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Correlation Between Self-Reported Adherence to Highly Active Antiretroviral Therapy (HAART) and Virologic Outcome

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ABSTRACT

The Patient Medication Adherence Questionnaire Version 1.0 (PMAQ-V1.0) is a patient-reported adherence instrument to assess medication-taking behaviors and identify barriers to adherence with antiretroviral therapy. To assess the correlation between adherence and virologic outcome, the PMAQ-V1.0 was administered to 194 antiretroviral-experienced adults with HIV infection enrolled in a 16-week evaluation of protease inhibitor–containing regimens featuring a lamivudine/zidovudine combination tablet. At baseline, plasma HIV-1 RNA levels were less than 10,000 copies/mL and CD4+-cell counts were equal to or greater than 300×10^6/L; patients had been receiving a conventional regimen of lamivudine + zidovudine (separately) plus a protease inhibitor for at least 10 weeks immediately prior

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to the study. Forty-eight percent of patients who reported missing at least one dose of a nucleoside reverse-transcriptase inhibitor (NRTI) during the study had detectable plasma HIV-1 RNA, compared with 26% of patients who reported no missed doses ($P = .002$). Patients who missed at least one dose of an NRTI or protease inhibitor were 2.5 times more likely to have quantifiable HIV-1 RNA than those who reported no missed doses. Patients who reported fewer barriers and more motivators to adherence had better virologic outcomes ($P = .001$). Several dimensions of the PMAQ-V1.0 did not function as well as hypothesized. In this study, self-reported adherence derived from the PMAQ-V1.0 predicted virologic outcomes, but further refinement of the dimensions appears warranted.

Keywords: Patient Medication Adherence Questionnaire; HIV-1 RNA; adherence

INTRODUCTION

Highly active antiretroviral therapy (HAART) has been demonstrated to reduce human immunodeficiency virus (HIV)-1 RNA, elevate CD4-cell counts, decrease morbidity and mortality due to acquired immunodeficiency syndrome (AIDS),[1,2] and improve quality of life.[3] As many HAART regimens involve complicated schedules with a large number of doses, strict dietary restrictions, and interruption of daily activities, adherence to therapy exactly as prescribed may be difficult, if not impossible, to achieve.[4] Estimates of nonadherence to antiretroviral therapy have varied widely, depending on the method of measurement, definition of nonadherence, the population studied, and the time over which adherence was monitored. When nonadherence was defined as taking less than 80% of prescribed doses, rates have been 44% by pill counts, 32% by physician perception, and 29% by patient self-report.[5] In a study of HAART adherence,[6] approximately one third of patients missed a mean of four doses in the previous week.

Nonadherence to HAART may lead to suboptimal drug levels, with the possible outgrowth of resistant HIV-1 variants and subsequent drug failure.[4,7,8] Poor adherence also poses a potential public health threat because it may prompt widespread sexual transmission of drug-resistant and cross-resistant HIV strains.[9] Nonadherence may increase medical costs, as patients progress to more costly stages of HIV disease,[10] and lead to misinterpretation of clinical trial results.

Although pharmacy claims data, antiretroviral-drug plasma concentrations, physician reports, electronic monitoring devices, and returned pill counts are potentially useful for detecting adherence, they are vulnerable to measurement error or bias, or both. These methods can be expensive to implement in clinical practice and resource-intensive to administer and analyze.[4] Self-reporting, in contrast, may be a simpler and more reliable way to determine the degree of adherence to antiretroviral regimens and could prove useful for interventional patient monitoring as well.

The self-administered Patient Medication Adherence Questionnaire Version 1.0 (PMAQ-V1.0) is being developed by GlaxoSmithKline for use in clinical trials and routine clinical practice to assess patient-reported medication-taking behaviors and to identify barriers and motivators to adherence.[11] Selection and initial deletion of items have been based on discussions with leading HIV practitioners and clinical

psychologists, feedback from patients, and a review of the published literature (see Appendix). Content has been validated through an analysis of data collected from a focus group composed of 67 HIV-infected patients taking combination antiretroviral therapy.[11] These patients reported that the PMAQ-V1.0 was easy to complete and sufficiently brief, and contained relevant questions.

The utility of the PMAQ-V1.0 was recently evaluated in a 16-week phase IIIB/IV, multicenter, open-label trial that demonstrated the virologic equivalence of protease inhibitor (PI)–containing regimens including a lamivudine/zidovudine combination tablet and PI-containing regimens including lamivudine and zidovudine as separate dosage forms (NZTA4001).[12] In this paper, we report the results from the PMAQ-V1.0 component of the trial. The primary objective of this aspect of NZTA4001 was to determine a correlation between medication-taking behavior and virologic outcome. Barriers and motivators associated with adherence and some psychometric properties of the PMAQ-V1.0 were also evaluated.

PATIENTS AND METHODS

Male and female participants had the following characteristics: seropositivity for HIV-1 infection confirmed by enzyme-linked immunosorbent assay; age at least 18 years; baseline plasma HIV-1 RNA level less than 10,000 copies/mL; baseline CD4+ count 300 cells or more $\times 10^6$/L; and triple-combination antiretroviral therapy (ART) with lamivudine 150 mg twice daily, zidovudine 600 mg daily (300 mg twice daily or 200 mg three times daily), and a marketed PI (indinavir, saquinavir, nelfinavir, or ritonavir at recommended doses) for at least 10 weeks just prior to the study. Eligible patients were randomly assigned to receive one of two treatments for 16 weeks: the conventional regimen of zidovudine and lamivudine, plus the PI they had been receiving prestudy, or a regimen consisting of one combination lamivudine/zidovudine 150/300-mg tablet (Combivir®*) administered twice daily, plus their PI regimen. The study was conducted between May 1997 and June 1998 at 19 outpatient sites in the United States and Puerto Rico. All patients provided written informed consent to participate, and the study protocol was approved by each site's institutional review boards.

The PMAQ-V1.0 was administered prospectively to patients at baseline and at weeks 8 and 16 of the study. Section 1 contains six items pertaining to medication-taking behaviors and asks patients to rank on an ordinal scale how often they missed individual doses or days of study medication over the past 4 weeks. Section 2 contains 25 items pertaining to barriers and motivators to taking medications. Items, such as "I don't want people to see me taking my medicines for HIV," are rated on a Likert scale from 1 ("definitely true") to 5 ("definitely false") and scored to produce a patient profile across five hypothesized dimensions: memory and recall, scheduling and timing, physical effects, social support, and knowledge and attitudes. These dimensions were created a priori and were based on opinions of patients and information about medication adherence from the published literature.[11] Responses were scored as follows: After the positively worded items were reverse coded, the actual raw score was calculated as the sum of the reverse-coded

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responses. The transformed dimension score was calculated as 100 (raw score–lowest possible raw score)/(highest possible raw score–lowest possible raw score). A total score using all 25 individual items was derived in the same fashion. The dimension and total adherence scores thus ranged from 0 to 100, with higher scores indicating fewer barriers and more motivators to adherence.

Plasma HIV-1 RNA was measured at baseline and at weeks 4, 8, and 16 by the reverse-transcription polymerase chain reaction (RT-PCR) technique with the Amplicor HIV Monitor assay (Roche, Nutley, New Jersey, USA) (lower limit of quantification, 400 [2.6 $\log_{10}$] copies/mL). Log_{10} plasma HIV-1 RNA values were summarized by the arithmetic mean of the assessments. Plasma HIV-1 RNA was categorized into unquantifiable (≤400 copies/mL) or quantifiable levels (>400 copies/mL) and was computed for weeks 4, 8, and 16 to determine whether patients had plasma HIV-1 RNA above the lower limit of quantitation on at least one visit. Intent-to-treat analysis of HIV-1 RNA was employed; missing plasma HIV-1 RNA at any visit was treated as quantifiable. HIV-1 RNA levels at weeks 4, 8, and 16 were summed and divided by three. Log_{10} plasma HIV-1 RNA was treated as a continuous variate in the rank linear correlation analyses and as a binary variate in the logistic regression analyses, according to the described classification. Data were pooled over treatment arms and PI strata.

Spearman rank correlation and logistic regression were used to determine the correlation between PMAQ-V1.0 results and virologic outcome. Adherence assessments at weeks 8 and 16 were summed and divided by two. Psychometric evaluation of the PMAQ-V1.0 used Cronbach's alpha and scale-scale and item-scale Pearson correlations. Cronbach's alphas at weeks 8 and 16 were summed and divided by two to produce mean reliability estimates across both weeks.

RESULTS

Of 223 randomized patients, 194 (87%) completed the PMAQ-V1.0. Eighty-five percent were male; 68% were white, 17% black, 12% Hispanic, and 3% Asian. The mean age was 40.5 years. At baseline, 72% of the patients had unquantifiable HIV-1 RNA. Median baseline values were 2.6 $\log_{10}$ copies of HIV-1 RNA and 522 CD4+ cells/mm^3. Most patients were receiving regimens containing indinavir (n = 121, 62%) or nelfinavir (n = 43, 22%). Baseline characteristics did not differ in the subgroups of PMAQ completers and noncompleters. The overall 17% dropout rate was similar in both treatment arms. The 39 patients who withdrew prematurely from the study did so for the following reasons: loss to follow-up (11), adverse event (9), insufficient viral load response (7), consent withdrawn (5), protocol violation (4), and others (3).

Forty-eight percent (51/107) of patients who reported missing at least one dose of a nucleoside reverse-transcriptase inhibitor (NRTI) during the study had detectable plasma HIV-1 RNA, compared with 26% (23/87) of those who reported no missed doses (odds ratio [OR] = 2.5; P = .002; 95% confidence interval [CI] = 1.4, 4.7). Similarly, patients who missed at least one PI dose were 2.1 times (P = .014; 95% CI = 1.2, 4.0) more likely to have quantifiable HIV-1 RNA than those who reported no missed PI doses. An intent-to-treat logistic regression analysis of PMAQ-V1.0 results showed that patients who missed at least one dose of an NRTI or PI were 2.5 times (P = .006; 95% CI = 1.3, 4.8) more likely to have quantifiable HIV-1 RNA than those who reported no missed doses. These results remained significant in sensitivity

analyses that employed as-treated populations and adjusted for baseline CD4+-cell count, treatment (combination-tablet versus conventional regimen), and current PI (OR = 2.711; $P = .0020$). Spearman rank correlation analysis also indicated a trend of higher plasma HIV-1 RNA with the frequency of missed NRTI (r = 0.28; $P = .0001$) and PI (r = 0.24; $P = .0008$) doses. In general, patients who reported fewer barriers and more motivators to adherence had better virologic outcomes ($P = .001$) (Table 1).

Memory and recall barriers were most highly associated with individual missed doses and missed days (Table 1). The correlation between barriers and motivators to medication-taking behavior was more strongly associated with missed doses than with missed days.

Table 1. Correlation Between PMAQ-V1.0 Dimensions and Medication-Taking Behaviors and Plasma HIV-1 RNA Levels

Dimension	Missed NRTI Doses	Missed PI Doses	Missed NRTI Days	Missed PI Days	Log_{10} HIV-1 RNA
Memory and recall	–0.60*	–0.57*	–0.28*	–0.33*	–0.20*
Scheduling and timing	–0.41*	–0.49*	–0.19*	–0.19*	–0.09
Physical effects	–0.34*	–0.34*	–0.06	–0.10	–0.18†
Knowledge and attitudes	–0.23*	–0.30*	–0.22*	–0.26*	–0.07
Social support	–0.01	–0.06	–0.06	–0.01	–0.08
Total	–0.42*	–0.46*	–0.24*	–0.27*	–0.18*

*$P<.01$.
†$P<.05$.

Reliability coefficients for each dimension and the total score by study week are shown in Table 2. Although mean Cronbach's alphas for each dimension were lower than had been hypothesized, reliability was considered reasonable enough to warrant further research and development of the PMAQ-V1.0. The reliability for the total score was 0.76. These results did not vary appreciably over the duration of the study. Scale-scale correlations indicated some degree of overlap among dimensions. Scale-total correlations were ranked from highest to lowest as follows: scheduling and timing, memory and recall, physical effects, social support, and knowledge and attitudes. A relatively low correlation (r = –0.18) was noted between total PMAQ-V1.0 scores and log_{10} HIV-1 RNA as a continuous variate.

Table 2. Scale-Scale Correlations for PMAQ-V1.0 Dimensions

	Memory/ Recall	Scheduling/ Timing	Physical Effects	Knowl-edge/ Attitudes	Social Support	Total
Mean Cronbach's alpha	0.53	0.60	0.48	0.24	0.44	0.79
Memory and recall	1					
Scheduling and timing	0.63	1				
Physical effects	0.45	0.37	1			
Knowledge and attitudes	0.35	0.33	0.20	1		
Social support	0.23	0.28	0.20	0.28	1	
Total	0.77	0.77	0.62	0.60	0.65	1

DISCUSSION

The PMAQ-V1.0 results described herein indicated that quantifiable HIV-1 RNA was more than twice as likely in patients who reported missing one or more doses of an NRTI or a PI over the 16-week study. This finding is consistent with results of other clinical trials showing an inverse relationship between HIV-1 RNA levels and rates of adherence to ART.[13,14] Unlike these early studies, however, which culled adherence data from pill counts, medication-refill records, self-reporting, face-to-face direct questioning, or Medication Event Monitoring System (MEMS®; APREX Corporation, Union City, California) technology, information in the present study was acquired through a self-administered questionnaire. Given the importance of adherence to ART for positive clinical outcomes, this is a significant and strong observation. Self-reports would certainly be more efficient and practical in the clinical setting than other "gold standards" for assessing adherence, such as those mentioned above.

The self-administration feature of the PMAQ-V1.0, along with adherence counseling by a healthcare professional, is important because it affords patients an opportunity to understand and potentially modify their medication-taking behaviors and, hence, therapeutic response. Additionally, the PMAQ-V1.0 can identify missed doses of component drugs within a multidrug-class regimen. A search on MEDLINE and Current Contents databases, and of abstracts presented at recent infectious diseases meetings (January 1997–April 2001), revealed other self-administered questionnaires to assess ART adherence, although none have been sufficiently validated.[15-20] The items used to predict adherence in the PMAQ-V1.0 performed reasonably well, given that they were based on information from patients and a literature review rather than on the refinement of studies unconfounded with a clinical trial. This study clearly revealed that the dimensions do not function as hypothesized. While the dimensions are likely not adequate and need revision, the observed

results could reflect a limitation of the current clinical trial that used only two regimens. This study also revealed the need for further work to identify factors that affect ART adherence. Nevertheless, these preliminary findings could and should advise others with similar interests, particularly because no other "gold standard" self-reporting ART adherence instruments currently exist.

The PMAQ-V1.0 results suggest consistency in the relationship between clinical outcome and adherence, even though the magnitude of the relationship as measured by r^2 may be low. Many factors could have attenuated the magnitude of the correlation, most notably the short timeframe of the study, and factors other than adherence (eg, resistance or achieved therapeutic drug levels) that would have affected viral load. The relatively low correlation ($r = -0.18$) between total PMAQ-V1.0 scores and $\log_{10}$ HIV-1 RNA as a continuous variate may be a result of the restriction of range induced by the ordinal scoring of the responses or the relatively high level of adherence and infrequency of virologic failure observed in this study. These results are consistent with those of an observational clinical cohort of HIV-1 infected patients monitored in routine clinical practice.[21] Whether the ultrasensitive HIV-1 RNA assay (lower limit of quantification, 50 copies/mL) would affect the interpretation of our viral load–adherence correlation is not known. However, more quantitative information on HIV-1 RNA would be expected to produce a higher correlation.

The finding that memory and recall barriers are most associated with missed doses is not surprising in view of other reports of forgetfulness as the key problem in preventing complete adherence to ART.[4,6] Indeed, in one study,[6] forgetting accounted for 90% of all missing antiretroviral doses. In general, the more complicated the dosing regimen—number of drugs, doses per day, or pill burden—the greater the likelihood that patients will forget to take a dose, self-administer doses at the wrong time, or double-dose.[4,6,22] Forgetting to take doses because of dosing complexity leads to inadequate suppression of viral load. A meta-analysis of 22 clinical trials evaluating triple-combination therapy in ART-naïve, HIV-infected patients[23] uncovered a correlation between higher pill burden and lower percentage of patients achieving plasma HIV-1 RNA levels at or below 50 copies/mL at 48 weeks. Although the lamivudine/zidovudine combination tablet can be used to lower pill burden and theoretically improve the odds for better adherence and virologic outcome, nonadherence with this formulation could potentially jeopardize the effectiveness of two drugs rather than one.

Our results confirm previous psychometric findings from several focus groups conducted to evaluate the structure, reliability, and validity of the PMAQ-V1.0.[11] Indeed, in 67 participants with HIV infection who completed the PMAQ-V1.0 during its initial evaluation, scale scores for memory and recall and scheduling and timing likewise established a high correlation with missed individual doses of ART; knowledge and attitudes showed the lowest correlation.[11] The assessment of correlation represents the *mean* for all patients who completed the PMAQ-V1.0, however; for individual patients, different correlations may be present (eg, knowledge and attitudes may be more important to nonadherence than other dimensions). Our study confirmed that patients did not have huge barriers or difficulties with the regimen evaluated, and our findings have since been used to improve the instrument and design additional validation studies for the dimensions.

Possible deficiencies of the PMAQ-V1.0 are its inability to estimate adherence rates to specific antiretroviral drugs and the time over which patients are asked to report medication-taking behaviors (4 weeks). These have been addressed by the inclusion of specific questions about the frequency and timing of drugs during the last week in a revised version called the PMAQ-3W (available for research purposes from the corresponding author). The observed correlation between self-reported adherence and virologic outcome could have been biased in favor of significance because missing plasma HIV-1 RNA was treated as quantifiable according to the intent-to-treat principle. Our results were robust when analyzed according to the as-treated principle, however.

Although the PMAQ may not accurately estimate percentage of doses missed, it may help to identify patients experiencing difficulty with adherence who are therefore at increased risk for virologic failure. It is also impossible to verify the accuracy of self-reports and putative objective measures, such as MEMS, relative to the true adherence rate. Self-reporting has been shown to overestimate adherence as measured objectively,[24] but the observed correlation between our results and virologic outcome supports the validity of the PMAQ-V1.0 for assessing individual adherence. There is no proof that simply recognizing poor adherence through the PMAQ-V1.0 will improve virologic outcome. Nevertheless, when this instrument does identify adherence as the major contributor to poor clinical response, steps can be taken to improve adherence, and virologic outcome, by positively influencing the nonadherence-associated behaviors. The correlations reported herein suggest that the PMAQ may be able to accurately rank adherence behaviors in a given clinic population and that accurate ranking, rather than an exact measurement of adherence, is essential to identify those most in need of support.

In this study, we pooled the viral load data over treatment and PI arms. As viral load response in the two treatment arms was not significantly different,[12] this pooling was appropriate, and sensitivity analysis adjusted for treatment produced consistent results. This study had several limitations. First, data on treatment duration and pretherapy viral load were lacking. Second, the patients were highly selected by virtue of their participation in a clinical trial. Thus, the high level of adherence (narrow range) reported may diminish the strength of the relationship between adherence and viral load as a continuous variable. A broader range of adherence is likely in routine clinical practice. In general, conclusions from a clinical trial in which virologic and immunologic measures are well controlled at entry may not be easily extrapolated to a more severely ill, real-world population of HIV-infected patients. Third, although the composition of our population (85% male, 68% white) was generally consistent with that in other clinical trials, it is not representative of many clinical practices. Fourth, inclusion of an objective measure of adherence (such as antiretroviral plasma concentrations) to validate the observations and investigation of a relationship between adherence and the frequency of adverse events would have been desirable. Finally, the size of the subgroups was too small to permit subgroup analysis.

Overall, however, the PMAQ-V1.0 is useful as a self-administered adherence instrument that is sensitive to a patient's virologic status. Consequently, its value may be extended to assessing adherence in other chronic viral infections, such as hepatitis B and herpes simplex. The PMAQ-V1.0 has adequate psychometric properties (good reliability and validity). Further in-depth analyses to explore its factor structure are underway. In conclusion, administration of the PMAQ-V1.0 in clinical

settings may enhance understanding of the barriers and motivators associated with adherence, improve compliance with therapy and ultimately foster better virologic outcomes and more effective management of HIV infection.

The results of this study were presented, in part, in Abstract 94 at the 6th Conference on Retroviruses and Opportunistic Infections; January 31-February 4, 1999; Chicago, Ill.

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APPENDIX

Initial Items in the Adherence Barriers and Motivators Section of the PMAQ-V1.0*

Scheduling and Timing

Taking HIV-related medicines on time
Convenience of dosing
Problems with storing medicines
Difficulty taking medications at prescribed times
Difficulty taking medications when away from home
Difficulty taking medications when tired

Physical Effects

Disincentive to take medicines when experiencing side effects
Difficulty swallowing medicines
Medications resulting in better sense of health
Discontinuing medicines when health is improved
Difficulty taking medicines because of unacceptable taste

Knowledge and Attitudes

Familiarity with prescribed regimen
Having to take more medications than are acceptable
HIV status reinforced by having to take medications
Difficulty taking medications because too busy

Social Support

Family and friends encourage use of HIV-related medications
Patient-provider relationship facilitates discussion of medications
Difficulty taking medications when privacy is compromised
Uncomfortable with people knowing medications are for HIV
Embarrassment felt when having HIV-related medications filled at drugstore

Memory and Recall

Took all HIV-related medications in the past week
Always remember to take HIV-related medications
Difficulty remembering to take medications when leaving place of residence
Having more medications to take causes more frequent "forgotten" doses
Difficulty remembering to have prescriptions refilled

*Descriptors under each dimension are a summary of each item and do not represent actual wording.