# COMPARISON OF ANTIRETROVIRAL SCHEMES USED IN INITIAL THERAPY FOR TREATMENT OF HIV/AIDS

## Luana LENZI[1]; Astrid WIENS[1] & Roberto PONTAROLO[1*]

Universidade Federal do Paraná. Departamento de Farmácia. Paraná, Brasil.
* Autor para correspondência: pontarolo@ufpr.br

## RESUMO

Um dos problemas da terapia antirretroviral (TARV) em pacientes com HIV é a sua adesão ao tratamento. O objetivo desse estudo foi relacionar os esquemas adotados na terapia inicial destes tratamentos com suas taxas de adesão, as mudanças de TARV e os custos do tratamento. Participaram do estudo pacientes acima de 16 anos de idade, HIV positivos, com tratamento há mais de 30 dias. A adesão à TARV foi calculada baseada na retirada dos medicamentos, que foi relacionado ao tempo total de tratamento. Avaliou-se em quantos pacientes a TARV foi alterada. Os custos de cada esquema terapêutico também foram estimados relacionando com os benefícios de cada tratamento. 142 pacientes que realizaram entre 38 e 1.150 dias de tratamento foram incluídos (57,7% homens). Os esquemas com menor custo, maior adesão e menor necessidade de mudança de tratamento foram efavirenz com biovir e efavirenz com lamivudina e tenofovir. Esse estudo sugeriu quais os esquemas terapêuticos mais vantajosos para inicio do tratamento, tanto do ponto de vista do paciente, como do sistema de saúde. Essa informação pode servir de subsídio aos médicos na decisão do início da TARV.

**Palavras-chave**: HIV; Antirretroviral, terapia combinada, adesão, efetividade.

## ABSTRACT

**Comparison of antiretroviral schemes used in initial therapy for treatment of HIV / Aids.** A problem of highly active antiretroviral therapy (HAART) in HIV patients is their adherence to treatment. The aim of this study was to compare the schemes adopted in the initial therapy of these treatments with their adherence, changes in HAART schemes and treatment costs. The study included patients over 16 years old, HIV positive, in treatment for more than 30 days. Adherence to HAART was calculated based on the withdrawal of the drug, which was related to the total treatment time. We evaluated how many patients changed HAART. The costs of each regimen were also estimated and related to the benefit of each treatment. 142 patients who were between 38 and 1,150 days of treatment were included (57.7% women). The schemes with lower costs, highest adherence and greater benefit were efavirenz with biovir and efavirenz with lamivudine and tenofovir. This study suggested the advantageous therapeutic regimens to start of treatment, both from the point of view of patients and the health system. This information can serve as a subsidy to clinicians in the decision of starting HAART.

**Keywords**: HIV; Anti-Retroviral; Combinated therapy; adherence; effectiveness.

## 1 - Introduction

The start of highly active antiretroviral therapy (HAART) may be one of the most difficult moments for individuals living with HIV. For this reason, set the best time to start treatment is one of the most important decisions in patient follow up.

Treatment is recommended in asymptomatic individuals with CD4 T-lymphocyte counts between 200 and 350/mm3. The closer to 200 cells/mm3 is the count of CD4 + T lymphocytes, the greater the risk of progression to AIDS, especially if associated with higher plasma viral loads (greater than 100,000 copies/mm3). Furthermore, the initiation of therapy depends on the downward trend in CD4 T-lymphocyte count and / or elevation of viral load, the patient's motivation to start treatment, their capacity to adherence and comorbidities. In asymptomatic patients with CD4 T-lymphocyte counts above 350/mm3 is not recommended to start treatment, since the benefits are not clear enough to offset potential risks of HAART (BRASIL, 2008).

The goals of HAART are sustained suppression of viral replication, preserve, and when possible restore the immune system, improve the quality of life and also reduce morbidity and mortality associated with HIV. These benefits have been clearly demonstrated both in patients with advanced symptomatic disease and in asymptomatic patients (BASTOS, 2006; TEIXEIRA *et al.*, 2000; WOOD *et al.*, 2004).

The first antiretroviral scheme is the moment of greatest possibility of suppression of viral replication and immune response. The rate of viral response to subsequent treatment is progressively smaller after each failure. For this reason, the importance of adherence to the therapy should be understood and accepted by the patient, since the effectiveness of treatment is associated with the use of the treatment regimen in a percentage equal to or greater than 95% of prescribed doses (PATERSON *et al.*, 2000; SMITH, 2004).

The clinician's decision regarding the composition of the initial antiretroviral regimen takes into account factors such as: the potential for adherence to the prescribed regimen, immediate and long term potency and toxicity, the presence of comorbidities, concomitant use of other drugs, the adequacy of the scheme to the routine of life of patients, interaction with food and the cost of the drugs (BRASIL, 2008).

According to the guidelines of clinical protocols, initial therapy should always include a combination of three drugs: two nucleoside analogues reverse transcriptase inhibitors (NRTIs) associated with a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an protease inhibitor reinforced with ritonavir (PI/r). Particularly in sequential therapy strategies, there are no published data from long term to determine which approach is associated with better outcomes (BARTLETT *et al*., 2006).

This article aims to relate the schemes adopted in the initial therapy of patients living with HIV with their adherence to treatment rates, changes in ART and treatment costs in order to establish the most advantageous schemes to initiate therapy, both from the point of view of the patient and the health system.

## 2 - Material and Methods

HIV+ patients were selected from the State of Paraná, who initiated treatment between October 2008 and December 2011. Inclusion criteria were age over 16 years and having been treated for at least 30 days.

All data regarding gender, age, initial regimen and withdrawals of antiretroviral drugs were inserted into the database. To calculate the adherence, it was considered as a total treatment time interval between the first and last date of take of drugs in the health system. Patients should take medication each month, once the bottles containing the required number of tablets for 30 days of treatment. Thus, we calculated the interval occurred between each date and this value was subtracted from 30, obtaining the number of days the patient was without any medication, or medication left on the withdrawal date of the next month, indicating in both situations, not doses administered. This result was added throughout the treatment period and related to the total time, thus obtaining the percentage of adherence.

The occurrence of changes in the initial treatment was observed in each case. For the groups for each initial therapeutic regimen were recorded the number of patients who underwent treatment changes in relation to the total number of patients in each group and the amount of times needed to exchange therapy.

The monthly and annual costs of drug regimens were obtained from the Table of Clinton Foundation's drug pricing, version August 2009 [9]. The monthly values were obtained by summing the values of vials of each drug that composes the schemes, since each container contains the number of tablets needed for 30 days of treatment. For the annual values, the annual costs of each value were added up.

The initial regimen was associated with adherence, with the occurrence of changes in treatment and the annual costs of treatment. The relationship between these variables was analyzed using S.P.S.S. version 17.0. This work follows the Declaration of Helsinki principles*, meets the specific legislation of Brazil and was approved by the Ethics Committee for Institutional Research, under the registration number CAAE: 0036.0.091.000-11.

## 3 - Results

Follow-up time ranged from 38 to 1,150 days. We included 710 patients, 410 (57.7%) were male. The mean age of patients was 38.9 (16-70) years. The drugs belonging to the class of NNRTIs used were 600 mg efavirenz (EFZ) and 200mg nevirapine (NVP). Among the NRTI drugs were biovir (ATC), composed by the combination of 300mg zidovudine (AZT) and 150mg lamivudine (3TC), 400 mg enteric didanosine (DDI400), 300mg tenofovir (TDF) and 150mg lamivudine (3TC). Among the drugs of the class of PI / r were 200mg lopinavir boosted with 50mg ritonavir (LPV / r), 300 mg atazanavir (ATV300), and 100mg ritonavir (RTV).

The treatment regimens used as initial therapy in these patients, the average rates of adherence, the percentage of patients who underwent treatment changes for each scheme and the cost of each treatment are shown in table 1.

**Table 1:** Characteristics of antiretroviral regimens.

| HAART | Class | Doses/day | N | Adherence** (%) | Changes (%) | Costs $ Month | Year |
|---|---|---|---|---|---|---|---|
| ATC*, EFZ | 2 ITRN + ITRNN | 3 | 385 | 83,5 | 28,6 | 18,33 | 220 |
| 3TC, TDF, EFZ | 2 ITRN + ITRNN | 4 | 175 | 86,3 | 25,0 | 19,83 | 238 |
| ATC*, NVP | 2 ITRN + ITRNN | 4 | 15 | 55,6 | 0,0 | 12,91 | 155 |
| DDI400, 3TC, EFZ | 2 ITRN + ITRNN | 4 | 5 | 40,2 | 0,0 | 31,58 | 379 |
| ATC*, LPV/R | 2 ITRN + IP/r | 6 | 100 | 74,0 | 25,7 | 48,75 | 585 |
| ATC*, ATV300, RTV | 2 ITRN + IP/r | 4 | 10 | 68,1 | 40,0 | 39,16 | 470 |
| 3TC, TDF, ATV300, RTV | 2 ITRN + IP/r | 5 | 20 | 86,5 | 33,3 | 40,66 | 488 |

HAART = highly active antiretroviral therapy. ATC = biovir. EFZ = efavirenz. 3TC = lamivudine. TDF = tenofovir. NVP = nevirapine. DDI400 = didanosine. LPV/R = ritonavir. ATV300 = atazanavir. NRTI = nucleoside analogues reverse transcriptase inhibitors. NNRTI = non-nucleoside reverse-transcriptase inhibitor. PI/r = protease inhibitor reinforced with ritonavir .N = Number of patients. *(AZT+3TC). **Mean.

Figure 1 shows the relationship between the variables cost and adherence in the initial treatment.
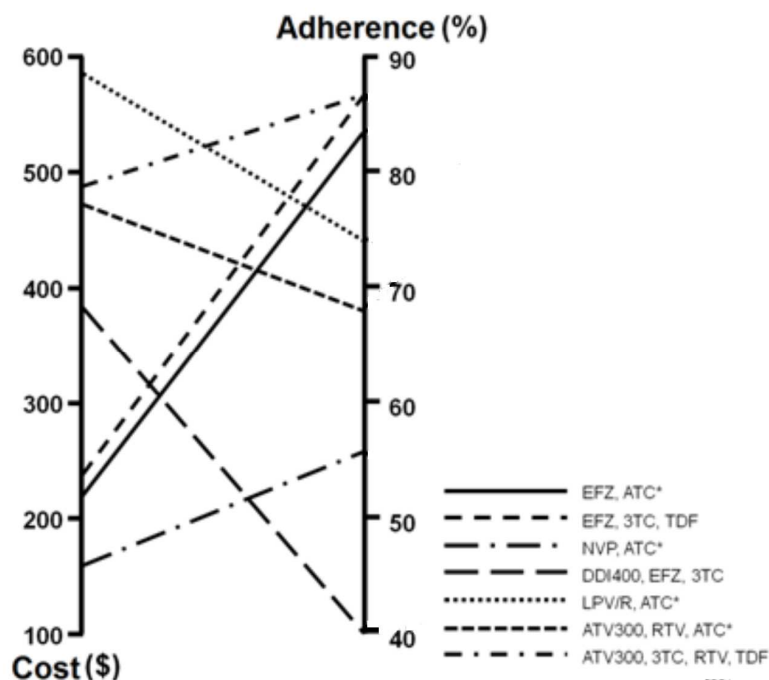


**Figure 1** – Parallel graphic relating annual cost vs. treatment adherence.

The graphic suggests that the best schemes for starting treatment were composed of EFZ and ATC (AZT+3TC) and EFZ, 3TC and TDF, which showed low-cost, high adherence and low percentage of changes in treatment regimen. Both schemes refer to the combination of 2 NRTI + NNRTI and require a lower daily intake of tablets, as shown in Table 1.

## 4 - Discussion

Several comparative studies involving treatment-naïve patients showed that rates of viral success (measured by the proportion of viral undetectability) in regimens containing two NRTIs + NNRTI were mostly equivalent than rates obtained in groups using regimens containing PI or PI / r (BARTLETT *et al.*, 2006).

Assessing the percentage of adherence in Table 1, it is observed that the rates ranged from 40.2% to 86.5%. However, to ensure the sustained viral suppression, prevent viral resistance and to ensure greater effectiveness of treatment is necessary for the patient to take more than 95% of the prescribed dose (BRASIL, 2008). There are numerous factors that can affect adherence to treatment, such as the complexity of the regimen (the number of doses and pills that must be ingested daily), lack of social support, emotional and / or material / instrumental; low education; non-acceptance of HIV status, presence of mental disorders such as depression and anxiety; side effects; user unsatisfactory relationship with the doctor and other professionals in the health team, negative beliefs and misinformation about the disease and treatment, abuse of alcohol and other drugs; difficulties of organization to suit the demands of daily routines treatment.

With the power of current antiretroviral therapy, adherence becomes one of the most important variables that influence the effectiveness of the first antiretroviral regimen. The partial suppression leads to early virological failure and emergence of viral resistance resulting in the need for changes in treatment. Changes in general occur due to four factors: the occurrence of adverse reactions; virologic failure (non-attainment or non-maintenance of undetectable viral load), immunological failure (progressive decline in CD4 T lymphocyte count) or clinical failure (progression of clinical infection expressed mainly by opportunistic infections or tumors). Thus, a low number of patients requiring changes in the treatment, suggesting a better tolerance and acceptance of scheme (BRASIL, 2008; RABOUD *et al.*, 2002; MALCOLM *et al.*, 2003).

Brazil has about 220,000 patients with HIV-AIDS under treatment and about 600,000 people infected. Since 1996, the year of publication of the Act 9,313, the Ministry of Health provides antiretroviral treatment to all HIV positive patients who meet the current therapeutic recommendations in Brazil. The annual cost of antiretrovirals reaches about $ 1 billion dollars. 15 antiretroviral drugs are distributed in public health, and eight of those produced domestically, which significantly reduces costs by importing antiretrovirals. Without domestic production spending would reach U.S. $ 1,325 billion, making the free universal distribution unviable (BRASIL, 2012).

The free and universal access to antiretroviral drugs has allowed a reduction of approximately 50% of the number of deaths between the years 1995 to 2001, and decrease in 80% of hospitalizations due to opportunistic infections such as tuberculosis and pneumonia or severe symptoms of AIDS, which led to a substantial saving of resources (BRASIL, 2010; BASSO *et al.*, 2007).

In addition to increased effectiveness and safety of antiretroviral therapy, is important that the standard regimens for initial treatment have great benefits and low costs. The decrease in spending and ensuring access to medicines is directly reflected in the improvement of quality of life of HIV / AIDS. As noted in this study, the schemes composed of EFZ + ATC and EFZ + 3TC + TDF showed high rates of compliance, low cost and low percentage of treatments change, when compared to regimens consisting of ATC + NVP, DDI400 + 3TC + EFZ, ATC + LPV / R, ATV300 + ATC + RTV and TDF + 3TC + RTV + ATV300 for use in initial therapy. The scheme consists of TDF + 3TC + RTV + ATV300 showed a high compliance rate, however its cost and the highest percentage of patients who underwent treatment changes disfavor this scheme. In general, schemes that use two NRTIs + NNRTI dosage is simpler, which probably facilitates adherence to treatment.

## 5 - Conclusion

Despite the limitations found in this study, the results allowed comparing the options for the initial treatment of HIV / AIDS. The advantages of the treatment by patient's point of view is the high percentage of adherence and the lowest rates of changes in the treatment, which suggests a higher tolerability of the scheme, particularly regarding the occurrence of adverse reactions. From the standpoint of the health system, it is advantageous to use effective drugs with low costs, reducing spending on drugs and hospitalizations resulting from health problems caused by infection.

### Limitations

This study had some limitations. Given the small number of patients in each group with regard to treatment, the results allow only suggest evidence of the superiority of compared drugs. This limitation can be justified by standard criteria currently using the protocol for treatment of adult HIV positive patients, which recommends that the initiation of ART is performed with 2 NRTI + NNRTI, particularly EFZ600 + ATC. Thus, other therapeutic regimens are not usual in the beginning of treatment, being adopted in special cases where the patient has incompatibility with the standard regimen, explaining the small number of individuals in these groups. Therefore, the choice of antiretroviral therapy by the physician may be based on inherent characteristics of the patient, they do differentiate the choice of antiretrovirals. Studies with more patients are needed to confirm these results. Furthermore, the rates of adherence are based on calculations relating to the dates in which patients withdrew the drugs and not from the daily take of the drug.

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