Predictor	Slope	P-Value
LPV trough concentration	0.032	0.905
Time (study day)	9.447	<0.001
Study		<0.001
Study*Time interaction		<0.001
Baseline plasma HIV-1 RNA	–2.833	<0.001
Baseline CD4+ T-cell count	–0.001	0.631
Body weight	0.007	0.567
Age	0.007	0.715
Gender		0.107
Race		0.429

Figure 4. LPV Trough Concentration vs. Actual and Predicted Virologic Suppression Responses (Model 2)



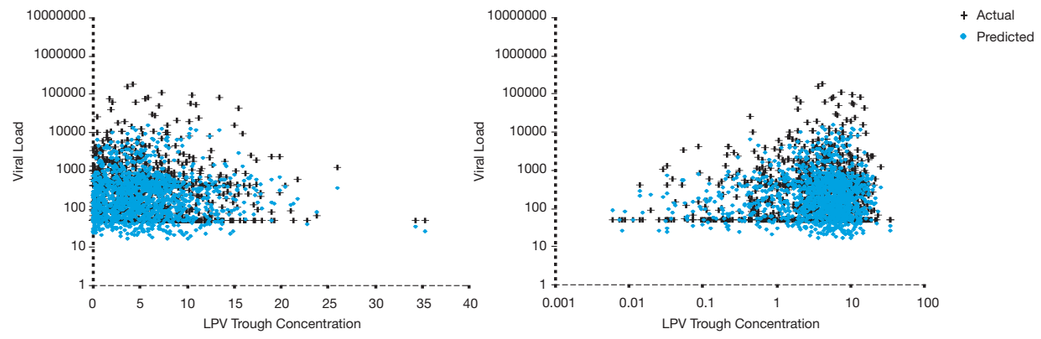
Result 3

Model 3: LPV trough concentration does not predict HIV-1 RNA levels at each time point.

Table 5. Mixed Effects Analysis for Plasma HIV-1 RNA Levels

Predictor	Slope	P-Value
LPV trough concentration	0.00002	0.999
Time (study day)	–0.663	<0.001
Study		<0.001
Study*Time interaction		<0.001
Baseline plasma HIV-1 RNA	0.209	<0.001
Baseline CD4+ T-cell count	–0.00002	0.734
Body weight	–0.0011	0.223
Age	0.0005	0.701
Gender		0.265
Race		0.628

Figure 5. LPV Trough Concentration vs. Actual and Predicted Plasma HIV-1 RNA Levels (Model 3)



Conclusions

For antiretroviral-naïve subjects treated with lopinavir/ritonavir plus 2 NRTIs:

- 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 4 clinical studies.
- These data question the clinical utility of therapeutic drug monitoring to assess virologic response of lopinavir/ritonavir in patients on an initial antiretroviral drug regimen.

Acknowledgments and References

- Studies M97-720, M98-863, M99-056 and M02-418 subjects.
- Abbott Laboratories: Balakrishna Hosmane and Guang Yang.

‡ 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.

§ Yeh V, Barros C, Easterbrook P, Lutz FB, Naylor C, Luff K, Chiu Y-L, Bertz R, King M, Brun S. “Virologic Response to a Once-Daily Lopinavir/ritonavir (LPV/r) Based Regimen in ARV-Naïve Patients Is Not Associated with Trough Lopinavir Concentrations or Baseline HIV RNA and CD4 Count.” The 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). American Society for Microbiology. Washington DC, October 2004.