Risk factors for non-compliance to treatment with highly effective antiretroviral therapy*

FATORES DE RISCO PARA A NÃO ADESÃO AO TRATAMENTO COM TERAPIA ANTIRETROVIRAL ALTAMENTE EFICAZ

FACTORES DE RIESGO PARA LA NO-ADHERENCIA AL TRATAMIENTO CON TERAPIA ANTI-RETROVIRAL ALTAMENTE EFICIENTE

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ABSTRACT

The purpose of the study was: to measure the prevalence of non-compliance to highly active antiretroviral therapy (HAART) by AIDS patients; to identify whether some of the factors listed in health literature were associated with non-compliance; to establish the predictive values of non-compliance to HAART-related factors. An analytic prevalence study (N=60) was performed, in which the three days prior to the interview were considered. Those classified as compliant were the patients who ingested 95% or over of the total amount of pills prescribed a day. Compliance appeared as 73.3%. The multivariate logistic regression analysis indicated that the black subjects presented 6.48 times higher risk for non-compliance. Those who did not present side effects showed 7.6 times higher risk, and a risk of 1.12 for each pill taken. The compliance observed in the study proved to be higher than in literature. The sociodemographic and cultural factors may interfere in the compliance with HAART.

KEY WORDS

Acquired immunodeficiency syndrome.
Antiretroviral therapy, highly active.
Treatment refusal.
Risk factors.

RESUMO

O estudo objetivou: mensurar a prevalência de não-adesão à terapia anti-retroviral altamente eficaz (HAART) em pacientes com AIDS; identificar se alguns fatores relacionados na literatura estavam associados com a não-adesão; estabelecer o valor preditivo dos fatores associados à não-adesão à HAART. Foi realizado um estudo analítico de prevalência (N=60). Foram considerados os três dias anteriores à entrevista e os pacientes classificados como aderentes quando ingeriam 95% ou mais do total de comprimidos prescritos por dia. A adesão foi de 73,3%. A análise de regressão logística multivariada indicou que indivíduos da raça negra apresentaram 6,48 vezes mais risco de não-adesão; aqueles que apresentaram ausência de efeito colateral tiveram um risco 7,6 vezes maior, e a cada comprimido ingerido o risco foi de 1,12. A adesão observada foi maior que a encontrada na literatura. Os fatores sociodemográficos e culturais podem interferir na adesão à HAART.

DESCRITORES

Síndrome de imunodeficiência adquirida.
Terapia anti-retroviral de alta atividade.
Recusa do paciente ao tratamento.
Fatores de risco.

RESUMEN

Objetivo del estudio: medir la prevalencia por falta de seguimiento al tratamiento anti-retroviral altamente eficaz (HAART) en pacientes con SIDA; identificar si algunos factores relacionados en la bibliografía se encuentran asociados con la falta de seguimiento; establecer el valor preditivo de los factores asociados con la falta de seguimiento al HAART. Para lo cual fue realizado un estudio analitico de prevalencia (N=60), considerándose los tres días anteriores a la entrevista, donde aquellos pacientes con ingesta del 95% o más del total de comprimidos prescritos por día eran clasificados como seguidores del tratamiento. El seguimiento fue de 73,3%. El análisis de regresion logística multi-variable mostró que sujetos de raza negra presentaron 6,48 veces mayor riesgo de no continuar con el tratamiento; aquellos individuos sin efectos colaterales tuvieron un riesgo 7,6 veces mayor, asimismo, cada comprimido ingerido produjo un riesgo de 1,12. El seguimiento observado fue mayor al encontrado en la bibliografía existente. Los factores socio-demográficos y culturales pueden influir en el seguimiento de la HAART.

DESCRIPTORES

Síndrome de inmunodeficiencia adquirida.
Terapia antirretroviral altamente activa.
Negativa del paciente al tratamiento.
Factores de riesgo.

INTRODUCTION

Since ancient times, when humans began to use medication, there has been concern regarding compliance to treatments. The importance of studying compliance to treatment of the Acquired Immunodeficiency Syndrome (AIDS) is mainly related to the severe consequences that this disease implies to the individuals, families and communities. Furthermore, the literature has shown that there is relation among viral resistance, therapeutic failure and low compliance[1].

Estimates show that 38.6 million (33.4 – 46 million) people worldwide were living with the Human Immunodeficiency Virus (HIV) in 2005; 4.1 million (3.4 – 6.2 million) individuals have recently been infected by the HIV and 2.8 million (2.4 – 3.3 million) lost their lives because of AIDS[2]. In Brazil, since the identification of the first case of AIDS, in 1980, until June 2005, 371.000 cases of the disease have been reported [3].

The treatment results with a Highly Active Antiretroviral Therapy (HAART) show the effectiveness of the therapy and, consequently, prove the importance that the public health service has to attain better results. Studies show that non-compliance occurs to a certain extent both in poor and rich countries. The average rate is 50%[4-5]. Researchers have strived to measure compliance by means of direct questions, indirect estimates, manual or electronic counting, biological markers or metabolite dosage.[6-7].

The literature has shown several predictive factors for non-compliance with HAART treatment that may be grouped in factors related to the following items: person in treatment; disease; healthcare service and social support[5,7-8].

These indicators show that some interventions are required so as compliance is constructed in a continuous process between professionals and clients. The latter should comply with treatment, understand and commit to perform the guidance dispensed[9].

It should be taken into account that in order to favor compliance to treatment among individuals with the HIV virus, it is fundamental that the health team knows the factors that may interfere in compliance. It is imperative that the clientele's specificities are recognized[10]. Thus, this study's goal was to identify the factors that could predict non-compliance in a more appropriate approach regarding individuals with HIV at a Day Bed Unit (DB) of a teaching hospital in the countryside of the State of São Paulo.

OBJECTIVES

This study had the purposes of measuring the prevalence of non-compliance to HAART in the sampling; identifying whether some factors related to individuals under treatment, healthcare service and social support were associated with non-compliance to HAART; and establishing the predictive value of factors associated with non-compliance to HAART.

METHOD

This was an analytical study of prevalence[11]. Data were collected in a private place at the referred BD Unit during the month of March in 2002.

The patients were contacted at the study place and informed about its objectives and the interview procedures. The interview data were registered in the questionnaire specifically created for the study.

The term of consent was thoroughly read with the patients so as to obtain authorization to proceed with the research. Their questions were answered and their privacy was ensured. The research was approved by the Ethics Committee in Research of the Institution (no. 326/2001).

The sample was composed by HIV-positive patients, registered at the BD Unit and participants of the bed-day program in the month of March 2002, with 79 patients.

In order to be included in the study, the individual had to be able to answer the questions directly and should be using antiretrovirals for at least a week, at home. The excluded individuals were inmates who were likely to have difficulty in following the therapeutics prescribed due to the penitentiary conditions. Furthermore, the presence of police officers at the moment of the interview could inhibit the answers to the questions. Patients who were living in support houses were also excluded. In these places, they were not responsible for their own drug treatment. The presence of a nursing professional to administer medication was compulsory.

To collect data, a form was elaborated with questions regarding variables to characterize the sampling, independent variables (factors associated with non-compliance) and dependent variables (non-compliance with the treatment).

Prior to beginning data collection, the complete instrument was pre-tested in order to check its adequacy, at the ambulatory of infectious diseases in the month of February/2002, with eight patients (four males and four females).

To identify the factors associated with non-compliance, a literature review was performed in the Medline and Lilacs databases, with the two uniterms: compliance and adherence. As AIDS is a recent disease, so are the studies on specific compliance to highly effective antiretroviral therapy. Hence, in this review, classic studies of chronic diseases in general were excluded. They have been used by the AIDS-related literature and dated back to the beginning of highly effective antiretroviral therapy.

> (...) that some interventions are required so as compliance is constructed in a continuous process between professionals and clients. The latter should comply with treatment...

Thus, based on the literature, the following factors (independent variables) were investigated: ethnicity; age; gender; sexual orientation; educational background, social isolation; absence of therapeutic advantage; need of periodic control; length of treatment (including the number of doses, number of medication, side effects and lifestyle changes); access to service; convenience to schedule consultations and procedures; social support; suitable information; feeling well; feeling bad; drug use; psychiatric disorder or syndrome; evaluation of the laboratorial results; disease gravity and perception of control over their own health[4-8,12-13].

Non-compliance was considered as a dependent variable, which was defined with the aid of the patients' reports that showed how many pills they had taken per day, in the past three days. The pill intake was verified. The individuals who reported taking less than 95% of the prescribed medication were considered non-compliant[8,12]. There are several methods to evaluate non-compliance and all of them contain important limitations. However, the direct questioning method has often been used so as not to overestimate compliance. When appropriately used, it turns out to be a good compliance indicator[13]. The self-report was the chosen method for this study. It is easily applied and incorporated to the Unit routine, with low operational cost.

The data were inserted in a databank by using the software EPI-INFO. For the statistical analysis, The SAS System software for Windows[14] was used.

To verify the association among the category variables and the dependent variable, the chi-square test was used, or Fisher's exact test, when indicated. The Mann-Whitney test was used to compare the continuous variables among the individuals who were compliant and non-compliant with the treatment.

Logistic regression analysis with a logit model and Stepwise criterion to select the most significant variables was used to analyze the variable influence over the profile of the compliant and non-compliant individuals. Initially, there were univariate analyses and afterwards, the most significant variables were selected by the multivariate analysis. The significance level for the statistical tests was 5%, that is, $p<0.05$.

RESULTS

In the month of March/2002, there were 79 patients registered in the BD Program. Of them, 17 (21.5%) did not meet the inclusion criteria and two (2.5%) interrupted the interview because they could not answer the questions. Therefore, 60 (76%) patients were interviewed.

The study showed a prevalence of 16 (26.7%) non-compliant patients and 44 (73.3%) compliant patients.

There was predominance of whites (39 or 65%) and the age group of 30-39 years (30 or 50%). The youngest was 21

years old and the oldest was 66 years old, and the average age was 37.49 (SD= 9.3), and median of 36.78.

The sampling showed a male/female ratio of 2:1 and 44 (73.3%) reported being homosexuals. Regarding educational background, the average was 7.25 (SD= 4.3) years of study, ranging from 0 to 20 years of study, with 6.5 years on average. No interviewed individual was a student.

Of the 60 patients who participated in this study, 26 (43.3%) identified some social isolation. In addition, 13 (50%) regarded this situation as a consequence of their becoming distant from their families, friends and/or partners.

The return to the BD happened monthly for 30 (50%) participants. Of the 19 (31.7%) patients who had some difficulty in accessing the Unit, eight mentioned the lack of transportation as the main hindrance. The remaining patients cited the fact that they depended on other people, financial difficulties and time expenditure. For 46 (76.7%) patients, the consultation scheduling was in accordance with their daily activities.

The time span of treatment was 4.22 years (SD= 3.46), with the shortest time span being 1 month and the longest 12.22 years. The median was 3.22 years. The time interval between HIV infection and the beginning of treatment was 1.37 years (SD= 3.54), varying from 0 to 15 years. The treatment was initiated at the moment of the diagnosis by 47 patients (78.3%).

For 27 (45%) patients, the frequency of the antiretroviral pills was twice a day. The prescribed therapeutic framework varied from five to 25 pills a day (average = 11.48; SD = 5.25; median = 11 pills).

Of the interviewed individuals, 45 (75%) were under prophylactic or therapeutic treatment associated with other diseases (tuberculosis, pneumocystosis, toxoplasmosis, cryptococcosis) and, besides antiretroviral medication, they had an average intake of six (SD= 3.8) pills a day, varying from one to 16 pills (median=5). When the antiretrovirals and the medication for other diseases were added, the average value obtained was 15.9 (SD = 6.9) pills a day, varying from a minimum of 5 to a maximum of 33 pills (median=16).

In the opinion of 48 (80%) interviewed individuals, there were improvements with the received treatment. Thirty-eight of them (63.3%) reported *not feeling side effects* after taking the antiretroviral pills. Fifty (83.3%) reported that, when they were feeling better, they did not discontinue the treatment. Likewise, 47 (78.3%) did not interrupt the treatment. Not even when they felt ill.

For 43 (71.7%) patients, there were some changes in the life routine in function of treatment and 46 (76.7%) did not see difficulty in carrying out the treatment.

Social support was present for 29 (48.3%) interviewed patients. It was characterized in this study as the presence of solidarity or collaboration from other people, financial

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support from official institutions or charities, and provision of food.

When questioned about the information provided to the healthcare team regarding disease, treatment, care required during social and sexual relationships, among others, 47 (78.3%) considered that they were enough to clarify aspects related to the disease, treatment and required care. For 13 (21.7%) patients, the information was partially sufficient.

It was found that in the past, 38 (63.3%) patients consumed alcohol and/or drugs (inhalatory and/or intravenous) and acknowledged dependency. Of them, 19 (50%) used only alcohol, 8 (21.1%) only drugs and 11 (29%), both. When questioned about the use of alcohol and drugs at the moment of the interview, 10 patients answered that they continued to use alcohol and/or drugs and acknowledged dependency.

It was verified that 34 (56.7%) improved their laboratorial results after the classification of the last values of viral load and CD4+. It is worth mentioning that, although 12 individuals had undetectable viral load, 51 (85%) were classified as C3, that is, they showed defining conditions of AIDS and CD4+ <200 T-lymphocytes/mL, according to the disease classification attributed by the Center for Disease Control (Centro de Controle de Doenças – CDC)[15].

The univariate analysis showed that the proportion of non-compliant individuals was higher among the blacks (p=0.012). The age of the compliant group was significantly lower (p=0.0476) when compared with the age of the non-compliant, although the p-value was near the 5% limit. The absence of side effects was associated with non-compliance (p=0.019) and the variable result of the total number of prescribed pills a day was seen to be significant (p=0.0402). Non-compliant individuals showed lower educational background than those who were compliant (p=0.0273). There

were associations between educational background that were equal or lower than six years and non-compliance (p=0.02).

The findings showed that the variables ethnicity (black), age (40 to 49 years), educational background (£ 6 years), side effects (absence) and the total number of prescribed pills were associated with non-compliance to treatment. Further comparisons were carried out, seeking to identify whether the ethnicity factor was associated with some socio-economic characteristics, namely family income, living conditions, occupation and type of work and educational background. There were only associations between black ethnicity and educational background lower or equal to six years (p=0.010).

Through univariate logistic regression analysis, there were associations between non-compliance and the variables: age (11.0 times more risks for the 40-49 year-olds), side effects (5.8 times more risk for absence of effects), ethnicity (5.0 times more risk for black ethnicity, educational background (4.3 times more risk for £6 year-olds). The number of pills prescribed a day variable was not significant when the results were analyzed separately (number of antiretroviral pills and others). However, by adding the total number of pills, the result showed a trend (p=0.0546) with 1.09 more risk for non-compliance.

Following the univaried analysis, a multivariate logistic regression analysis was performed, (Table 1) with *Stepwise* selection. The following variables were associated with non-compliance: ethnicity, side effects and total number of pills prescribed a day. The black ethnicity showed 6.48 more risk for non-compliance than whites or Asians; those who reported the absence of side effects had 7.6 more risk for non-compliance, and each pill increased the risk in 12% – that is, the risk was 1.12. It can also be stated that the risk was 3.2 (1.1 – 9.7) for every 10 pills.

Table 1 – Multivariate logistic regression analysis, with Stepwise, of factors associated with non-compliance – Campinas – 2002

Variable	Comparison level*	p	O.R.	TI 95% O.R.
Ethnicity	Black/White or Asian	0.0110	6.48	1.54 – 27.36
Absence of side effects	No/Yes	0.0229	7.60	1.32 – 43.63
Total number of prescribed pills a day	Each pill**	0.0397	1.12	1.01 – 1.26

Note: BD Unit (N=60)
OR ("Odds Ratio") = Odds ratio for non-compliance (44 compliant and 16 non-compliant). TI 95% OR = Trust Interval of 95% for the Odds Ratio.
* Comparison level/reference level ** Comparison level could not be determined

DISCUSSION

Non-compliance in this study was 26.7%. It is a result that is lower than what is shown in the literature[4-6]. This may have occurred due to several factors, among them: data collection was performed in a single interview, without client accompanying; the sampling was homogenous; there may have been the involvement of a multiprofessional team, with real understanding of their role in assisting the patient

to construct compliance on a daily basis, and, therefore, improve antiretroviral intake.

The multivariate logistic regression analysis, with Stepwise selection, demonstrated that only some variables maintained association with non-compliance: ethnicity, side effects and the total number of pills prescribed a day.

Black individuals showed 6.48 times more risk of non-compliance than white or Asian individuals.

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Researchers verified that the non-Caucasian patients were significantly more non-compliant than Caucasian patients[16]. In another study, the authors showed that there was a relative risk of 1.7 regarding non-white ethnicity [8]. A study on tuberculosis evidenced that no sociodemographic variable was consistent to measure non-compliance to treatment, except for complexion. However, there was no specification of the risk it represented[17].

The *absence of side effects* increased 7.6 times the risk for non-compliance. In contrast, other authors argue that compliance decreases as side effects increase[6-7].

The literature offers data that may explain such result. Two studies evidenced that HIV patients were more likely to bear the side effects than less severe chronic diseases such as hypertension or diabetes. Negative attitudes regarding medication and diseases may interfere in the patients' compliance. The perception of how treatment influences the disease outcomes would be associated with compliance[8,18].

A study carried out in Pelotas, RS, about compliance with tuberculosis treatment evidenced that the drug effects and treatment reactions involve equally important questions for compliance. The treatment and cure expectations, motivation to maintain health, personal advantages in complying with the therapeutic and other therapeutic benefits outline some behaviors[17]. The role of culture in popular disease conceptions should not be disregarded. It has been largely discussed, contrary to the positivist view. A popular conception of AIDS medications, the antiretrovirals, causing side effects, is likely to still exist. This reinforces the belief that in order to cure, they ought to show such effects. However, as the study was cross-sectional, it was not possible to evaluate whether the *absence of side effects* variable was antecedent or subsequent to non-compliance. That is, non-compliant individuals may have shown lower side effects because they either did not take the medication or as did not show these effects, they discontinued the treatment for considering it ineffective. Thus, longitudinal studies are recommended to clarify the association found.

Another component of the treatment complexity that showed significant results was the total number of pills prescribed a day. The results show that for each pill, the risk for non-compliance increased by 1.12 (12%) and it was 3.2 times every 10 pills. Researchers reported that non-compliance increases as the number of prescribed pills increases. Nevertheless, the risk was not evaluated in their works. There was direct association between low compliance and regime complexity (number of different medications) because they interfere in the daily routine of patients[19-20].

A research carried out in the city of Campinas, SP, with patients under antiretroviral treatment showed that the most frequent mistakes were related to the combined use of drugs. The drugs most associated with mistakes were Didadosina and Indinavir[19].

CONCLUSIONS AND CONCLUDING REMARKS

In the present study, ethnicity, side effects and total number of prescribed pills a day were associated with non-compliance.

In order to better understand the results found, it is imperative to reproduce this study with larger samples and different characteristics. The results indicate the need of performing longitudinal studies that can also evaluate sociocultural aspects, beliefs, etc. related to ethnicity and antiretroviral side effects.

During the interviews, the day of the week may interfere in the compliance evaluation because some patients would not take medication on the weekends. The difficult factor was the hours and the social commitments. They felt embarrassed to take medication in front of people with whom they maintained occasional contacts.

For a more precise compliance to AIDS treatment, the pertinent literature recommends that the 95% or more of the prescribed pills are taken. In the present study, this rate allowed to identify differences between the group of compliant and non-compliant individuals.

As a perspective of further researches, it is important to amplify the studies to other assistance sites, establishing conditions to evaluate the quality of the assistance provided, and also the relationships of the client with the multiprofessional team, so as to favor the establishment of strategies that improve patient compliance to HAART.

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