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Cross-Sectional Study to Evaluate Factors Associated with Adherence to Antiretroviral Therapy by Brazilian HIV-Infected Patients

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ABSTRACT

Antiretroviral therapy success is highly dependent on the ability of the patient to fully adhere to the prescribed treatment regimen. We present the results of a cross-sectional study that evaluates the predictive value of a self-administered questionnaire of adherence to antiretroviral (ARV) therapy. Study participants were interviewed using a 36-item Patient Medication Adherence Questionnaire (PMAQ) designed to assess knowledge about ARV therapy, motivation to adhere to treatment, and behavioral skills. Plasma HIV-1 RNA levels were correlated with the results obtained from the PMAQ. Of the 182 study participants, 82 (45%) were receiving their initial ARV regimen. Of the remaining patients, 39 (21%) and 61 (34%) were on a second or additional ARV regimen, respectively. An undetectable viral load was documented in 47/62 (76%) patients on their first regimen who reported missing medication on less than 4 days in the last 3 months. The PMAQ had a higher predictive value of plasma viral suppression for patients in the initial regimen than for patients in salvage therapy. The overall predictive value of the PMAQ to identify adherence was 74%, and 59% for nonadherence, with an overall efficacy of 64%. Of the 74 patients (45%) who did not understand the concept of antiretroviral therapy, 80% were failing or had previously failed the ARV treatment. Of 35 patients with doubts about their HIV status or skeptical of the benefits of ARV therapy, 29 (84%) were nonadherent. Despite the positive predictive value of PMAQ in identifying adherence, self-reported adherence is not a sufficiently precise predictor of treatment success to substitute for viral load monitoring. On the other hand, the use of such an instrument to identify factors associated with nonadherence provides an excellent opportunity to apply early intervention designed to specifically address factors that might be contributing to the lack of adherence prior to regimen failure.

INTRODUCTION

Contemporary antiretroviral therapy, termed highly active antiretroviral therapy (HAART), has greatly reduced the morbidity and mortality associated with HIV-1 infection. The long-term success of HAART is dependent on a high level of adherence to the regimen prescribed.[1] The unforgiving nature of the virus requires that levels of adherence be higher and more sustained than in most other areas of medicine. In one study, an adherence level of less than 95% was associated with a reduction in treatment success.[2,3] An array of tools has been employed to assess the level of adherence to antiretroviral ARV therapy.[4–8] Self-administered structured sets of questions related to self-reported adherence are among these tools.[9,10] Most studies of adherence to antiviral therapy have been undertaken in industrialized settings.[4] The Patient Medication Adherence Questionnaire (PMAQ) is one of the most widely used questionnaires for assessing adherence in HIV-infected patients, especially in clinical trials.[5,11] In this investigation of self-reported adherence among HIV-1-infected Brazilian patients, we determined the accuracy of PMAQ to predict viral suppression and identify predictors of adherence for patients on initial and salvage ARV treatment.

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MATERIALS AND METHODS

The study population consisted of 182 patients followed in the HIV/AIDS outpatient clinics of the Hospital Universitário Prof. Edgard Santos (HUPES) and at the AIDS Reference Center of Salvador, Bahia, Brazil (CREAIDS).[2] Patients eligible for this cross-sectional study were required to have a previous diagnosis of HIV infection, to have received ARV therapy for at least 6 months, to be over 18 years of age, and to have at least one measure of CD4 count and viral load collected within 2 months of completing the PMAQ. Consenting patients who spontaneously came to the outpatient clinics were interviewed by one of the authors. The PMAQ was adapted from a previously described adherence tool and consisted of 36 questions designed to evaluate the level of knowledge of participants regarding ARV therapy, their level of motivation to take therapy, and their behavioral abilities.[5] The assessment of adherence was based on participant responses to questions about the extent to which the regimen prescribed was taken as directed. Other potentially important dimensions of adherence such as food intake related to antiretroviral administration were not investigated. Results of the PMAQ were correlated with HIV-1 RNA levels by comparing the HIV-1 RNA value obtained closest to the time when the questionnaire was completed. CD4 cell counts could not be matched with viral load determinations because most patients had different times of collection of the samples for the two studies. Plasma HIV-1 RNA levels were available for 180 of the 182 subjects. Nonadherence was defined as a patient report of omitting at least one dose of drugs on 4 or more days in the last 3 months (90 days). Study participants missing ≤4 days of therapy over the prior 90 days were considered to have taken >95% of prescribed medications. ARV drugs were prescribed according to the Brazilian National Guidelines for the treatment of Adults with AIDS/HIV infection.[12] For treatment-naive patients, these guidelines stipulate a combination of two nucleoside analog reverse transcriptase inhibitors and either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor. Treatment-experienced patients taking other combination drug regimens were allowed to participate in the study if their regimens consisted of at least three ARVs. A change in the regimen was considered for virologic failure. Viral suppression was defined as a value below the limit of quantification (400 copies/ml) of the NucliSens HIV-1 assay (Bio-Merieux).

Statistical methods

The association between patient characteristics assessed by the PMAQ and self-reported adherence was analyzed using the chi-square test and the Mann–Whitney test, for categorical and continuous variables, respectively. The association between self-reported adherence and viral suppression was analyzed using Fisher's exact test. The proportion of subjects with viral suppression, together with an asymptotic 95% confidence interval, was computed and plotted for the adherent and nonadherent subjects, overall and separately for subjects within their first, second, and third or later regimen. In addition, the predictive value of adherence on viral suppression (true positive,

Table 1. Demographic and Clinical Characteristics of the Study Population

		Number of patients (%)		
	Total	*Adherent*	*Nonadherent*[a]	p *value*
Number of patients	182 (100)	116 (64)	66 (36)	NR
Gender				
Male	95 (52)	59 (51)	36 (54)	NS
Female	87 (48)	57 (49)	30 (46)	
Age (mean ± SD)	37.7 ± 8.0	37.8 ± 8.1	37.8 ± 7.6	NS
Level of Education (years)				
≤8	77 (42)	46 (40)	31 (47)	NS
>8	105 (58)	70 (50)	35 (53)	
Annual Income Salary (US$)[b]				
≤100 USD monthly	33 (23)	22 (23)	11 (25)	NS
>100 USD monthly	107 (77)	74 (77)	33 (75)	
Partner				
Stable	37 (20)	20 (17)	17 (26)	NS
Nonstable	145 (80)	96 (83)	49 (74)	
Lenght of ARV (months)				
(mean ± SD)	42.0 ± 28.5	37.9 ± 24.9	49.4 ± 32.8	0.002
Time or ARV regimen				
≤24 months	71 (39)	52 (45)	19 (29)	0.04
>24 months	111 (61)	64 (55)	47 (71)	
Desire to keep treatment[c]				
Scale 0 to 10 (mean ± SD)	7.7 ± 1.1	8.1 ± 0.9	7.1 ± 1.4	0.007

[a]Missing 4 days or more of treatment in the last 90 days.
[b]Data on 140 patients
[c]Eliminating the extremes (0 and 10). Wilcoxon rank test.

TABLE 2. ASSOCIATION BETWEEN SELF-REPORTED ADHERENCE AND VIRAL SUPPRESSION (<400 COPIES/ML) ACCORDING TO REGIMEN OF THE ARV TREATMENT[a]

		PMAQ self-reported adherence				
		Adherent		*Not adherent*		
	N	*Supp. (%)*	*Not supp. (%)*	*Supp. (%)*	*Not supp. (%)*	p *value*
Regimen						
Initial	82	47 (76)	15 (24)	5 (25)	15 (75)	<0.001
Second	37	14 (67)	7 (33)	7 (39)	9 (61)	0.20
Add	61	16 (52)	15 (48)	15 (50)	15 (50)	1.0
Total	180	77 (68)	37 (32)	27 (41)	39 (59)	<0.001

[a]Supp., viral suppressed; not supp., not viral suppressed; add, patients that were on the third or more ARV regimens. The percentages are computed for each adherence group and treatment regimen. The *p* values are from Fisher's test.

true negative, and overall) was computed for each regimen and for all subjects. The trend in the proportion of subjects with viral suppression between the first and later regimens was analyzed using the asymptotic chi-square test of homogeneity of risk ratios across 2×2 tables. The analysis was performed using SPSS v. 9.0 (SPSS, Inc., Chicago, IL) and R (The R foundation, http://www.r-project.org) statistical analysis software.

RESULTS

Table 1 presents the characteristics of the 182 subjects in the study. Ninety-five (52%) were male and 87 (48%) female. The median age was 37 years (range 18–64 years). The adherent and nonadherent groups were similar in gender, age, education, income, and stable partnership distributions. Annual income data (calculated in U.S. dollars) were available for 140 patients. No significant difference in annual income was noted between the adherent and the nonadherent patients. At the time of the survey, the mean duration of ARV was 42.0 ± 28 months. Eighty-two subjects (45%) were receiving their initial ARV regimen, whereas 39 subjects (21%) and 61 subjects (34%) were on a second or additional ARV regimen (third or more), respectively. The adherent group had a significantly shorter duration of therapy (37.9 months vs. 49.4 months for the nonadherent group, $p = 0.002$, Table 2).

Self-reported adherence was predictive of virologic suppression for subjects in the initial ARV regimen: 47 of 62 (76%) of the subjects reporting adherence had viral suppression, versus only 5 of 20 (25%) of the subjects reporting nonadherence, $p < 0.001$. In contrast, adherence was not predictive of viral suppression in the second regimen (67% versus 39%, respectively, $p = 0.20$) or in the additional regimen subgroups (52% versus 50%, $p = 1.0$). Figure 1 shows the proportion of subjects with viral suppression (and 95% confidence intervals) for adherent and nonadherent subjects for each treatment group. There was a significant trend toward a higher difference in viral suppression between adherent and nonadherent group for subjects with initial treatment versus second or additional treatment, $p = 0.017$.

Further analysis of PMAQ items revealed several interesting associations. Seventy-four patients (45%) had no knowledge of ARV; of these, 80% did not have viral suppression. Belief in the value of ARV treatment and in the severity of HIV-1 infection also correlated with adherence. Of 35 patients who doubted their HIV status or the benefit of ARV treatment, 29 (84%) were not adherent. Although there was no difference between the number of pills prescribed to adherent versus nonadherent patients, (8.4 ± 3.9 vs. 8.8 ± 4.0, $p > 0.10$), the patients with the simplest drug scheme, two nucleoside analogs (two pills daily) plus an NNRTI (two or three pills daily) were more likely to be among the highly adherent group (47/116, 40%) than among the less adherent group (10/66, 15%), $p < 0.001$).

Table 3 displays the reasons reported by patients for missing doses of medication. Among the 145 patients reporting missing at least one dose of drugs, the most frequent cause of not taking medication was being "away from home" (76/145, 56% of patients). Other reasons given included the requirement for a change in daily routine (55/145, 38%) and "simply forgot" (50/145, 34.5%). Depression (28 subjects, 19%), feeling sick (19, 13%), and sleepiness (33, 23%) were observed in the majority of nonadherent subjects. In the behavioral skill category of the questionnaire, 95 patients (68%) reported that ARVs interfered with their lives, 29 (19%) reported that ARVs inter-

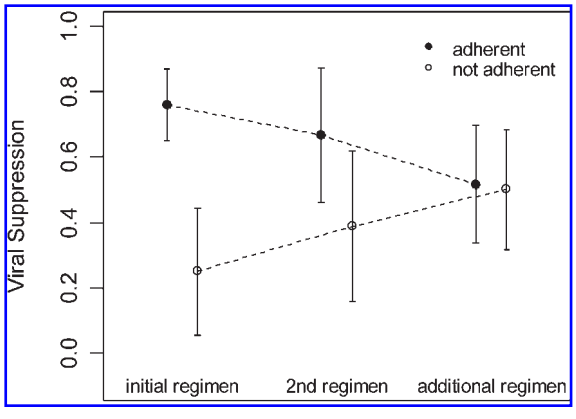

FIG. 1. Proportion of subjects with viral suppression and 95% CI for initial, second, and additional ARV regimens.

Table 3. Reasons Reported for Having Missed Medication among 145 Patients Reporting Incomplete Adherence

Reasons[a]	*Total number of patients*	*(%)*
Away from home	76	(52)
Change in daily routine	55	(38)
Simply forgot	50	(34)
Being busy	49	(34)
Found it difficult to take pills	40	(28)
Was sleeping	33	(23)
Depressed	28	(19)
To avoid side effects	24	(17)
Feeling sick	19	(13)
Too many pills	18	(12)
Was intoxicated	14	(10)
Job demand	29	(17)
Friendship difficulties	46	(28)
Interference of ARV in their life	95	(95)
Total	145	

[a]Many patients had more than one reason, so the total number of each individual reason does not necessarily reflect the total number of patients who reported that specific reason for having missed medication.

fered with job demands, and 46 (28%) reported that ARVs posed difficulties in personal relationships.

DISCUSSION

In this cross-sectional study of ARV adherence using the PMAQ we documented a high predictive value (76%) to detect viral suppression for patients on initial drug regimens. The tool is much less capable of predicting viral suppression for patients on second or later ARV regimens. Most prior studies of adherence have been undertaken in nonresource-limited settings. Our study noted both parallels and differences when factors related to adherence were compared to those identified in U.S. and European populations. Our results are consistent with those reported by the AIDS Clinical Trials Group and by the French APROCO cohort study, which also demonstrated a high level of adherence for patients on the initial drug regimen.[11,13] In our study undertaken in Brazil, we noted no significant associations between adherence or viral suppression and gender or annual income.[14,15] Unlike another study undertaken in Brazil that noted that having less than 2 years of formal education predicted lower adherence, we did not note that level of education was predictive of adherence.[16] Our study, however, evaluated potential differences in adherence based on whether or not patients had 8 years of education. In other studies alcohol consumption, drug toxicity, poor material living conditions, education level, depression, negative life events, social support, and behavioral skills and attitudes (being away from home, forgetting to take medication, being busy) are reported to be most frequent reasons for nonadherence to ARV therapy.[10,14,17–19] We noted a different set of challenges to adherence among the Brazilian population. Drug toxicities were less frequently cited as barriers to adherence in our study while issues like being away from home were more important. It should be noted that less frequent reporting of toxicities, especially subjective ones, does not mean that there are substantial differences in toxicity of the regimens used in the Brazilian population.

Persons from cultures that are more likely to defer to medical professionals may be less likely to report toxicities despite having toxicity rates similar to those in less deferential populations. Other investigators have noted that being extremely sure of the subject's own ability to take all ARV drugs directly influences the rate of adherence.[19] We found that the patient's desire to keep the treatment coupled with the understanding that failure of adherence will lead to viral resistance and ultimately to virologic failure were reported significantly more by the adherent patients compared to the nonadherent patients.

Depression, which has been commonly identified in nonadherent patients in other studies, was also reported by about 20% of our patients.[17] Reports about the role of financial resources on regimen adherence in resource-limited settings are conflicting. One report from Africa cited the cost of ARV as a barrier to patients with limited financial resources to adhere to ARV.[20] Another study noted that patients who contributed a part of the cost of the ARV drug for their treatment showed a higher level of adherence compared to those who received free medication.[21] In this study in Brazil, where free access to ARV is widely available on a national scale to all Brazilian citizens, no correlation was found between adherence and either income or level of education.[12]

Continuing to study treatment adherence in different settings using simple treatment assessment tools is important in order to accurately identify factors that interfere with adherence and thereby reduce the effectiveness of ARV therapy. In certain settings such as prison populations directly observed treatment (DOT) is a very effective strategy to maximize adherence.[22] Such approaches are generally not feasible in the general population or for massive ARV treatment programs such as in Brazil. In these settings, it may be more important to develop simple strategies that overcome lapses of adherence caused by leaving medications at home such as the creation of emergency drug dispensaries located close to patients' workplaces. These would avoid missed doses because the patient "simply forgot" or was "away from home," which were two of the most frequently cited reasons for nonadherence in our study, as was the case in a study reported from South Africa and one from the United States.[23,24] In a study undertaken in Costa Rica patients who were nonadherent were more likely to report being unable to find transportation to the clinic.[25] These free, one-day DOT dispensaries, strategically located close to where patients live and work for those already on ARV therapy, may be a cost-effective alternative to investing in a sophisticated armamentarium to detect virologic resistance for those who fail ARV therapy because they simply forgot their drugs, have no access to a spare pill, or could not travel to the clinic.

Although this adherence assessment tool was very useful in predicting successful antiretroviral therapy among patients receiving their first treatment regimen, the 76% positive predictive value is not sufficiently sensitive to substitute for plasma HIV-1 RNA monitoring in settings in which this tool is available. As has been reported by others, the tool did identify fac-

tors that strongly predicted nonadherence including a deficiency of knowledge about antiretroviral therapy and a lack of belief in its efficacy.[26] In addition, patients with doubts about the severity of HIV infection or who doubted their HIV status were likely to be nonadherent. Tools such as the PMAQ might be extremely useful in identifying those who are unlikely to adhere to therapy, thereby allowing interventions designed to counteract adherence barriers prior to regimen failure. Therapy usually fails in those who report not reliably taking their medications, but reports of adherence are no substitute for a documented plasma HIV-1 RNA level that is below the limit of detection.

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