13º PROGRAMA EDUCAÇÃO PELA CIÊNCIA

FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

- RELATÓRIO DE EXECUÇÃO MATERIAL -

MUDANÇA TERAPÊUTICA NOS DOENTES SEROPOSITIVOS PARA O VIH

AVALIAÇÃO RETROSPECTIVA DA INCIDÊNCIA E FACTORES ASSOCIADOS

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Integrado no estudo

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

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Frequency and Reasons for Antiretroviral Therapy Switching in HIV Patients

Abstract

Changing ART (antiretroviral) therapy is a complex decision, influenced by various reasons. Switching frequency at the end of first year of treatment had been estimated by 25-50%, mainly due to adverse effects. We conducted a cohort study with HIV patients followed at Infectious Diseases Day Clinic – Hospital de Santa Maria. Data of clinical records was collected for eligible subjects from a random sample of 320 subjects with at least two pharmacy refills between 2005 and 2008. Switches were considered if individuals changed at least one ART or stopped therapy. Frequency and reasons on first, second and third changes were characterized. 192 individuals were included, 122 had changed therapy at least once, 75 twice and 50 three times. Main reasons for first and second change were, adverse effects and resistance, and for third change both. We came to find a relevant frequency of changes, mainly due to adverse effects and resistance.

Introduction

HIV infection is a major public health problem in Portugal, where incidence and prevalence is higher than other European countries.[1] Since the introduction of Highly Active Anti Retroviral Therapy (HAART) in 1996, AIDS related mortality has been diminishing, with the HIV infection being now considered a chronic disease.

Given the central role of antiretroviral therapy (ART) in HIV infection, it is important to choose the best treatment for each patient, bearing in mind that the initial regimen is considered to have the highest probability of leading to a sustained virologic response and that pharmacological options are limited.[2]

Clinical decision on switching ART is then a complex decision, as it may lead to a lower probability of success and diminish future options. There are also many reasons to be taken into account besides immunologic/virologic failure. A 1999 Netherlands' study had determined a 30% frequency for first change.[3] More recent studies had estimate switching frequency in 25-50% of the naïve patients ending the first year of treatment. [2,4] At a national level, a 2004 study with patients followed between 1997 and 2004, determined the mean time to switch in 14.0 ± 4.1 months, and a mean of 2.2 ± 1.7 mean switches by patient.[5]

Reasons for switching HAART regimens are related to adverse effects, virologic/immunologic failure, co-morbidities and non-adherence. In previous studies, adverse effects were considered the main reason for changes, with gastro-intestinal intolerance being the most frequent adverse effect.[2] However, most of the studies on ART switching have described prevalence and reasons

on first HAART change, and few had analyzed the longitudinal pattern of switching or the reasons for second and third changes.

Our study aims to complete this information, by describing frequency and reasons on first, second and third changes.

Methods

The *Adherence To AntiRetroviral therapy in HIV infected subjects* (ATAR-VIH) study is an observational cohort study with a first retrospective data collection on a sample of HIV subjects followed at Infectious Diseases Day Clinic (Director: Professor Francisco Antunes) - Hospital de Santa Maria (HSM). From patients who had at least one ART refill (pharmacy records) between January 1st, 2005 and December 31st, 2008 a sample of 320 patients was randomly selected and clinical records were consulted. Eligible subjects fulfilled the following criteria:

1. Started ART with at least 18 years-old;
2. Started ART in Hospital de Santa Maria (HSM);
3. Had at least 2 medical appointments 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.

After the ART beginning criteria from 4 to 6 were considered as exit criteria.

For the purposes of our study, ART changes are defined as switching at least one of the antiretroviral drug (not including adjustments of intake frequency) or interrupting treatment by clinical decision or non-adherence.

According to the written data on clinical records, reasons for ART changes were grouped into: [6]

- Immunologic/Virologic failure, not only by physician explicit annotation but also when LyT CD4+ >200 cells/ml or viral load > 40 (or > 50) copies;
- Non-adherence/Non-persistence – interruption of ART by patient decision;
- Side effects/Intolerance – side effects attributable to ART;
- Resistance – verified by genotypic resistance test registered on clinical record;
- Others – as pregnancy, drug interactions, co-morbidities, etc.

Descriptive statistics was used to determine frequency of changes and its reasons. Statistical analysis was performed with R software (www.r-project.org).

Results

From the 320 patients randomly selected 192 (60.0%) were included in the study. Exclusion of individuals was mainly due to beginning of ART out of the study's hospital (n=40, 31.3%) and participation in a clinical trial (n=34, 26.6%).

Table 1 presents demographic and ART regimen characteristics for the group of included subjects, which is mainly formed by white (n=115, 77.7%) young (mean age 36.5) male (37.0% of female subjects) individuals. Way of virus transmission was mainly from a heterosexual intercourse (n=85, 48.3%), even though injecting drugs users (IDU) are a significant group of transmission (n=42, 23.9%). The majority of subjects was infected with HIV type 1 (n=181, 97.8%).

Forty (20.8%) individuals had started ART with non-HAART regimens. For these subjects, the median time until a switch to HAART regimen occurred was 27.3 ($Q_{0.25}$-$Q_{0.75}$: 11.3 – 61.6) months.

When in HAART regimen 122 (63.5%) subjects changed at least once. The first change on HAART took a median time of 18.7 months ($Q_{0.25}$-$Q_{0.75}$: 5.8-30.2). A second and third change occurred for 75 and 50 subjects, respectively. Median time from first to second change was 20.0 months ($Q_{0.25}$-$Q_{0.75}$: 7.4-27.2) and 16.7 ($Q_{0.25}$-$Q_{0.75}$: 10.31 – 23.74) months from second to third change.

Table 2 resumes reasons for HAART changes. Main reason for first change was side effects/intolerance (n=31, 37.3%), while second change was mainly related to resistance (n=14, 35.0%) and third change was mainly due to side effects/intolerance and resistance (n=8, 26.7%).

Discussion

Demographic and transmission characteristics from this sample are compatible with data from official epidemiological surveillance organizations.[7,8]

Our study reveals that time elapsed between the beginning of follow-up and beginning of ART therapy is very short, with 50% of subjects beginning ART less than 1.3 months from first medical appointment. Even though nowadays some recommendations have considered the begin of ART therapy in a more early stage [8], our data reflects patients that, in some cases, have started to be followed years ago and may also show that most of these subjects have been diagnosed in a late stage of progression of disease. This hypothesis is also supported by the number of LyT CD4+ at the beginning of follow-up, which was less than 234.5 cell/mm^3 in 50% of subjects, as well as by the number of copies of the virus/ml (higher than 115700 for 50% of subjects). This fact reflects the reality in our country, where late presentations are a problem.[1]

Near 21% of subjects had started ART with a non-HAART regimen, and have a longer time until changing to HAART when compared to the other changes already on HAART. This may reflect the time elapsed until the beginning of HAART era (around 1996) and the difficulties in choosing a good HAART regimen for subjects that had already been on ART medication [8]. First regimen was mainly formed by 2 NRTIs (Nucleoside Reverse Transcriptase Inhibitors) for the subjects on a non-HAART regimen and by 2 NRTIs plus a NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitor) for the remaining.

While in HAART, 63.5% of subjects had one first change, which occurred on less than 18.7 months for 50% of the cases. First change was mainly related to adverse effects. Reason on first is consistent with other studies[2,6,9], while median time on first change is similar to that obtained by de la Torre et al [6] but superior to that reported by Kirstein et al[4]. Second change was mainly due to resistance and the median time between first and second change was 20.0 months, similar to the time until first change. Main reasons for third change were both side effects and resistance (n=8, 26.7%). Time between second and third change seems slightly inferior to the ones observed in prior changes.

An important limitation of our study is that information was collected in the written clinical record and, despite an important percentage of missing information (approximately 40% for each change), that doesn't mean that the physician doesn't know the reason to change.

Our study came to find a significant percentage of changes, mainly related to side effects and resistance, and reflecting the chronic treatment of HIV infection. Work on researching ART with fewer side effects should be continued, as well as the efforts on defining clinical interventions that may improve adherence and, thus, avoid resistance and virologic/immunological failure.

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Table 1. Main characteristics of the included subjects.

	Included subjects (n=192)
Mean age (S.D.)	36.5 (10.2) years
No. of female patients	71 (37.0%)
Ethnic group	
White people	115 (77.7% of 148)
Black	29 (19.6% of 148)
Others	4 (2.7% of 148)
Missing information	44
Type of virus	
HIV1	181 (97.8% of 185)
HIV2	3 (1.6% of 185)
HIV1 and HIV2	1 (0.5% of 185)
Missing information	7
Transmission	
Heterosexual	85 (48.3% of 176)
Injectable Drug Users	42 (23.9% of 176)
Men having Sex with Men	28 (15.9% of 176)
Other	21 (11.9% of 176)
Missing information	16
Time from first medical appointment to beginning of ART (median)	1.3 ($Q_{0.25}$-$Q_{0.75}$: 0.0-8.5)
Time of follow-up (median)	91.1 ($Q_{0.25}$-$Q_{0.75}$: 55.1-135.0)
Laboratory parameters	
Beginning of follow-up	
LyT CD4+ - median	234.5 ($Q_{0.25}$-$Q_{0.75}$: 84.25 – 430.0)
LyT CD4+ - *missing information*	8
Viral load – median	115700 ($Q_{0.25}$-$Q_{0.75}$: 35800 – 400400)
Viral load – *missing information*	49
Beginning of ART	
LyT CD4+ - median	255.7 ($Q_{0.25}$-$Q_{0.75}$: 229.0 - 365.0)
LyT CD4+ - *missing information*	21
Viral load – median	345900 ($Q_{0.25}$-$Q_{0.75}$: 126100 – 352700)
Viral load – *missing information*	62
First ART regimen	
Non-HAART	
1 NRTI	18 (9.4%)
2 NRTIs	28 (14.6%)
HAART	
2 NRTIs + NNRTI	74 (38.5%)
2 NRTIs + PI	64 (33.3%)
Others	8 (4.2%)
Time on ART	
Mean (S.D.)	86.5 (53.0)
Median	84.2 ($Q_{0.25}$-$Q_{0.75}$: 41.5 – 126.6)
Time on HAART	
Mean (S.D.)	78.4 (45.5)
Median	79.7 ($Q_{0.25}$-$Q_{0.75}$: 40.6 – 119.2)

Table 2. Main reasons of first, second and third changes.

Reason	1st change n (%)	2nd change n (%)	3rd change n (%)
Virologic / Immunologic failure	11 (13.3%)	8 (20.0%)	2 (6.7%)
Non-adherence	14 (16.9%)	5 (12.5%)	7 (23.3%)
Side effects / Intolerance	**31 (37.3%)**	**11 (27.5%)**	**8 (26.7%)**
Resistance	14 (16.9%)	**14 (35.0%)**	**8 (26.7%)**
Other	13 (15.7%)	2 (5.0%)	5 (16.7%)
Missing information	39 (32.0%)	35 (46.7%)	20 (40%)

Actividades desenvolvidas

As actividades desenvolvidas pela aluna encontram-se descritas na tabela abaixo.

ACTIVIDADES	DESCRIÇÃO
Transversais ao projecto	Identificação de artigos recentemente publicados sobre a mudança de TAR nos doentes seropositivos para o VIH.
	Participação nas reuniões da equipa de investigação do estudo ATAR-VIH.
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 processos clínicos
2. Recolha de dados no HSM	Colheita de informação a partir dos registos clínicos dos doentes seleccionados
3. Análise de dados	Inserção de dados na base informática
	Realização da análise estatística
4. Publicação de Resultados	Colaboração na submissão do resumo e respectivo poster no X Congresso Nacional de Doenças Infecciosas e Microbiologia Clínica & VIII Congresso Nacional sobre SIDA
	Apresentação do trabalho sob a forma de poster no 13º workshop "Educação pela ciência"
	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
- Leite A, Fernandes M, Nicola PJ. Mudança da Terapêutica Anti-Retrovírica em indivíduos seropositivos para o VIH. 13.º Workshop "EDUCAÇÃO PELA CIÊNCIA". Lisboa, Portugal. 2010. Poster presentation. **URL**: http://uepid.wikidot.com/local--files/projectos-de-investigacao/GAPIC - poster mudan%C3%A7a - 2010-12-14.pdf