

CLINICAL SCIENCE

DIFFICULTIES REPORTED BY HIV-INFECTED PATIENTS USING ANTIRETROVIRAL THERAPY IN BRAZIL

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OBJECTIVE: To describe the degree of difficulty that HIV-infected patients have with therapy treatment.

INTRODUCTION: Patients' perceptions about their treatment are a determinant factor for improved adherence and a better quality of life.

METHODS: Two cross-sectional analyses were conducted in public AIDS referral centers in Brazil among patients initiating treatment. Patients interviewed at baseline, after one month, and after seven months following the beginning of treatment were asked to classify and justify the degree of difficulty with treatment. Logistic regression was used for analysis.

RESULTS: Among 406 patients initiating treatment, 350 (86.2%) and 209 (51.5%) returned for their first and third visits, respectively. Treatment perceptions ranged from medium to very difficult for 51.4% and 37.3% on the first and third visits, respectively. The main difficulties reported were adverse reactions to the medication and scheduling. A separate logistic regression indicated that the HIV-seropositive status disclosure, symptoms of anxiety, absence of psychotherapy, higher CD4+ cell count (> 200/mm³) and high (> 4) adverse reaction count reported were independently associated with the degree of difficulty in the first visit, while CDC clinical category A, pill burden (> 7 pills), use of other medications, high (> 4) adverse reaction count reported and low understanding of medical orientation showed independent association for the third visit.

CONCLUSIONS: A significant level of difficulty was observed with treatment. Our analyses suggest the need for early assessment of difficulties with treatment, highlighting the importance of modifiable factors that may contribute to better adherence to the treatment protocol.

KEYWORDS: AIDS. Treatment. Patient Perception. Adherence. Modifiable Factors.

INTRODUCTION

Antiretroviral therapy (ART) has brought important benefits to HIV-infected patients, such as increased survival, better quality of life, significant reduction in the incidence of opportunistic infections and lower costs

related to ambulatory care and hospitalization.^{1,2,3} The Brazilian National STD/AIDS Program of the Ministry of Health has guaranteed universal and free access to ART since 1996.⁴ Patients diagnosed in that year had a median survival three times longer than those diagnosed in 1995, clearly indicating the benefits of ART.⁵ The clinical goals of HIV treatment and care, including maximizing survival and improving quality of life, are optimally accomplished only through a high-level of adherence to ART and, consequently, a durable suppression of the HIV viral load.⁶ Non-adherence has become a common cause of therapy failure, with failure rates varying from 7.0% to 43.0% in different health care settings worldwide.⁷⁻¹⁴ Factors poten-

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tially associated with non-adherence include characteristics related to the antiretroviral regimen (e.g., complexity of therapy, pill burden, food requirements, adverse reactions), a patient's perception of the treatment, the interference of ART in a patient's daily life, symptoms of AIDS and level of education, among others.⁸⁻¹⁵ However, there are few published epidemiologic studies that investigate the difficulties reported by patients initiating antiretroviral therapy, and to our knowledge, none in Brazil. Patients may feel emotionally unprepared for treatment due to a lack of understanding and/or belief in ART, leading to increased difficulties with everyday treatment management.¹⁶⁻¹⁷ Identifying and understanding the difficulties that arise in the beginning of treatment may help prevent further episodes of non-adherence and potentially increase long-term adherence with sustainable clinical benefits and improvement in patient quality of life.^{16,17} The present study aimed to describe the degree of difficulty with ART reported by HIV-infected patients in public AIDS reference centers using two cross-sectional analyses issued subsequent to the beginning of treatment (after one and seven months). In addition, we explored potential factors associated with such difficulties, including sociodemographic, psychosocial, clinical and health care-related variables.

MATERIALS AND METHODS

Subjects

This analysis is part of a prospective concurrent study conducted at two public health referral centers in a large metropolitan city in Brazil. The objective of the main project was to estimate the incidence of non-adherence to ART among patients initiating treatment and the factors associated with it. Briefly, eligibility criteria were serologic-confirmed HIV infection; no prior history of antiretroviral use; age over 18 years old (or 16 years old for pregnant women); having had one's first antiretroviral regimen dispensed in one of the centers and voluntarily participation consent. Patients were interviewed after first receiving medication (baseline interview), and subsequently in the first, fourth and seventh month of follow-up. The project was approved by the Ethical Committee Board of both participating centers and the Federal University of Minas Gerais (ETIC 106/99).

Exposure and event measurements

Data were collected using a pre-tested semi-structured questionnaire consisting of closed and short open-ended questions. Face-to-face interviews were conducted by trained research personnel in private rooms. Sociodemographic (e.g.,

gender, age, schooling, income), behavioral (e.g., disclosure of HIV-seropositive status, condom use and alcohol and injection drug use), health services and clinical characteristics (e.g., difficulty of access to services, embarrassment, understanding of medical orientation) were obtained during baseline interviews, while data on ARV use (e.g., difficulties with the treatment, prescribed regimens, change in regimen, pill burden, adverse reactions and adherence) were obtained from each follow-up interview. Additionally, the CDC clinical classification¹⁸ and CD4+ T-lymphocyte count were obtained from medical charts during the study period. Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale during the baseline interview.¹⁹ Disclosure of one's HIV-seropositive status was self-reported and defined as having communicated an HIV positive result to a close acquaintance such as a relative, friend or sexual partner.

For the current analysis, the outcome measurement (i.e., the difficulty of antiretroviral therapy use) was assessed in a cross-sectional approach at the first (first month) and third (seventh month) visits. We used only these visits as points of comparison because the time between the first and second visits was brief. Patients were asked to classify the degree of difficulty of their treatment at each visit as very high, high, medium, low, or very low and to justify their choice. The reported reasons were classified as problems associated with adverse reactions, scheduling, pill burden, emotional status, adaptation, social interactions, health care service, organoleptic properties of the drugs or dietary interference.

Data analysis

Descriptive analysis was conducted for the reported difficulties while crude associations were assessed by chi-square test. The degree of difficulty was categorized as a dichotomous variable, comparing all values falling between medium and very high difficulty to those in the range of low to very low difficulty, due to power considerations. The magnitude of the associations between putative risk factors and the degree of difficulty with treatment was estimated by the odds ratio (OR) with a 95% confidence interval (95% CI). The independent effect of potential exposure variables was assessed by multivariate analysis using logistic regression for each visit. All variables with p-values equal to or less than 0.20 obtained in the univariate analysis were used to begin multivariate modeling. A backward deletion strategy was applied, and those variables with p-values equal to or less than 0.05 remained in each of the final models. Goodness of fit was evaluated using the Hosmer-Lemeshow test,²⁰ while the SAS System[®] and EGRET for Windows[®], were used for data analysis, and Paradox[®] was used for data storage.

RESULTS

Of the 406 participants enrolled in the study, 362 (89.2%) patients returned for the first and 218 (53.7%) for the third visit after initiating ART. Twelve and nine patients did not classify the degree of difficulty of their treatment in the first or third visits, leaving 350 (86.2%) and 209 (51.5%) patients for analysis, respectively. No difference was observed when comparing the two visits for most variables, although there were fewer participants in the third visit. Descriptive data indicated that, for both visits, most participants were male, younger than 35 years old, and had less than 8 years of schooling, a low individual monthly income and no health insurance (Table 1). While more than half of the sexually-active participants reported always using condoms in the last month, fewer patients reported alcohol or injection drug use for both periods. Similarly, most patients had disclosed their HIV-seropositive status to relatives or friends while fewer participants declared embarrassment during clinic visits, reported some difficulty of access to the health service or were receiving psychotherapy. Clinical markers indicated high proportions of patients with lower CD4+ T-lymphocyte count (≤ 200 cells/mm³) or with CDC clinical classification B or C. Protease inhibitors were commonly prescribed, while a reasonable proportion of patients reported more than four adverse reactions or had a low understanding of their prescription's medical orientation.

Overall, 51.4% (n=180) patients found their treatment to be of medium to high difficulty in the first visit while this rating frequency dropped to 37.3% (n=78) in the third visit (Table 2). Adverse reactions were the main reason reported (33.3%), followed by complex scheduling (23.9%), among those reporting medium to high degree of difficulty in the first visit. Less frequent reasons were those associated with emotional status (9.4%), social interaction (7.2%), pill burden (6.7%), health care service (6.1%) and the organoleptic properties of the drugs (5.6%). On the other hand, adverse reactions only accounted for 19.2% and scheduling became the foremost difficulty by the third visit (37.2%). Among those with less difficulty with the treatment overall, the main reason reported was scheduling, while there was an increase in treatment adaptation over time (23.5% and 32.1%, for the first and third visits, respectively) (Table 2).

Univariate analysis indicated similar proportions of patients with increased difficulty with treatment across age, schooling, income, condom, alcohol or injection drug use, for both visits. Although more patients reported a change in regimen in the first visit, this was not associated with greater difficulty with treatment (data not shown). On the other hand, at the first visit, an increased degree of difficulty (p-value < 0.05) was found for those who disclosed their

Table 1 - Descriptive characteristics of participants in the first (n=350) and third (n=209) follow-up visits, ATAR Project, 2001-2003

Characteristics	1 st visit n (%)	3 rd visit n (%)
Sociodemographic:		
Gender (male)	195 (55.7)	124 (59.3)
Age (≤ 35 y.o.)	208 (59.4)	110 (52.6)
Schooling (< 8 years)	184 (52.6)	99 (47.6)
Individual monthly income (\leq USD 80)*	212 (61.6)	123 (60.0)
No health insurance	276 (78.9)	152 (72.7)
Behavioral:		
HIV-seropositive status disclosure**	297 (86.3)	181 (87.9)
Always used condom in the last month**	95 (55.6)	52 (57.8)
Alcohol use in the last month**	127 (36.9)	74 (35.9)
Lifetime injection drug use**	17 (4.9)	13 (6.3)
Clinical and health service related:		
Difficulty of access to health service**	33 (9.6)	22 (10.7)
Embarrassment during clinic visits**	48 (14.0)	28 (13.6)
Anxiety (Moderate/Severe)**	123 (36.0)	78 (38.0)
Low understanding of medical orientation**	108 (30.9)	65 (31.1)
ART regimen (with protease inhibitor)***	161 (46.0)	94 (45.0)
Change in ART***	39 (11.1)	13 (6.2)
Pill burden (> 7 pills a day)***	180 (51.4)	101 (48.3)
Use of other medication***	187 (53.4)	94 (45.0)
≥ 4 adverse reactions***	161 (46.0)	77 (36.8)
Time between 1 st office visit and 1 st ART prescription (> 90 days)**	112 (32.0)	63 (30.1)
Clinical category B or C (CDC 1993)**	166 (49.8)	107 (53.0)
CD4+ T-lymphocytes count (< 200 cells/mm ³)**	132 (52.4)	96 (59.3)

* US dollar; ** Baseline data; *** Follow-up data

HIV-seropositive status, reported embarrassment during clinic visits, had a higher CD4+ T-lymphocyte count (> 200 cells/mm³), presented moderate to severe symptoms of anxiety, had ≥ 4 adverse reactions and had experienced a longer time period between the first HIV medical visit and the first antiretroviral prescription (> 3 months). Borderline significance was observed for difficulty of access to services,

Table 2 - Number and distribution of the degree of difficulties and reasons reported by patients in the first and third visits. ATAR Project, 2001-2003

Degree of Difficulty (Reasons reported)	First visit n=350	Third visit n=209
	n (%)	n (%)
Medium to Very High	180 (51.4) *	78 (37.3) *
Adverse Reactions (Nausea, Diarrhea, Nightmares, Feeling bad with medication)	60 (33.3) **	15 (19.2) **
Scheduling (I forget to take the drugs, The regimen is complex)	43 (23.9) **	29 (37.2) **
Emotional status (I'm feeling too depressed, I feel hopeless)	17 (9.4) **	9 (11.5) **
Social Interactions (It's difficult to take the drugs at work, I can't go out in the weekends)	13 (7.2) **	6 (7.7) **
Pill burden (Too many pills, So many pills make me anxious)	12 (6.7) **	8 (10.3) **
Health care service (I don't understand the treatment, I live far from the clinic)	11 (6.1) **	3 (3.8) **
Organoleptic properties of drugs (Bad taste, The pills are too big, they are difficult to swallow)	10 (5.6) **	3 (3.8) **
Adaptation (It's hard to get used to it)	9 (5.0) **	3 (3.8) **
Dietary interference (Sometimes I forget fasting, I have to take with meals)	3 (1.7) **	2 (2.6) **
Reason not reported	2 (1.1) **	-
Low to Very Low	170 (48.6) *	131 (62.7) *
Scheduling (Easy schedule, Only two times a day)	51 (30.0) **	45 (34.4) **
Adaptation (The regimen is easy to adapt)	40 (23.5) **	42 (32.1) **
Health care service (Medicines are free, I was well oriented)	23 (13.5) **	11 (8.4) **
Adverse Reactions (I don't feel anything, No adverse reactions)	19 (11.2) **	19 (14.5) **
Emotional status (I'm feeling better, More hopeful)	16 (9.4) **	5 (3.8) **
Social Interactions (My family helps me, Don't need to hide)	8 (4.7) **	-
Pill burden (Few pills, Only two medicines)	4 (2.4) **	4 (3.1) **
Organoleptic properties of drugs (It's easy to swallow)	-	1 (0.8) **
Dietary interference (It doesn't need fasting)	2 (1.2) **	3 (2.3) **
Reason not reported	7 (4.1) **	1 (0.8) **

* Percent from total in each visit; ** Percent from each category (medium to very high and low to very low) in each visit

psychotherapy attendance and being clinically asymptomatic (Table 3). Fewer factors were statistically associated (p -value < 0.05) with difficulty with treatment in the third visit, including higher CD4+ T-lymphocyte counts (> 200 cells/mm³), ARV antiretroviral regimen with protease inhibitor, daily pill burden (≥ 7 pills), use of other medication, ≥ 4 adverse reactions and low understanding of medical orientation. It should be noted that women had more difficulties with treatment in the third visit, although this result is only of borderline significance ($p=0.068$).

Adjusted OR with 95% CI are shown in Table 4. Because women showed a statistically-independent borderline association during the third visit ($p=0.081$), we decided to retain this variable in the final model of each visit for comparison

purposes. HIV-seropositive status disclosure, ≥ 4 adverse reactions reported, presence of symptoms of anxiety and absence of psychotherapy were independently associated with the degree of difficulty in the first visit while CDC clinical category A, pill burden (> 7 pills), use of other medication, ≥ 4 adverse reactions reported and low understanding of one's medical orientation were associated with difficulties during the third visit, in addition to gender.

DISCUSSION

By using several simple questions, we were able to assess patient perception of difficulties related to initial ART. We chose to compare visits at two separate, cross-sectional

Table 3 - Univariate analysis of the degree of difficulty according to selected characteristics (p-value < .020) in the first and third visits, ATAR Project, 2001-2003

Characteristics	First Visit (n=350)				Third Visit (n=209)			
	Total	n (%) [*]	OR (95% CI)	p-value	Total n	n (%) [*]	OR (95% CI)	p-value
Gender								
<i>Male</i>	195	101 (51.8)	1.00		124	40 (32.3)	1.00	
<i>Female</i>	155	79 (51.0)	0.97 (0.63 – 1.48)	0.878	85	38 (44.7)	1.70 (0.96 – 3.00)	0.068
HIV-seropositive status disclosure^{**}								
<i>No</i>	47	18 (38.3)	1.00		25	7 (28.0)	1.00	
<i>Yes</i>	297	160 (53.9)	1.88 (1.00 – 3.54)	0.047	181	71 (39.2)	1.66 (0.66 – 4.18)	0.278
Difficulty of access to health service^{**}								
<i>No</i>	309	155 (50.2)	1.00		183	72 (39.3)	1.00	
<i>Yes</i>	33	22 (66.7)	1.99 (0.93 – 4.24)	0.071	22	6 (27.3)	0.58 (0.22 – 1.55)	0.271
Embarrassment during clinic visits^{**}								
<i>No</i>	295	146 (49.5)	1.00		178	65 (36.5)	1.00	
<i>Yes</i>	48	32 (66.7)	2.04 (1.07 – 3.88)	0.027	28	13 (46.4)	1.51 (0.68 – 3.36)	0.315
Attendance to psychotherapy^{**}								
<i>Yes</i>	35	13 (37.1)	1.00		22	6 (27.3)	1.00	
<i>No</i>	308	165 (53.6)	1.95 (0.95 – 4.02)	0.065	184	72 (39.1)	1.71 (0.64 – 4.59)	0.279
Clinical category (CDC 1993)^{**}								
<i>B or C</i>	166	79 (47.6)	1.00		107	36 (33.6)	1.00	
<i>A</i>	167	95 (56.9)	1.45 (0.94 – 2.24)	0.089	95	41 (43.2)	1.50 (0.85 – 2.65)	0.165
CD4+ T-lymphocytes count^{**}								
<i>≤ 200/mm³</i>	132	60 (45.5)	1.00		96	34 (35.4)	1.00	
<i>> 200/mm³</i>	120	73 (60.8)	1.78 (1.14 – 2.80)	0.011	66	30 (45.5)	1.65 (0.91 – 2.99)	0.010
<i>Unknown</i>	98	47 (48.0)	0.82 (0.52 – 1.32)	0.206	47	14 (29.8)	0.64 (0.32 – 1.31)	0.206
Degree of anxiety^{**}								
<i>None / Mild</i>	209	101 (46.1)	1.00		127	50 (39.4)	1.00	
<i>Moderate / Severe</i>	123	75 (61.0)	1.83 (1.17 – 2.86)	0.008	78	28 (35.9)	0.86 (0.48 – 1.55)	0.619
Anti-retroviral therapy^{***}								
<i>Without protease inhibitor</i>	189	93 (49.2)	1.00		115	33 (28.7)	1.00	
<i>With protease inhibitor</i>	161	87 (54.0)	1.21 (0.80 – 1.85)	0.367	94	45 (47.9)	2.28 (1.29 – 4.04)	0.004
Pill burden^{***}								
<i>≤ 7 pills</i>	170	82 (42.8)	1.00		108	30 (27.8)	1.00	
<i>> 7 pills</i>	180	98 (54.4)	1.28 (0.84 – 1.95)	0.245	101	48 (47.5)	2.36 (1.33 – 4.18)	0.003
Use of other medication^{***}								
<i>No</i>	162	83 (51.2)	1.00		115	36 (31.3)	1.00	
<i>Yes</i>	187	96 (51.3)	1.00 (0.66 – 1.53)	0.985	94	42 (44.7)	1.77 (1.01 – 3.12)	0.047
Report of adverse reactions to ART^{***}								
<i>< 4</i>	189	81 (42.9)	1.00		132	42 (31.8)	1.00	0.031
<i>≥ 4</i>	161	99 (61.5)	2.13 (1.39 – 3.27)	0.001	77	36 (46.8)	1.88 (1.01 – 3.36)	
Time between 1st office visit and 1st prescription of ART								
<i>≤ 3 months</i>	238	111 (46.6)	1.00		146	52 (35.6)	1.00	
<i>> 3 months</i>	112	69 (61.6)	1.84 (1.16 – 2.90)	0.009	63	26 (41.3)	1.27 (0.69 – 2.33)	0.438
Degree of understanding of medical orientation^{**}								
<i>High</i>	242	124 (51.2)	1.00		144	46 (31.9)	1.00	
<i>Low</i>	108	56 (51.9)	1.03 (0.65 – 1.61)	0.916	65	32 (49.2)	2.07 (1.14 – 3.76)	0.017

*Number and proportion of medium to high degree of difficulty in each category; **Baseline data; ***Follow-up data

Table 4 - Final multivariate analysis of the degree of difficulty in the first and third visits, ATAR Project, 2001-2003

Characteristics	OR (95% CI)	p-value
First Visit (n=350)*		
Gender (female)	0.91 (0.57 – 1.45)	0.691
HIV-seropositive status disclosure	2.00 (1.01 – 3.97)	0.046
No psychotherapy	2.20 (0.99 – 4.91)	0.053
CD4+ T-lymphocytes count(> 200/mm ³)*	2.07 (1.21 – 3.53)	0.007
≥ 4 adverse reactions	1.82 (1.14 – 2.90)	0.012
Moderate or severe anxiety	1.69 (1.02 – 2.80)	0.040
Third Visit (n=209)**		
Gender (female)	1.79 (0.93 – 3.42)	0.081
Clinical Category “A” (CDC 1993)	2.17 (1.12 – 4.20)	0.021
Pill burden (> 7 pills)	3.06 (1.60 – 5.86)	<0.001
Use of other medication	2.29 (1.19 – 4.38)	0.013
> 4 adverse reactions	1.81 (0.94 – 3.46)	0.074
Low understanding of medical orientation	2.27 (1.16 – 4.46)	0.017

* Hosmer-Lemeshow test: $\chi^2=6.965$ (degrees of freedom=8); p-value=0,540;

** Hosmer-Lemeshow test: $\chi^2=6.655$ (degrees of freedom=7); p-value=0,466

time points due to power considerations, despite the known limitation of cross-sectional designs with regard to causal inferences. However, we should emphasize that no difference was observed with regard to non-participation rates and most variables were similarly distributed between the two periods. In addition, patients at these centers represented approximately 90% of all reported AIDS cases during the study period for the region.

Notably, a high proportion of patients indicated a high degree of difficulty in the beginning of treatment (51.4%). Health care-related variables seem to have played a more important role in the first visit, while treatment and clinical characteristics were more prominent in the third visit. Although most sociodemographic variables were not statistically associated with our outcome of interest, women tended to report more difficulties, but only for the third visit, and this with borderline significance. This is corroborated by other data indicating that women may have higher rates of non-adherence²¹ or a poorer quality of life.²² Because of the need to cope with their partners' and/or children's treatment, women often fail to adhere to their own treatment, which may partially explain the finding from the third visit.²³

Factors related to health care providers are crucial for patients initiating ART therapy, including compliance to regular clinic visits, counseling, availability of support services and a multidisciplinary approach. A complete understanding of the complexity of the regimen, side effects and scheduling, among other concerns, may help patients deal with their medication with less difficulty. In addition, earlier access to care and counseling before actual ART may help prepare pa-

tients for long-term treatment effects and reinforce the need for high adherence. As shown, patients with a longer time between their initial medical visit and their antiretroviral prescription and those who reported embarrassment were more likely to have increased difficulties with the treatment in the first visit, although these results did not remain in the final statistical model. Factors such as irregular medical visits, discontinuation of their clinical follow-up²⁴ and poor health professional-patient relationships^{25,26} may indirectly explain such findings. In addition, particularly related are the lack of psychotherapy and the presence of moderate-to-severe symptoms of anxiety, which were also associated with increased difficulty in the first visit. This may clearly indicate the lack of adequate psychiatric counseling by trained professionals in these services before treatment started, as shown in other studies²⁷.

Clinical- and treatment-related factors were found to be barriers for good adherence. Although adverse reactions remained statistically significant in both visits, they were more common in the first visit and indicated a stronger early effect of treatment. They were also more commonly cited as the main reason for difficulty with treatment in the first relative to the third visit, at rates of 33.3% and 19.2%, respectively. This is consistent with the literature, which indicates that adverse effects are related to a decrease in the quality of life and low adherence among HIV-treated patients.^{21,28-30} However, ART is a dynamic phenomenon, which changes over time, as patients tend to adapt their daily routine to regimen scheduling and more readily learn how to identify and deal with side effects.³¹ As shown, better scheduling and easier adaptation were the most common reasons reported by those patients with low to very low difficulty in the third visit (34.4% and 32.1%, respectively). However, pill burden, the inclusion of regimens with protease inhibitor and the additional use of other medications over time are factors which also tend to create more difficulties. Additionally, it should be noted that poor understanding of medical orientation remained a predictor of difficulties only for the third visit. This may indicate that, even if adequately counseled when beginning treatment, long-lasting and sustained good levels of information may not be feasible if routine counseling and reminders by health professionals are not continuously received by patients. Finally, the association of a higher CD4+ cell count and the asymptomatic patient designation (CDC classification A) with increased difficulties may reflect a lower perception of these patients with regard to the need for treatment, and thus a lower threshold for dealing with the daily burden of ART regimens.

Findings from these analyses suggest the need for early assessment of factors associated with increased difficulties and therefore the need to identify patients who are at a great-

er risk of lower adherence before starting treatment. Health care professionals and AIDS referral services must develop focused interventions to address modifiable factors such

as compliance with medical visits, counseling, improved physician-patient relationships and better ARV orientation to achieve immediate and sustainable adherence.

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