ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2004, p. 979–984 Vol. 48, No. 3
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.3.979–984.2004

Intrapatient Variability of Efavirenz Concentrations as a Predictor of Virologic Response to Antiretroviral Therapy

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Received 28 March 2003/Returned for modification 6 September 2003/Accepted 15 November 2003

Intrapatient variability of drug concentrations over time has not been evaluated as a predictor of drug response but may provide information on the onset and maintenance of response and a patient's adherence to therapy. Our objective was to develop a pharmacologically based measure of intrapatient variability of concentrations and investigate its association with a patient's response to antiretroviral therapy. Efavirenz concentrations were obtained for 50 children enrolled in Pediatric AIDS Clinical Trials Group study 382, a concentration-controlled trial of efavirenz plus nelfinavir and at least one nucleoside reverse transcriptase inhibitor. Efavirenz pharmacokinetic parameters were determined from 24-h concentration-time profiles at weeks 2 and 6 and used to predict trough concentrations obtained during 1 year of therapy. A concentration predictability score, defined as the fraction of measured trough concentrations that fell within a ±50% range of the predicted concentration, was used to place subjects into high and low concentration predictability groups. Relationships between this score and human immunodeficiency virus RNA levels in plasma were investigated. Eight of 33 children (24%) in the high-predictability group experienced viral rebound, compared with 9 of 17 children (53%) in the low-predictability group ($P = 0.042$). Children with low predictability scores exhibited a significantly shorter time to their first viral rebounds and were significantly more likely to experience viral rebound; the latter finding persisted after adjustment for baseline viral load and efavirenz exposure at week 6. This novel method for the quantitation of intrapatient concentration variability was independently predictive of virologic rebound. This measure may allow interventions to minimize therapeutic failure and is applicable to other drugs.

Variability in response to antiretroviral therapy has been attributed to differences in virologic, immunologic, pharmacologic, and behavioral characteristics. In the field of human immunodeficiency virus (HIV) therapeutics, substantial interpatient pharmacokinetic variability has been demonstrated and relationships between drug exposure and viral response have been observed for all three classes of antiretroviral agents (2, 6). Importantly, dose adjustment strategies designed to achieve target drug exposures and thereby reduce pharmacokinetic variability have resulted in improved virologic and immunologic outcomes (7, 8).

In addition to pharmacokinetics, another source of variability in outcomes is adherence. Therapeutic drug monitoring and pharmacokinetics have been discussed as approaches to monitor adherence but have not been systematically studied, partly because adherence has not been conceptually integrated into the basic pharmacologic dose-response paradigm. In the standard model, pharmacokinetics describes the relationship between dose and concentration and pharmacodynamics describes the relationship between concentration and response. While this paradigm has proven quite useful in modeling these relationships, it relies on the administration of a known dose. This requirement is a major limitation in the clinical setting, since the dosing regimen followed by the patient does not necessarily coincide identically with the prescribed regimen. This mismatch is due to nonadherence, and the standard pharmacokinetic-pharmacodynamic paradigm can be altered to accommodate it (Fig. 1). Pharmacological principles suggest that if a patient's pharmacokinetic parameters are known, concentrations can be predicted and compared with observed values at any point in time following any dosing regimen. If the actual dosing regimen used by the patient reasonably approximates the prescribed regimen, the predicted concentrations should be close to the observed concentrations. A certain degree of discrepancy is expected and occurs, for example, because of analytical variability, time dependencies in pharmacokinetic parameters, and pharmacokinetic model misspecification. However, if the patient is not taking a drug as prescribed, i.e., is nonadherent, it follows that the observed and predicted concentrations could become quite discrepant. As discrepancies increase beyond the expected amount, medication nonadherence becomes a dominant contributor to the mismatch. We hypothesize that nonadherence can be detected by evaluating discrepancies between observed and predicted concentrations. Since these concentrations will directly reflect the actual and prescribed dosing regimens, the extent of nonadherence will be incorporated into the discrepancy. Hence, this approach yields an integrated pharmacokinetic adherence measure (IPAM). It is acknowledged that other sources of intrapatient variability of concentrations will be incorporated into this assessment and

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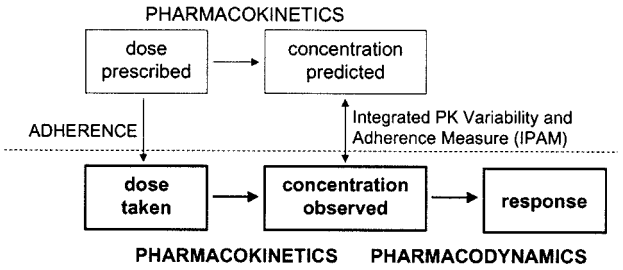

FIG. 1. Standard pharmacokinetic-pharmacodynamic paradigm (in bold) with modifications to include adherence and illustrate the utility of concentration monitoring in assessing integrated pharmacokinetic variability and adherence.

cannot be separated from nonadherence. These collective sources of intrapatient variability of concentrations over time have not been carefully evaluated as a predictor of drug response. This omission represents a potentially important oversight, as such a measure may contain information on the onset and particularly the maintenance of a therapeutic response and on a patient's adherence to therapy.

The objective of this work was to develop a score that quantitates intrapatient variability of concentrations over time and to evaluate whether this measure is associated with a patient's virologic response to antiretroviral therapy. This effort was undertaken with 50 HIV-infected children who participated in Pediatric AIDS Clinical Trials Group (PACTG) study 382. PACTG study 382 was a phase I/II, open-label, area-under-the-curve (AUC) controlled study designed to determine the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz in combination with nelfinavir and at least one nucleoside reverse transcriptase inhibitor in children. The viral dynamics (13) and primary results through 48 weeks (14) of this study have previously been reported.

MATERIALS AND METHODS

Study design and pharmacokinetic evaluations. Pharmacokinetic and virologic data on 50 subjects were collected. Plasma samples for quantitation of efavirenz concentrations were obtained before an observed morning dose and at 2, 5, 6, 8, 12, and 24 h postdose at week 2 of therapy. A 24-h steady-state AUC was computed with the linear trapezoidal rule. If the AUC for efavirenz was not within the prespecified target range of 190 to 380 $\mu M \cdot h$, the efavirenz dose was adjusted proportionately, up to a 200-mg maximum dosing increase. This procedure was repeated for all 50 subjects at week 6. Subjects were seen at monthly intervals for clinical evaluations that included an efavirenz trough concentration and a determination of plasma HIV-1 RNA levels. By use of the efavirenz concentrations for AUCs from week 2 and week 6, individual pharmacokinetic parameters were obtained by a population pharmacokinetic approach. Briefly, all concentration-time data for all subjects were appropriately pooled and analyzed with a nonlinear mixed-effects regression model (3). By use of the first-order conditional estimation (FOCE) procedure, Bayesian estimates of individual pharmacokinetic parameters were provided in addition to the population means and variances. The clearance, volume of distribution, and first-order rate constant determined for each individual were used to predict values for each observed trough concentration. An acceptable range for each observed concentration was defined as ±50% of the predicted concentration. This range was selected based on investigator judgment to account for analytical uncertainty, intrapatient pharmacokinetic variability, inaccuracies in the recording of the times of drug dosing and sample collections, and inadequacies in the pharmacokinetic model. The discrepancy between predicted and observed concentrations was expressed as the ratio of the observed concentration to the predicted concentration. For each subject, the number of ratios within this range was determined and the IPAM score was defined as the fraction of available ratios within the acceptable range. With this approach, a high score is indicative of high concentration predictability (or low intrapatient concentration variability), while a low score indicates low predictability (or high intrapatient concentration variability). Up to 12 efavirenz concentration ratios were available for each subject over a 1-year period. These trough concentrations were not available in real time, and no provisions were made in the protocol for the use of the knowledge of the concentrations in patient management. Although nelfinavir AUCs were obtained in PACTG study 382, nelfinavir concentrations in the monthly samples were not quantitated. Viral rebound was defined as an RNA measurement of >400 copies/ml for a patient after at least two consecutive values of <400 copies/ml or a >0.75-$\log_{10}$ increase from the nadir otherwise. Confirmed viral suppression of <400 copies/ml was defined as two consecutive RNA measurements of <400 copies/ml for a patient.

Efavirenz concentrations in plasma were determined by using a validated high-performance liquid chromatographic method. The total variability of the assay was 1 to 4.5% over the standard curve range of concentrations.

All efavirenz concentrations and HIV-1 RNA determinations obtained for this study were approved as part of the PACTG study 382 protocol by the institutional review boards at each site. Written informed consent was obtained from parents or guardians of all children.

Statistical analyses. The times to the first viral rebound and the first confirmed RNA level of <400 copies/ml were estimated by the Kaplan-Meier method (9). The relationship between the IPAM score and the time to the first viral rebound from the nadir was examined by using the Cox proportional hazards regression model (4) and the Kaplan-Meier method (9). Risk ratios and 95% confidence intervals were evaluated by Cox regression models with and without adjustment for baseline covariates and the efavirenz AUCs at weeks 2 and 6. Analyses were conducted using $\log_{10}$-transformed plasma HIV-1 RNA levels (RNA), $\log_2$-transformed CD4 percentages, and week 2 AUCs. Week 6 AUCs had a narrower range and were analyzed as a binary variable. Raw weight measurements were converted to age- and sex-adjusted *z* scores (weight-for-age *z* scores) (5). Correlations between the covariates were assessed by the nonparametric Spearman rank correlation coefficient (10). The chi-square test and Fisher's exact test were used to compare the viral rebound rates between children with high and low IPAM scores, as defined below. All reported *P* values are two-sided.

(i) TSSA. Tree-structured survival analysis (TSSA) (11, 12) was used as an exploratory tool to identify subgroups with homogeneous covariates within groups and distinct time-to-viral-rebound outcomes across groups. Given the study sample size, we developed two subgroups by using binary recursive partitioning. Separation between two candidate subgroups was measured by a two-sample log rank test statistic that compared their time-to-viral-rebound distribution curves. A binary split having the largest log rank test statistic over all possible binary splits was chosen to yield the maximum difference in the time-to-viral-rebound distribution outcomes between the two resultant subgroups. This split was used to define the high- and low-IPAM groups.

(ii) Sensitivity analyses. The statistical analyses were repeated with an expected range of concentration ratio deviation of ±40% rather than ±50% to determine whether changing this criterion strongly influenced results. The analyses were also repeated with only the first six concentration ratios in the computation of the IPAM to evaluate whether fewer observations may be useful in discriminating the times to various virologic outcomes across subjects.

RESULTS

Fifty-seven subjects were enrolled in PACTG study 382; seven were taken off study treatment at or prior to study week 2. These subjects did not have the intensive 24-h AUC for efavirenz at week 2 that was necessary for this analysis and were excluded. The baseline characteristics of the remaining 50 children were similar to those reported for the 57 children in the overall study (14). These children ranged in age from 3.8 to 16.8 years (median, 7.8 years) and had baseline CD4 percentages of 1 to 56% (median, 30%) and HIV-1 RNA levels of 2.6 to 5.7 $\log_{10}$ copies/ml (median, 4.1 $\log_{10}$ copies/ml).

Figure 2 displays data from all subjects in this study and illustrates the range of IPAM scores. Several features can be noted. First, this approach was able to detect differences among subjects with scores ranging from 0 to 1.0. Three subjects had ratios that were all within the acceptable range and

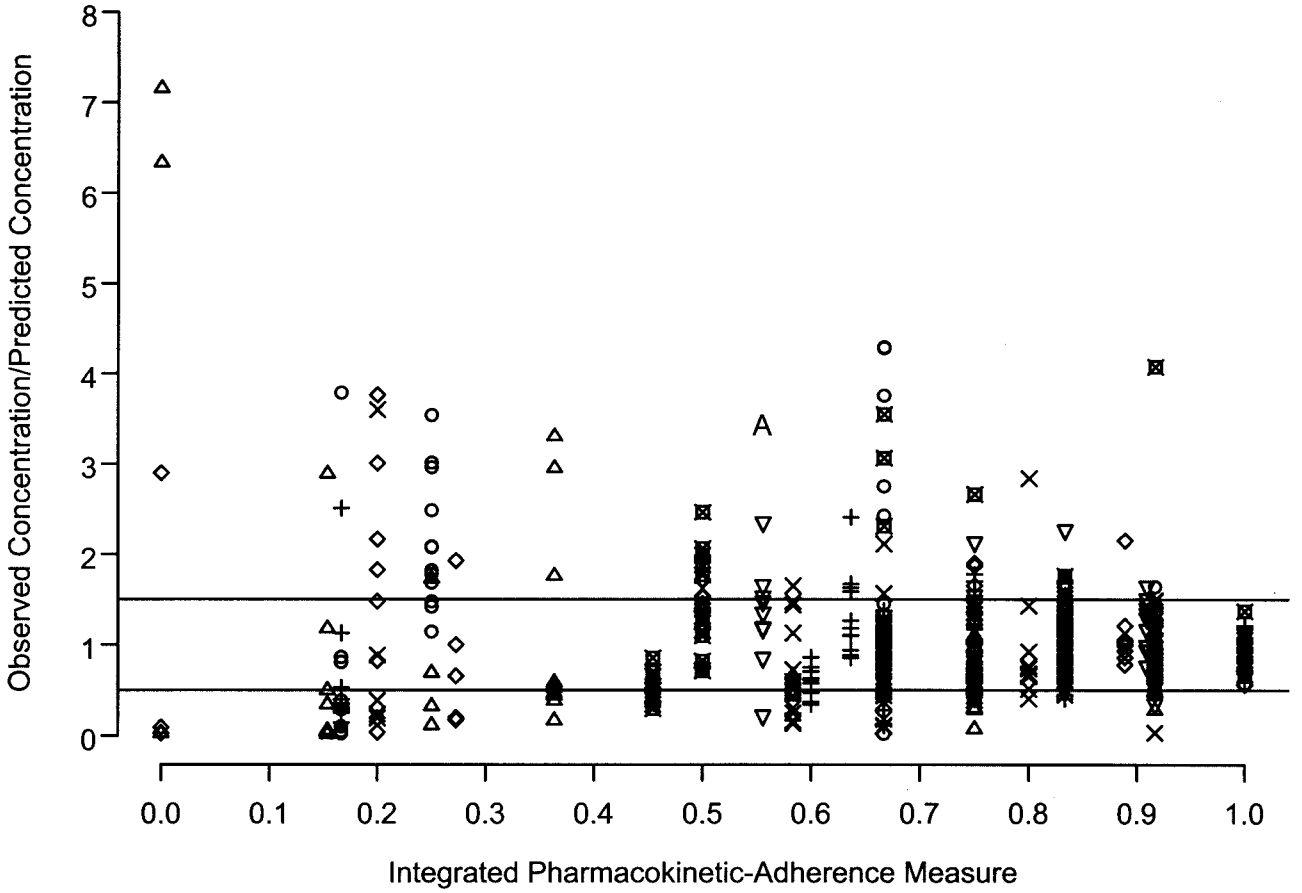

FIG. 2. Ratio of observed trough concentration to predicted concentration versus the IPAM. Ratios within the range of 0.5 to 1.5 identified by the two horizontal lines were within an acceptable range of deviations (±50%) from unity. For each IPAM, concentration ratios from the same subject are denoted by the same symbol; multiple symbols at a given IPAM represent different individuals with the same score.

therefore had an IPAM of 1.0; for two subjects, all ratios fell outside the acceptable range and produced a score of 0. To further illustrate the IPAM calculation, subject A can be seen to have 5 of 9 ratios in the acceptable range, which gave an IPAM of 0.56. Finally, some observed concentrations are noted to be less than 50% of the predicted concentration, and others are more than 150% of the predicted concentration. A histogram of the 50 IPAMs is provided in Fig. 3. Table 1 shows the IPAM summary statistics and the number of observations (or ratios) used to compute the IPAM for each subject. For 45 subjects (90%), at least nine observations were used to compute the IPAM.

TSSA. We examined the effect of the IPAM on the time to the first viral rebound by using TSSA. The maximum prognostic discrimination was observed with a cut point of 0.592, which closely corresponds to the 33rd percentile of the IPAM in the study population. This cut point was used to classify the 33 subjects (66%) with IPAMs of >0.592 as a high-IPAM, or high-predictability, group and the remaining 17 subjects (34%), with scores of ≤0.592, as a low-IPAM, or low-predictability, group (Table 1).

Time-to-first-viral-rebound analysis. Eight of 33 children (24%) in the high-predictability group, versus 9 of 17 children (53%) in the low-predictability group, experienced viral rebound (chi-square test; $P = 0.042$). The low-predictability group exhibited a significantly shorter time to the first viral rebound (Fig. 4) (log rank; $P = 0.012$). Subjects in the high-predictability group were less likely to experience a viral rebound than subjects in the low-predictability group in the univariate analysis (risk ratio, 0.31; $P = 0.017$ [Table 2]). This finding persisted after baseline viral load was controlled for (adjusted risk ratio, 0.34; $P = 0.028$ [Table 2]). Other covariates, including weight-for-age z scores, $\log_2$-transformed CD4 percentages, and $\log_2$-transformed week 2 AUCs for efavirenz, were not significant factors in the analysis with multiple covariates. With TSSA, a binary cutoff value of 186 $\mu M \cdot h$ was determined for the week 6 efavirenz AUCs, and subjects with higher week 6 AUCs were less likely to experience viral rebounds. Adjusted by this covariate and baseline viral load, the IPAM remained a significant explanatory factor in the likelihood of experiencing a viral rebound. Table 2 summarizes the results of the Cox regression analysis.

Time to first viral load of <400 copies/ml. Twenty-nine of 33 children (88%) in the high-IPAM group, versus 11 of 17 children (65%) in the low-IPAM group, had confirmed viral suppressions of <400 copies/ml (chi-square test; $P = 0.052$). There was a statistically significant difference in distributions of times to first viral loads of <400 copies/ml between the high- and the

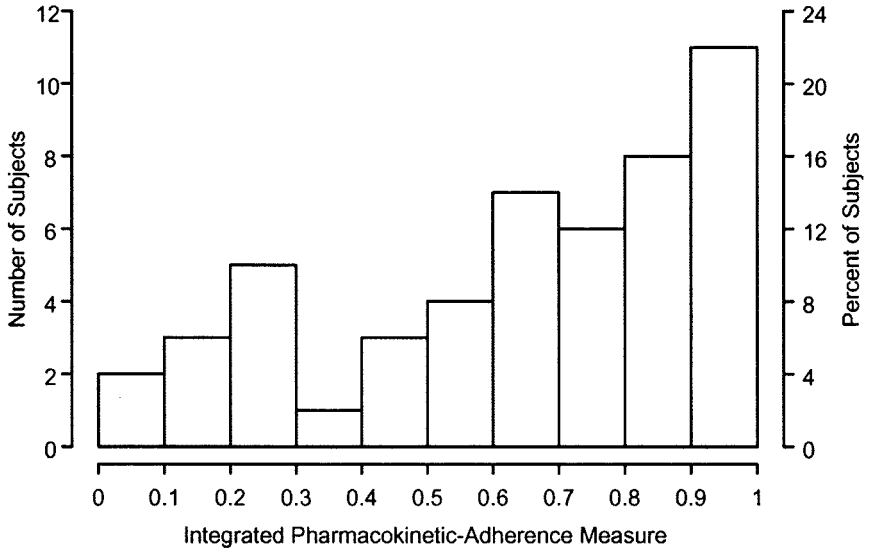

FIG. 3. Histogram of the 50 IPAMs obtained in the study.

low-IPAM groups (log rank; $P = 0.044$). The median times to reach confirmed viral suppressions of <400 copies/ml were 4 weeks for the high-IPAM group and 12 weeks for the low-IPAM group.

Correlation of IPAM with AUC. Spearman rank correlation coefficients (ρ) between IPAM, baseline $\log_{10}$ RNA, week 2 AUC, week 6 AUC, weight-for-age *z* score, and CD4 percentage were computed. IPAM and week 2 AUC were moderately correlated ($\rho = 0.47$, $P = 0.0006$). None of the other variables were significantly correlated with each other.

Sensitivity analysis. When the above analyses were repeated with a narrower range (±40%) of expected deviation being used to compute the IPAM, the results of all statistical analyses were qualitatively and quantitatively similar to those obtained with the ±50% range. We also used only the first six pairs of observed and predicted concentrations available and a criterion of ±50% to compute the IPAM. The results of most statistical tests for this reduced data set were qualitatively similar to those for the full data set, though some results became less statistically significant.

DISCUSSION

The identification of pharmacodynamic relationships is typically approached through quantitation of systemic exposure and exploration of relationships between that measure and one of response. Our approach was different. We chose to quantitate intrapatient variability in concentrations and to use this information to evaluate a metric which reflected integrated pharmacokinetic and adherence information for its relationship with response. We approached the development of this method by defining an expected range of deviation between measured efavirenz concentrations obtained during 1 year of therapy and those predicted based upon individual pharmacokinetic parameters determined from two observed-dose, 24-h, steady-state AUCs. With this method, close agreement between the measured and the predicted concentrations over 12 months of therapy provided a high IPAM (i.e., high predictability or low intrapatient variability), while poor agreement gave a low IPAM (i.e., low predictability or high intrapatient variability). We found that the IPAM was independently prognostic of viral rebound and that this finding persisted in a Cox regression analysis which controlled for baseline viral load and efavirenz exposure.

This approach to the quantitation of intrapatient variability over time was conceived to capture variability that arises from a variety of sources, including analytical variability, intrasubject pharmacokinetic variability, errors in reporting times of doses and blood sample collections, imperfectly characterized pharmacokinetic parameters, and medication adherence. In the course of implementing the mixed-effects model to identify individual pharmacokinetic parameters, this particular data set also allowed the identification of interoccasion variability

TABLE 1. Summary statistics for IPAM

Variable	No. of subjects	IPAM statistic(s)			
		Mean ± SD	Median	25th, 75th percentiles	Range
All IPAMs	50	0.64 ± 0.28	0.71	0.50, 0.83	0.00–1.00
No. of observations (for each subject) used to compute IPAMs	50	10.7 ± 2.4	12	10, 12	3–13
IPAMs in the high-IPAM group (>33rd percentile)	33	0.81 ± 0.11	0.83	0.75, 0.92	0.60–1.00
IPAMS in the low-IPAM group (≤33rd percentile)	17	0.31 ± 0.19	0.25	0.17, 0.50	0.00–0.58

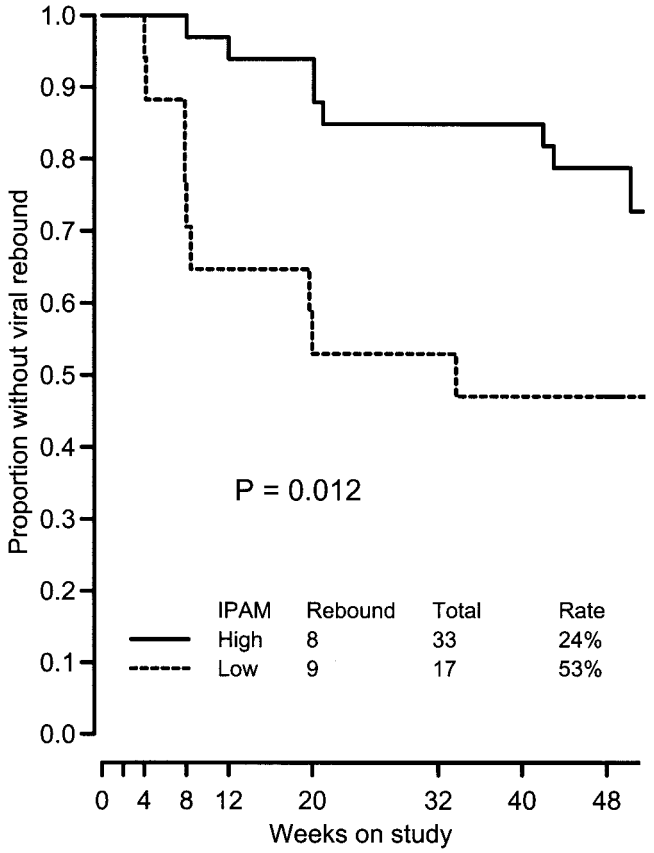

FIG. 4. Proportion of subjects without viral rebound. Shown is a Kaplan-Meier plot of the proportion of subjects who did not experience a viral rebound versus study weeks for subjects in the high-IPAM group (solid line) and subjects in the low-IPAM group (dashed line). A two-sample log rank test statistic between the two groups yielded a *P* value of 0.012.

TABLE 2. Cox regression analysis results for time to viral rebound

Variable	Risk ratio	(95% confidence for time-to-viral-rebound interval)	*P* value
Univariate analysis			
IPAM (per 0.1-unit increase)	0.73	0.62–0.87	0.0005
IPAM group (high vs low)	0.31	0.12–0.81	0.017
Baseline $\log_{10}$ RNA (per unit increase)	2.62	1.16–5.91	0.021
CD4 percentage (per twofold increase)	0.60	0.38–0.94	0.025
Weight-for-age *z* scores	0.66	0.41–1.06	0.087
Week 2 AUCs (per twofold increase)	0.54	0.24–1.21	0.136
Week 6 AUCs (>186 vs ≤186 μM · h)	0.22	0.08–0.57	0.002
Analysis with multiple covariates			
IPAM group (high vs low)	0.34	0.13–0.89	0.028
Baseline $\log_{10}$ RNA (per unit change)	2.54	1.09–5.90	0.031
IPAM (per 0.1-unit increase)	0.72	0.59–0.86	0.0005
Baseline $\log_{10}$ RNA (per unit change)	3.00	1.24–7.24	0.015
IPAM (per 0.1-unit increase)	0.75	0.62–0.90	0.003
Baseline $\log_{10}$ RNA (per unit change)	3.32	1.42–7.76	0.006
Week 6 AUCs (>186 vs ≤186 μM · h)	0.22	0.08–0.63	0.005

[a] Adjusted risk ratio for analysis with multiple covariates.

(IOV), which represents the extent of variability in pharmacokinetics between visits. The IOVs for clearance and volume of distribution were estimated to be 38 and 35%, respectively. From a theoretical perspective, the threshold chosen for the IPAM should be larger than the IOV, since concentration variability includes nonadherence and other nonpharmacokinetic sources. In this application of the IPAM, we used an expected range of deviation between measured and predicted concentrations of ±50%. Decreasing the range of acceptable concentration ratios to ±40% had the predictable effect of shifting the IPAM distribution to lower values. The TSSA breakpoint placed 33% of the subjects in the lower IPAM group when either ±50% or ±40% was used as the acceptable range. The similarity in the results of all statistical analyses suggests that the implementation of the IPAM for efavirenz may be relatively insensitive to the choice of an acceptable range of ratios. In part, this insensitivity may arise because efavirenz has a long plasma half-life (≥24 h). As a consequence of the long half-life of efavirenz, an observed concentration reflects doses administered over the previous 7 to 10 days. The predictability of efavirenz concentrations and the long half-life form a scientific basis on which to suggest that as the deviations between measured and predicted concentrations increase beyond the expected amounts, the sources of variability that are common across all individuals, such as intrasubject pharmacokinetic variability, errors in reporting times of doses and blood sample collections, and imperfectly characterized pharmacokinetic parameters, become more unlikely to be explanatory factors and medication nonadherence becomes suspect as the primary contributor to the deviation between measured and predicted concentrations. The present study offers some insight into this hypothesis as it applies to efavirenz. With the ±50% criterion for expected variability in drug concentrations, subjects were significantly more likely to fail therapy when fewer than 60% of concentrations were within the acceptable range (IPAM < 0.6). Having more than 60% of ratios within the ±50% range was compatible with virologic success for this efavirenz-based treatment regimen in children. The larger numbers of deviations are more likely due to extensive nonadherence and emphasize the obvious: a drug is not likely to be effective if it is not taken. Unfortunately, other measures of adherence (counts of returned medication, electronic monitoring system data) were not obtained in PACTG study 382, and there are no traditional adherence data for a comparison with the IPAM.

As a potential surrogate marker of adherence, this approach has some particular strengths. One is that it uses measured drug concentrations as objective evidence of adherence. Therefore, it is one step closer to assessing the drug that was actually ingested than is recording when medication vial tops are removed, as with a medication event monitoring system (MEMS caps), or relying on patient recall, as with questionnaires. The IPAM method does not require patients to use any specialized devices that might impact their daily routines; MEMS devices, for example, do not allow patients to remove a day's worth of medication. The time commitment required to complete and interpret extensive patient questionnaires is also

avoided with this approach. Unlike questionnaires, neither IPAMs nor MEMS caps can provide reasons for nonadherence. A patient determined to appear falsely adherent is likely to be able to disguise nonadherence to some extent, regardless of the method. However, it is unlikely that many individuals possess the pharmacokinetic expertise to calculate the exact dose necessary to produce the expected concentration at the time of a clinic visit. Disadvantages of applying the IPAM in a clinical setting include the requirement for an accurate and precise analytical method and the need to obtain timed blood specimens. In a clinical research setting, however, an assay often has already been developed, and phlebotomy is scheduled at several study visits. These qualities and the results of the present study indicate that further evaluation of this method, including a comparison with other putative measures of adherence, is warranted.

In this study, we found that the IPAM was independently prognostic of viral rebound when baseline viral load and efavirenz exposure were controlled for. This finding suggests that concurrent knowledge of drug concentrations over time might be used to improve pharmacotherapy for HIV infection. Therapeutic drug monitoring has been suggested as a strategy to improve the response of patients to antiretroviral therapy (1). This argument arises because of data showing considerable interpatient variability in concentrations among patients who take the same dose and data indicating relationships between concentration and effect. A potential obstacle to the implementation of therapeutic drug monitoring for any agent is intrapatient variability, as a high degree of intrapatient variability makes dose adjustments designed to achieve a specific target value futile. An integration of the concepts used here to quantitate intrapatient variability with therapeutic drug monitoring represents an area for future investigation. In addition, there are particularly intriguing possibilities for the application of the IPAM in the patient care setting, similar to the model of diabetes monitoring for which blood glucose provides integrated information on adherence to therapy and diet. An IPAM could be generated from concentrations obtained during the routine clinical care of a patient and used by the health care provider as timely quantitative information on integrated adherence and variability in concentrations over time. We can envision a role for drug concentration information in the management of HIV therapy; however, the tool developed in this work, as well as other strategies, such as therapeutic drug monitoring, must be shown to be useful to the clinician through rigorous controlled trials.

ACKNOWLEDGMENTS

We are indebted to Lane R. Bushman and Dennis Weller for performing the efavirenz measurements and to Sheila Cabral for the virologic assays.

This study was supported by the PACTG (protocol 382); General Clinical Research Centers, National Center for Research Resources (at several participating sites); DuPont Pharmaceuticals Company; Agouron Pharmaceuticals, Inc.; and RO1 AI33835-10 (to C.V.F.) from the National Institute of Allergy and Infectious Diseases.

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