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Trough Lopinavir Concentrations do not Predict Virologic Response to Lopinavir/Ritonavir-Based Three-Drug Regimens in Antiretroviral-Naïve Patients

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Abstract

Background: Therapeutic drug monitoring (TDM) guidance suggests that lopinavir trough concentration < 1 or < 3 mcg/mL may be associated with virologic failure. The aim of this analysis was to evaluate the association between lopinavir exposure and virologic response in antiretroviral-naïve subjects.

Methods: Data from previously antiretroviral-naïve subjects enrolled in 5 clinical trials of lopinavir/ritonavir (administered BID or QD) plus 2 NRTIs were utilized. Plasma HIV-1 RNA and lopinavir trough concentrations were collected simultaneously at multiple post-baseline visits. Lopinavir exposure and virologic response relationship were analyzed.

Results: At Week 48, the suppression rates were similar between subjects with concentration below or above TDM cutoff values. Similar results were obtained when subjects who received lopinavir/ritonavir QD were evaluated separately. In the exposure-response models, there was no significant association between lopinavir trough concentration and virologic response.

Conclusions: Trough lopinavir concentrations did not predict the virologic outcome in 856 antiretroviral-naïve subjects treated with lopinavir/ritonavir plus 2 NRTIs. No threshold value for trough lopinavir concentration which resulted in a suboptimal response was identified raising question as to the clinical utility of therapeutic drug monitoring to assess virologic response to lopinavir/ritonavir based therapy in patients on an initial antiretroviral drug regimen.

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ABBREVIATIONS

TDM: Therapeutic Drug Monitoring; **HAART:** Highly Active Antiretroviral Therapies; **NRTIs:** Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

INTRODUCTION

Lopinavir/ritonavir is a potent protease inhibitor (PI) combination for the treatment of HIV. Lopinavir has demonstrated approximately 10-fold greater *in vitro* potency than the protease inhibitor ritonavir against wild type HIV-1. When co-administered with low-dose ritonavir, which acts exclusively as a pharmacokinetic enhancer by blocking the cytochrome P450 3A (CYP3A)-mediated metabolism of lopinavir, plasma concentrations of lopinavir are significantly raised and half-life is prolonged. This interaction is utilized clinically in the approved co-formulation of lopinavir/ritonavir. The high drug exposures achieved with co-formulated lopinavir/ritonavir have the advantage of providing a pharmacologic barrier to the emergence of HIV-1 viral resistance in patients with wild-type virus, as well as enhanced activity against some strains of drug-resistant HIV-1. The average trough lopinavir concentration at steady state (mean ± SD) is 5.5 ± 4 μg/mL at the clinical twice-daily dose of 400 mg of lopinavir in combination with 100 mg ritonavir, and 3.2 ± 2 μg/mL at the once daily dose of lopinavir/ritonavir 800/200 mg [1-3]. These plasma drug concentrations exceed the inhibitory concentration (IC_{50}) of the wild-type virus corrected for protein binding (0.07 μg/mL) with a ratio of mean lopinavir trough concentration to IC_{50}, or inhibitory quotient (IQ), of 78 for twice daily and 46 for once daily doses. This high IQ likely contributes to lopinavir/ritonavir's high barrier to the emergence of viral resistance and durable activity [4,5].

The effectiveness of highly active antiretroviral therapies (HAART) depends on a number of factors including patient adherence, intrinsic drug potency, pharmacokinetic factors, and the likelihood of emergence of drug resistant virus; among these factors, poor adherence has been cited as the leading contributor to treatment failure [6].Therapeutic drug monitoring (TDM) has been proposed as a strategy to manage pharmacokinetic factors that may contribute to inadequate virologic response. An underlying assumption of TDM is that measured drug concentration correlates with virologic outcome. Among "first generation" protease inhibitors including saquinavir, indinavir, nelfinavir and amprenavir, observational studies have suggested that drug exposure does correlate with virologic suppression in patients prospectively followed up in phase II studies [7,8]. However, a similar correlation between drug concentration and virologic response has not been observed for lopinavir. While a study in 20 nucleoside pretreated children suggested that lopinavir trough concentrations less than 1 μg/mL may be associated with viral load rebound [9], and French guidelines have recommended maintaining lopinavir trough concentrations above 3 μg/mL, a prospective lopinavir/ritonavir trial in 190 antiretroviral-naïve subjects showed no association between trough lopinavir concentrations and virologic response at Week 48 of therapy [3]. The current analysis was performed to assess the relationship between lopinavir exposure and virologic response in a larger data set with multiple time points from 5 prospective clinical trials.

MATERIALS AND METHODS

Data from previously antiretroviral-naïve subjects enrolled in 5 controlled clinical trials (720, 863, 056, 418 and 730) [2,3,10-12] of lopinavir/ritonavir plus 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs: stavudine [d4T] and lamivudine [3TC] for studies 720, 863 and 056, tenofovir DF [TDF] and 3TC or emtricitabine [FTC] for 418 and 730) who had post-baseline plasma HIV-1 RNA levels and lopinavir concentration values were included in the analysis. Plasma HIV-1 RNA levels and lopinavir trough (pre-dose) concentrations were collected simultaneously during multiple visits from Day 3 to Day 728 of therapy. Patients were randomized to receive lopinavir/ritonavir 400/100 mg twice daily (BID) (all 5 studies), 200/100 mg twice daily (720), 400/200 mg twice daily (720), or 800/200 once daily (QD) (056, 418, and 730). These studies all enrolled HIV-1 infected subjects who were at least 18 years old and had no more than 7 days of any prior antiretroviral treatment. Patients were excluded if they had been treated for an active opportunistic infection within 30 days before screening or if they had an alanine aminotransferase and/or aspartate aminotransferase level greater than 3 times the upper limit of normal at screening. Women who were pregnant or breast-feeding were excluded from participation in Studies 720, 863, 056 and 418. All of the studies were approved by the institutional review board or ethics committee at each of the participating institutions, and all subjects gave written informed consent prior to study participation.

Demographic features including gender, race, age and weight, as well as plasma HIV-1 RNA level and CD4+ T-cell count, were obtained at baseline. After the initiation of the lopinavir/ritonavir therapy, blood samples were periodically measured for pharmacokinetic and virologic results. Lopinavir trough concentrations were scheduled to be collected immediately prior to the morning dose (12 ± 2 hours from the previous BID dose and 24 ± 2 hours from the previous QD dose). The timing of the trough concentration collection relative to the previous dose was recorded to the nearest minute. Lopinavir concentrations were determined by measured by liquid chromatography with tandem mass spectrometry (LC/MS/MS for 418 and 730) or a validated high performance liquid chromatography (HPLC) assay method with ultraviolet detection (720, 863 and 056). The lower limit of quantitation (LOQ) for lopinavir was 5 ng/mL (with LC/MS/MS) or 6 ng/mL (with HPLC). Individuals who did not have any measurable lopinavir concentrations from the first pharmacokinetic collection through Week 48 were analyzed and discussed separately since, due to the sensitivity of the lopinavir assay; the absence of detectable lopinavir concentrations suggested extremely poor adherence. In addition to the drug concentration as a tangible measure for adherence, additional compliance data such as pill counts from these subjects were summarized. Efficacy was evaluated using assessments of plasma HIV-1 RNA levels. The proportion of subjects with plasma viral load (HIV RNA) below the LOQ (<400 or <50 copies/mL using Roche Amplicor or Roche Amplicor ultrasensitive) at each time point was also calculated at each visit. For the virologic binary response (suppressed if < 50 copies/mL) at Week 48, an intent-to-treat, dropouts-as-censored analysis was used. In this analysis, subjects who discontinued early in the study (before Week 8), and those who discontinued while HIV-1 RNA was <50 copies/mL between week 8 and week 48, were censored from

the analysis. In typical primary endpoints, subjects discontinuing for reasons unrelated to virologic response are considered non-responders. Such subjects are excluded from the dropouts-as-censored analysis to avoid the dilution of potential viral load-related effects. To associate with the Week 48 clinical endpoint, the trough concentrations during the study were averaged across all the visits for each subject, as lopinavir concentrations quickly reach steady state by Day 7. If a subject did not have a trough concentration at Week 48 but had the virologic endpoint, the average concentration data from all other visits was employed for this subject.

Since trough concentrations for lopinavir of 3.0 or 1.0 μg/mL have been proposed as targets for TDM, [5,13-15] the virologic response rates at Week 48 were compared between subjects who had lopinavir trough concentrations above and below each suggested target value (3 or 1 μg/mL). A range of other thresholds from 0.1 to 1.0 μg/mL was also assessed, and binary recursive partitioning was used to evaluate whether any other thresholds would constitute a viable target value. To formally characterize the exposure-response relationship, a logistic regression analysis was employed to evaluate the association between the average trough lopinavir concentrations and virologic response at Week 48. Three repeated-measure analyses were also performed to include all the time points for the evaluating the correlation between the lopinavir trough concentrations and virologic response. The first one used the proportion of subjects with plasma HIV-1 RNA below LOQ as the response variable. The second one assessed the correlation between the lopinavir concentrations and the log-transformed plasma HIV-1 RNA levels. As HIV-1 RNA levels decreased with time after the initiation of lopinavir/ritonavir therapy, to investigate whether subjects who had lower lopinavir concentrations would tend to have a slower viral load decline, the decreasing trends in time were compared between subjects above and below 1 μg/mL in the third analysis. All analyses were conducted using SAS version 8.2 (SAS Institute Inc., Cary NC), with the exception of binary recursive partitioning, which was conducted using CART version 6.2 (Salford Systems, San Diego, CA).

RESULTS AND DISCUSSION

One thousand three hundred eighteen (1318) antiretroviral-naïve HIV positive patients met the inclusion/exclusion criteria and were enrolled in the 5 clinical studies. Of these, 856 subjects who had at least one lopinavir trough concentration and the efficacy endpoint based on HIV-1 RNA level at Week 48 were included in the analysis. Most of the subjects had additional post-baseline visits for both the lopinavir trough concentrations and HIV-1 RNA levels. The baseline characteristics of these 856 subjects are summarized in Table 1.

At Week 48, 84% (717/856) of the subjects had HIV-1 RNA levels below the limit of detection (≤50 copies/mL) and were categorized as virologic responders. The overall mean lopinavir trough concentration was 5.42 with SD of 3.48 μg/mL. The mean (± SD) lopinavir trough concentration was similar between non-responders (detectable or virologic failure) and responders (undetectable or suppression): 5.81 (±4.19) *vs.* 5.34 (±3.32), respectively, Figure 1. The average trough value was slightly higher numerically in subjects with HIV-1 RNA >50 copies/mL; the difference did not reach statistical significance (p=0.88, two-sample *t* test with unequal variances) despite the large number of subjects.

Approximately 7% and 25% individuals had trough concentrations below the previously proposed TDM threshold of 1 or 3 μg/mL, respectively. To understand the potential utility of various lopinavir trough concentration cutoff values, the proportions of subjects who had successful virologic response (≤50 copies/mL) at Week 48 between subjects who had lopinavir trough concentration below and above proposed TDM thresholds were compared. The proportion of responders was similar between the two groups: 83.6% (178/213) *vs.* 83.8% (539/643) for subjects with lopinavir trough concentration < 3 μg/mL *vs.* ≥

Table 1: Summary of Demographic Characteristics (N=856).

Variable		N (%)	lopinavir/ritonavir doses (mg)	
Study Number	M720	46 (5%)	200/100*, 400/100, or 400/200 BID*	
	M863	178 (21%)	400/100 BID	
	M056	35 (4%)	400/100 BID or 800/200 QD	
	M418	156 (18%)	400/100 BID or 800/200 QD	
	M730	441 (52%)	400/100 BID or 800/200 QD	
Gender	Male	688 (80%)		
	Female	168 (20%)		
Race	White	612 (71%)		
	Black	184 (22%)		
	Other	60 (7%)		
	Mean	**SD**	**Min**	**Max**
Age (yrs)	39	9.7	19	75
Weight (kg)	74	15.2	33	171
Plasma HIV-1 RNA (copies/mL, log10 scale)	4.94	0.7	1.72	6.98
CD4+ T-cell count (cells/μL)	241	179	2	1086

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

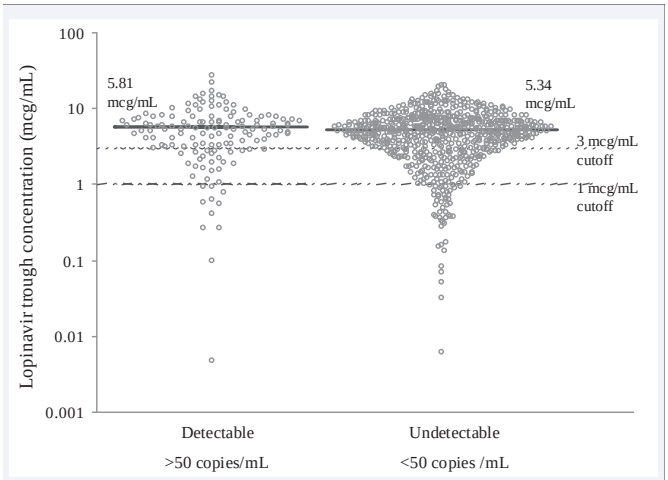

Figure 1 Comparison of Lopinavir Trough Concentrations Between Responders (Undetectable HIV-1 RNA < 50 copies/mL) Versus Non-Responders (Detectable HIV-1 RNA > 50 copies/mL) at Week 48.

3 µg/mL, respectively; p=0.92 using Fisher's exact test (95% CI for the difference, –6.0% to 5.5%). Similar results were observed when the threshold value of 1 µg/mL was used (83.9% vs. 81.4%; 95% CI for the difference, –12.8% to 7.7%; p=0.58). As shown in Table 2, response rates based on other ad hoc thresholds remained consistently around 80% (p>0.48 for all comparisons). Thirteen subjects did not have any measurable lopinavir concentrations. The absence of detectable lopinavir at any time point is likely explained by failure to take their medication; these subjects were therefore deemed unevaluable and not included in the statistical analysis. Most of these subjects (9/13) had virologic failure (>50 copies/mL) at Week 48. The absence of a meaningful threshold to predict virologic response was confirmed by binary recursive partitioning analyses. In an analysis of the 856 subjects in the primary analysis set, no lower threshold was identified. In an analysis of all 869 subjects (i.e., including the 13 subjects with no detectable lopinavir concentration), the only threshold identified was 0.005 µg/mL. This cutoff segregated the 13 subjects with no detectable concentration plus 1 subject with a concentration of 0.005 µg/mL from the remaining 855 subjects, with response rates of 29% (4/14) in the former group and 84% (717/855) in the latter group.

To account for other potential covariates, logistic regression analyses were performed to assess the correlation between the proportion of responders at Week 48 and the following predictors: average lopinavir trough concentrations, baseline plasma HIV-1 RNA viral loads, baseline CD4 counts, study, race, gender, body weight and age. There was no significant association between mean lopinavir trough concentration and virologic response assessed at Week 48 (p=0.98), Figure 2.

When incorporating multiple visits per patient into the analysis by accounting for inter- and intra-subject variability, 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. Table 3 summarizes the slope (for continuous various) and p-value for trough concentration and demographic characteristics from the three exposure-response modeling analyses.

Based on the exposure-response models, lopinavir trough concentrations did not predict the virologic response at Week 48, or all visits collectively. To understand whether there was a difference in time for the HIV-1 RNA level decline between subjects who had high or low trough concentrations, data were further analyzed and plotted by high (≥1 µg/mL) *vs.* low (< 1 µg/mL) concentration groups. HIV-1 RNA levels significantly decreased with time (study days) for both groups (p<0.0001). Decreasing HIV-1 RNA level trends with time were similar between the two groups (p=0.63), indicating that the subjects with lower concentrations did not have a slower viral load decline, Figure 3. As the viral load decline curves were fitted based on all the observed data (n=5077), due to large number of

Table 2: Proportions of Responders‡ for Different Lopinavir Trough Values.

N (%)	<0.1 µg/mL	<0.2 µg/mL	<0.3 µg/mL	<0.4 µg/mL	<0.5 µg/mL	<0.6 µg/mL	<0.7 mg/mL	<0.8 µg/mL	<0.9 µg/mL	<1.0 µg/mL	≥1.0 µg/mL
Nonresponders (Failure)	2 (29%)	2 (18%)	4 (29%)	4 (17%)	5 (18%)	7 (21%)	8 (20%)	9 (20%)	9 (18%)	11 (19%)	128 (16%)
Responders (Suppression)	5 (71%)	9 (82%)	10 (71%)	20 (83%)	23 (82%)	27 (79%)	32 (80%)	37 (80%)	41 (82%)	48 (81%)	669 (84%)

‡ Patients who had undetectable HIV-1 RNA (<50 copies) were classified as responders. Formal statistical tests for cutoffs below 0.5 µg/mL were not performed due to small number of subjects (< 5).

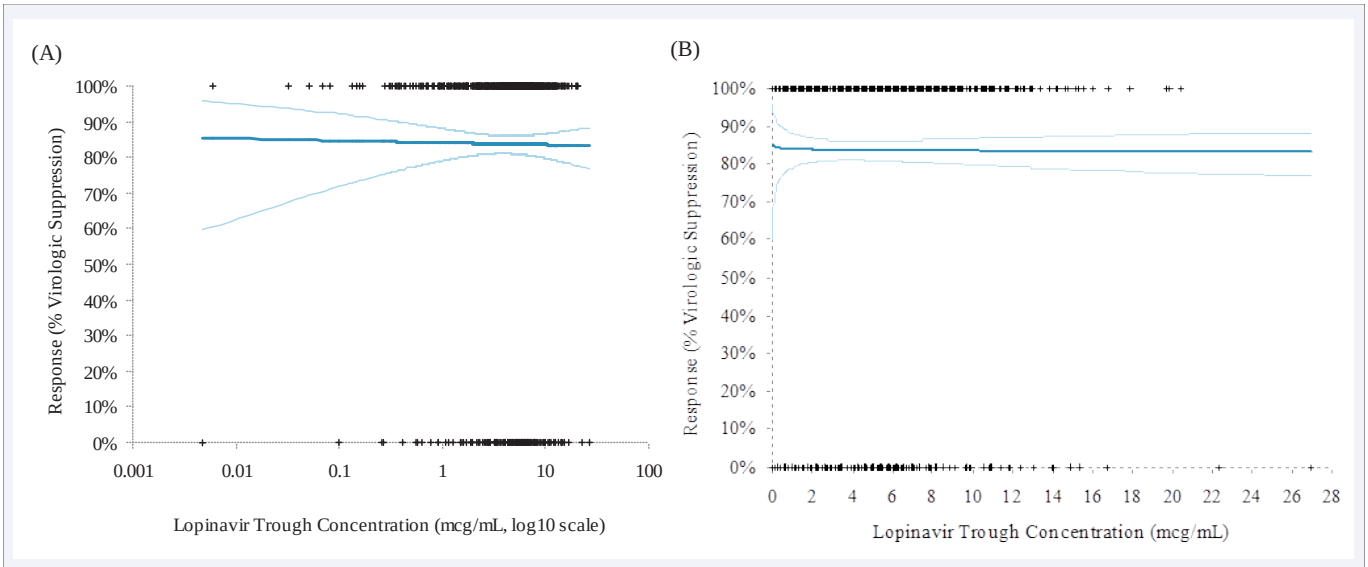

Figure 2 Relationship between lopinavir trough concentration and virologic response (HIV-1 RNA < 50 copies/mL) at Week 48. Observed (+) and the Predicted Response (;;) and the 95% Confidence Interval (;;). (A) concentration on log scale (B) concentration on linear scale.

observations, 1000 and 50 random samples of high (≥1 μg/mL) and low (<1 μg/mL) concentrations (approximately 20% of the original data), respectively, were plotted in the figure.

In clinical practice, the benefit of adjusting medication regimens on the basis of measured drug concentration is uncertain. TDM, entailing a limited number of measurements of drug concentrations, may not accurately reflect true drug exposures in patients with poor adherence, because patients who know they are due to have drug concentrations quantified in the clinic may improve their adherence prior to their visit (so-called white coat compliance), but return to poor adherence after the plasma concentration is measured [16,17]. In addition, target drug concentrations may not be well defined, and the value of dose adjustment to meet these target concentrations is uncertain for many antiretroviral agents. Thus, additional research is still needed to clarify the most appropriate roles for TDM in the clinic.

There are multiple challenges to investigating the utility of TDM for antiretroviral therapies. In clinical trials, only a fraction of patients would be expected to have drug concentrations lower than the proposed/targeted TDM threshold [18]. Thus, a large sample size would be required to have sufficient power to demonstrate the presence or absence of a meaningful association between the drug concentration and virologic response. Few large studies assessing the benefit of TDM for antiretroviral therapy have been conducted. In a randomized controlled trial in 190 treatment naïve and experienced HIV-1 infected patients receiving PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, subjects below the TDM targets tended toward worse virologic response [18]. However, a recent study in 194 HIV-1 infected patients showed no overall benefit of TDM [19]. In that study, all approved PIs were allowed with the exception of darunavir, which was not available at the time of the study. Of note, the median trough concentrations increased significantly more in the TDM arm compared with standard of care for all PIs except fosamprenavir. The inability of the investigators to achieve the desired experimental conditions for fosamprenavir was considered as a limitation for this study. Approximately half the patients used dual PIs; all except for nelfinavir were co-administered with ritonavir. Both of these studies pooled subjects from a number of drug regimens in order to study a sufficient number of subjects. However, the variety of different treatments resulted in relatively small number of subjects per drug regimen within each study, making it difficult to identify treatment-specific effects.

It is important to recognize that not all drugs and patients are the same; TDM may be more beneficial in specific patient populations, and in the setting of specific drug regimens. For

Table 3: Exposure-Response Analyses to Explore the Association Between Lopinavir Trough Concentration and HIV-1 RNA, Adjusting for Potential Effects of Baseline Characteristics.

Explanatory Variable	Week 48 Virologic Response (% Suppression)		All Visits Virologic Response (% Suppression)		All Visits HIV-1 RNA Level (copies/mL)	
	Slope	P-Value	Slope	P-Value	Slope	P-Value
Lopinavir trough concentration (μg/mL)	0.0030	0.98	-0.0829	0.67	0.1071	0.42
Gender		0.95		0.13		0.16
Race		0.44		0.25		0.68
Age at baseline (years)	0.0039	0.70	0.0097	0.39	-0.0006	0.55
Body Weight at baseline (kg)	-0.0023	0.72	0.0047	0.55	-0.0005	0.49
Note: All models also adjusted for potential effects of baseline HIV-1 RNA, baseline CD4+ T-cell counts, and study.						

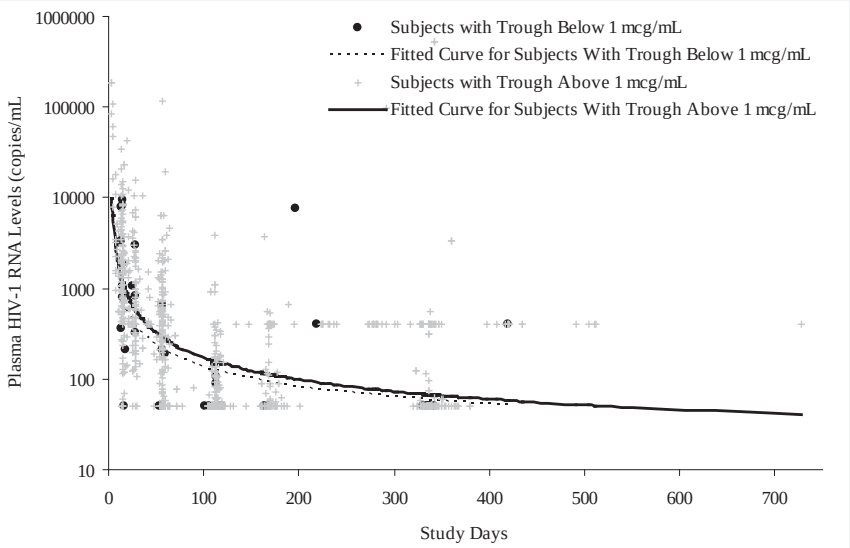

Figure 3 HIV-1 RNA Level vs. Time Profiles for Subjects With Lopinavir Trough Concentration Below and Above 1mcg/mL Cutoff Value.

NNRTIs, multiple studies have suggested that patients treated with nevirapine may benefit from TDM since the plasma nevirapine concentration correlated with both antiviral effects and toxicity [20-22]. In contrast, results are inconsistent for efavirenz; one study showed that efavirenz plasma concentrations can predict treatment failure and central nervous system side effects in HIV-1-infected patients [23], while the study by Fiske and colleagues concluded that the knowledge of efavirenz concentrations would have had no impact on side effects or response [24-26]. For PIs, it has been reported that treatment-naïve patients with lower plasma concentrations tended to have worse virologic response, but this relationship was observed for older agents dosed without ritonavir boosting, such as indinavir, nelfinavir [27,28], and saquinavir, agents that achieve relatively low plasma concentrations compared to boosted PIs [7,29].

Analysis of the utility of TDM with newer PIs suggests a possible role in treatment-experienced patients, when drug concentration data were combined with data on baseline resistance mutations as a genotypic inhibitory quotient (GIQ, ratio of plasma concentration to number of baseline resistance mutations). For atazanavir (including both boosted with ritonavir and unboosted), no significant relationship was observed between atazanavir plasma trough concentration and antiviral response in 82 patients starting atazanavir without PI mutations, but a significant relationship was demonstrated between atazanavir GIQ and treatment response in 26 patients starting atazanavir while having PI mutations [30]. Similarly, for a cohort of 116 treatment-experienced patients treated with lopinavir/ritonavir-based regimens, drug concentration alone was not associated with virologic response, but in patients with 3 or more mutations at baseline, lopinavir GIQ was significantly associated with response [31,32]. Importantly, however, the GIQ value is determined primarily by the number of baseline resistance mutations; for a given subject, dose modifications can lead to only modest changes to the GIQ value [31]. Overall, these data suggest a possible role for TDM when trough drug concentrations only marginally exceed those necessary for viral suppression, as with unboosted protease inhibitors or in the setting of reduced viral susceptibility.

Another challenge with TDM research is the complexity of drug interactions and the subsequent impact on drug concentrations. While attention and effort have been given to demonstrate that dose changes resulting from TDM can lead to a significant increase in percentages of subjects above a proposed TDM cutoff value [5,6] there is still no evidence that increasing lopinavir concentrations is associated with improved virologic outcomes in these studies. Such studies do not prove the effectiveness of TDM with regard to virologic response, since the given TDM target values had not been validated as predictors of virologic response.

In this current study of lopinavir/ritonavir including 856 HIV positive, antiretroviral treatment-naïve subjects pooled from 5 similar clinical trials, formal statistical analyses did not identify a TDM threshold concentration that predicted virologic response. Similar results were obtained when subjects who received lopinavir/ritonavir QD (N=295) were evaluated separately (data not shown). Of note, for the unevaluable subjects who did not have any measurable lopinavir concentrations during the pharmacokinetic collections, a much lower virologic response rate was observed (4/13) than that of the evaluable 856 subjects. Given the lopinavir assay sensitivity, these nonmeasurable lopinavir concentrations would suggest poor adherence. Indeed, 5 of these 13 subjects received study drugs dispensed with electronic adherence measures; recorded compliance for all 5 subjects was 0-25%. Among the remaining 8 subjects, all but one had adherence below average as assessed by pill counts. TDM was therefore of value in these individuals as apparent evidence of lack of adherence. In clinical practice, TDM may be useful to identify the small minority of patients who do not have any measurable lopinavir concentration. To date, the current analysis is the largest study to investigate the utility of TDM for a specific antiretroviral therapy in a specific population (lopinavir/ritonavir with NRTIs in antiretroviral-naive patients). Additional study of other PIs and of treatment-experienced patients is needed to understand the utility of TDM in those situations.

CONCLUSION

Trough lopinavir concentrations did not predict the level of plasma HIV-1 RNA at the same visit or virologic outcome in this meta-analysis of 5 clinical studies in 856 antiretroviral-naïve subjects treated with lopinavir/ritonavir plus 2 NRTIs. No threshold value for trough lopinavir concentration which resulted in a suboptimal response was identified raising question as to the clinical utility of therapeutic drug monitoring to assess virologic response to lopinavir/ritonavir based therapy in patients on an initial antiretroviral drug regimen.

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CONFLICT OF INTEREST

Yi-Lin Chiu, Martin S King, Cheri E Klein, Daniel Cohen and Barry Bernstein are AbbVie Employees and have no additional conflict of interest to report.

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