Four Measures of Antiretroviral Medication Adherence and Virologic Response in AIDS Clinical Trials Group Study 359

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Summary: AIDS Clinical Trials Group (ACTG) 359 was a randomized, partially double-blinded factorial study of 6 antiretroviral regimens, all including saquinavir, among HIV-infected persons in whom prior therapy had failed (n = 258). Counts of remaining saquinavir capsules were determined between weeks 0 and 4; at weeks 4, 8, and 16, self-reported adherence was estimated from 2-day report of doses skipped, therapeutic coverage, and percent of doses taken were determined by electronic monitoring devices applied to saquinavir bottles, and the saquinavir 24-hour area under the curve (AUC) was estimated. Relationships were evaluated among these 4 adherence measures and the primary endpoint of week 16 HIV RNA change. Thirty percent of 254 subjects had HIV RNA ≤500 copies/mL at week 16. Only self-reported adherence and saquinavir AUC were significantly associated with week 16 HIV RNA change ($P = 0.019$ and 0.023, respectively), and these measures were higher in subjects with week 16 HIV RNA ≤500 copies/mL ($P = 0.03$ and 0.008, respectively). The ability to detect a correlation between electronically monitored adherence and virologic response was limited by the small sample size. Self-reported adherence and saquinavir AUC were significant predictors of virologic response, in this evaluation. These findings provide insight into methods of assessing and improving adherence to antiretroviral regimens.

Key Words: adherence, antiretroviral therapy, pill counts, self-reported adherence, virologic response

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Adherence to an antiretroviral regimen is a critical determinant of virologic success. Studies in HIV-infected individuals have indicated that a very high (>90%–95%) degree of adherence is necessary for optimal suppression of HIV RNA levels in plasma.[1,2] Poor adherence results in virologic failure and the emergence of drug-resistant strains of HIV, although the relationship between adherence and resistance is complex.[3–7] Unfortunately, there is no gold standard by which to measure medication adherence.[8] The methods most frequently used to quantitate adherence include counts of returned medications, patient self-report, electronic monitoring of the opening of a medication bottle, and measured drug concentrations. Each method has certain limitations. Investigations of adherence to antiretroviral regimens have used these methods individually and in combination. At least 2 studies have combined 3 of these methods, specifically counts of returned medications, patient self-report, and electronic monitoring of medication vial opening[1,9]; no studies, however, have combined all 4.

AIDS Clinical Trials Group (ACTG) study 359 was one of the first trials of antiretroviral therapy in persons in whom prior therapy had failed. The complete details and the week 16 and week 48 results have been published.[10,11] In ACTG 359, only 77 of 254 subjects (30%) achieved the primary virologic endpoint of ≤500 copies/mL of HIV RNA at week 16.[10] Four putative methods of measuring adherence were evaluated in ACTG 359: counts of returned medications, patient self-report, electronic monitoring of medication bottle opening, and quantitation of protease inhibitor concentrations in plasma. The objective of this report is to describe relationships among these 4 adherence measures and relationships between the adherence measures and virologic response.

METHODS

Study Design, Subject Selection, and Study Procedures

ACTG 359 was a randomized, partially double-blinded, 48-week factorial study of 6 antiretroviral regimens.[10,11] The regimens were saquinavir soft gelatin capsules (hereafter referred to as saquinavir) plus ritonavir together with delavirdine (group A), adefovir dipivoxil (group B), or both (group C), and saquinavir plus nelfinavir together with delavirdine (group D), adefovir dipivoxil (group E), or both

(group F). Study subjects were HIV-infected adults who had taken indinavir for at least 6 months and had screening plasma HIV RNA levels of 2000–200,000 copies/mL (Amplicor HIV Monitor Test, version 1.0, Roche Diagnostic Systems, Branchburg, NJ; lower limit of quantification, 500 copies/mL). Subjects had never taken nonnucleoside reverse transcriptase inhibitors or adefovir dipivoxil. The institutional review boards at each site approved this study and all subjects provided written informed consent.

Study participants had study visits every 4 weeks through week 24; subjects who met criteria for virologic response continued to week 48. Blood samples for determination of HIV RNA in plasma were obtained every 4 weeks through week 16 and every 8 weeks through week 48. The primary virologic endpoint was the proportion of participants with ≤500 copies/mL of HIV RNA at week 16.

Medication Counts

A count of returned medications was performed for all drugs in each of the treatment arms for all patients. The counts were performed at weeks 4, 8, and 16. The medication-count adherence measure was computed as the total number of dosage units dispensed, minus the number of dosage units returned, divided by the number of dosage units dispensed, expressed as a percent. Only the week 4 medication count was used in data analyses. This decision was made before any analyses were conducted because information regarding the dates and quantity of drug dispensed, extra doses provided, as well as prescribed dose reductions were not recorded reliably after week 4. As saquinavir was the agent common to all 6 regimens in ACTG 359, the primary medication-count variable was the count of returned saquinavir for the interval between study entry and week 4. To adjust for the different number of saquinavir capsules taken among the 6 arms of the study, this measure is reported as the percent of medication units taken by week 4 based on a 28-day supply dispensed at entry.

Self-Reported Adherence Questionnaire

The self-reported adherence questionnaire was administered at baseline with follow-up at weeks 4, 8, and 16. Data were collected on forms developed by the AACTG Outcomes Committee,[12] which included a baseline adherence questionnaire and 2 follow-up adherence questionnaires. At baseline, subjects were asked: "How many pills did you skip taking" for "yesterday?", "the day before yesterday (2 days ago)?", "3 days ago?", and "4 days ago?" for each drug in their prior-to-study-entry indinavir-containing regimen. Baseline adherence was calculated in 2 ways using different weightings. In the first method, for each drug recorded, the proportion of the drug regimen taken as prescribed was computed and averaged over the 4 days. The drug-specific proportions were then averaged to obtain a total baseline adherence score. This method assigned equal weighting to the individual drugs, and if a drug was not listed, the total baseline adherence was the average of those listed (method 1). In the second method, the number of total dosage units skipped across all drugs was divided by the total number prescribed across all drugs for "yesterday" and "2 days ago" and then averaged to get a total baseline adherence. No imputation for missing data was performed (method 2). The correlation between total medication adherence using methods 1 and 2 was 0.65 ($P < 0.0001$).

At the follow-up visits, subjects were again asked to rate the frequency of each of the reasons for missed medications. The total numbers of dosage units missed during the period through week 16 and across the 2 responses for "pills skipped yesterday" and "pills skipped the day before yesterday" were averaged for each drug. The number of missed dosage units was transformed to a drug-specific adherence score by computing [1 − (number of missed dosage units ÷ number of dosage units prescribed)]. The Cronbach α coefficient (a correlation test of internal consistency among the 6 drug-specific adherence measures) was >0.95; therefore, an overall regimen adherence score (proportion of regimen taken) was considered a valid summary measure and was calculated by averaging the 6 drug-specific adherence scores.

Electronic Monitoring

The Medication Event Monitoring System (MEMS, Aprex Union City, CA) device, which records each time a medication bottle is opened, was used to assess saquinavir adherence because saquinavir was common to all treatment arms in ACTG 359. Only centers participating in an intensive pharmacokinetic substudy participated in the electronic monitoring adherence assessments; MEMS caps were applied to the saquinavir bottles of 76 subjects. The MEMS caps were read at weeks 4, 8, and 16 by the AACTG Pharmacology Laboratory at Stanford University. Removal of the MEMS cap was used as an indication that a medication dose was taken. Two measures were determined from the MEMS data. The "percent of dose taken" measure was computed as the total number of doses taken divided by the total number of doses prescribed during the study period. This measure was expressed as a percent and was uncorrected for the timing of the cap opening across days and within dosing intervals. The therapeutic coverage measure corrected for the timing of MEMS cap removals and was calculated as the proportion of time doses were taken within the correct time interval. For example, if an individual was prescribed every-12-hour dosing and the vial was opened at 7 AM and again at 11 PM (4 hours late), therapeutic coverage would be 83% of the 24-hour day, whereas the percent taken would be 100% for that day.

Measured Saquinavir Plasma Concentrations

One blood sample for quantitation of saquinavir concentrations was obtained in all study participants at weeks 4, 8, and 16. In addition, at one of these visits randomly selected by the site, a second blood sample was obtained at least 1 hour after the first. These blood samples were obtained following unobserved doses. Subjects provided the times of their last 3 doses of study medications, which were recorded along with the time the blood samples were obtained. Plasma was obtained and frozen at −70°C until analyzed for saquinavir by validated, quality-controlled high-performance liquid chromatography.[13] All concentration–time data from all subjects were appropriately pooled and analyzed using a nonlinear mixed-effects regression model.[14] Using the first-order conditional estimation procedure, Bayesian estimates of individual pharmacokinetic parameters were obtained in

addition to the population means and variances. The individualized parameters were used to estimate the corresponding 24-hour area under the curve (AUC) for saquinavir, which was the primary pharmacokinetic variable. The details and results of the population pharmacokinetic evaluation as well as the intensive pharmacokinetic substudy have been previously published.[15,16]

Statistical Analysis

Statistical analyses employed parametric and nonparametric tests to evaluate between-group differences, χ^2 tests of association between categorical variables, parametric and nonparametric tests of correlations, general linear models (regression and analysis of variance), and logistic regression to model the probability of self-reported adherence >95% and virologic failure (week 16 HIV RNA >500 copies/mL). Age, sex, alcohol use, race, and treatment (based on delavirdine use) were included as covariates in the logistic regression models of virologic failure. Two-sided tests of significance are reported. A natural log transformation of HIV RNA was used in the correlation analyses to reduce the heterogeneity of variance.

RESULTS

A total of 277 subjects were randomly allocated to 1 of the 6 treatment arms in ACTG 359.[10] A total of 231 of the 277 study participants (83%) were male and 46 (17%) female; 49% were white (non-Hispanic), 29% black (non-Hispanic), 19% Hispanic, and 3% other. The median age was 40 years. The median baseline HIV RNA was 31,746 copies/mL and the CD4 cell count was 229 cells/μL. At week 16, 30% (77/254) of participants had HIV RNA ≤500 copies/mL.

Baseline Self-Reported Adherence

The baseline self-report and questionnaire was completed by a total of 266 study participants (96%). A baseline adherence score (method 1) was available for 239 subjects with a mean of 93% ± 19%, median of 100%, and a 25th percentile of 96%. Using method 2, 220 patients reported a mean baseline total adherence of 94% ± 15%, and indinavir-specific adherence was 93% ± 16%. Of the 259 subjects responding, 33% reported that they never skipped their medication, 26% reported skipping during the past week, and the remainder reported skipping medication prior to the past week. Of the 166 individuals reporting their primary reasons for skipping medications, social reasons such as "being away from home," "difficulty with timing the dose," "being too busy," and "simply forgot" were the most frequent reasons. Problems with "too many pills," "avoiding side effects," and "feeling that the drug was too toxic or harmful" were the reasons least cited.

Adherence to and Baseline Predictors of On-Study Adherence

Among the variables, age, sex, race (white vs. nonwhite), and alcohol use, both white race ($P = 0.03$) and older age ($P = 0.04$) were significantly associated with a higher odds of self-reported adherence of ≥95%. When both age and race were included in the logistic regression model, for each additional year of age, the odds of higher adherence increased by 3% (odds ratio [OR] = 1.03, 95% CI: 1.01 to 1.06), whereas white race was associated with 79% higher odds for the probability of adherence >95% (OR = 1.79, 95% CI: 1.07 to 3.02). Sex ($P = 0.13$) and alcohol use of ≥3 drinks per week ($P = 0.85$) were not significant predictors. The self-reported adherence measure obtained at baseline was significantly correlated with the self-reported measure obtained during treatment ($\rho = 0.19$, $P = 0.005$). Those who stated they never missed a dose at baseline (n = 83) vs. those who stated they missed a dose during the past week (n = 65) had statistically significant differences in their follow-up self-reported adherence scores (mean ± SE = 88% ± 3% vs. 73% ± 4%, $P = 0.007$).

Associations Among Measures of Adherence and Virologic Failure

The summary statistics for the 4 adherence measures are presented in Table 1. Subjects in arms A, B, and C, who took a saquinavir dose of 400 mg twice daily (8 capsules per day), had slightly lower medication count adherence than those in arms D, E, and F, who took a saquinavir dose of 800 mg thrice daily (12 capsules per day). Median medication count adherence was 89% for the former group and 92% for the latter group ($P = 0.049$). Otherwise, these 4 measures did not differ significantly among the 6 treatment regimens.

As shown in Table 1, median MEMS therapeutic coverage was 10% lower than MEMS percent of doses taken; however, they were highly colinear ($r = 0.988$, $P < 0.0001$). The distribution of the "percentage of doses taken" measure indicated a large ceiling effect with a 75th percentile of 98% as compared with therapeutic coverage, which had a 75th percentile of 86%. Adherence as measured by returned medication counts was significantly correlated with therapeutic coverage and percentage of doses taken (n = 54, $r = 0.35$ and 0.34, $P = 0.01$; $\rho = 0.26$ and 0.24, $P = 0.056$ and 0.077). Self-reported adherence was marginally correlated with therapeutic coverage and percent of doses taken (n = 61, $r = 0.25$ and 0.24, $P = 0.054$ and 0.065; $\rho = 0.19$ and 0.20, $P = 0.15$ and 0.13). All other pairwise correlations among the 4 adherence measures were nonsignificant ($P > 0.10$).

Measures significantly associated with the week 16 changes in HIV RNA were self-reported adherence ($\rho = -0.15$, $P = 0.019$, n = 244) and the saquinavir AUC ($\rho = -0.17$, $P = 0.023$, n = 180). Subjects who had week 16 HIV RNA ≤500 copies/mL compared with those who had values >500 copies/mL had significantly higher self-reported adherence and saquinavir AUC measures (Table 2; Wilcoxon rank sum test, $P = 0.03$ and 0.008, respectively). Logistic regression also demonstrated that self-reported adherence and saquinavir AUC, when modeled individually, were significant predictors of week 16 virologic response (after adjusting for treatment effect). Self-reported adherence >95% increased the odds of virologic response by approximately 86% (OR = 1.86, 95% CI: 1.02 to 3.41, n = 254, $P = 0.044$) compared with those who reported <95%. The odds of virologic response increased by approximately 3.5% per unit increase in AUC (OR = 1.035, 95% CI: 1.01 to 1.06, n = 180, $P = 0.004$). However, when both self-report and AUC adherence measures were included in the model, only AUC was found to be an independent predictor of virologic failure.

TABLE 1. Description and Summary Statistics of Adherence Measures Plus Correlations Among Adherence Measures and Week 16 in HIV RNA Change From Baseline

				Correlation Pearson's *r*, Spearman's rho (n)				
Adherence Measure and Units (n)	**Measurement Method**	**Mean (SD)**	**Median (25th–75th Percentile)**	**MC (n)**	**SR (n)**	**MEMS Therapeutic Coverage and Doses Taken (n)**	**SQV AUC (n)**	**Change in HIV RNA (week 0–16) (n)**
Medication Count (%) (MC) (n = 220)	Percent saquinavir taken for interval between study days 0–28 by count of returned medications	83 (23)	91 (72–99)	—	−0.001 0.106 (n = 211)	0.348,* 0.337* 0.262,† 0.243 (n = 54)	−0.013 0.008 (n = 165)	−0.011 0.003 (n = 199)
Self-Report (%) (SR) (n = 258)	Percent of total regimen medication taken by patient self report	82 (32)	100 (75–100)	—	—	0.248,† 0.238 0.187, 0.196 (n = 61)	−0.104 −0.042 (n = 186)	−0.177* −0.150‡ (n = 244)
MEMS (%)								
Therapeutic Coverage	Percent time per 24-hour day of active medication coverage	64 (27)	72 (47–86)	—	—	—	−0.177 −0.034 (n = 58)	−0.004 −0.048 (n = 62)
Doses taken (n = 62)	Percent of total doses taken	72 (29)	82 (50–98)				−0.168 −0.051 (n = 58)	−0.009 −0.057 (n = 62)
SQV AUC (mg × h/L) (n = 186)	Saquinavir area under the plasma concentration time curve for 24 hours by pharmacokinetic modeling	20.4 (15.4)	15.9 (10.2–25.0)	—	—	—	—	−0.147‡ −0.169‡ (n = 180)

*$P < 0.01$.
†$P < 0.06$.
‡$P < 0.05$.
SQV indicates saquinavir.

Cox survival analysis revealed a marginally significant relationship between treatment regimen and time to first grade 3 or 4 laboratory toxicity ($P = 0.074$); however, overall adherence (binary or continuous) was not related to this outcome. The time to grade 2 or higher laboratory toxicity and the time to the first grade 3 or 4 signs/symptoms were not explained by either treatment regimen or adherence.

TABLE 2. Comparison of Self-Reported Adherence and Saquinavir AUC With the Proportion of Patients ≤500 Copies/mL vs. >500 Copies/mL of HIV RNA

	Adherence Measure			
	Self-Report (%)		**SQV AUC (mg × h/L)**	
Week 16 HIV RNA	**Median (and number)**	**25–75th Percentile**	**Median (and number)**	**25–75th Percentile**
≤500 copies/mL	100 (n = 74)	91–100	19.2 (n = 50)	12.8–31.4
>500 copies/mL	100 (n = 170)	72–100	14.5 (n = 130)	9.6–23.5
P value*		0.03		0.008

*Wilcoxon rank sum test.
SQV indicates saquinavir.

DISCUSSION

In this evaluation of 4 different methods of measuring medication adherence in antiretroviral therapy–experienced persons, 2 important findings emerged. First, we found that only counts of returned medication and therapeutic coverage and percent of doses taken as determined with electronic monitoring were significantly correlated. Second, only self-reported adherence and measured saquinavir concentrations were correlated with the primary virologic endpoint, HIV RNA suppression at week 16. Subjects who had week 16 HIV RNA ≤500 copies/mL had better self-reported adherence and a higher AUC compared with subjects who had HIV RNA >500 copies/mL. Logistic regression demonstrated that self-reported adherence and AUC, when modeled individually, were significant predictors of response after adjusting for treatment effect. These findings are consistent with those of another recent study that validated both self-reported adherence and measures of protease inhibitor concentrations as predictors of virologic response.[17] As each of the 4 methods measures a different aspect of the overall medication-taking behavior continuum, the finding of little correlation among the methods is not surprising. That only 2 of the approaches employed in this study to quantify adherence showed a significant association with virologic suppression was somewhat

unexpected. These findings illustrate the complexity of measuring the medication-taking process and the challenges in finding adequate surrogate measures for observing the patient take each dose of medication.

The ability of the present study to evaluate strengths of correlation among the different adherence measures is hampered by the sample size and by the differences in the quality of measurement among our measures. For example, whereas self-report with n = 258 had 90% power to detect a correlation of $\geq$0.20, therapeutic coverage with n = 62 only had 34% power. Furthermore, the self-reported adherence measure was comprised of multiple items within assessment, across drugs, and between visits in contrast to the "count of returned medication" measure, which was based on a single assessment. These differences in measurement quality limit our ability to compare directly the measures with regard to their predictive validity for virologic failure. The lack of a strong association among electronic monitoring–derived measures, self-reported adherence, and counts of returned medications, however, has been found in other studies.[1,18] There are most likely several reasons for these findings. First, although the underlying construct of adherence is common across the various measures, the elements measured by the various methods are different and the variability introduced by the different methods of measurement may be quite large. Counts of returned medication most precisely measure patient adherence with returning a medication bottle to the clinic. Self-reported nonadherence, although qualitatively accurate, reflects the ability of a person to recall accurately their medication-taking behavior and their willingness to report missing doses to their healthcare provider. Electronic monitoring devices provide evidence for the frequency of opening a medication bottle. Correlations among these measures would not be expected unless the between-measure error introduced by these different techniques was small relative to each measure's ability to estimate the underlying true adherence score. Moreover, the degree to which each measure might deviate from a common adherence construct has not been clearly established. As such, there remains an ongoing need for rigorous validation of adherence measurement techniques.

Measured concentrations of drugs provide objective proof of the presence of drug in the body but have not been widely used as a measure of adherence. The formal interpretation for an AUC is the drug concentration integrated over time. As such, it is generally a metric used to reflect the overall systemic exposure achieved following a given dose of a drug. Exposure is not equivalent to adherence as an individual with a low exposure could be completely adherent to his or her medication regimen, and another individual with a high exposure could be quite nonadherent. The design of the pharmacokinetic evaluations in ACTG 359 required 1 or 2 concentrations on 3 different study visits over a 3-month period. The AUC derived from these data is most precisely interpreted as a time-averaged exposure over 3 months. In this application, AUC is clearly a function of an individual's pharmacokinetic characteristics and his or her medication-taking behavior, and nonadherence will result in a lower AUC.[19] Our findings confirm that a low AUC was a significant predictor of virologic failure.

Adherence as measured by electronic monitoring was not correlated with virologic suppression. However, because of the small sample size of this study, only correlations of $\geq$0.40 could be detected with a fairly high power. In contrast, others have described significant associations between electronic monitoring and virologic response.[1,2,9,20] However, electronic monitoring was found to be a less sensitive predictor of virologic response than self-reported adherence in a prospective observational cohort study of 235 HIV-infected adults.[21] Limitations in the present study include not only the small sample size of the electronic monitoring evaluation, but the study regimens. These regimens were complex, involving matching placebos and components administered once to thrice daily, resulting in a high dosage unit burden, and are not commonly used today. There are also differences among the various studies in terms of how the adherence measure was calculated from electronic monitoring data. For example, the studies of Liu et al[9] and Paterson et al[2] calculated an adherence measure based on the number of medication bottle openings divided by the number of expected openings. The study of McNabb et al[1] as well as the present study calculated the percentage of time a patient had drug coverage based on actual and expected bottle opening times and the dosing interval. Studies have not validated that these MEMS-derived metrics are equivalent. We do not believe that the lack of correlation arose because the MEMS device was only placed on saquinavir bottles as opposed to all of the drugs in a regimen, as others have shown a concordance of medication taking among all of the drugs in a regimen.[20] Lastly, the 4-week assessment for medication counts, and the 16-week duration for the other adherence assessments in this study, was a limitation; clearly, long-term adherence is essential for the durability of antiretroviral regimens.

The link between poor adherence and poor virologic outcomes is indisputable. Our data demonstrated that individuals reporting adherence >95% had an 86% higher rate of virologic response compared with those reporting lower adherence. In addition, for each unit increase in saquinavir AUC, there was a 3.5% increase in virologic response. However, significant methodologic challenges remain in understanding the medication-taking continuum and developing validated measures to quantify adherence behavior. For patient care, the most urgent need is to develop tools that are convenient and useful to evaluate adherence early and concurrently during therapy. If poor adherence behavior can be diagnosed and modified early in treatment as a preventive measure, the impact on reducing virologic failure could be substantial. In this regard, self-reported adherence and measured drug concentrations offer ideas for early intervention programs that can identify adherence problems and allow efforts to improve adherence prior to virologic failure. Certainly, a patient who reports missing doses is quite likely describing an adherence problem and thereby provides an opportunity for early intervention. We can envision a role for measured drug concentrations as objective evidence of medication-taking behavior, similar to the model of monitoring blood glucose to obtain integrated information on adherence to therapy and diet in persons with diabetes. The application of such an approach does add complexity to patient care and presents certain challenges.

Whereas measured concentrations of drugs with short plasma half-lives provide extremely limited information on past doses, the widespread use of ritonavir-boosted protease inhibitor regimens, which results in longer half-lives, and drugs such as efavirenz that have half-lives of >24 hours, provides evidence of drug taking for a week or longer. Because antiretroviral therapy is expensive, therapeutic choices limited, and the consequences of widespread emergence of resistance and cross-resistance are severe, methods to quantify and enhance medication adherence need aggressive development, validation, and implementation as strategies to improve the health outcomes associated with antiretroviral therapy.

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