13º PROGRAMA EDUCAÇÃO PELA CIÊNCIA

FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

- RELATÓRIO DE EXECUÇÃO MATERIAL -

AVALIAÇÃO RETROSPECTIVA DA ADESÃO À TERAPÊUTICA ANTI-RETROVÍRICA

(REF. 2010041)

Integrado no estudo

ATAR-VIH – Adesão à Terapêutica AntiRetrovírica em indivíduos seropositivos para o VIH

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Non-adherence to antiretroviral treatment: a retrospective analysis, José Alexandre Sousa Freitas | Tutor: Paulo Nicola; Co-Tutor: Milene Fernandes | Preventive Medicine Institute, FML

Abstract

Maintaining a high adherence to antiretroviral therapy (ART) decreases the progression of HIV / AIDS infection, the likelihood of viral resistance and it contributes to lower health costs. With this study, we aimed to determine the prevalence of non-adherence to ART and to identify its associated factors. A retrospective cohort study was conducted with the analysis of a random sample of patients followed in the Hospital de Santa Maria (Lisbon, Portugal), that received ART therapy at least once between 2005 and 2008. The pharmacy records and the clinical record of each patient were consulted.

So far, data from 60 patients was analyzed, determining a non-adherence prevalence of 38%. No statistically significant differences were found between adherents and non-adherents, regarding age, sex, HIV transmission and time elapsed from diagnosis to ART beginning. With the conclusion of the study, we aim to determine non-adherence to ART in a more accurately way, and to test new hypothesis of related factors.

Background

After the recognition of the first cases of AIDS and the discovery of HIV, many efforts were made to better understand this disease, especially regarding its prevention and treatment. However, it was with the implementation of HAART, together with the prevention and treatment of opportunistic infections, that mortality and morbidity associated with HIV/AIDS infection started to decline. [1,2]

With an increased survival rate, HIV/AIDS infection came to be considered as a chronic illness and it began requiring more prolonged therapies. With this in mind, several countries – including Portugal – started to distribute free antiretroviral therapy (ART) to the patients according to medical prescription.[2] However, the success of this public health strategy depends on the therapeutic adherence. In fact, high levels of adherence are linked to better virological and immunological outcomes and a decrease in likelihood of viral resistance.[2,4,6] Additionally it reduces health expenditures.[3,5]

For the reasons described above, Recommendations for the Portuguese Treatment of HIV/AIDS in 2008 defined that "therapeutic adherence constitutes a critical factor in the success of therapeutic, conditioning from the beginning of it, the durability of the therapy efficacy." They also claim that it "[...] is absolutely essential that all efforts are made to optimize the motivation and adherence of the patient." [7]

It is then required a thorough and contextualized knowledge of ART adherence, to delineate and carry out interventions more effective in increasing adherence and consequently improving not only individual health but also public health.[8]

However, assessing adherence and any associated factors is complex, and a multi-method approach is recommended.[9,10] Among the available study methods, the review of dispense records of pharmacy is more viable than the electronic monitoring of medication or the measurement of serum drug levels. Additionally it tends to be more objective than the auto-report, showing an high correlation with ART failure.[5,11] However, in order to link factors to adherence to therapy, other method as the review of the clinical record has to be made.

With this study, we aimed to determine the prevalence of non-adherence to ART by analysing dispense records of pharmacy. Also, in a first analysis, we aimed to explore non-adherence associated factors.

Methods

Study design

Observational cohort study with a retrospective analysis of HIV-positive patients followed in the Infectious Diseases' Day Hospital (Director: Professor Francisco Antunes) of Hospital de Santa Maria (HSM, Lisbon, Portugal) and with at least two dispensations of ART in the period from January 1st, 2005 and December 31st, 2008.

Sample selection process

The list of all patients who had at least two dispensations of ART during the period from January 1st, 2005 to December 31th, 2008 was requested to HSM Pharmaceutical Services. From that list, they were sampled 320 subjects and those who fulfilled the following criteria were included in the study:

1. Started ART with at least 18 years-old;
2. Started ART in Hospital de Santa Maria (HSM);
3. Had at least 2 consultations between 01-01-2005 and 31-12-2009;
4. Had no participation on ART clinical trial;
5. At the beginning of ART, was not arrested or under a social institution care; and
6. Was not dependent of other person for taking their medication.

Of the included participants, those who fulfilled the criteria 4 to 6 after starting ART were censored. Note that, if the censor was made before 2005 or it just left a consultation between 2005 and 2009, the participant was excluded for not fulfilling criterion 3.

Data Collection

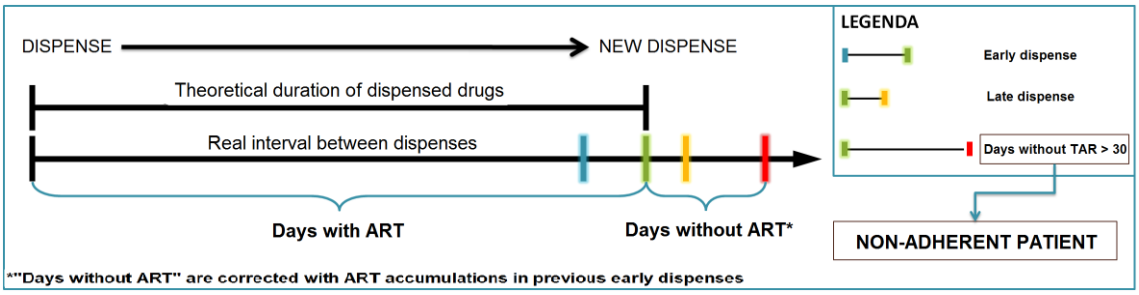
Dispense records of pharmacy and clinical records were consulted, for all patients included in the study. From pharmacy records, it was collected information on ART regimen, including the intervals between dispenses of ART. Clinical and socio-economic data was collected from clinical records, through the completion of a specific form. The first clinical apointment, the first

ART prescription, and every consultation between 2005 and 2009 were registered. All data was gathered in a central electronic database, with randomized individual numbering attributed to each patient.

Data analysis

From the pharmacy records, we determined the intervals between two consecutive dispenses (intervals between dispenses) of every patient. By knowing how many pills were given and the drug intake frequency, we assessed whether in each interval there were days in which the patient theoretically had no medication (days without ART). If the patient had an interval between dispenses that had more than 30 days without ART, it was considered as non-adherent.

Figure1. Explanatory scheme of the analysis of the intervals between dispenses



From this analysis we determined the prevalence of ART non-adherence and set up two groups: adherent *vs*. non-adherent subjects. After the validation of the database, we tested differences between the two groups regarding their socio-economic and clinical data. The following hypothesis (α <5%) were tested:

- Is there any age or gender difference between adherents and non-adherents?
- Is any infection route associated with non-adherence?
- Is time elapsed from diagnosis to the beginning of TAR associated with non-adherence?

Results

So far, 60 subjects were analyzed, with an average age of 32.7 ± 8.9 years (reaching a maximum of 59 years-old). From the participants, 38% were female, 32% were of Portuguese nationality and 18% were born in African countries. Information on nationality was not recorded in 45% of the clinical records consulted. As for race, 52% were Caucasian, 12% were black, and 2% were Asian. Again, for the remaining cases (34%), information was not found. The transmission of the HIV was EV drug-addiction in about one third of the cases, while 50% of the cases were related to sexual behaviours (33% heterosexual, 12% homosexual and 5% bisexual). Information was missing for 13% cases.

At the beginning of the study period (2005), HAART therapies were those most frequently prescribed (90%). From these, 43% were the association between two nucleoside reverse

transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitors (NNRTIs), followed by the association of two NRTIs with a protease inhibitor (PI), boosted or not with ritonavir.

From the 60 participants, 1791 intervals between dispenses were analyzed, of which 38% contained days without ART (11% with less than three days without ART, 21% with three to seven days, 31% with seven to thirty days and 28% with more than thirty days). Each participant had an average of 11.4 ± 8.9 intervals with days without ART.

A 38.3% of non-adherence was determined (patients with at least one interval with more than thirty days without ART). However, 5% of patients had days without ART in every interval and 92% of the patients had at least an interval with at least one day without ART, distributed according to Table 1.

Table1. Distribution of intervals in patients with at least one interval with days without TAR

Days without ART	< 3 days	3 - 7 days	8 - 30 days	> 30 days
Median (number of intervals)	3	2	2	0
Min – Max (number of intervals)	0-13	0-17	0-17	0-8

The following hypothesis for differences between adherents and non-adherents were tested by bivariate analysis:

- Distribution by **age** didn't show any statistical significant difference. (p=0.62 by Wilcoxon test with continuity correction).
- Difference in distribution by **sex** (59% males in the adherent group and 65% in non-adherent) was not statistically significant. (p=0.86 by qui-square test with Yales continuity correction)
- Statistically significant differences were also not found amongst the different **HIV transmission** routes. (p=0.55 by the qui-square test).
- **Time elapsed from diagnosis to beginning of ART** did not statistically significantly influenced adherence. (p=0.62 by Wilcoxon test with continuity correction)

Discussion

It was determined a ART non-adherence prevalence higher than 38%, a value higher than in previous studies in Portugal: 22.3% in Hospital de Santa Maria, Lisbon in 2004[14] and 31.3% in Hospital Joaquim Urbano, Oporto in 2006 [13]. However, both studies included only subjects that had persisted in treatment and for a study period of one year, which may explain the higher prevalence observed in our study.

In addition, only a small minority of the patients had no days without ART in all intervals between dispenses. In fact, 50% of the participants that had at least one interval with a days without ART had more than 2 intervals between dispenses with more than 8 days without ART. However it's important to keep in mind that these are preliminary results.

There weren't found factors associated with ART non-adherence, which may be due to the small sample size (60 participants), and because there were only tested four hypotheses of association yet. Other factors will be evaluated in the near future, such as: ART duration, number of ART switches, number of missed consults, recommendations records in the clinical process, number of hospitalizations, presence of opportunistic infections and co-morbidities and taking other medication.

Also, with the conclusion of the study, we aim to define more accurately non-adherence prevalence, and to calculate the ART drop-outs percentage, as well as collecting information on other factors related to the patient and not available in the clinical records. The aim is also to evaluate adherence variation over time and its correlation with immunological failure and / or viral resistance emergence.

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Actividades desenvolvidas

ACTIVIDADES	DESCRIÇÃO
Transversais ao projecto	Identificação de artigos recentemente publicados sobre a adesão à terapêutica anti-retrovírica e seus condicionantes.
	Participar nas reuniões da equipa de investigação do estudo "*ATAR-HIV*"
1. Revisão do protocolo do estudo e instrumentos de recolha de dados	Revisão do protocolo de estudo e dos formulários para recolha de dados a partir dos registos de dispensa de TAR na farmácia hospitalar e dos processos clínicos.
2. Recolha de dados no HSM	Recolha de informação a partir dos registos clínicos e de dispensa de medicação dos doentes seleccionados
3. Análise de dados	Desenho e Construção da base de dados informática
	Inserção de dados na base informática
	Discussão da análise estatística
4. Publicação de Resultados	Colaboração na submissão do resumo no X Congresso Nacional de Doenças Infecciosas e Microbiologia Clínica & VIII Congresso Nacional sobre SIDA
	Elaboração de poster e comunicação oral para o 13ºWorkshop do GAPIC
	Elaboração do Relatório de Execução Material, de acordo com o previsto no Regulamento do Programa Educação pela Ciência

Publicações

- Fernandes M, Caldeira L, Leite A, Freitas JA, Nicola PJ, Nogueira P, Martins AP, Maria V. Patient Refill of Antiretroviral Therapy: how frequent it is for a patient to have days without medication? (Dispensa de Terapêutica Anti-Retrovírica: quantosdias sem medicação e qual a frequência desses períodos?). X Congresso Nacional de Doenças Infecciosas e Microbiologia Clínica & VIII Congresso Nacional sobre SIDA. Coimbra, Portugal. 2010. Poster presentation. **URL**: http://uepid.wikidot.com/local--files/projectos-de-investigacao/poster adesao 2010-10-05.pdf
- Fernandes M, Caldeira L, Leite A, Freitas JA, Nicola PJ, Nogueira P, Martins AP, Maria V. Frequency and reasons for antiretroviral therapy switching in HIV patients. (Prevalência e razões para mudança da terapêutica anti-retrovírica em indivíduos seropositivos para o VIH.). X Congresso Nacional de Doenças Infecciosas e Microbiologia Clínica & VIII Congresso Nacional sobre SIDA. Coimbra, Portugal. 2010. Poster presentation. **URL**: http://uepid.wikidot.com/local--files/projectos-de-investigacao/poster mudan%C3%A7a2010-10-05.pdf
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