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*Full Length Research Paper*

# Description of pharmaceutical care to assess their effectiveness on adherence to antiretroviral therapy--A randomized clinical trial

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**In the framework of pharmaceutical care, pharmacotherapy follow -up requires developing, implementing and monitoring an individual care plan to solve drug-related problems (DRP). HIV/AIDS patients use complex regimens, factor that could lessen adherence, which in turn, is associated with increased viral replication and the development of drug-resistance. Studies have shown that perception of side-effects also lessens adherence, reinforcing the need to prevent, identify and solve problems during antiretroviral treatment and to avoid DRP through pharmaceutical care. We describe a program of pharmaceutical care for HIV/AIDS patients and our planned randomized controlled trial. To evaluate pharmaceutical care program for HIV-infected patients using antiretroviral treatment, through the Dáder method. Randomized clinical trial method was used for this study. Patients will be interviewed when they collected drugs or have their medical visit. Data will be collected through questionnaires demographic and self-reported adherence to the antiretrovirals and self-efficacy, for 12 months. Viral load and CD4 will be measured. The pharmaceutical care program will consist of color labeling the antiretrovirals and giving patients a card with prescription information. This study will provide information about HIV-infected patients' pharmaceutical care and will hopefully provide a validated model of pharmaceutical care for specialized health centers that will supplement their care.**

**Keywords:** Patient compliance, pharmaceutical care, anti-retroviral agents; HAART; HIV, Dáder method.

## INTRODUCTION

Pharmaceutical care is a new concept in professional practice, in which the patient is the main beneficiary of the pharmacist actions (WHO, 1993). In the framework of pharmaceutical care practice, pharmacotherapy follow-up requires developing, implementing and monitoring an individual care plan to solve drug-related problems (DRP) (Ministerio da Saúde do Brasil, 2006b; Ivama, 2002).

HIV/AIDS antiretroviral therapy aims to reach maximum viral replication suppression and to restore immune function, in order to improve quality and length of patients' life (Bartlett et al., 2001). However, for these goals to be achieved, high treatment adhesion is required (adherence rate>= 95%) (MS, 2006a).

Suboptimal adherence was found to be the most common cause for virologic failure in the early treatment phases of HIV infection and in analysis of causes of virologic failure (Descamps et al., 2000; Paterson et al., 2000). Research has demonstrated that suboptimal adherence (i.e., taking less than 90-95% of prescribed doses) is associated with increased viral replication and the development of drug-resistant HIV strains (Gifford et al., 2000; Liu et al., 2001; Wainberg et al., 1998), and it is also the cause of clinically significant health-related setbacks (Paterson et al., 2000). Prior studies conducted in our clinic showed a low antiretroviral adherence rate (56%) (Silveira et al., 2002; Pinheiro et al., 2002), similar to overall Brazilian rates (MS, 2006a).

HIV/AIDS patients use many drugs and complex regimens, factors that could lessen adherence (Silveira et

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al., 2003). Studies show the perception of drug reactions by the patient also lessens adherence, reinforcing the need to prevent, identify and solve problems that may appear during antiretroviral treatment and to avoid drug related problems through pharmaceutical care (Pinheiro et al., 2002; Pádua et al., 2006). Authors have already demonstrated high incidence of adverse reactions to ARV (approximately 33.7%) (Pádua et al., 2006).

Recent research has shown that pharmaceutical care increases adherence to antiretrovirals (Bluml et al., 2000; Haddad et al., 2002; McPherson-Baker et al., 2000) and significantly contributes to the care of HIV-infected patients (Calderón et al., 2004; Colombo et al., 1997; Emmerick, 2004; Foisy & Akai, 2004; Marshall et al., 1997). Aiming to evaluate the effect of a clinical pharmacist's intervention on duration of antiretroviral-related errors in hospitalized patients, Heelon M et al (Heelon et al., 2007) studied 199 hospital admissions, and 73 HAART errors were confirmed in 41 patients. The most common type of error was an incomplete regimen (Heelon et al., 2007), and the researchers concluded that the duration of prescribing errors decreased when a clinical pharmacist was monitoring patients receiving HAART and intervened to solve errors. Others authors demonstrated that patients who were managed by pharmacists had significant improvement from baseline in their CD4+ lymphocyte counts, viral loads, and drug-related toxicities (March et al., 2007; Cantwell-McNelis & James, 2002).

In a study by Marshall (1997), over 85% of HIV-infected man interviewed referred satisfaction with assistance given by pharmacists, but said they wanted more oral and written information and more personal interaction. On the other hand, the barriers most commonly cited by pharmacists in the development of pharmaceutical care are "lack of time", ''lack of specific training'' and ''lack of communication skills with patients''(Uema et al., 2008), suggesting that the description of a pharmaceutical care method is important. To our knowledge, there are no published prospective data regarding pharmaceutical care in HIV-infected Brazilian patients. Thus, the objective of our paper is to describe a method used in pharmaceutical care of HIV-infected patients on antiretroviral treatment and our plans to evaluate it using a randomized controlled trial design.

## MATERIALS AND METHODS

### Design

Randomized clinical trial, controlled by non-intervention, to be carried out in accordance with CONSORT prescriptive. Trial is registered as number NCT00959361 on ClinicalTrials.gov. Patients and statistical analysts will be blinded.

### Sample size

Considering adherence of 56% in the control group and relative risk of 1.3 of adherence to the antiretroviral treatment for the intervention group, a level of significance of 0.05 and power of 80%, we estimated that 138 patients in each group would be necessary. Adding 20% in order to account for losses and refusals, the final calculated sample size is 166 patients in each group.

### Inclusion criteria

Adults (>=18 years), habitants of the urban zone of Pelotas, not pregnant, using antiretroviral treatment independent of the time under treatment, consecutively registered in Serviço de Assistência Especializada em HIV/AIDS de Pelotas-RS- Brazil (SAE-Pelotas), agreeing to participate in the study and to sign written informed consent.

### Exclusion criteria

Refusal to sign written informed consent, inability to fill out the instruments of data collection, patients who could not be followed for 12 months.

### Data collection

All patients in both the groups will be interviewed at the time of drug collection at the pharmacy or at the time of their medical visit. Data will be collected through structured questionnaires, including demographic information and self- reported adherence to the antiretroviral regimen (Silveira et al., 2002; Pinheiro et al., 2002; Silveira et al., 2003). All interviewers will be trained.

Adherence to the treatment and other cited questionnaires will be applied at baseline and every 3 months in both groups (accounting for 4 measures of adherence during a 12-month period) (Figure 1).

### Intervention: Pharmaceutical care

### Research team and structure

*I- Managers:* Students in the Pharmacy course of the Catholic University of Pelotas have been previously trained. The training was performed by the infectious disease physician responsible for the service (CP), and was 8 hours. The training in pharmaceutical care, the Dader method and on drugs used by HIV patients was conducted by MS and was 8 hours. In total there have been 16 hours of initial training. Monthly meetings will be held where the training reinforced.

*II- Place:* Serviço de Assistência Especializada em HIV-AIDS, Pelotas (SAE-Pelotas).

*III- Development:* Patients randomized to the pharmaceutical care group will be interviewed at the moment of drug collection at the pharmacy or at the time of their monthly medical visit in a private room. Pharmaceutical care will deliverd using the Dáder method. The following steps will also be carried on monthly:

1st - Patients will be asked if they understood the prescription and asked to repeat it to evaluate possible misunderstandings.

2nd - Patients will receive a card with information regarding the prescribed medication, schedule and amount, and the date of next clinical visits. (Figure 2)

3rd - The prescription will be repeated by the student while showing the card to the patient and providing drugs labeled with different colors, to identify each antiretroviral and to facilitate patient understanding. (Figure 3)

The medicines will be identified by colors (a different color for each medicine) in order to facilitate its identification since many patients cannot read or have vision impairment. All drugs' boxes and bottles are identified.

4th - The patient receives verbal information about the probable side effects and oriented to seek medical attention or aid through the pharmacy's telephone without discontinuing drug use.

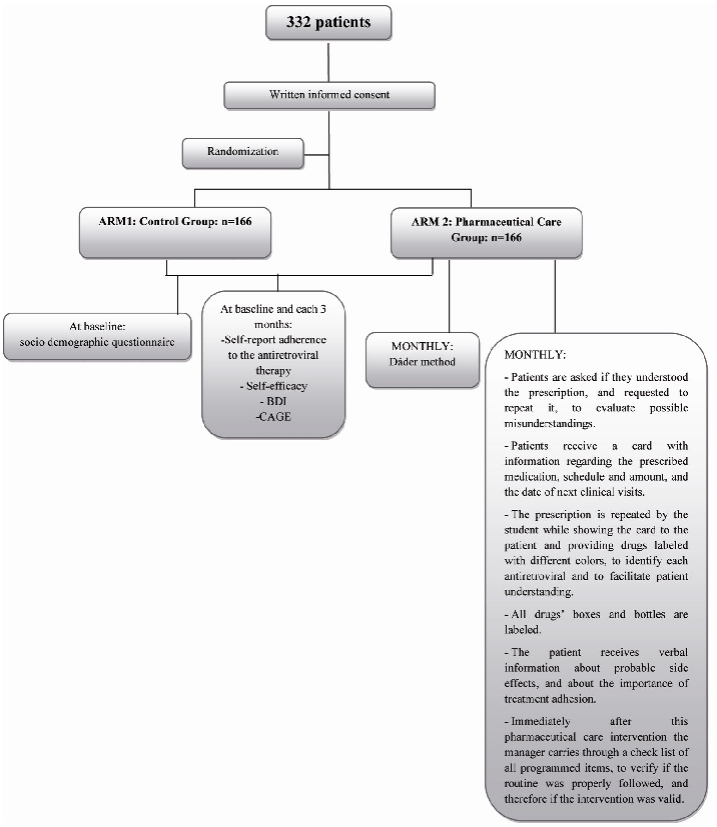


**Figure 1**. Framework of study

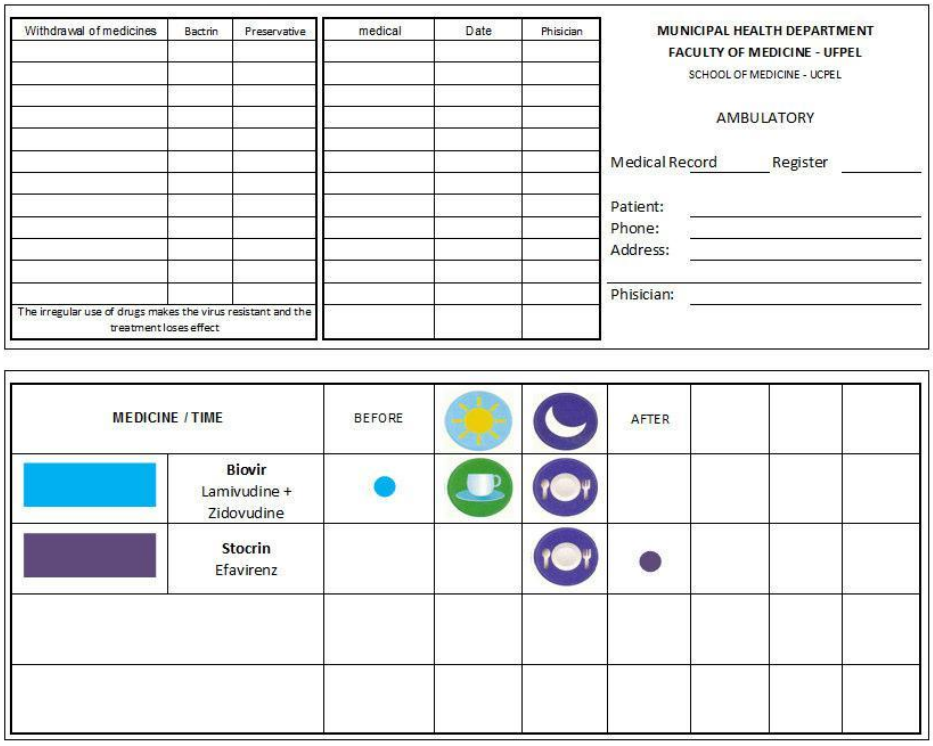


**Figure 2.** Example of Card: information regarding the prescribed medication


**Figure 3**. Description of antiretroviral´s colors

5th - The importance of treatment and adherence will be reinforced.

6th - Immediately after this pharmaceutical care intervention the manager will review a check list of all programmed items to verify that the routine was properly followed, and therefore if the intervention was valid.

Patients who do miss visits to collect medication will be contacted by telephone or receive home visits if necessary, and requested to return to the service.

**Brief description of the Dáder method (Programa Dader, 2004)**

The Dáder method consists of a series of previously scheduled interviews.

First interview: This interview begins with an open question about health problems that concern the patient and about drug-related problems. The patient's medication bag is reviewed in order to identify drugs and register how they are being used. From this information a situational analyses and a global evaluation are performed to identify, prevent and seek solutions to drug-related problems. The definition proposed by the Brazilian Consensus of Pharmaceutical Care of drug-related problem will be used (Ivama et al., 2002): "any health problem related or suspected to be related to drug therapy that interferes or may interfere in the results of therapy or in the quality of life of the patient". A drug-related problem will be considered to be present whenever there is an issue regarding need, effectiveness, or safety, and these conditions are not optimal. The most common reasons and possible solutions for the occurrence of drug-related problems will be investigated by the pharmacist and by the physician when necessary.

Second interview: The second interview identifies drug-related problems listed by the patient and proposed strategies to solve them (pharmaceutical intervention).

The evaluation continues on the following interviews, always focusing on drug-related problems. According to the method, there is no need for monthly encounters unless there is change in the treatment or if the patient requests it.

## RESULT

### Definition of the outcomes (dependent variable)

### Adherence to antiretrovirals

**T**he use of antiretrovirals in the last 3 days will be investigated by self-report. A time sheet will be used to help the patient remember his/her routine activities (e.g., breakfast, lunch) and report the medicines in use, doses and time of administration. Individual drug adherence will be calculated dividing the number of tablets of each drug taken in three days by number of tablets prescribed in the same days. Rate of regimen adherence will be calculated by arithmetic mean of all individual drug adherences. Patient will be considered adherent if reporting an intake 95% of the prescribed dose during the three days of evaluation (MS, 2006a).

### Viral load

Plasma viral load will be measured subsequently to the adherence evaluation (viral load and CD4 counts are routinely measured every four months for patients on antiretroviral therapy) . The viral load measurements will be performed by the bDNA method ( *branched DNA)* in periods of clinical stability, at least four weeks after immunizations or recovery from infections, and always at the same laboratory accredited by the Ministry of Health in Brazil. The detection limit with this method is 50 copies/ml (MS, 2006a).

### Control variables (potential risk factors)

### Sociodemographic conditions

Sex, age, years of study, household income (as a proportion of minimum wage – R$ 350.00 = US$ 153.21), work status, government benefit dependence and living situation will be assessed through individual questions.

### Evaluation of depression symptoms

This will be assessed through the self-report Beck Depression Inventory (BDI) . It has been extensively used in depression studies and was shown to be valid and reliable in measuring depressive symptoms. The BDI has 21 items, which reflect cognitive, affective, behavioral, and somatic symptoms of depression. Each item is composed of four statements, and the patient is asked to pick the one that best describes how he/she has been feeling for the past week. Statements are scored on a scale value of 0 to 3, according to the intensity of the symptom. Final scores are obtained by adding all points. The BDI cutoff score will be 12. The following score ranges will be considered are 0-11, non-depressed; 12-19, mildly depressed; 20-35, moderately depressed; and 36- 41, severely depressed (Cunha, 2001). If necessary the patients will be referred to clinical assistance.

### Evaluation of problems with alcohol

This is assessed through CAGE questionnaire.

### Evaluation of smoking

Patients will be asked about smoking and amount of cigarettes consumed per day in the last 30 days.

### Expectation of self-effectiveness

This will assessed through a specific scale (Pinheiro et al., 2002). Each item of the scale corresponds to one of five answers: I will not take the medication, I think I will not take the medication, I do not know, I will take the medication and I will certainly take the medication. This will be considered an independent continuous variable, because each score 0-5 points. Means and standard deviation will be calculated for patients with and without pharmaceutical care.

### Expectation of results; perceived social support and perception of negative affection and physiological states

Collected through appropriate scales (Pinheiro et al., 2002), each item of the scales admits five answers: I completely disagree, I disagree, I do not know, I agree and I completely agree. This will be considered an independent continuous variable. Means and standard deviation will be calculated for patients with and without pharmaceutical care.

Information obtained from records will be used to create the following variables:

*Viral load previous to the first adherence measurement:* last plasma viral load (quantification of the RNA of the HIV) available before this protocol.

*Duration of antiretroviral treatment*: number of months between the beginning of the antiretroviral therapy and the date of the final viral load count (when the outcome is viral load) or the date of the last interview (when the outcome is adhesion to treatment).

*Group of drugs in the antiretroviral regimen currently prescribed:* drugs will be grouped according to their mechanism of action: (a) nucleoside reverse transcriptase inhibitors (NRTI), (b) non-nucleoside reverse transcriptase inhibitors (NNRTI), (c) protease inhibitors (PI), and (d) fusion inhibitors.

*Number of drugs* : drugs will be grouped into triple, quadruple regimens or 5 or more drugs in use.

*Total of antiretroviral pills prescribed per day:* numbers of pills prescribed per day.

*Changes in antiretroviral regimens*: investigation of previously prescribed antiretrovirals regimens and of new prescription changes.

*Current immune status*: determined by the CD4 lymphocyte count measured closest to the interview, using flow cytometry. Counts of 200 cells/mm $^3$ or higher indicate a stable immune status (Bartlett et al., 2001; MS, 2006a).

*Clinical stage of disease caused by HIV*: classified according to the recommendations of the United States Centers for Disease Control and Prevention (CDC, 2000) and modified according to the criteria adopted in Rio de Janeiro/Caracas. Patients will be classified as stage A (asymptomatic), stage B (with symptoms related to HIV) and stage C (with diseases that define AIDS or with 10 or more points in criteria adopted by the Rio de Janeiro/Caracas consensus) (MS, 2006a; CDC, 2000).

## Statistical analysis

Data will be entered in duplicate. The variables will be described by measures of central tendency and proportions. In view of the repeated measures, the associations will be analyzed using generalized linear models using SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA). Covariates will be selected using a hierarchical model. At the first level, we entered socioeconomic variables (sex, age, family income and schooling). At the second level, we added social variables (living alone, alcohol use, regular employment), at the third level clinical variables (immune status, viral load and depressive symptoms), at the fourth level treatment-related variables (treatment period, group of antiretroviral medications and total of tablets) and, finally, at the fifth level, the intervention variable (PC). Variables significantly associated with adherence at a significance level of $p < 0.2$ will be included in the next level.

## Ethical aspects

The guidelines of direction and norms of research involving human beings established by Resolution 196/96 of the National Advisory of Health will be followed. Only after written informed consent is obtained will the patient be randomized and the study's evaluation instruments applied. This study has been approved by the staff of the service, by the Scientific Commission of the Catholic University of Pelotas and by the Ethic Committee of the Federal University of Rio Grande do Sul.

## Conclusion

This study will provide important information about HIV-infected patients' pharmaceutical care and will hopefully provide a validated model of pharmaceutical care for specialized health centers that will supplement their care. This will we hope, improve the quality of their services, the quality of patients' life, and also value the professional practice of the pharmacist.


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