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Durability of the first combined antiretroviral regimen in patients with AIDS at a reference center in Belo Horizonte, Brazil, from 1996 to 2005

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ABSTRACT

Finding a better first antiretroviral regimen is one of the strategies used to improve span and quality of life of HIV/AIDS patients. 891 patients were followed during 24 months or until interruption/abandonment of treatment, changing regimen or death. At the end of 6 months, 69% of the patients were still being treated with the first regimen, 54% at 12 months, 48% at 18 months and 39% at 24 months. AZT-3TC-EFV was the most prescribed regimen and with the lesser discontinuation. NNRTI regimens showed high effectiveness and durability compared to PI regimens. Irregular medication dispensation was the only risk factor for failure/interruption of treatment in multivariate analyses. Intolerance/adverse effects were mainly responsible for first regimen discontinuation, followed by abandonment/non-adherence and virologic failure. Results showed significant difference between causes of interruption of first HAART with higher percentage of intolerance/adverse effects with PI regimens and higher immunologic failure with NNRTI regimens. Even with the availability of more potent and tolerable drugs, lack of adherence to HAART and high level of adverse effects are still the most important barriers to prolonged success of treatment. This study adds relevant information about durability and effectiveness of HAART in the first decade of its use in Brazil.

Introduction

The widespread use of highly active antiretroviral therapy (HAART) has led to major reductions in morbidity and mortality associated with HIV infection.[1-4] The choice of initial HAART therapy has potential implications not only for short-term success of therapy but also for long-term durability of antiretroviral activity, for immune system restoration and for adherence to the regimen, as well as to potential emergence of drug resistance.[5] Effectiveness of first regimen is a debated topic in the world and several questions on the subject need more consistent answers. In Brazil, since 1996 access to antiretroviral (ARV) therapy has been universal and free of charge to all individuals who qualify for treatment according to national guidelines. Nonetheless, despite the well recognized public health impact of the Brazilian AIDS program, there are important issues to be addressed regarding durability and determinants of HAART discontinuation. In the present

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study, we assessed durability and determinants of initial HAART regimens discontinuation in a cohort of treatment-naive patients who started ARVs between 1996 and 2005 in a referral center for infectious and parasitic diseases (CTR/DIP Orestes Diniz) in Belo Horizonte, Brazil.

Material and methods

Study population included all treatment-naive HIV-infected adults aged 18 or more on follow-up at CTR/DIP Orestes Diniz, for whom HAART had been prescribed between 1996 and 2005. Pregnant women were excluded from this analysis. The main objective was to ascertain the duration of the first HAART regimen in patients with HIV/AIDS. Secondary objectives were: to describe the main regimens prescribed and the temporal evolution; to identify possible risk factors associated with durability and effectiveness of the first antiretroviral regimen; and to identify the reasons for discontinuation or replacement of the first HAART regimen.

Data were abstracted from the medical records, from a database of laboratory tests and from antiretroviral inventory sheets at the local pharmacy.

Data analysis included all patients who received their first antiretroviral combination containing at least three drugs throughout 24 months or until the suspension, abandonment or replacement of the regimen or death. Antiretroviral regimens were categorized in two major groups: protease inhibitor (PI) (regimens containing 2 nucleoside reverse transcriptase inhibitors [NRTIs] plus at least 1 PI, including ritonavir-boosted regimens) and non-nucleoside reverse transcriptase inhibitor (NNRTI) (regimens containing 2 NRTIs plus 1 NNRTI). Demographic variables included gender, age, risk category, ethnicity, education level and marital status.

The main endpoint was the time period for discontinuation of HAART, defined as the time at least one of the drugs in the regimen was stopped. Time-to-event was defined as the time from start of HAART to date to discontinuation. Regimen discontinuation or switch, date of occurrence and reason were documented. The reason for discontinuation was characterized as abandonment/non-adherence, pharmacological interaction, regimen inadequacy, therapeutic failure (virological, immunological or clinical), death or intolerance/adverse events. Only one category was considered as the reason for replacement or discontinuation. Virological failure was defined as viral load persisting above 400 copies/mL six months after beginning of HAART (primary virological failure) or viral RNA detection in at least two consecutive exams after having achieved complete viral suppression (secondary virological failure). Immunological failure was defined as reduction of more than 25% in the absolute number or in the percentage of T-CD4+ lymphocytes in at least two consecutive exams, in the absence of documented virological failure, according to Brazilian guidelines.[6,7] Any AIDS-defining opportunistic infection (CDC/93) in patients with T-CD4+ lymphocyte nadir higher than 200 cells/mm^3 was considered clinical failure.[8] In the absence of laboratory results, failure was deemed to be clinical. In other words, for virological failure of the regimen, the date of the viral load result was considered. For immunological failure, the date of the T-CD4+ count that led to HAART discontinuation was considered. In relation to clinical failure, the date of diagnosis of an opportunistic event was considered.

When therapeutic failure was detected secondarily to abandonment/non-adherence to treatment, the latter was considered as the reason for discontinuation. When replacement was due to intolerance/adverse events, the suspected drug(s) and the type of adverse event(s) were identified. Other variables included reports of irregular use of medication in the medical records and irregular dispensing of medication; the latter based on the dispensing sheets of the CTR/DIP pharmacy and defined as dispensing less than 95% of the doses in the period.

For patients who had not discontinued the initial combination, follow-up visits were discontinued after 24 months (730 days) of therapy.

Data were entered into the Epi-info 3.3.2 software and analyzed with the SPSS 13.0 (2004) software, initially in a descriptive manner. Type-I error of 5% was considered for comparison among groups. Survival curves were used to assess HAART duration and of the several antiretroviral regimens. Wilcoxon (Gehan) test was used for paired comparison among the most frequent regimens and comparison of treatment duration among drug classes. Chi-square test was used to evaluate: association between the level of T-CD4+ lymphocytes at the beginning of treatment and the class of the third drug in the regimen, reasons for discontinuation/failure for each drug class, and between gender and marital status and drug classes. In order to evaluate the relation between drug classes and education level, *t* test for independent samples was used. Mann-Whitney test was used for income and age and Cox proportional hazard model was to evaluate the relative risk of treatment discontinuation.

Ethics

The study was approved by the Ethical Committee of the Universidade Federal de Minas Gerais (COEP 569/07).

Results

Among the 916 patients who fulfilled the eligibility criteria, 25 (2.8%) were not included because the medical records were not found or the necessary information was missing. Thus, the study sample comprised 891 patients (Table 1). The majority of the patients were male (69.2%), single (52.1%), white (53.5%), from the city of Belo Horizonte (63.9%), with an average age of 36.3 years and education level of 8 years or less (65.8%). All patients had sexual risk for contracting the infection and 57.4% of men declared themselves as heterosexual. Most patients (548/62.5%) were on a regimen that included a PI. The groups had a similar socio-demographic profile. Regarding CDC/93 classification, it was observed that, at the beginning of HAART, 66.6% (578/859) had T-CD4+ lymphocytes count below 200 cells/mm^3 (categories A3, B3 and C3) and 31% (266/859) had an AIDS-defining condition (categories C1, C2 and C3), with

26% (221/859) presenting both an AIDS-defining condition and T-CD4+ lymphocyte count below 200 cells/mm^3 (category C3).

T-CD4+ lymphocyte count at the beginning of therapy was lower among those who started with a regimen containing a PI, as shown in Table 1.

Thirty-seven different combinations were prescribed as first combined antiretroviral regimen and 75% of the prescriptions comprised the eight more frequent combinations. The combination azidothymidine + lamivudine + efavirenz (AZT + 3TC + EFV) was the most commonly prescribed, accounting for 21.3% of the regimens.

Between 1999 and 2001 there was a significant decrease in ritonavir use as the sole PI, as opposed to an increase of other regimens, especially the combination of AZT, 3TC and EFV. During the study period there was also a decrease in the prescription of regimens containing a PI as first line antiretroviral regimen (Fig. 1).

Table 1 - Baseline characteristics of 891 patients starting antiretroviral therapy from 1996 to 2005

Variable	Median, n/n (%)
Median age (y)	36.3
Male	620/891 (69.2%)
White	418/780 (53.5%)
Single	455/873 (52.1%)
Heterosexual male	356/620 (57.4%)
Less than 8 years of education	570/865 (65.8%)
CD4 < 200 cells/mm^3	578/859 (66.6%)
AIDS diagnosis	266/859 (31%)
Regimen type	
PI	548 (62.5%)
NNRTI	329 (37.5%)
PI and CD4 < 200 cells/mm^3	424/538 (78.8%)
NNTRI and CD4 < 200 cells/mm^3	154/329 (46.8%)

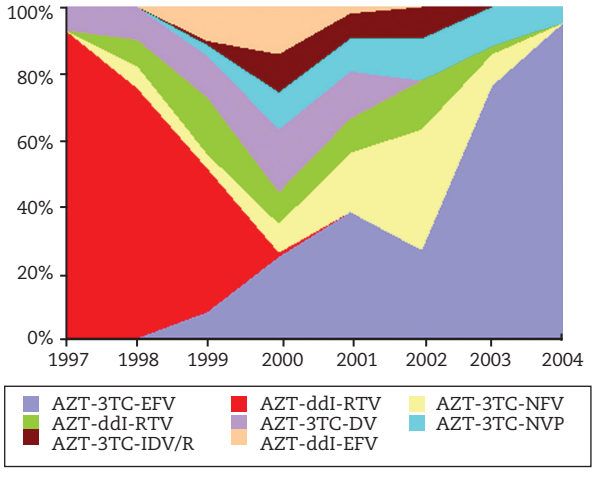

Fig. 1 - Evolution of the percentage of the most frequent regimens per year of introduction of HAART.

Duration of the first combined antiretroviral regimen

Six months after the initiation of therapy, 69% were still on their first regimen, 54% after 12 months, 48% after 18 months and 39% after 24 months. For half of the patients, the duration of the initial antiretroviral regimen was equal or shorter than 14.7 months (441 days) (Fig. 2).

Factors related to the discontinuation of the first antiretroviral regimen

Cox proportional hazard model was used to evaluate the relative risk of treatment discontinuation. After excluding cases with missing values in the demographic variables, 718 cases were available for the survival analysis. The risk of interrupting treatment was not associated with initial CD4, marital status, gender, age group or education level.

Irregular dispensing and reports of irregular use of medication were evaluated as an indirect measure of patients' non-adherence and in univariate analysis both were risk factors ($p < 0.001$) for HAART discontinuation. Adding the variable "regular dispensing" to Cox proportional hazard model did not change these results.

Only 318/891 (35.7%) of the patients had a viral load exam before starting treatment. Viral load before treatment was divided into three categories: up to 9,999; from 10,000 to 99,999 and higher than 100,000 copies/mL and there was no difference in treatment discontinuation in relation to pre-treatment values.

When the main therapeutic classes were compared, a significantly lower discontinuation rate was noticed for NNRTI containing regimens at all intervals, as shown in Table 1.

A significant difference ($p < 0.001$) was observed when comparing duration of regimens containing NNRTI to those containing PI, when adjusted to baseline CD4+ category and to combination of NRTI. In pair-to-pair comparison among the eight most frequent regimens, it was noticed that

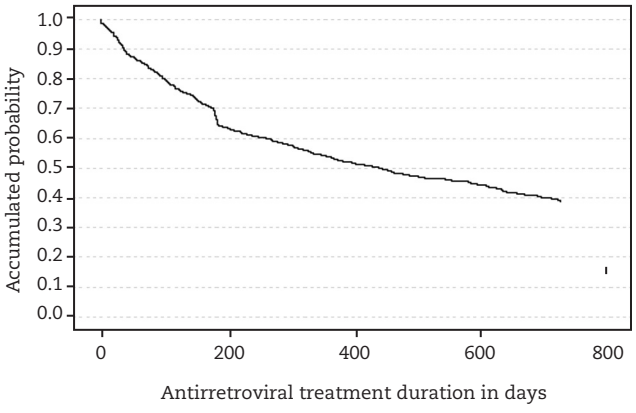

Fig. 2 - Duration of the first antiretroviral regimen in days.

the combination AZT + 3TC + EFV showed a significantly lower discontinuation rate in comparison to other regimens ($p < 0.05$) (Fig. 3).

For 543 participants the first antiretroviral regimen failed during the study period. Intolerance/adverse events were the main reasons for regimen discontinuation (49.5%), followed by virological failure (21.2%) and by abandonment/non-adherence (21%). In 12 patients the antiretroviral regimen was replaced for regimen adequacy, which was not considered as discontinuation. In 61 patients the reason for discontinuation could not be retrieved from the medical records.

Regarding the drug classes evaluated, a significantly higher percentage of patients on NNRTI discontinued their regimens due to immunological failure. Discontinuation due to adverse events was more common among those using PI-containing regimens. Intolerance/adverse events were responsible for the discontinuation of 235 regimens. The least tolerated drug was ritonavir (RTV) (full dose), which was responsible for 27.6% of regimen switches, followed by AZT (18.3%) and didanosine (DDI) (17%). Interruption of the initial antiretroviral regimen could have been caused by more than one drug.

In relation to adverse events leading to discontinuation of the first antiretroviral regimen, gastrointestinal intolerance was responsible for 44.2% of the cases, followed by anemia (14.6%) and neuropsychiatric disturbance (6.2%) (Table 2).

Table 2 – Frequency of adverse events* responsible for discontinuation of medication

Adverse event	Frequency	Percentage (%)
Gastrointestinal intolerance	121	44.2
Anemia	40	14.6
Neuropsychiatric disturbances	17	6.2
Drug allergy	15	5.4
Hepatitis	10	3.6
Peripheral neuropathy	7	2.5
Acute pancreatitis	6	2.2
Nephrolithiasis	6	2.2
Dyslipidemia	4	1.5
Lipoatrophy	4	1.5
Hyperlactatemia	3	1.1
Central fat accumulation	3	1.1
Lactic acidosis	3	1.1
No information	35	12.8
TOTAL	**274**	**100**

*The two main adverse events described as the reason for regimen discontinuation were considered for this analysis.

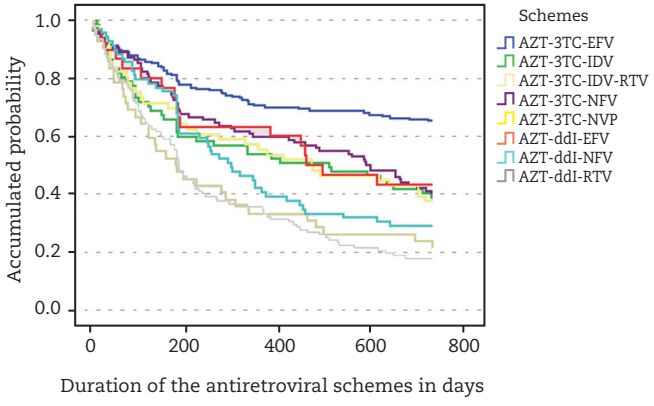

Fig. 3 - Duration of the 8 most frequent antiretroviral regimens in treatment-naive patients.

Discussion

Socio-demographic characteristics of the evaluated population were similar to the Brazilian reported AIDS cases.[9] Since 1996, HAART is recommended as an option to initial therapy in Brazil, when the PIs became available. Until 2001, double therapy was the recommended option for patients without symptoms or advanced immunodeficiency. In 1998, NNRTI-class drugs were introduced and the preferential use of PIs was recommended for symptomatic patients and/or for those with advanced immunodeficiency. In 2000, RTV was restricted to use as pharmacological adjuvant and PI and NNRTI classes were equally indicated for initial therapy. Since 2004, NNRTIs have been recommended as first option and PI-containing regimens as an alternative for initial therapy. In our sample, a higher proportion of PI use by patients with T-CD4+ lymphocyte count under 200 cells/mm^3 was observed, reflecting the national guidelines recommendations at the beginning of the study period. Changes in the antiretroviral therapy observed over time correspond to modifications in Brazilian guidelines for treatment for adults and adolescents infected by HIV.[10-17]

Late arrival to treatment in this cohort was elevated and is probably related to the study period (1995-2005). We do not know if that was an exclusive finding for the city of Belo Horizonte at that time as there is not much data from other Brazilian cities in that period. Currently, the available data for Brazil shows that late arrival comprises approximately 40% of cases, which is just a bit higher than what is reported for the US and western Europe. In Brazil, Souza Jr et al.[18] evaluated 84,964 patients aged 15 or over with an initial T-CD4+ lymphocyte count done between 2003 and 2006, and whose HAART initiation was subsequent to the initial CD4+ T cell count determination. One third of patients had less than 200 cells/mm^3 and, when combined with number of symptomatic individuals, 41% of total group should have received immediate antiretroviral drugs (ARV).

In the multivariate analysis, none of the socio-demographic variables nor the T-CD4+ lymphocyte count at the beginning of HAART turned out to be risk factors for treatment failure and/or discontinuation. Although this study was not aimed at evaluating the influence of adherence on HAART duration,

this variable was indirectly measured. A significant association was observed between regular dispensing plus regular use of medication and longer duration of the first antiretroviral regimen. Although both measurements demonstrated a clear association with HAART duration, we noticed that irregular dispensing was a more accurate marker of discontinuation in the initial regimen, especially in the first months of treatment. This difference suggests that some patients may have omitted or denied their irregular use of medication to their physician. One limitation of this analysis was that it was not possible to be sure that patients regularly seeking medication at the pharmacy actually made regular use of it, as it has also been seen in previous studies carried out in the same outpatient clinic.[19,20] Irregular dispensing of medication remained as a risk factor for treatment discontinuation in the multivariate analysis, when this variable was added to Cox proportional hazard model. In the analysis of reasons for abandonment/non-adherence leading to regimen discontinuation, no differences were observed between drug classes PI and NNRTI, despite the pill burden and worse tolerability to PIs, especially those most often used by patients in this study.

In univariate analysis, pretreatment viral load was not a risk factor for treatment discontinuation. This finding is not in accordance with some previous reports. As described in the literature, high viral load at the beginning of treatment has been shown to be a risk factor for treatment discontinuation.[21,22] In the present study, this analysis may have been compromised by the small number of patients (318/891) that had this test available.

When comparing the main therapeutic classes, a lower discontinuation rate was observed for the NNRTI class at all periods, even after adjusting for T-CD4+ lymphocyte count and NRTI backbone at the beginning of treatment. In the pair-to-pair comparison amongst the eight most frequent regimens, combination AZT + 3TC + EFV showed a significantly lower discontinuation rate than the other regimens ($p < 0.05$). Three major randomized clinical studies initiated between 1997 and 1999 to evaluate the safety and effectiveness of regimens containg either a PI or an NNRTI showed similar increases in T-CD4+ lymphocyte count, and higher viral suppression in the group using NNRTI.[23-25] In a metanalysis of 53 clinical trials performed from 1994 to 2004 and involving 14,264 patients, Bartlett et al.[26] observed a significantly higher percentage of viral load below 50 copies/mL in week 48 among patients on regimens containing either a PI/r (ritonavir-boosted protease inhibitors) or in those containing a NNRTI when compared to regimens containing a PI without booster.

Intolerance/adverse events were the main reason for discontinuation of the initial regimen. The least tolerated drug was RTV alone, which was responsible for 27.6% of the regimen switches due to intolerance, followed by AZT (18.3%) and DDI (17%). Gastrointestinal intolerance to RTV is well documented and in the studied population it was the only protease inhibitor in 150 patients. Currently, RTV is only recommended in small doses, as a pharmacological adjuvant, as even at full dose is less efficacious and is associated with a high frequency of adverse events.[22,27] Myelosuppression related to AZT, leading especially to anemia and neutropenia, is a well described adverse event.[26] It is possible that the large percentage of patients with advanced immunosuppression and symptoms at the beginning of HAART might have contributed to the lower tolerance to AZT. As previously reported, several adverse events are common to all antiretroviral classes, limiting future options of antiretroviral regimens.[27-29]

As for duration and reasons for discontinuation of initial HAART, some observational studies corroborate the results here obtained. O'Brien et al.[22], in a retrospective cohort of 345 patients, observed after an average follow-up of 8.1 months that 61% of the patients interrupted initial HAART, with a cumulative probability of 51% of interrupting treatment after one-year of follow-up. Adverse events were the main reason for treatment discontinuation (24%), the most common of which being gastrointestinal intolerance. Therapeutic failure was the reason for treatment discontinuation in 12% of patients. The study regimens of the above-mentioned study corresponded to 43.5% of the prescriptions of the present study, in which a similar average duration was observed after one year follow-up (54%). In the current study we found similar results, with a higher proportion of therapeutic failure, probably due to the longer follow-up period. In another Brazilian observational study with 498 patients, Brito et al.[30] reported that 36% interrupted initial HAART within the first six months of treatment. They did not observe either the association of T-CD4+ lymphocyte count or the type of antiretroviral treatment with regimen discontinuation. There was a significant association with low education level and age between 25 and 34 years, which was not observed in this study.

Regarding differences in the initial therapy duration between the PI- and NNRTI-containing regimens, Dorucci et al.[21] evaluated the use of combined therapy as first regimen, initiated between 1997 and 2000, to compare the discontinuation rates among patients on PI versus NNRTI. Average follow-up time was 9.7 months (11 months for patients on PI and 5.6 months for those on NNRTI). The majority was receiving a PI-containing regimen (85.4%). Eight hundred and fifty-seven patients interrupted the first antiretroviral regimen, 777 (45.5%) of then were on PI and 80 (27.3%) on NNRTI. Toxicity was the reason for discontinuation for 42.7%, followed by therapeutic failure (28.5%) and non-adherence (23%). These results are similar to the current study, although the cumulative probability of interrupting treatment after one year was lower (37.5%) and there was no significant difference between drug classes regarding time for discontinuation considering all reasons. In relation to therapeutic failure, Dorucci et al.[21] reported a tendency for less discontinuation of the NNRTI group, differently from what was observed in this study. Other published data have indicated that overall discontinuation or modification of HAART regimens ranges from 8% to 59% (median 33%).[26]

The high frequency of regimens known to be less tolerated or less effective at the beginning of the period evaluated may have had an influence on the worse performance of PI-containing regimens. Current literature demonstrates the superiority of NNRTI-containing regimens when compared to PI-based regimens without a pharmacological booster. Therefore, the results of the current study were as expected. RTV boosted PI-containing regimens (IP/r), however, have shown an efficacy similar to those containing an NNRTI, with a lower chance of virological failure, but with higher frequency of adverse events.[26,31-33] However, RTV-boosted regimens correspond

to only 9.6% of the regimens herein evaluated, most of them with saquinavir/R (SQV/R) and indinavir/R (IDV/R), following the recommendations at that period. Also, the numbers were too small to analyze such regimens separately. On the other hand, this study provides important information about NNRTIs, especially EFV, and corroborates its use as drug of choice to compose the initial regimen in the current Brazilian recommendations. Furthermore, the long observation period and the large number of patients evaluated, combined with the similarity of the population studied with the Brazilian reported AIDS cases provide useful information for choosing the initial regimen in the country. Observational studies such as this complement the results obtained in clinical trials, as the former include patients with several socio-demographic characteristics in real life situaions.[34]

Medical records with incomplete information were a limitation in this study. Variables not found were considered as missing answers, which limited the analysis of some important variables, such as viral load. As only 96 patients had virological failure as the reason for discontinuation, this analysis was not performed. We do believe that if this evaluation would be done now, in a situation where there is ample access to viral load determination we would probably find more virological failure and drug substitution would have occurred sooner.

Conclusion

This study presents relevant information about several aspects of the first highly active antiretroviral regimen in Brazil. Even with free access to antiretroviral medication, for 61% of the patients there was failure or discontinuation of the regimen in the first 24 months of treatment. Nonetheless, these results are similar to those reported in industrialized countries.[2,35] NNRTI-containing regimens, especially with EFV, were more durable and effective than those of PI-containing regimens. Irregular dispensing of medication was a risk factor for treatment failure and/or discontinuation. Although more powerful and better tolerated antiretroviral drugs have been developed, poor adherence and the high rate of adverse events remain as the main obstacles for a long-term success of the treatment. Furthermore, it must be emphasized that a substantial percentage of patients initiated therapy with advanced symptoms and/or immunosuppression, which reduces the chances of therapeutic success and increases mortality in the assisted population.

Conflict of interest

The authors declare to have no conflict of interest.

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