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ORIGINAL ARTICLE

Analysis of the duration of and reasons for changing the first combination of antiretroviral therapy

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Abstract
Objective: To determine the duration of and reasons behind changing the various combinations of drugs used for the initiation of antiretroviral treatment in naïve patients.
Methods: A retrospective observational study that included all patients with HIV infection who started antiretroviral therapy in a high-tech university reference hospital during the period from 1 January 2003 and 31 December 2005. Patients were followed until 31 December 2008. To estimate the cumulative probability of discontinuation the Kaplan- Meier method was used.
Results: A total of 441 patients were included. The average duration of the first treatment was 384 (interquartile interval 84-1290) days. The regimen based on non-nucleoside reverse transcriptase inhibitors and those that included as nucleosides abacavir or tenofovir in combination with lamivudine or emtricitabine showed a significantly longer duration than the rest. The main reasons for termination were the side effects, although in a lesser percentage than that obtained in previous studies. No associations were found between the rest of the characteristics of the patients or of the treatment and the risk of termination.
Discussion: Although the duration of the first antiretroviral treatment remains short, currently fewer changes are made due to side effects and due to loss to follow-up. The reasons may be better tolerance and less complexity. However, more studies are needed to determine the benefits of one regimen or another, and to be able to generalise the results.

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PALABRAS CLAVE
VIH;
TARGA;
Interrupciones;
Efectos adversos

Análisis de la duración y los motivos de cambio de la primera combinación de tratamiento antirretroviral

Resumen
Objetivo: Conocer la duración y los motivos de cambio de las distintas combinaciones de fármacos utilizadas como inicio del tratamiento antirretroviral en pacientes naive.
Métodos: Estudio observacional y retrospectivo en el que se incluyeron todos los pacientes con infección por VIH que iniciaron tratamiento antirretroviral en un hospital universitario de referencia de alta tecnología durante el periodo comprendido entre el 1 de enero de 2003 y el 31 de diciembre de 2005. El seguimiento se realizó hasta el 31 de diciembre de 2008. Para estimar la probabilidad acumulada de interrupción del tratamiento se utilizó el método de Kaplan-Meier.
Resultados: Se incluyeron un total de 441 pacientes. La mediana de duración del primer tratamiento fue de 384 (intervalo intercuartil 84-1.290) días. Los regímenes basados en inhibidores de la transcriptasa inversa no análogos de nucleósidos y aquellos que incluían como análogos de nucleósidos abacavir o tenofovir en combinación con lamivudina o emtricitabina presentaron una duración significativamente mayor que el resto. Los principales motivos de finalización fueron las reacciones adversas aunque en un porcentaje menor que el obtenido en estudios anteriores. No se hallaron asociaciones entre el resto de características de los pacientes o del tratamiento y el riesgo de interrupción.
Discusión: Aunque la duración del primer tratamiento antirretroviral sigue siendo corta, actualmente se producen menos cambios por reacciones adversas y por pérdidas de seguimiento. Los motivos podrían ser una mejor tolerancia y una menor complejidad. No obstante, son necesarios más estudios para determinar el beneficio de un régimen frente a otro y poder generalizar estos resultados.

Introduction

The introduction in the mid-90s of protease inhibitors and, with them, highly active antiretroviral therapies (HAART), provoked a major change in the evolution of the infection caused by HIV.[1,2] Since then, new antiretroviral drugs have appeared virtually on a yearly basis. In 2009, 27 commercialised drugs were available, as well as several new molecules being researched.

The treatment of the infection caused by HIV is based on three-drug combinations. The goal with this method is to achieve the maximum viral suppression for the longest period of time possible, re-establishing or conserving immunological function, improving quality of life, and reducing the HIV-related morbidity and mortality.[3,4]

The number of antiretroviral drugs currently available allows for multiple treatment combinations. Since many of these combinations have similar effectiveness, other aspects must be evaluated when selecting the course of treatment, such as the number of pills, the frequency of administration of the treatment, the appearance of adverse reactions, adherence to previous treatments, pharmacological interactions, cost, and updated recommendations from when the prescription was given.[5]

The availability of a large number of antiretroviral drugs along with the rapid appearance of different modifications from new studies makes the treatment of patients infected with HIV a complex process that is subject to frequent changes.

Due to the chronic nature of the disease, one of the main objectives is to prolong the duration of these treatments, and so it is important to know the different prescriptions given and the reasons for changing them.

Several studies have estimated the duration of the first HAART combination. However, the majority of these were performed between 1996 and 2000.[6-9] Subsequently, nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) that were more widely used at the time, zidovudine (AZT), didanosine (ddI), and stavudine (d4T), have been replaced with tenofovir (TDF) and abacavir (ABC), because they are less toxic.[10-12]

The main aim of this study is to quantify the current duration of the various combinations of drugs used to start antiretroviral treatment in new patients. Our secondary aim is to understand the most frequent reasons for changing this first treatment combination.

Method

We performed a retrospective observational study that included all patients with HIV infection who started antiretroviral therapy in a high-tech university reference hospital during the period from 1 January 2003 to 31 December 2005. Patients that had started treatment in clinical trials with non-commercialised drugs or with non-approved indications were excluded from the study. Patients were followed until 31 December 2008.

The variables we focused on were the percentage of patients that stopped treatment and the median duration of time spent receiving each combination of drugs until then.

Treatment was defined as interrupted when the therapy was ceased, substituted by another drug or combination of drugs, or when treatment was halted altogether, whether due to doctor's orders or patient initiative. Those patients

that did not visit their attending physician for more than 6 months at a time were considered lost from the follow-up protocol.

The data was obtained by a retrospective review of digitalised clinical histories and from outpatient centre registries. We included the typical socio-demographic variables (age, sex) related to the disease and its treatment (method of transmission, coinfection with HCV and/or HBV, date of commencement and finalization of antiretroviral treatment), as well as the patient's baseline levels of viral load and CD4 lymphocytes.

The different combinations were classified into regimens based solely on NRTI, regimens based on non-nucleoside reverse transcriptase inhibitors (NNRTI) and regimens based on protease inhibitors (PI).

The NRTI used within each regimen were assigned to 3 groups: combinations including ddI o d4T, combinations that included AZT and combinations that included ABC or TDF. If the regimen contained NRTI of more than one group (eg. ddI and AZT), the regimen was assigned using the following hierarchy: ddI or d4T, then AZT and finally, ABC or TDF.

The change in commercialised drugs from individual doses to a fixed combination of the same medications was not considered a change in treatment. Neither was the change from lamivudine (3TC) to emtricitabine (FTC) considered a change in therapy because of their therapeutic equivalency.

With regard to the statistical analysis, we performed a descriptive analysis of the characteristics of the population studied, the percentage of interruptions in treatment, and the reasons for these. In order to study the influence of different variables on the duration of the HAART, we used Cox regression models, and the Kaplan-Meier method for estimating the accumulated probability of treatment interruption throughout the study period. All analyses were performed using SPSS statistical software, version 15.0.

Results

A total of 441 patients were included in the study. Of these, 131 started treatment in 2003, 137 in 2004, and 173 in 2005. Table 1 displays the baseline characteristics of this population. 78% of patients were men and the median age was 37 years (31-45). We observed no statistically significant differences in these variables between the different years of the study period. When assessing the population by the different drug combinations that were given, the distribution by sex was similar to the global distribution. Median baseline CD4 count and viral load were 186 (87–275) cells/µl and 5.06 $\log_{10}$ (4.69 $\log_{10}$-5.70 $\log_{10}$) copies/ml, respectively. With respect to the risk factors, almost half of the population was homosexual, 35% were heterosexual, and 15% had been addicted to intravenous drugs.

Table 2 summarises the most common treatment regimens that were used as the initial prescription. With respect to the NRTI, baseline treatments including ABC or TDF were used in 53.7% of cases, followed by AZT in 37% and ddI or d4T in 9.3%. These NRTI were generally combined with 3TC or FTC (85% of cases). 61% of patients received treatments based on NNRTI and almost 30% were based on PI. The most commonly used NNRTI was efavirenz (EFV), which made up 84.4% of NNRTI prescriptions. The most commonly used PI was lopinavir/ritonavir (LPV/r), in 78.7% of patients that received PI. The most commonly prescribed initial treatment during the study was 3TC or FTC along with TEN and associated with EFV (32%) followed by the association of these same analogues along with LPV/r (9%).

The global median duration of treatment was 384 days (interquartile range: 84-1290). That is, the probability of continuing with the same treatment was 75% at 84 days, 50% at 384 days, and 25% at 1290 days.

By comparing the duration of treatment between the different combinations of pharmacological groups (Figure 1), we observed that the regimens based on NNRTI had a significantly greater median duration [501 days (84-.)] than the regimens based on PI [286 days (152-722)] or that only included NRTI [137 days (31-766)] (P<.005). We observed no statistically significant differences when comparing the regimens based on PI with the prescriptions that only included NRTI.

With regard to the NRTI used (Figure 2), the combinations that included ABC or TDF had a greater duration of treatment [690 days (133-.)] than those including AZT [209 days (70–629)], or ddI or d4T [364 days (137-766)] (P<.005). The interquartile range is presented between the parentheses.

Table 1 Baseline characteristics of the study population

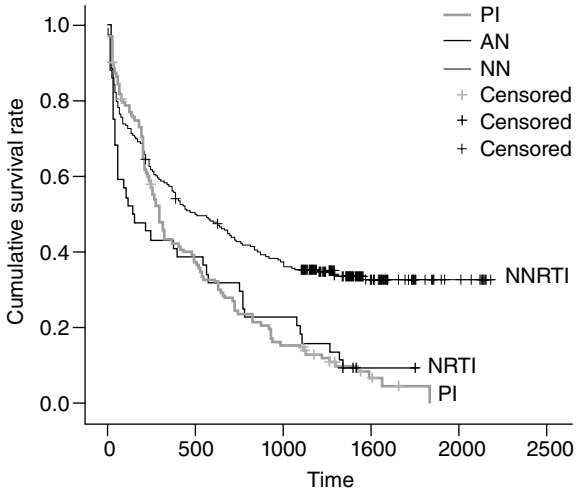
	Overall	2003	2004	2005
No. patients	441	131	137	173
Age, years*	37 (31-45)	37 (30-45)	38 (30-45)	37 (31-43)
Sex, males	78	77	77	79
Risk factors				
Intravenous drug addiction	67 (15.2%)	24 (18.3%)	23 (16.8%)	20 (11.6%)
Homosexual	202 (45.8%)	51 (38.9%)	60 (43.8%)	91 (52.6%)
Heterosexual	152 (34.5%)	48 (36.6%)	49 (35.8%)	55 (31.8%)
Other	20 (4.5%)	8 (6.1%)	5 (3.6%)	7 (4.0%)
Baseline viral load* $\log_{10}$ copies/ml	5.29 (4.69-5.70)	5.35 (4.79-5.78)	5.28 (4.69-5.69)	5.25 (4.63-5.64)
Baseline CD4* cell/µl	186 (87-275)	172 (92-285)	155 (51-264)	212 (111-284)

*Values expressed as median and interquartile range.

Table 2 Antiretroviral treatment combinations used as the initial treatment

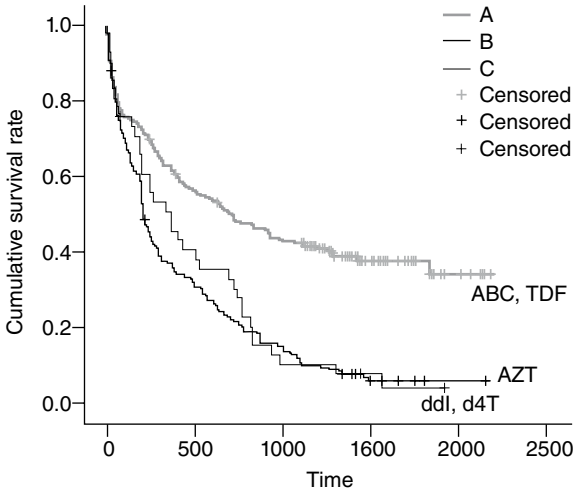
Type of treatment	Overall	2003 (n=131)	2004 (n=137)	2005 (n=173)
NRTI 44 (9.98%)				
ABC/TDF	10	10	–	–
AZT	31	6	1	24
ddI/d4T	3	3	–	–
NNRTI 270 (61.22%)				
ABC/ TDF	166	28	39	99
AZT	83	27	47	9
ddI/ d4T	21	16	3	2
PI 127 (28.80%)				
ABC/ TDF	61	13	17	31
AZT	49	19	24	6
ddI/ d4T	17	9	6	2

ABC/ TDF indicates regimens including abacavir or tenofovir; AZT, regimens including zidovudine; ddI/ d4T, regimens including didanosine or stavudine; NNRTI, regimens based on non-nucleoside reverse transcriptase inhibitors; NRTI, regimens that only included nucleoside reverse transcriptase inhibitors; PI, regimens based on protease inhibitors.



NRTI: regimens that only included nucleoside reverse transcriptase inhibitors
NNRTI: regimens based on non-nucleoside reverse transcriptase inhibitors
PI: regimens based on protease inhibitors

Figure 1 Kaplan-Meier survival analysis according to type of treatment.



ABC/TDF: regimens including abacavir or tenofovir
AZT: regimens including zidovudine
ddI/d4T: regimens including didanosine or stavudine

Figure 2 Kaplan-Meier survival analyses according to type of NRTI used.

Only one value is presented in two cases because there were no cases in the first quartile. We observed no statistically significant differences when comparing the regimens that included AZT with those that included ddI or d4t.

We observed no statistically significant relationship between duration of treatment and the rest of the study variables.

Table 3 summarises the reasons for changing from the first antiretroviral treatment. The main cause for change of treatment was adverse reactions, which caused the change in one fourth of the initial treatments. 7% of patients voluntarily abandoned the antiretroviral treatment, and 6% were lost during follow-up. The treatment was ineffective in 6% of cases. Only one fourth of patients still continued with the initial treatment at the end of the study.

By observing the reasons for halting the first antiretroviral treatment based on the year that treatment started, we wish to point out that the percentage of interruptions due to adverse reactions was lower in patients that started treatment in 2005 (23%) than in those that started in 2003 (27%) and 2004 (32%). The changes in treatment due to adverse reactions were similar for the different types of regimens.

Table 3 Reasons for terminating the initial antiretroviral treatment

Reason for changing treatment	Global (n=441)	2003 (n=131)	2004 (n=137)	2005 (n=173)
Adverse reaction	120 (27.2%)	23 (27.5%)	44 (32.1%)	40 (23.1%)
No change	102 (23.1%)	12 (9.2%)	23 (16.8%)	67 (38.7%)
Clinical trial	49 (11.1%)	26 (19.8%)	16 (11.7%)	7 (4.0%)
Simplification	40 (9.1%)	10 (7.6%)	19 (13.9%)	11 (6.4%)
Abandoned treatment	32 (7.3%)	10 (7.6%)	7 (5.1%)	15 (8.7%)
Loss	28 (6.3%)	6 (4.6%)	10 (7.3%)	12 (6.9%)
Failure	26 (5.9%)	12 (9.2%)	7 (5.1%)	5 (4.0%)
Pregnancy	19 (4.3%)	8 (6.1%)	2 (1.5%)	9 (5.2%)
Interaction	12 (2.7%)	5 (3.8%)	4 (2.9%)	3 (1.7%)
Death	6 (1.4%)	3 (2.3%)	2 (1.5%)	1 (0.6%)
Transfer	4 (0.9%)	2 (1.5%)	1 (0.7%)	1 (0.6%)
Dosage adjustment	3 (0.7%)	1 (0.8%)	2 (1.5%)	–

Table 4 Adverse reactions that motivated changing the antiretroviral treatment

Adverse reaction	No. of patients (percentage)
Hypersensitivity	32 (26.7)
CNS toxicity	29 (24.2)
Digestive intolerance	19 (15.8)
Anaemia	8 (6.7)
Lipodystrophy	7 (5.8)
Renal toxicity	6 (5.0)
Dyslipidemia	6 (5.0)
Hepatotoxicity	4 (3.3)
Other	9 (7.5)

Table 4 indicates the adverse reactions that motivated the change from the initial antiretroviral treatment. The main adverse reactions that provoked changes were hypersensitivity to prescriptions including efavirenz, nevirapine, and abacavir, toxicity to the central nervous system in prescriptions including efavirenz, and digestive intolerance, mainly in prescriptions that included PI.

Discussion

The results from this study show that the duration of the first antiretroviral treatment is short. In spite of the fact that treatments have changed considerably in recent years, the durations of each treatment in our study were similar to the results obtained from a study with similar methodology performed in patients that started treatment between 1998 and 2000.[6] However, we must point out that the reasons for switching treatment have changed. In the previous study period, adverse reactions were the cause for suspending almost half of the treatments that were interrupted, whereas in the 2003 to 2005 period, this was the cause in fewer than 30% of cases. On the other hand, although the percentage of abandoned treatments is similar (7%), the percentage of patients lost during follow-up is much lower (6% vs 15%). Taking into account these data, the length of treatment now should be higher. However, the inclusion of patients in clinical trials has contributed to shortening the duration of treatment in our study. This fact denies the possibility of extrapolating our data when comparing data from other centres that do not focus so much on research.

Previous studies that established the duration of the first antiretroviral treatment have referred to periods that range from 11.8 months to 1.6 years.[7-9] Chen et al[7] followed a cohort of 405 new patients that started antiretroviral treatment between 1996 and 2001 for 6 years, of which 65% received a combination with PI as the initial treatment. These authors obtained a median duration of treatment of 1.6 years. Palella et al[8] produced a median of 11.8 months duration of the first antiretroviral treatment in patients from the HOPS cohort that started antiretroviral treatment between 1996 and 1999. The combinations used were based on PI in over 80% of cases. In another study, Arribas et al[9] observed a length of the first treatment of 18.5 months in a retrospective study performed in Spain between January 1997 and April 2000, which included 401 new patients.

The differences observed between these studies can be explained by differences in study design, whether the patients were new or previously treated, the type of statistical analysis (if an analysis of survival was performed or the researchers simply calculated the difference between the date of initiation and finalization of treatment), follow-up time, whether or not follow-up was continued after the finalization of the study period, the inclusion or exclusion of patients lost in the follow-up period in the final analysis, the inclusion or exclusion of patients that participate in clinical trials, and the differences in the prescribed drug combinations. With respect to this last point, combinations based on PI were prescribed in the majority of studies performed between 1996 and 2001, in accordance with the recommendations of the time and the availability of medications. However, PI has gone from representing 92% of drugs prescribed in 1997 to 20% in 2005.

A more recent study compared the duration of the first antiretroviral treatment and the reasons for changing from it in an American health centre.[13] The authors compared two different time periods, from before and after August 2004 (when once-a-day regimens at fixed doses appeared in the

United States). The data obtained showed an increased risk of discontinuation in patients treated with regimens based on PI and in those that included analogues of ddI or d4t, similar to the results obtained in our study. Previous studies have demonstrated high rates of discontinuation of regimens that contain AZT, especially due to the suppression of bone marrow, and of d4t and ddI, which are occasionally related to mitochondrial toxicity. New NRTI have contributed to prolonging the duration of treatments due to their reduced toxicity. In the study by Willig et al, one of the reasons for a longer duration of treatments after August 2004 was attributed to the change from ddI, d4T and AZT to ABC or TDF. However, the results obtained regarding the duration of treatment are not superimposable, since all interruptions that were produced before 14 days within the start of treatment were excluded from this study. This methodology excludes the majority of hypersensitivity reactions that in our case constituted one of the primary reasons for changing treatment and contributed to shortening the global mean duration.

On the other hand, in spite of the fact that the follow-up period was shorter in patients that started HAART in 2005, the median duration of treatment was higher to that obtained in previous years. This leads us to believe that with currently used regimens, the duration of HAART will be even greater due to the reduced complexity and toxicity of new drugs. Taking into account that HIV infections have become a chronic disease, it is of interest to interrupt the treatment as little as possible once it has been commenced and to keep it active for as long as possible.

As we have already mentioned, the duration of treatment was significantly longer ($P<.005$) in combinations based on NNRTI than in those based on PI or NRTI and in those that included ABC or TDF than in those that included AZT, d4t, or ddI.

We observed no statistically significant relationship between a worsened initial immunological or viral state and reduced duration of initial treatment. These results coincide with those obtained in other studies.[7]

A median duration of the first antiretroviral medication of 384 days can seem short for an infection like that produced by HIV, which requires continuous treatment. Therefore, it is important to understand the causes that motivate changing the first treatment. Adverse reactions have been cited by many authors as the main cause for changing treatment, both in new and previously treated patients.[14-18] In studies by Chen et al[7] and Arribas et al,[9] adverse effects were responsible for the change in treatment in 50% and 46.2% of cases, respectively. In the study by Willig et al,[13] adverse reactions were also the main reason for changing treatment, and were diminished after August 2004 as compared to beforehand (43% vs 64% at one year of follow-up). In our study, adverse reactions continue to be the main cause for changing treatment, although at a lower percentage than those obtained earlier.

The adverse reactions that caused changes in treatment in our study were different from those described in previous publications. The changes were primarily due to hypersensitivity reactions and toxicity to the central nervous system, reactions that were mainly produced by the NNRTI. This is an expectable result when taking into account that the majority of drugs prescribed were NNRTI. If we focus on PI, the most frequent adverse reaction observed, and that responsible for over 40% of changes in treatment, was digestive intolerance. This result is similar to those obtained in previous studies that primarily used prescriptions based on PI.[14]

Undoubtedly, these results confirm that adverse effects are a serious problem of antiretroviral treatment. This fact is of the utmost importance, since, apart from the large number of changes in treatment that it causes, it can provoke a reduction in adherence and therefore lead to resistance, increasing the number of virological failures. We must also point out that, although the adverse effects have continued to be the main reason for changing or terminating treatment during the entire study period, the percentage was lower in 2005 than in either of the two previous years.

The results of this study must be interpreted while taking into account its limitations. Given the size of the sample, we could not make comparisons in duration of treatment at the individual level. Another limitation is that the study was performed at one single centre, and therefore, we cannot generalise.

In conclusion, the results obtained from our study show that, although the duration of the first antiretroviral treatment remains low, currently there are fewer changes due to adverse reactions and loss of patients is reduced during the follow-up period. The reasons for these changes could be improved tolerance and reduced complexity of the medications. More studies are needed to determine the benefits of one regimen compared to others, and in order to apply these results to the general population.

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