Characteristics of HIV Antiretroviral Regimen and Treatment Adherence

Vera Lúcia da Silveira, Maria de Lourdes Drachler,
José Carlos de Carvalho Leite and
Cézar Arthur Tavares Pinheiro

Faculty of Medicine of the Federal University of Pelotas and Municipal Secretary of Health of Pelotas; University of Caxias do Sul, Rio Grande do Sul, Brazil

The relationship between characteristics of HIV antiretroviral regimens and treatment adherence was studied in adolescent and adult patients who underwent antiretroviral therapy from January 1998 to September 2000, at the Service for Specialized Assistance in Pelotas. The patients were interviewed on two occasions, and the use of antiretrovirals during the previous 48 hours was investigated by a self-report. Adherence was defined as use of 95% or more of the prescribed medication. Social-demographic variables were collected through direct questionnaires. The antiretroviral regimen and clinical data were copied from the patients' records. Associations between the independent variables and adherence were analyzed by means of logistic regression. The multivariate analysis included characteristics of the antiretroviral regimens, social-demographic variables, as well as perception of negative effects, negative physiological states, and adverse effects of the treatment. Among the 224 selected patients, 194 participated in our study. Their ages varied from 17 to 67 years; most patients were men, with few years of schooling and a low family income. Only 49% adhered to the treatment. Adherence to treatment regimens was reduced when more daily doses were indicated: three to four doses (odds ratio of adherence to treatment (OR)=0.47, 95% confidence interval (CI) 0.22-1.01) and five to six (OR=0.24, 95% CI 0.09-0.62); two or more doses taken in a fasting state (OR=0.59, 95% CI 0.11-0.68), and for patients who reported adverse effects to the treatment (OR=0.39, 95% CI 0.19-0.77). Most of the regimens with more than two daily doses of medication included at least one dose apart from mealtimes. The results suggest that, if possible, regimens with a reduced number of doses should be chosen, with no compulsory fasting, and with few adverse effects. Strategies to minimize these effects should be discussed with the patients.
Key Words: HIV/AIDS, adherence, antiretroviral therapy.

HIV infection is a serious public health problem. According to estimates from the World Health Organization (WHO), in 2000 there were more than 36 million infected people and 22 million had already died [1]. Another 5.3 million were infected in 2000, which means more than 15,000 people per day or 11 per minute [2].

Antiretroviral therapy has changed the prognosis of patients infected with HIV [3]. This treatment causes a reduction of viral load count to undetectable levels [3], thus reducing the incidence of infections [4,5], hospitalizations [5], and mortality [4,5]. Treatment effectiveness requires high levels of adherence [5-8]. RNA levels higher than 400 copies/ml were found in only 22% of the patients whose treatment adherence was ≥95%; on the other hand these high levels were found in 80% of the patients whose adherence was <80% [5]. Other studies have also found low adherence

to be associated with detectable viral load (>400 [9] or 500 copies/ml [7]), and with cross-resistance to other antiretrovirals [6,8,10]. Cross-resistance interferes with future therapeutic options for the individual being treated and for those who subsequently become infected with the resistant virus. Therefore, low adherence can have a devastating effect on the individual and can also pose an even greater problem for public health.

Nowadays, according to the Brazilian Ministry of Health, an adherent patient is defined as one who takes $\geq 95\%$ of the prescribed dose [1,5,7]. However, a significant proportion of patients do not reach high levels of adherence. In one study, 37% of the patients used less than 80% of the prescribed medication [11]. More recent data reveal that 31% of the patients took $\leq 90\%$ of the doses [12]. In Brazil, it is estimated that 30-40% of all patients do not adhere to treatment (they take less than 80% of the medication prescribed). These data were obtained by means of a self-report analysis [13].

The effect of the characteristics of the antiretroviral regimen and treatment adherence has been studied [12, 14-22]. Increased numbers of antiretroviral drugs used in the treatment regimens is expected to make it more difficult for the patient to follow the prescription. A majority of trials confirm this hypothesis [16,18-21, 23-25]. However, there was no evidence of such an effect in other studies [7,11-13,22,26-28].

The number of doses is another important variable. Some studies support the hypothesis that the number of doses is more important than the number of drugs used [16, 18, 28], as a small number of medication sessions tends to fit more easily into the patient's daily routine [19,24,28-30]. Nevertheless, other studies did not find this association [12,13,22], which suggests a need for more comprehensive studies concerning this issue.

The effect of the number of pills has also been studied. Taking a larger number of pills is likely to affect adherence due to the greater difficulty involved [18,21,24,28]. In one study [19], the difficulty of taking a large number of pills was the fourth most frequent cause of non-adherence; it was reported by 50% of

the non-adherent patients. Other authors did not find a link between this variable and adherence [4,11-13,15,30,31]; thus, the possibility of an effect of the number of pills on adherence was deemed inconclusive.

Some antiretroviral regimens require that the medication be taken with food, during a hearty meal or in a fasting state [19,24,32-34] in order to attain full absorption. In one study [19], the primary cause of non-adherence was hunger, due to the fasting requirement. In another study [25], 23% of the patients reported difficulty in following this recommendation. Although no studies were found involving taking medication with meals, adherence is expected to be higher in this case.

Most of the review studies [18,34,35] and research papers [4,19,36-38] on this subject suggest that adverse effects are contributing factors to non-adherence. Other factors, such as little schooling [13,21], emotional dysfunction (anxiety [21] and depression [11,39-41], were also considered risk factors for non-adherence.

We examined the effect of antiretroviral regimen characteristics and treatment adherence in an HIV/AIDS reference center in southern Brazil.

Materials and Methods

Design and data collection procedures. We studied all patients aged 13 and over registered at the Service of Specialized Assistance for HIV/AIDS of the city of Pelotas-RS (SAE), who were prescribed antiretroviral therapy for treatment of HIV infection from January 1998 to September 2000.

Data collection took place between May and December of 2000; it included two interviews with each patient. Well-trained personnel interviewed the patients after obtaining written consent. Interviews took place at the SAE, when patients went there for a medical appointment or to obtain their medication at the center's pharmacy. Patients who did not attend the outpatient clinic (n=53) were interviewed at home and were advised to return to the outpatient clinic.

During the first interview, patients answered a questionnaire that included social-demographic data,

the use of antiretrovirals and other medications, as well as perception of adverse effects to antiretroviral treatment, of negative effects and of negative physiological states. The second interview, with a minimum interval of one month after the first one, investigated the use of antiretrovirals and other medications. Two medical researchers, experts in HIV/AIDS, copied all data on clinical evaluations, duration of treatment and use of antiretrovirals directly from the patients' records. The variables studied were:

Social-demographic characteristics. Data that included social details, such as age, gender, formal education and family income were collected with semi-open questions.

Clinical, viral and immunological characteristics. Current viral load was estimated by means of the serum HIV-RNA quantification made closest to the time of the interview, using the NASBA technique; the data was obtained from the patients' records.

Flow cytometry CD_4 counts were copied from the patients' records. The most recent CD_4 counts were used as an indication of the current state of the immune system. Figures lower than 200 have been considered indicators of serious immunological debilitation [42]. The lowest CD_4 figure of each patient was used as part of the criterion for classifying the clinical stage of infection. Clinical stage of HIV infection was estimated according to CDC (Centers for Disease Control and Prevention) criteria [43]; patients were classified as: stage A, asymptomatic; stage B, having symptoms of HIV infection but without criteria for diagnosis of the disease; and stage C, having diseases that define AIDS (Kaposi's sarcoma, for example), with a total of 10 or more points according to the Caracas criterion [42]. The CD_4 counts and viral load counts were extracted from the patient's records for this purpose.

Aspects of treatment and other clinical information. The following variables were obtained from the patients' records: time of diagnosis of HIV/AIDS carrier, date when antiretroviral treatment was initiated, current antiretroviral regimen, and other antiretroviral regimens previously used by patients (including names of medications, number of daily doses, number of pills per treatment session, compulsory fasting or medication taken with a meal), adverse effects and use of other medications.

Perception of negative effects and negative physiological states. These perceptions were measured by means of a scale developed for this study. This scale includes five items: "I have been sad and feeling low," "I have been nervous and irritable," "I have been feeling bad," "I have been having problems with my day-to-day activities," "I feel debilitated and sick." A Likert scale was added to each item, where the patient expressed the degree of agreement with the situation described by the item. Items were classified as (o):"strongly disagree", (1) "disagree", (2) "don't know", (3)"agree", (4) "agree strongly." A score of perception of negative effects and negative physiological states was generated after the first main component of the exploratory analysis of the main components. This score was designed in a standardized z-scale and measured, in standard deviations, how much the individual's perception was above or below the sample mean. This scale showed acceptable levels of internal consistency, as indicated by a Cronbach's alpha value of 0.75.

Adherence to antiretroviral regimen during the study period. The use of antiretrovirals was investigated at first and second interviews (interval of approximately one month between them) by means of a self-report, using a questionnaire that investigated the medications in use, schedule of administration and doses during the previous 48 hours.

Adherence to the regimen during this period was estimated as follows: initially, adherence to each separate medication was calculated by dividing the number of pills that the patient declared he took by the number of pills prescribed (first and second interview). After that, adherence to the regimen during this period was estimated by an arithmetic mean of adherence to medications. A patient was considered adherent if he or she took ≥95% of the prescribed dose during the four days of evaluation.

Statistical analyses. Percentages of adherent patients and crude and adjusted odds ratios of adherence were estimated for each variable of the treatment regimen. Gender, clinical stage, time since diagnosis, and duration of treatment were not considered potential confounding factors because they did not show evidence of any association with adherence (they all presented p>0.30, both in the crude model and in the model adjusted for age, family income, schooling, perception of negative effects and negative physiological states). Age, family income, schooling, perception of negative effects and negative physiological states were included as potential confounding factors of the effect of treatment regimen on adherence (they all gave a significant correlation with adherence, p<0.05). It was determined that all variables of treatment regimen that had any significant or nearly significant effect on adherence (p<0.30), either in the crude model or in a model adjusted for age, family income, schooling, perception of negative effects and negative physiological states, would also be included as potential confounding factors for the other variables of this regimen. The only exception was the number of doses taken in a fasting state, which was not included in the other models because it was too closely related to the number of daily doses.

Results

Two hundred and forty four patients eligible for the study were registered at SAE. Among those, 10 had died, 27 were not found and 194 participated in the study. Most (60.8%) of the patients who participated were men. Their ages ranged from 17 to 67 years, with a mean of 34. Schooling varied from 0 to 15 years, with a mean of 5 years; family income ranged from 0 to 46 minimum wages, and it was less than 1.5 minimum wages in 50% of the patients. The time since diagnosis ranged from 0 to 9 years, with a mean of 2 years. A third of all patients had less than six months of treatment. Most of the patients (60.3%) had stage C disease and 28.4% had stage A. The current immune status of 73.7% of patients was good, which was evidenced by a CD_4 count of >200 cells/ml. Viral load count was <400 copies/ml in 64.7%; 49% of the patients had adhered to treatment.

More than half of the patients used four or more pills per session, three or four drugs in each regimen, three or more daily doses, and one or more doses administered in a fasting state. Most patients never changed their antiretroviral regimen, never used other medications and did not report adverse effects to antiretroviral treatment (Table 1). The vast majority of antiretroviral regimens with more than two daily doses (88.9%; n=111) required at least one dose administered in a fasting state.

Patients with a prescription of three to four daily doses were 53% less likely to adhere (odds ratio of adherence to treatment (OR) = 0.47, 95% confidence interval (CI) 0.22-1.01) than patients who had been prescribed a two-dose regimen; for those who had been prescribed 5 to 6 doses, the likelihood of adherence was 76% lower (OR=0.24, 95% CI 0.09-0.62), after adjustments for age, family income, schooling, use of other medications and perception of negative effects, negative physiological states and adverse effects (Table 1).

Two or more daily doses taken in a fasting state reduced the likelihood of adherence by 73%, when compared with absence of compulsory fasting (OR=0.27, 95% CI 0.11-0.68), adjusted for age, family income, schooling, perception of negative effects, negative physiological states, adverse effects and use of other medications (Table 1).

The perception of adverse effects reduced the likelihood of adherence by 61% (OR=0.39, 95% CI 0.19-0.77) as compared with the absence of these effects, after adjustments for age, family income, schooling, perception of negative effects, negative physiological states, adverse effects and use of other medications (Table 1). The most frequent adverse effects were gastrointestinal symptoms (n=47), mood swings, thinking and behavioral changes (n=15), neurological symptoms (n=13) and headaches and diffuse pain (n=10).

The use of other combined medications did not affect the adherence in the crude model (p=0.363). However, after adjustments for age, family income, schooling, perception of negative effects, and negative physiological states, the likelihood of adherence was reduced by 42% compared with those who did not have other medications prescribed (OR=0.58; 95%

Table 1. Number of patients, percentages of individuals adhering to treatment, and Odds Ratio of adherence to antiretrovirals

Variables	Patient n	Adherence %	OR (CI 95%) Crude	OR (CI 95%) Adjusted
Maximum number of tablets per dose				
1-3	69	49.3	1	
4	85	49.4	1.01 (0.53-1.97)	
≥5	40	46.5	0.93 (0.43-2.03)	
			p = 0.987	
Number of drugs per Regimen				
2	26	34.6	1	
3	152	51.3	2.01 (0.83-4.74)	
4	16	50.0	1.89 (0.53-6.72)	
			p = 0.283	
Daily Doses (1)				
2	69	62.3	1	1
3 a 4	79	45.6	0.51 (0.26-0.98)	0.47 (0.22-1.00)
5 a 6	46	34.8	0.32 (0.15-0.70)	0.24 (0.09-0.62)
			p = 0.011	p=0.007
Administered with a meal				
No	177	48.6	1	
Yes	17	52.9	1.20 (0.44-3.22)	
			p = 0.731	
Administered in a fasting state (1)				
None	82	59.8	1	1
1	68	47.1	0.60 (0.31-1.14)	0.59 (0.27-1.26)
≥2	44	31.8	0.31 (0.15-0.69)	0.27 (0.11-0.68)
			p = 0.010	p = 0.014
Change of Regimen				
No	119	48.7	1	
Yes	84	49.3	1.02 (0.57-1.82)	
			p = 0.935	
Other medications (2)				
No	110	57.8	1	1
Yes	84	45.2	1.30 (0.74-2.30)	0.57 (0.28-1.17)
			p = 0.363	p = 0.126
Adverse Effects (3)				
Not reported	118	57.6	1	1
Reported	76	35.3	0.41 (0.22-0.74)	0.39 (0.19-0.77)
			p = 0.002	p = 0.006

(1) Adjusted for age, family income, schooling, perception of negative effects, negative physiological states, adverse effects, and use of other medications; (2) Adjusted for age, family income, schooling, perception of negative effects, negative physiological states, daily doses, and use of other medications; (3) Adjusted for age, family income, schooling, perception of negative effects, negative physiological states, daily doses, and use of other medications.

CI 0.30-1.10; p=0.092) (data not shown), and therefore it was included as a confounding factor of other variables of the therapeutic regimen (Table 1).

Percentages of adherence were similar among various categories of variables, including maximum number of pills administered per session, the number of drugs in each treatment regimen, medication administered with a meal, and changes in the treatment regimen. There was no evidence of a significant effect of these variables on adherence (crude and adjusted odds ratio; p>0.283) (Table 1).

Discussion

Currently there is no gold standard for measuring adherence [13,18,41]; some methods of doing so include interviews with patients, manual counting of pills, counting of opened bottles and serum or urinary dosing of drug metabolites [14,39]. Interviews [15,41] and counting of pills [13,14, 22, 29] tend to overestimate adherence, but their main advantages are low cost and readiness to obtain the desired information [13,14,36]. Dosing of metabolites can be affected by the medication's half-life [13,44]; therefore, it does not offer accurate information about the last dose taken by the patient [39]. Electronic counting is expensive and tends to overestimate adherence because patients may open the bottles and not take the tablets [13]. In our trial, prevalence of adherence was evaluated by means of a self-report from the patient. Nowadays, this is the most widely used method [7,8,12,15,16,21,40,41,45,46], and it has been useful to identify patients at risk for non-adherence and to forecast the results of short-term treatment as assessed by viral load counts [7,8,25,41].

Adherence during this period was estimated by the information collected in the two interviews regarding the mean use of antiretrovirals; each interview involved medication taken during the previous 48 hours. Adherence was defined as the use of ≥95% of the prescribed dose, a level that was recommended by the Brazilian Ministry of Health [1], as it is associated with therapeutic effectiveness. The vast majority of older studies used a cut-off point of 80% [11,13,16,30]. Nowadays, some studies use even more stringent cut-off points of as high as 100% [21,25].

This study was carried out in a reference service of the Unified National Health System (SUS, Sistema Único de Saúde) for HIV/AIDS in the city of Pelotas, where 79.5% of the patients registered in that service participated in our study. Adherence to drug regimens was low (49%) compared with another study that found 69% adherence and also used 95% of the prescribed medication as a cut-off for defining adherence [7]. Low adherence might be explained in part because of the low level of schooling of the patients from SAE in the city of Pelotas.

Our research about the effects of the characteristics of the treatment regimen on adherence had a cross-sectional design; we were unable to establish causal relations between these variables and treatment adherence. Nevertheless, in agreement with other studies, we suggest that regimens with three or more daily medication doses, with two or more doses taken in a fasting state, or those which produce adverse effects noticed by the patient (such as gastrointestinal problems, mood swings, thinking and behavioral changes, neurological effects and diffuse pain) tend to reduce treatment adherence. In our study, the amount of medication taken in a fasting state was very much related to the number of daily doses, and it was impossible to measure the effect of one separately from the other. Other studies and reviews also found an association between non-adherence and the number of daily doses [16,18,19,28], compulsory fasting [19,24,32-34], and adverse effects of treatment [4,18,19,34-38].

One study indicated that patients who took four drugs had a less rigorous adherence than those who took only one or two drugs [25]. In our study, regimens using three and four drugs had a likelihood of adherence approximately two times lower than that seen in two-drug regimens, but this effect was not significant, probably due to the low power of this study to detect effects of such magnitude. Studies with larger sample sizes are necessary to examine the association that between adherence and the number of drugs used.

Parameters such as the maximum number of pills per medication session, changes in the antiretroviral regimen and compulsory administration with food did not reveal any relationship with adherence (p values >0.30 and effect ≤30%). Other studies also found no association between treatment adherence and the number of pills per medication session [4,11-13,15,31,39] or with changes in the antiretroviral regimen [25].

Based on our study, we suggest a need for strategies to increase treatment adherence. Efforts must be made towards simplifying the therapeutic regimen, to reduce the number of daily doses and substituting with regimens that are accompanied by fewer adverse effects, wherever possible [14,18,47]. Emphasis on instruction of patients to take the medication is fundamental, as well as patient's participation in some treatment decisions [12,18,22,29]. It has been recommended that the physician discuss with the patient potential adverse effects and means to minimize them [14,19,21,22,29,47]. It is also important to stimulate the patient to implement the therapeutic regimen in his or her daily routine, pointing out, at each consultation, the importance of adherence. Adherence groups, as well as the participation of friends and family members have also been recommended as potentially beneficial for adherence [14,29,47]. It is crucial to explain to those patients whose medications need to be taken in a fasting state, that the absorption of the drug is reduced when there is food in the digestive tract [22,29,33].

Acknowledgements

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