Factors determining changes in initial antiretroviral therapy

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Summary

Objective: To investigate factors determining changes in initial antiretroviral therapy (ART) in patients attended to in an AIDS tertiary care hospital in Ceará, Brazil. **Methods:** This descriptive and exploratory study used the analysis of request to initiate or change treatment forms in the year of 2008, and the changes in therapy were followed through the first year of treatment. Data were analyzed with SPSS and EpiInfo by using ANOVA and the exact test of the coefficient of contingency, with significance at $p < 0.05$. **Results:** From 301 patients initiating ART, 22.1% (n = 68) needed a change in the first year. These patients were mostly males, aged 20 to 39 years; with only one ART changed needed in 86.8% of the cases (n = 59). Reports of two or three changes in regimen were observed. Zidovudine was the drug most often changed, followed by lopinavir/ritonavir and efavirenz. A significant association was found between changes in initial regimens and the report of adverse reactions ($p < 0.001$). **Conclusion:** The main factor determining changes in the initial ART was an adverse reaction report. Most patients had one change in the initial ART over the first year of treatment. ART monitoring contributed to a better control of the specific drug therapy.

Keywords: Acquired immunodeficiency syndrome; highly active antiretroviral therapy; drug toxicity.

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Introduction

AIDS, for its pandemic character, represents one of the greatest current public health problems. In Brazil, approximately 506,000 cases were reported as of 2008[1]. In the state of Ceará, 254 deaths from AIDS were reported in 2007, and 945 new cases of the disease were reported in 2008[2]. These data may be related to the policy of access to antiretroviral treatment and to early diagnosis[1,2].

Since 1996, through the Law 9313, the Ministry of Health (Ministério da Saúde – MS) has ensured free access to antiretroviral therapy to all HIV carriers, thus promoting a positive impact and a noticeable improvement in morbidity, mortality, and quality of life indicators[3].

The study was conducted in a HIV-AIDS tertiary care hospital in Ceará, which currently attends to 2,600 patients (adults, pregnant women, and children) receiving antiretroviral therapy (ART). Among these patients, the number of those who need a rescue therapy is large because they have often used several treatment regimens and had more than one therapy failure in prior trials. Thus, the hospital staff has members of the Interinstitutional Committee of Antiretroviral Therapy (Comissão Interinstitucional de Terapêutica Antirretroviral – CITA), which regulates the changes in patients' therapies and supervises these interventions based on specific forms and on data endorsed by the MS.

Consensus recommendations for the chosen rescue therapy are few, due to the small number of clinical trials comparing different strategies. The majority of current studies provide data about experience in rescue therapy focusing on new drugs. In addition, the heterogeneity of patients presenting therapy failure does not allow for the adoption of an absolute rule[3].

With the increasing number of patients on ART, treatment monitoring from its onset has become a priority in public health. Rescue therapy not only has an elevated cost, but non-adherence can result in mutations and resistant virus selection, which justifies the need for follow-up for these patients[4].

In the United States and in Europe, the average time the patient uses the initial ART is lower than one year and, although data are not numerous, this time seems to be considerably higher in Brazil and in other developing countries[5].

Better understanding of the factors associated with the initial ART change, of the documentation of the information regarding the patient and the pharmacotherapy in the proposed change is important for managing patients in the drug context. Thus, the current study aimed to describe and analyze changes in the initial ART in patients attended to in our hospital, so that a basis for treatment quality, safety, and effectiveness can be provided, as well as for judicious use of these drugs.

Methods

This descriptive, exploratory, retrospective, and documentation-based study was performed in the pharmacy service of an infectious disease-specialized tertiary care hospital of the Department of Health of the State of Ceará. The Request Forms for Initial Treatment or Treatment Change of all outpatients initiating antiretroviral therapy in the year 2008 and whose medication had been changed over the first year of treatment were sequentially analyzed. Thus, the patients were followed-up for one year after treatment initiation and, therefore, had their data acquired until the year 2009.

From 301 patients investigated, 68 had an ART change request and, among these, some had more than one change request, resulting in the generation of 78 forms. These forms prepared by CITA were filled by the physician attending to the patient on ART and submitted to the committee through the facility's pharmacy service. After being analyzed, the forms were sent back to the pharmacy in order to enable dispensation, and the forms were archived for five years.

The request form contained items regarding the patient identification, symptom presence or absence, treatment naïve status, drugs already used, current drugs, $CD4^+$ T lymphocyte count (CD4), viral load (VL), reason for requesting a therapy change, new regimen requested, and a field for the committee's opinion about the request. This information, obtained from the form during the study period, was organized, quantified, and analyzed in a spreadsheet containing clinical indicators and variables, such as: age, gender, CD4, VL, reason for changing the initial ART, time on the same ART regimen, number of favorable and unfavorable CITA opinions regarding the change request, and percentage of changes that were in accordance with Brazilian consensus on ART[3].

Patients under the age of 18; pregnant women who, in some settings, used ART only during the gestational period; and those who did not stay in the hospital's outpatient follow-up over the first year of treatment were excluded from the study. The results were expressed in tables, in the case of qualitative variables, and in central tendency and dispersion measures (mean ± standard deviation) in the case of quantitative variables. Data were analyzed using the Statistical Package for the Social Sciences – SPSS version 15.0 (SPSS Inc. – Chicago, IL) and EpiInfo version 6.04b (Centers for Disease Control and Prevention – Atlanta, GA) softwares. The parameters were compared through analysis of variance (ANOVA) and the exact test of the coefficient of contingency, considering a $p\text{-value} < 0.05$ as statistically significant.

The study was designed in accordance to regulatory standards and guidelines of research involving humans[6], ensuring patients' privacy and data confidentiality. It was approved by the hospital's ethics and research committee under the protocol no. 048/2009.

Results

Over the year 2008, 391 patients were registered into the Drug Logistical Control System (Sistema de Controle Logístico de Medicamentos – SICLOM) to initiate ART at the hospital. 72 patients who did not continue the treatment, 16 children, and two pregnant women were excluded.

From the 301 patients suitable for analysis, 22.1% (n = 68) changed ART over the first year of treatment, 61,8% (n = 42) of males and 38.2% (n = 26), females, with intervals of 49.9-73.6 and 26.4-50.1, respectively, a statistically non-significant difference in number of changes between genders. The predominant age group among patients was 20 to 39 years (69.1%; n = 47), followed by patients aged 40 to 59 (25%; n = 17) years.

Among the 68 patients experiencing changes in the ART regimen in the first year of treatment, 86.8% (n = 59) had only one change; 11.8% (n = 8) had two changes, and only one patient had three changes, amounting to a total of 78 change request forms analyzed.

At the initiation of treatment, 60.3% (n = 41) of patients were reported as symptomatic, and 16.2% (n = 11) as asymptomatic. Some forms did not show information about symptomatology (23.5%; n = 16).

The presence of AIDS-related opportunistic diseases was reported in the forms of 73.2% (n = 30) of the symptomatic patients, with one occurrence being described in 63.4% (n = 19), and two occurrences in 3.3% (n = 10) of patients. The occurrence of three diseases appeared on only one form, and no disease was mentioned in 26.8% (n = 11) of the symptomatic patients' forms. The diseases predominantly cited were: neurotoxoplasmosis, candidiasis, tuberculosis, histoplasmosis, diarrhea, cytomegalovirus disease, and herpes.

CD4 absolute count was present in 62.7% (n = 52) of forms, with results between 2 and 755 cells/mm^3. On the other hand, VL was present in 60.3% (n = 47), ranging from undetectable (< 50 copies/mL) to > 500,000 copies/mL.

In the forms of patients with a CD4 count < 500 cells/mm^3, the mean VL was 66,314 copies/mL (standard error 17,175), and it was higher than the VL in patients with a CD4 count > 500 cells/mm^3, i.e., 875 copies/mL (standard error 101), representing a statistically significant result (p = 0.018).

Initial ART regimens using a combination of two nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) were observed in half of the patients (n = 34); the predominant association zidovudine + lamivudine (AZT + 3TC) combined with efavirenz (EFV) was found in the forms of 54% (n = 27) of patients.

Initial regimens introducing two NRTIs associated with one ritonavir (RTV)-boosted protease inhibitor (PI) were observed in 44.1% (n = 30) of patients' forms, with the combination AZT+3TC plus lopinavir/ritonavir (LPV/r) predominantly used in 70% (n = 21) of patients' forms. Other regimens (2 NRTIs + 1 PI, 3 NRTIs + 1 NNRTI, and 2 NRTIs + 2 PIs) were observed in four (5.9%) patients.

Among NRTIs, the most often used was 3TC, found in 66 (97.1%) regimens, followed by AZT, in 59 (86.8%). LPV/r was the most often used PI, present in 22 (62.9%) regimens, followed by atazanavir (ATV) boosted by RTV, found in 10 (28.5%). The drugs ATV and fosamprenavir (FPV) were observed in three (8.6%) regimens. In NNRTI class, EFV was the drug most frequently chosen, found in 30 (85.7%) regimens, followed by nevirapine (NVP), in five (14.3%).

Table 1 shows the panel for all the drug changes during the study time, including the modifications for the patients who required more than one ART change over the first year of treatment.

The reports of adverse drug reaction (ADR) represented the main reason for the initial ART change in the analyzed forms, causing 88.5% (n = 69) of the substitutions, followed by five (6.4%) caused by non-adherence to the proposed treatment, three (3.8%) modifications caused by a report of a rifampin, isoniazid, and pyrazinamide (RIP) regimen initiated in patients with tuberculosis, and one change aiming to boost the therapeutic regimen already selected for the patient. The correlation of main change reasons with the drugs changed had a significant value (p < 0.0001), as shown in Table 2.

From the 59 patients who initiated ART with AZT, 42.4% (n = 25) changed to another regimen. Anemia reports occurred from a minimum time of seven days to a maximum time of 350 days. From 30 patients initially using EFV, the drug was changed in 63.3% (n = 19), eight of which (42.1%) due to reports of dizziness, insomnia, bad dreams, and hallucinations. The reactions occurred over periods ranging from 14 to 229 days.

LPV/r was related to a change in 77.3% (n = 17) of the 22 initial regimens in which the drugs were used, with gastrointestinal reactions being the most frequently cited reason for change, presenting from 15 to 154 days.

ATV was related to a change in 3 of the 10 initial regimens it was found in, two (66.7%) of them resulting from jaundice reports within a minimum of 72 days and a maximum of 329 days. Abacavir (ABC) was changed in the 4 (5.9%) regimens in which it was initially used: in one patient, from a hypersensitivity report, and in the remaining, from drug shortage in dispensation units in the country. A significant value (p < 0.001) was found when the association between the changes to the initial regimens was compared with the reported reasons for their occurrence, regarding ADR.

Table 1 – Panel of changes in antiretroviral therapy[a]

	Initial ART			Final ART		
	Among drugs		Percentage among patients	Among drugs		Percentage among patients
	n	%		n	%	
AR drugs found in forms						
AZT	66	24.4	84.6	43	15.6	55.1
3TC	76	28.0	97.4	78	28.3	100.0
LPV	27	10.0	34.6	22	8.0	28.2
RTV	37	13.7	47.4	42	15.2	53.8
ABC	7	2.6	9.0	11	4.0	14.1
ddI	2	0.7	2.6	4	1.4	5.1
d4T	2	0.7	2.6	2	0.7	2.6
EFV	35	12.9	44.9	28	10.1	35.9
NVP	4	1.5	5.1	4	1.4	5.1
ATV	10	3.7	12.8	23	8.3	29.5
TDF	5	1.8	6.4	19	6.9	24.4
Total	271	100.0	347.4	276	100	352.8

[a]Source: Request forms for initial therapy or change in antiretroviral therapy (ART) stored in the hospital pharmacy service. AR, antirretroviral; AZT, zidovudine; 3TC, lamivudine; LPV, lopinavir; RTV, ritonavir; ABC, abacavir; ddI, didanosine; d4T, stavudine; EFV, efavirenz; NVP, nevirapine; ATV, atazanavir; TDF, tenofovir.

Table 2 – Correlation between main reasons for change and each drug changed[a]

	Reason for change							
	Anemia		Hypersensitivity		Gastrointestinal reaction		Non-adherence	
	n	%	n	%	n	%	n	%
Drugs changed								
AZT	22	100.0	0	0.0	1	5.9	0	0.0
LPV	0	0.0	1	7.1	16	94.1	0	0.0
ABC	0	0.0	1	7.1	0	0.0	0	0.0
EFV	0	0.0	11	78.6	0	0.0	1	50.0
NVP	0	0.0	0	0.0	0	0.0	1	50.0
ATV	0	0.0	1	7.1	0	0.0	0	0.0
Total	22	100	14	100	17	100	2	100

[a]p-value < 0.0001 with reasons for changes and drugs changed compared in patients initiating antiretroviral therapy in the year 2008. They were followed up to 2009. AZT, zidovudine; LPV, lopinavir; ABC, abacavir; ddI, didanosine; d4T, stavudine; EFV, efavirenz; NVP, nevirapine; ATV, atazanavir; TDF, tenofovir.

No correlation was found either between the drug changed and the opportunistic disease reported (p = 0.709), or between the mean time from the treatment initiation until the regimen substitution regarding drugs (p = 0.688).

From the 78 Request Forms for Initial Treatment or Treatment Change analyzed, 89.7% (n = 70) of them showed a drug substitution and, in six (7.7%), two drugs were substituted. A four-drug substitution was observed in one form, and in another one, RTV was requested to be added in order to boost the regimen. The substitution panel of drugs used in the study first regimens is shown in Table 3.

Out of the total of forms (n = 78) submitted to CITA approval, 96.2% (n = 75) were directly approved, and in 3.8% (n = 3) the new proposed regimen was criticized and suggestions on a new regimen to be adopted were made, based on recommendations endorsed by MS, which were posteriorly accepted.

Discussion

There are few studies approaching the problem of ART changes over the first year of treatment, which represents a limitation to further discussion. Most studies depict factors associated with non-adherence as a priority[7,8]. In fact, studies conducted during early ART would be highly

Table 3 – Panel of drug substitutions in initial regimens of antiretroviral therapy

Initial ART drugs (n)	Drug substitutions (n and percentage)			
AZT	**TDF**	**ABC**	**ddI**	**d4T**
n = 25	n = 14 (56%)	n = 8 (32%)	n = 2 (8%)	n = 1 (4%)
EFV	LPV/r	ATV/r	NVP	ABC
n = 20	n = 10 (50%)	n = 7 (35%)	n = 2 (10%)	n = 1 (5%)
LPV/r	ATV/r	EFV	NVP	–
n = 19	n = 11 (57.9%0	n = 7 (36.8%)	n = 1 (5.3%)	
ABC	AZT	TDF	ddI	–
n = 5	n = 3	n = 1 (20%)	n = 1 (20%)	
ATV/r	EFV	LPV/r	–	–
n = 6	n = 4 (66.7%)	n = 2 (33.3%)		
NVP	EFV	–	–	–
n = 3	n = 3 (100%)			
TDF	AZT	–	–	–
n = 1	n = 1			
FSP/r	LPV/r	–	–	–
n = 1	n = 1			
d4T	ABC	–	–	–
n = 1	n = 1			
ddI	d4T	–	–	–
n = 1	n = 1			

n, number of regimens entered into the patients' forms. ART, antiretroviral therapy; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; d4T, stavudine; ddI, didanosine; EFV, efavirenz; LPV, lopinavir; NVP, nevirapine; r, ritonavir; TDF, tenofovir.

valuable, as the earlier the detection of problems, the lower the likelihood of the appearance of a resistant strain and other associated problems that make treatment harder[9].

In this study, the patients considered on ART were only those who continued treatment in the hospital for one year, from 2008 to 2009. Those who discontinued were excluded, and the reasons for their discontinuation (drop-out, transfer to another dispenser unit, death, or other reasons) were not investigated.

Over recent years, an increased number of women with HIV was observed, due to increased heterosexual transmission[10]. According to the AIDS-STD Epidemiological Bulletin, there was a reduction in gender ratio (M:F) for AIDS cases, showing a 1.5:1 ratio in 2007, compared to 6.5:1 in 1988[11]. However, over the year 2008, in the facility where the study was conducted, the number of male patients registered for the initial ART was higher than the number of female patients. Despite the data on the increased number of females, this study found values similar to a study from Caribbean and Latin America countries, in which only 35% of patients were females, with a mean age of 37 years[12]. This study also showed that female patients had a higher number of ART changes in the first year of treatment[12]. In the present study, no statistically significant difference could be observed in the number of changes regarding genders.

Concerning opportunistic diseases, an increase in the number of tuberculosis and neurotoxoplasmosis cases has been reported among patients with HIV/AIDS in the northeastern states of Brazil[10]. Perhaps this is correlated with a predominance of cases of these diseases. Tuberculosis is the main cause for morbidity and mortality in HIV-positive patients all over the world, and is found as the second most frequent disease in Brazil[13].

The determination of VL and $CD4^+$ cell count demonstrated that lower viral loads account for higher CD4 levels in treated patients, being referred as important laboratory monitoring tools to investigate virologic failure in ART follow-up and management, including circumstances where drug changes are required[4,3,8,13,14]. When VL and CD4 measurements are not available, clinical monitoring will assess the patient status and determine ART change[4,8]. In the present study, VL and $CD4^+$ recording was not found in every analyzed form, which does not mean that these data are missing, rather that they were not entered in the appropriate field.

In certain situations where the viral load is monitored, the ART regimen changes tend to occur earlier and within higher CD4+ levels, compared to programs with no VL follow-up[14]. In a study conducted in India, no correlation between CD4+ count and therapeutic failure was observed, as failures occurred in patients with various levels of this marker[15].

The antiretroviral therapy guidelines for adults infected by HIV[3] are periodically revised and, at times, changed. However, as this study database was from the year 2008, results were assessed based on the references from that year.

Most initial regimens consisted of two NRTIs + one NNRTI, followed by regimens with two NRTIs + one PI/r, with AZT + 3TC + EFV and AZT + 3TC + LPV/r being the predominant combinations in each case, respectively, in accordance with the Brazilian consensus on ART[3] and the findings of the Caribbean and Latin-American study[12]. However, in a study conducted in Africa, South America and Asia, the stavudine (d4T) regimen was also quite prevalent[14]. Other regimens with three NRTIs were found in a low ratio, similarly to that found in a study conducted in 23 countries[16]. In the present study, 3TC was the most used drug in initial regimens, as well as the drug with the lowest number of substitutions, in accordance with the results reported from the Caribbean and Latin-America[12]. AZT was the drug with the highest number of substitutions.

No significant association between drug changes and the variables "gender" and "age" was observed. However, results expressively indicated the report of ADR occurrence as the main reason for ART change requests, in accordance with studies conducted in Switzerland and South Africa[17], and in the Caribbean and Latin-America[12]. The treatment of opportunistic diseases occurring simultaneously with ART in AIDS patients likely affects antiretroviral tolerance, increasing the toxicity risk[12].

Following the results reported, AZT, the drug with the highest change percentage, was indicated as causing anemia in many patients. Accordingly, the study in the Caribbean and Latin America revealed anemia cases in over 70% of patients[12]. The guidelines on ART mention this hematologic change, as well as lipodystrophy, which is more common after one-year treatment[3]. Other considerable changes include LPV/r, which, in first regimens, was the most substituted drug regarding gastrointestinal reactions, and EFV, related to hypersensitivity reaction reports, confirming data already reported in the literature[18].

In most cases of initial ART changes, only one drug in the regimen was changed, in contrast with the findings of the study conducted in Africa, South America, and Asia, in which most changes (54.9%) involved two NRTIs and occurred due to toxicity in 10% of patients, and therapeutic failure in 74%[14].

In regimens where AZT was the reason for a change request, TDF was the main drug chosen, followed by ABC, didanosine (ddI), and d4T. In the case of EFV, it was most often replaced by LPV/r, followed by ATV/r. Such changes were in accordance with the consensus recommendations endorsed for antiretroviral therapy[3].

The number of approvals of the proposed regimens in the change forms was high, indicating that they were in accordance with the recommendations of the Brazilian consensus on ART[3]. Forms that were not initially approved received suggestions from CITA physicians, and these suggestions were followed by the attending physicians who requested the changes. It is also noteworthy that a number of forms were not appropriately filled and information requested was missing. However, generally speaking, despite these limitations, this context denotes the hospital's control in the management of ART, having an active committee with rules and regulations aiming at quality, efficacy, and safety of the treatments proposed to HIV-positive patients.

Conclusion

The main factor determining the initial ART change in the first year of treatment was the occurrence of adverse reactions, with AZT and LPV/r being the most implicated drugs, and anemia and gastrointestinal reactions, respectively, the most often reported events.

The majority of patients had only one change in the initial ART over the first year of treatment. These changes were in accordance with the Brazilian consensus. In this regard, the presence of CITA members in the reference center contributed to better management and control of specific drug therapy.

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