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Impact of Adherence to Antiretroviral Therapy in HIV-1–Infected Patients at a University Public Service in Brazil

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ABSTRACT

The objective of this study was to assess if a simple evaluation, adherence to antiretroviral therapy, would correlate to clinical and laboratory outcomes. We followed an open cohort of patients from a public teaching hospital AIDS outpatient clinic. Patients were categorized according to adherence as: regular (Reg), optimal, all doses all days, tolerating only irregular timing (±2 hours) of intake; quasi-regular (qReg), those missing up to four doses or 1 full day during a month; irregular (Irreg), all other irregular regimens, and ignored (Ign), those without information. The results from a simple questionnaire were compared to $CD4^+$ cell counts and human immunodeficiency virus type 1 (HIV-1) RNA plasma viremia. One hundred eighty-two HIV-1–infected patients (126 males, 69%; 56 females, 31%) were analyzed. Information on adherence was available for 168 (90%). Reg adherence was reported by 75 (41%) patients, qReg adherence by 35 (19%), and Irreg by 53 (29%) of patients. The main reasons for nonadherence were forgetfulness, intolerance, use of alcohol, and misunderstanding of prescription. A significant increase of $CD4^+$ T-cell counts and absolute gain were only observed among Reg and qReg users ($p < 0.001$). The median viral RNA load $\log_{10}$ decreases were −1.68, −1.45, −0.9 log, respectively, for Reg, qReg, and Irreg patients ($p = 0.043$, Kruskal-Wallis). Development of and death from AIDS occurred almost exclusively among those with Ign or Irreg adherence. Previous use of antiretroviral therapy may have had an impact in treatment response. Individuals who were treatment-naive were more likely to be Reg users (41%). Although more refined methods to assess adherence should be implemented when available, the inability to do so should not prevent simple, albeit subjective measurements that also correlate with favorable outcome. Mechanisms to improve adherence should be considered an integral part of antiretroviral therapy.

INTRODUCTION

CLINICAL TRIALS have unquestionably supported the benefit of combined antiretroviral therapy (ART) for human immunodeficiency virus type 1 (HIV-1)–infected patients. In fact, ART is now indicated for all patients with symptoms and/or laboratory markers

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suggestive of immune dysfunction such as high viremia and low $CD4^+$ T-lymphocyte counts, but the threshold for treatment indication varies among recommendations.[1–3]

In Brazil the law has guaranteed free public access to ART since the early 1990s, and to highly active antiretroviral therapy (HAART) since 1996. Today, more than 100,000 patients are currently using some ART.[4] However, in many instances, these assets are implemented in poor health care settings. This may favor inadequate combinations and irregular use of these medications, an appropriate environment for virologic failure and the development of resistance. Although viral resistance, drug pharmacokinetics, and cellular metabolism are fundamental to drug efficacy, adherence to treatment regimens is one of the cornerstones of adequate ART.

Adherence is a problem in many clinical settings[5,6] and anecdotal information suggests that it is a prevalent problem. Little information is available concerning adherence in Brazil,[7–9] and there is no assessment of the impact on therapy outcome in Brazil. Moreover, nonobjective measurements, and simple assessments used in the past are often seen as highly unreliable, and thus not pursued.

To address this issue, we analyzed the correlation of a simple, subjective assessment of adherence to clinical and laboratory measurement of HIV-1 outcome.

METHODS

This prospective study was developed in an open cohort from an acquired immune deficiency syndrome (AIDS) outpatient clinic in a public teaching hospital, Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, Brazil, and included HIV-1–infected individuals who were using or had initiating the use of ART. Patients were followed, with visits of 3–4 times per year. Patients used available local ward facilities whenever necessary. Patients who entered the study were either ART-naive or had previous, unmonitored regimens. $CD4^+$ cell counts were done by Coulter flow cytometry, and HIV-1 RNA plasma viremia was quantified by Amplicor (Roche Diagnostic, USA), Nasba, and more recently Nuclisens (Organon Teknika, Holland) following the manufacturer's instructions. The detection level of the least sensitive plasma viremia method (500 copies per milliliter) was used as the limit of detection. All treatments, including double nucleoside reverse transcriptase inhibitors (NRTIs), 2 NRTIs, and hard-capsule saquinavir or HAART (2 NRTIs plus either nelfinavir, indinavir, or ritonavir) combinations were analyzed. HIV-1 transmission major risk factor, social-demographic characteristics, clinical status, and laboratory tests were obtained from interviews with patients during visits and from medical records. Adherence to ART during the last 30 days was determined by a simple questionnaire with four closed questions and one open question, which allowed a subjective evaluation of ART adherence and the reasons for suboptimal adherence. Patients were categorized according to adherence as regular (Reg), optimal, all doses all days; tolerating only irregular timing ($\pm$2 hours) of intake; quasi-regular (qReg), those missing up to 4 doses or 1 full day during a month; irregular (Irreg.), all other irregular regimens; and ignored (Ign), those without any information. The lower adherence category was assumed whenever divergent results where obtained.

Procedures

Patients seen at the clinic weere approached and the study was explained to them. Patients were asked to participate but only those who gave written informed consent were included. The Medical Ethical Committee of the HCFMUSP approved the protocol.

Analysis

The database and preliminary analysis were carried out using the EpiInfo 6.04 and Prisma 3.0 programs. Descriptive analysis was followed by univariate analysis using STATA 6.0. To examine associations among gender, transmission route, clinical status, education, and previous ART use a Kruskal-Wallis test was used, Yates corrected χ^2 tests were used to compare proportions, and paired t test was used to test variation in $CD4^+$ T-cell counts and viral

load from inclusion to follow-up assessment. Analysis of variance (ANOVA) was used for analysis of adherence between groups. Multiple regression analysis was used to evaluate whether any association could be caused by a confounding fact.

RESULTS

One hundred eighty-two HIV-1–infected patients (126 males, 69%; 56 females, 31%) who were attending the clinic had initiated or changed to a new, monitored antiretroviral regimen that lasted for a median of 12 months. Patients were followed for a median of 50 months. For 168 (90%) patients, information on adherence was available. Patients' baseline characteristics are presented in Table 1. Regular adherence (Reg) to a prescribed regimen was reported by 75 (41%) patients; suboptimal adherence (qReg) by 35 (19%) patients; and irregular adherence (Irreg) by 53 (29%) patients. No information (Ign) was available for 19 (10%) patients. Therapy was modified according to clinical decisions based on clinical and laboratorial data.

The main reasons for irregularity in ART, i.e., forgetfulness and intolerance, were reported by 48% and 22% patients, respectively. Patients cited various other reasons for nonadherence including stopping ART to consume alcohol, misunderstanding of prescription, difficulty in following recommendations at the workplace, and lack of money for transportation to obtain medication. Seven percent of patients stated they did not believe in the efficacy of ART.

We observed no association of adherence with intravenous drug users (IDU). When women who had sexual partnerships with IDUs were analyzed separately from other heterosexual women, no differences among Reg and Irreg were observed (data not shown). This suggests that adherence is not directly associated to risk factors or vulnerability groups (Table 1). The median CD4, for IDU showed one of the highest increments after ART as compared to other HIV risk categories (median

Table 1. Demographic Characteristics of the HIV-1–Infected Patients in an Outpatient Clinic at a University Hospital in São Paulo City

		Adherence to ART			
		Reg	*Q reg*	*Irreg*	*IGN*
Mean age (range)		37 (22–67)	38 (25–58)	37 (21–67)	40 (18–53)
Gender	Female	26 (35%)	7 (20%)	15 (28%)	8 (42%)
	Male	49 (65%)	28 (80%)	38 (72%)	11 (58%)
Risk factor	IDU	9 (12%)	4 (11%)	4 (8%)	1 (1%)
	MSM	28 (37%)	12 (34%)	23 (43%)	7 (37%)
	PIDU	4 (5%)	0 (0%)	3 (6%)	2 (11%)
	WSM	17 (23%)	7 (20%)	9 (17%)	6 (32%)
	MSW	6 (8%)	8 (23%)	8 (15%)	1 (1%)
	Risk ign	11 (15%)	4 (11%)	6 (11%)	2 (1%)
Income	<$500	7/15 (47%)	3/12 (25%)	3/7 (43%)	2/3 (67%)
	>$500	8/15 (53%)	9/12 (75%)	4/7 (57%)	1/3 (33%)
Education (HS)		13/20 (65%)	9/14 (64%)	7/13 (54%)	2/3 (67%)
% AIDS baseline		22 (29%)	11 (33%)	14 (26%)	7 (37%)
$CD4^+$	At entry	338 (6–1,141)	335 (12–1,024)	340 (9–1,365)	330 (6–1457)
T-cell count	Pretreatment	270 (6–892)	248 (23–586)	208 (9–836)	190 (6–738)
RNA viral load	Pretreatment	4.88 (3–6)	4.77 (3.2–6.0)	4.98 (2–6.0)	5.08 (3.4–6.3)
ART	Double	25 (33%)	10 (29%)	22 (42%)	4 (21%)
	Triple/HAART	50/33 (67%)	25/15 (71%)	33/19 (58%)	15/7 (79%)
Naïve		31 (41%)	9 (26%)	14 (26%)	5 (26%)
Total		75	35	53	19

Reg, regular adherence; Q-reg, quasi-regular adherence; Irreg, irregular adherance; Ign, no information (see Materials and Methods for details); IDU, intravenous drug user; MSM, men who have sex with men; MSW, men who have sex with women; WSM; women who have sex with men; HS, high school level education; Income, total of the family income; ART, antiretroviral therapy; Naïve, absence of monotherapy before double or triple ART; HAART, highly active antiretroviral therapy.

CD4 gain for IDU, 223; for women with IDU partner 268; for men with only heterosexual exposure [MSW], 141; and among men who have sex with men [MSM], 82). The CD4 at entry was lower for IDU (339) and MSW (340) as compared to MSM (397), and to all women (452). Moreover, the CD4 pretreatment that was used to calculate the CD4 gain was also higher among all females (332) and lower among IDU (209) (mostly males) and the other male groups (MSM, 203; MSW, 230).

When analyzing laboratory marker modifications, a significant increase in $CD4^+$ T-cell counts during the first treatment was observed only among Reg and qReg users ($p < 0.001$) but not among Irreg users ($p > 0.5$). $CD4^+$ T-cell gains were also superior among Reg and qReg users when only patients using HAART were analyzed (Table 2). Similarly, the percentage of undetectable viremia (viral load <500 copies per milliliter) was higher in the Reg or qReg users as compared to the other groups (Table 2) and significantly higher in the former groups as compared to the latter ($p < 0.003$). No differences among qReg and Reg were observed ($p > 0.9$). When frequency of undetectable viremia was analyzed only among HAART users, albeit higher in Reg or gReg groups, the difference was nonsignificant (Table 2).

Although only a few clinical events occurred during the monitored treatment, the impact of adherence on long-term outcome, was also analyzed at the last visit at the service. Clinical and laboratory outcome were significantly worse in Irreg or Ign adherence patients as compared to those with either regular or qR adherence. At the last visit, the median gain in $CD4^+$ T-cell count was +122, +128, and +54 cells/mm^3 for Reg, qR, and Irreg, respectively ($p = 0.02$, Kruskal-Wallis test). Among HAART users the trend was similar (Table 3). Median gain was also higher among Reg and qReg users. The median viral RNA load $\log_{10}$ decreases were −1.68, −1.45, −0.9 log, respectively, for Reg, qR, and Irreg patients ($p = 0.043$, Kruskal-Wallis test).

AIDS development or death 60 days after initiation of treatment was significantly more frequent among Irreg and Ign adherents as compared to those with Reg or qReg therapy adherence (odds ratio [OR] 6.6, $1.3 < OR < 65$, $p < 0.016$). Regular users had a significantly lower number of clinical end points, AIDS or death, than did irregular ART users ($p < 0.029$) or those with ignored adherence ($p < 0.0011$).

Patients tended to improve treatment adherence with subsequent regimens. Forty-two percent of Irreg adherences became Reg or qR on subsequent ART regimens, while only 13% (Reg) and 22% (qReg) adherents becoming Irreg on introduction of a new regimen. As expected, a subsequent regimen introduced because of intolerance or failure of monitored regimen was more frequent among Irreg (77% of patients) then in Reg or qReg patients (53% and 54%, respectively).

The univariate analysis did not reveal any association among different variables such as gender, risk of transmission, clinical outcome, previous ART use, education level, and adherence.

Table 2. Laboratory Outcome by Adherence Categories During Monitored Treatment Regimen

	Adherence to ART			
Post treatment	*Reg*	*Q-reg*	*Irreg*	*IGN*
$CD4^+$ treatment	396 (30–1340)	288 (39–769)	215 (9–938)	229 (31–693)
Median CD4 gain (cells/mo)	79 (6.2)	102 (5.4)	3.5 (0.3)	0 (0)
Median CD4 gain (cells/mo) on HAART	116 (6.6)	125 (6.3)	55 (3.6)	51 (4)
Undetectable viremia (%)	105/220 (48%)	59/121 (49%)	24/90 (27%)	6/33 (18%)
Undetectable viremia (%) on HAART	62/107 (58%)	36/62 (58%)	20/42 (48%)	2/9 (22%)

Reg, regular adherence; Q-reg, quasi-regular adherence; Irreg, irregular adherance; Ign, no information; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy.

TABLE 3. CLINICAL AND LABORATORY OUTCOME BY ADHERENCE AT LAST FOLLOW-UP VISIT

	Adherence to ART			
Outcome	*Reg*	*Q reg*	*Irreg*	*IGN*
Asymptomatic	64 (85.3%)	31 (88.6%)	34 (64.2%)	11 (58%)
AIDS events	0	1	2	2
Death	0	1	2	2
Median $CD4^+$ T-cell count at last visit	437 (14–1340)	396 (2–871)	287 (2–938)	218 (3–700)
Median CD4 gain (cells/mo)	122 (4.8)	128 (4.4)	54 (2.2)	60 (2.2)
Median CD4 gain (cells/mo) among HAART users	112 (5.4)	111 (4.2)	69 (3.0)	149 (7.7)
Median viremia at last visit	3.20 (1.6–5.94)	3.32 (1.6–5.7)	4.08 (1.6–6.18)	4.15 (1.6–6.4)
Undetectable viremia (%)	28/73 (38%)	15/33 (46%)	12/50 (25%)	4/17 (24%)
Median viremia at last visit among HAART users	2.00 (1.6–5.61)	2.03 (1.6–5.49)	3.59 (1.6–6.18)	4 (1.6–4.9)
Undetectable viremia (%) among HAART users	17/31 (55%)	8/14 (57%)	6/18 (33%)	3/7 (43%)

Reg, regular adherence; Q-reg, quasi-regular adherence; Irreg, irregular adherance; Ign, no information; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy.

DISCUSSION

Fewer than half of the HIV-1–infected patients admitted to maintaining strict adherence (Reg) to prescribed ART in the outpatient clinic of a public teaching Hospital in Sao Paulo, Brazil. Adherence was associated with improvement in $CD4^+$ T-cell counts and frequency of undetectable viremia. Including those switching to subsequent regimens, the long-term decrease in plasma viremia was significantly improved among patients with better adherence to their first monitored antiretroviral regimen. Also, AIDS-defining conditions or death 2 or more months after the introduction of ART were more likely to occur among Irreg ART users. These findings are in accordance with studies conducted elsewhere.[6,10] Overall, clinical outcome was superior among self-admitted Reg or qReg users, with both development and death of AIDS occurring almost exclusively among those with Ign or Irreg adherence.

The expected association of irregular adherence to ART with IDU was not observed. Although this could have been because of a lower accuracy of reporting among patients in other HIV ??? groups that our simple assessment of adherence would not be able to detect, both laboratory outcome of IDU (better $CD4^+$ cell gain after treatment and similar clinical outcome (data not shown) do not support that. The small sample size does not allow us to address this issue directly, but provides preliminary information, already suggested by others,[7] that adherence is multifactorial and not directly associated with any specific risk factors or vulnerability groups.

Previous use of ART has an impact on treatment response. Individuals who were treatment-naive were more likely to be Reg users (41%) and this may have contributed to the better outcome observed in this group. Surprisingly, previous use of medication did not ensure adequate usage of a new monitored regimen, *per se* but a limited improvement of adherence to subsequent ART regimens was observed. One possibility is that the intervention during monitored therapy, albeit limited and punctual, had a positive impact on improving adherence overall. Plasma viremia and CD4 count determinations during monitored therapy may have also contributed to a patient's awareness of possible regimen failure, motivating them to improve their adherence. This is a multifactorial issue that could not be addressed in this study. Patients in the Irreg and Ign categories tended to initiate treatment later in the course of their illness (as suggested by their lower CD4 and higher viremia pre-

treatment values), and this might also have an impact on outcome. In addition, the type of treatment prescribed, constitutes an important aspect of ART. Use of HAART, as expected was associated with a better clinical and laboratory outcome. Even then, CD4 gain and viremia control had a better evolution in those acknowledging strict adherence. The small sample size in some subgroups might have an impact decreasing the significance of some analysis among HAART users.

The use of two reverse transcriptase inhibitors therapy, recommended at the time of the study Brazilian government guidelines, was frequent among irregular users suggesting that even simpler regimens, if prescribed without adherence reinforcement, may lead to low adherence. However, this might have had an impact on the efficacy in this group, because these regimens are less active than HAART regimens. Moreover, it may be that physicians could prescribe double therapy to patients who would be less likely to be adherent to more complex regimens, introducing a bias in the analysis. We were not able to address this issue. Nevertheless, the data support the idea that a simpler regimen (double NRTIs) *per se* does not necessarily mean better adherence to ART. This observation taken together with the information available[1,2] and the findings described above suggest that the use of these regimens should be reevaluated.

Several reasons for nonadherence were reported by patients. Forgetfulness and intolerance were the most frequent. Similar results have been obtained in studies from more developed countries.[11] Some problems were more typical of developing countries, such as difficulty in transportation to the hospital. This situation could be improved by providing transportation tickets, a policy already being implemented. Some of the patients (7%) simply did not believe in the efficacy of ART, and some reported problems in taking medication at the workplace, lack of appropriate orientation, and not taking their medication in order to drink alcohol as additional causes. It is worth noting that apart from intolerance because of side effects, all other causes could and should be circumvented by adequate social and psychosocial support and other measures that improve the patient's awareness of the need for adherence. These findings reinforce the concept that regular adherence to ART is part of an overall commitment to therapy and supports the concept that improving disease understanding may be a key issue in therapy success.

We must point out that these data about adherence were subjective and reflect patients' perceptions of their adherence. Although phrased as simple questions that could be understood by most of our patients, this study surely included responses that were more related to what patients wanted to transmit, or how they wanted to be seen by health providers, rather than to actual adherence. In some cases, poor adherence may indicate the existence of a factor common to irregular intake and worse response to treatment, rather than a causal association with outcome. Even if this is the case, determining and improving adherence constitutes an important aspect of treatment efficacy, and the lack of sophisticated objective measurements should not deter services for assessment or interfere with adherence.

Preparing patients for the rigors of adherence before initiating treatment includes an investment in a multidisciplinary team with an overall understanding of the disease and the way to combat it. This approach may be cost effective and may have a major impact on response to therapy in public services. This seems to be a neglected component in the antiretroviral therapy of HIV/AIDS.

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REFERENCES

1. BHIVA Guidelines Co-ordinating Committee. British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals. Lancet 1997;349:1086–1092.
2. Carpenter CCJ, Cooper DA, Fischl MA, et al. Anti-

retroviral therapy in adults. Updated recommendations of the International AIDS Society-USA Panel. JAMA 2000;283:381–390.
3. Ministério da Saúde/Programa Nacional de DST/AIDS. Infecção pelo HIV em adultos e adolescentes. Recomendações para a terapia anti-retroviral. Brasil, 1999.
4. AIDS: Boletim Epidemiológico. Ministério da Saúde/Programa Nacional de DST/AIDS 1999; Ano XII, N° 3.
5. Mehta S, Moore RD, Graham NMH. Potential factors affecting adherence with HIV therapy. AIDS 1999;11:1665–1670.
6. Markowitz M. Resistance, fitness, adherence, and potency: Mapping the paths to virologic failure [editorial]. JAMA 2000;283:250–251.
7. www.aids.gov.br/Estudo de Aderência em São Paulo.
8. Deeks S, Beatty G, Cohen PT, Grant R, Volberding P. Viral load and CD4+ T cell changes in patients failing potent protease inhibitor therapy [abstract]. Fifth Conference on Retroviruses and Opportunistic infections, Chicago, Illinois, February 1–5, 1998.
9. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. AIDS 1999;13:1099–1107.
10. Maher K, Klimas N, Fletcher MA, et al. Disease progression, adherence, and response to protease inhibitor therapy for HIV infection in an Urban Veterans Affairs Medical Center. J Acquir Immune Defic Syndr 1999;22:358–363.
11. Altice FL, Friedland GH. The era of adherence to HIV therapy. Ann Intern Med 1998;129:503–505.

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