

*Full Length Research Paper*

# A simple method for adherence evaluation to highly active antiretroviral therapy by Brazilian patients from healthcare unit: Focus on a adequately therapeutic compliance

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**In general, the indirect measures used to evaluate adherence to medication treatment are self-reporting, daily record of the medication use, pharmacy dispensing records, and others. This study used the indirect method analyzing the dispensing records to evaluate adherence of 295 patients treated with antiretrovirals in Health Unit of Ribeirão Preto (SP), from January 2009 to December 2011. The level of adherence, i. e., regularity, low irregularity, high irregularity and dropout presented values of 23.7, 26.1, 46.1 and 26.4%, and over the 3 years, the dropouts showed a significant increase, with a recidivism rate ranging from 1 to 6. The correlation studies showed a negative correlation ( $P<0.05$ ) between age and adherence, more pronounced in women ( $P<0.01$ ). On the other hand, the changes in therapeutic prescriptions was positively correlated with the abandon ( $P<0.05$ ). Based on these results, peculiarities of populations' adherence are useful in the development of actions aiming to improve the assistance.**

**Key words:** Acquired immune deficiency syndrome virus, highly active antiretroviral therapy, medication non-adherence, correlation studies.

## INTRODUCTION

After three decades of the human immunodeficiency virus (HIV) emergence, Brazil has occupied a prominent role, ensuring free access of the population to highly active antiretroviral therapy (HAART). This action contributed to the stabilization of the epidemic and increased the rates of longevity and quality of life, even though the growth was still observed in sub-populations in condition of vulnerability and mortality (Barreto et al., 2011; Brasil, 2013; Fonseca and Bastos, 2007). This growth can be attributed to the poor patient adherence to therapy

(WHO, 2003; Ceccato et al., 2004; Melchior et al., 2007), a challenge for the Brazilian Unified Health System (Crespo-Fierro, 1997; Figueiredo et al., 2001).

Despite the difficulty of establishing a measure of adherence to treatment effectiveness, studies show that the expected effects of viral sustainable suppression and improvement of the immune system occur when the patient ingest about 95% of prescribed doses (Paterson et al., 2000; Gross et al., 2006). Lower levels of adherence can lead to selection of resistant viruses resulting

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in treatment failure and new treatment schemes, more complex and costly (Martin-Sanchez et al., 2002; Munakata et al., 2006)

In general, patients present adherence of 20 to 50% to prescription of health care professionals and treatment recommendations, including medicine use ranged from 20 to 50% (WHO, 2003; Brasil, 2007; DiMatteo, 2004; Osterberg and Blaschke, 2005). Adherence is a dynamic and multidimensional phenomenon determined by the inter-relation of economic and social factors that requires shared and mutual responsibility between the individual diagnosed positive for HIV, the health equipment and social network (WHO, 2003; Brasil, 2007).

According to Nachega et al. (2006) is important to know the level of adherence to HAART, since some problems such as long distance from home, difficulty with the dosing schedules, and running out of pills can be identified soon and strategies focused on adherence maximized. However, there is no way to establish a "gold standard" for measuring adherence (WHO, 2003). Direct and indirect methods are used to evaluate medication adherence. Among the direct measures, we can include plasma concentration of antiretrovirals (ARVs) and their metabolites, drug assay in urine and direct observation of the patient receiving the medication (Crozzati, 2007). Among the indirect measures, self-report, the daily record of medicine use, manual/electronic counting of pills, electronic monitoring and drug dispensing records of pharmacies can be used (Bonolo et al., 2007; Carvalho et al., 2003; Johnson et al., 2009; Rocha et al., 2011; Polejack and Seidl, 2010).

For the computerized system and identification by bars code of the dispensed medication, the data records began to be highly accurate and reliable, providing precise and exact information. Although it does not ensure that medications dispensed will be used correctly, it is considered that there is a relation between medication dispensed and their correct use (WHO, 2003; Gomes et al., 2009).

In this context, a public unit for medication dispensing (PUMed) has a special role to the access and the coherent use of the medication (prescription, dispensation and patient use). This PUMed is generally linked to a basic healthcare unit (BHCU) which has multidisciplinary professionals in a city or district (Brasil 2010a, b). Consequently, studies directed towards a single PUMed can reveal the impact of a complete healthcare service for a specific group of patients (Brasil, 2007; Minas, 2008).

Therefore, the aims of this study were to evaluate the adherence of patients by using the individual dispensing records of ARVs and correlate adherence to age, gender and scheme's modifications.

## METHODOLOGY

The location of data collection was the pharmacy from PUMed Sumarezinho, situated at the West District of Ribeirão Preto city, State of São Paulo, Brazil. The records of dispensing ARVs (and

HAART) were collected during 36 months (from January 1st, 2009 to December 31st, 2011).

The PUMed is from a BHCU assisted by the Faculty of Medicine of Ribeirão Preto, University of São Paulo and the Municipal Secretariat of Health. The PUMed is part of the service of pharmaceutical care of the Municipal Health System of Ribeirão Preto (MHS). This PuMed is linked to the PN-DST/AIDS for providing the dispensing medication from strategic component of pharmaceutical care including ARVs beyond the municipal essential medicines (REMUME). Among the list of ARVs available for dispensing in the municipality are: (1) Nucleotide Reverse Transcriptase Inhibitors (NRTIs): abacavir (ABC), didanosine (ddl), stavudine (d4T), lamivudine (3TC), tenofovir (TDF), zidovudine (AZT) and lamivudine + zidovudine (AZT + 3TC, Biovir<sup>®</sup>); (2) Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): efavirenz (EFV) and nevirapine (NVP); (3) and protease inhibitors (PI): atazanavir (ATV), darunavir (DRV), fosamprenavir (FPV), indinavir (IDV), ritonavir (RTV), saquinavir (SQV) and lopinavir + ritonavir (LPV/r, Kaletra<sup>®</sup>); (4) fusion inhibitor (FI): enfuvirtide (T20) and; (5) integrase inhibitor (II): raltegravir (RAL).

## Population and sampling

The population of the west district is estimated at 151,218 inhabitants, according to IBGE (2013).

Antiretroviral drugs were dispensed mainly to resident population in the area of the BHCU. The data was collected from 341 patients who had personal registration of dispensation. Criteria for eligibility were: gender (male, female), age ( $\geq 18$  years) and on HAART. From these, were selected patients who had the registries in the system of management of the municipality's health, named HygiaWeb, and logistics control system of medications (Siclom) since January 1st, 2009. Patients were excluded based on: (1) did not pickup medication for a period longer than 12 months (n=26); (2) transfer registered (n=9); (3) obits (n=10) and; (4) pregnant women (n=1) due to the particularity of treatment (Gomes et al., 2009). Finally, after exclusions, the populations studied totaled 295 individuals (86.51%). All patients in use of HAART had their names coded to ensure anonymity (alphanumeric code).

In the present work, record on dispensing drugs to patients with HIV/AIDS dispensed the statement of consent. This study was approved by the Ethics in Research, Teaching Health Center, CONEP-CEP on 03/09/2012.

## Dispensing records

The ARVs are dispensed in the PUMed from a BHCU, through individualized assistance. Each patient, at the dispensing, receives the amount of pills for one month of treatment and the date of the next return, according to the medical prescription. For each dispensation along the 36 months of the study, the attendance records and individually dispensing drugs (individual records, HygiaWeb and Siclom) were analyzed. From both, individual form and Siclom/HygiaWeb, the following data were collected: ARVs, quantity dispensed, date of dispensing and changes in the scheme of treatment. Finally, the information was inserted into a database (Excel 2003, Microsoft<sup>®</sup>).

## Evaluation of dispensations

For the analysis, the following variables were considered: number of patients, gender (male and female), age ( $\geq 18$  years), use of medications and schemes (medications used and scheme according the methodology), as well as the modifications in HAART scheme (number of modifications on schemes during the period).

Regarding medications' dispensing were considered the frequency (monthly) during the period. Anticipated dispensations or dispensations for more than one month of treatment, time and counting pills were adjusted for the monthly period (Gomes et al., 2009; Grossberg et al., 2004). Thus, classification of dispensations were divided into three groups: regular, when there was no failure in withdrawing medications, including frequency (monthly) and amount of pills; Irregular, patients who did not pick up the medications in the correct frequency (monthly), remaining a period of 30 to 60 days without medications were considered; and dropouts, when the patient failed the pickup of medication for longer than 60 days (Bomtempo, 2000; Carmody et al., 2003; Seguy et al., 2007) with the possibility of the return to the treatment.

For each patient who abandoned (> 60 days) and returned to treatment, recidivism rates were calculated. Already for irregularities (up to 60 days) were classified as low and high irregularity. Low irregularity were considered, which is the frequency of pickup of ARVs  $\geq 95\%$ , or in other words, from one to two irregular pick up of medications over the period. For high irregularity were considered the patients who picked up the medication at a frequency  $\leq 95\%$ , in other words, three or more irregular pickups.

### Statistical data analysis

Statistical analyzes were performed by SigmaStat software (SigmaStat for Windows, Version 3.5, Systat Software Inc. 2006). One-way analysis of variance (ANOVA) was used for data analysis (regularity, irregularity and dropouts between the years). For the use of ARVs, the data presented as parametric and correlation test of "Pearson" was used. The P-value was set at  $P < 0.05$ .

## RESULTS

Table 1 presents the population's characteristics. From the total, 152 were male (51.5%) and 143 females (48.5%). The male population, female and total presented a normal distribution since the medians and percentiles were close, as well as the low standard deviation between ages. Male/female ratio was 1.06 (Table 1).

Regarding age, the main proportion of AIDS cases was observed between 40 and 49 years (42.7%), followed by age group 50 to 59 years (19.7%).

Comparisons between the rates of irregularities during the period (Figure 1) showed that there were no statistical differences between 2009 ( $17.2 \pm 7.3$ ), 2010 ( $17.1 \pm 4.3$ ) and 2011 ( $17.1 \pm 3.5$ ) with  $P > 0.05$ . The averages of dropouts in the first, second and third years were  $6.3 \pm 2.5$  (1 to 12 months),  $9.4 \pm 1.8$  (13 to 24 months) and  $12.3 \pm 1.8$  (25 to 36 months), respectively. Statistical analysis revealed a significant increase in the number of dropouts ( $P < 0.01$ ) from the first to the second year and from the second to the third year (Figure 1). The regularity ( $n = 295$ ), which involves dispensation of HAART within a period of 30 days, was detected for 70 individuals, or 23.7% of total adherence to treatment (Figure 2A and 3).

Considering low irregularity, the percentage achieved 26.1% (77 patients), however patients with high irregularity, i.e., time without pickup the medication is higher than 5%, was 46.1% (Figure 2A).

In this study, patients who dropout totalized 78, the percentage was 26.4% value higher than patients considered regular (Figure 2A). We should also consider the recidivism rate of these individuals (Figure 2B). In this study it was observed that 78.2% of these individuals ( $n=61$ ) dropout and returned to the treatment once or twice and 20.4% (17 subjects) did it more frequently, from 3 to 6 times during 3 years (Figure 2B).

Regarding the total population ( $n=295$ ), statistically significant correlations between the dropout rate and (1) age, (2) change in the treatment scheme of the individual and (3) regularity was observed (Table 2). The regularity demonstrated negative significant statistically correlation more substantial with the dropouts ( $r=-0.558$ ), in other words, the higher regularity, lower dropouts. In relation to age, the higher the age of the population the lower the dropouts ( $r=-0.196$ ) and more regularity ( $r=0.224$ ), as shown in Table 2. In contrast, the change in the treatment scheme is positively correlated to dropouts and negatively to the regularity. This implies that the higher the change in the treatment scheme of the individual the higher the dropout rate.

Concerning male ( $n=152$ ), a statistically significant influence on these correlations was not observed (Table 2). Only a statistically negative with respect to the regularity and dropout rate was observed ( $r=-0.534$ ). However, females ( $n=143$ ) had a strong influence on the correlations, particularly to dropouts and change in treatment scheme (Table 2). Finally, no correlation was observed between age and change in the treatment scheme of patients regarding the general population and genders.

Between January 2009 and December 2011, considering the first record of dispensing for each patient, 49 different HAART's schemes were detected. Therefore in the course of the records there was an increase in the number of schemes to 80, or an increase higher than 63% in the number of combinations of HAART for the treatment of patients during the period.

The combinations of HAART more prescribed were triple schemes combining two NRTIs with a NNRTI, being the most common medication AZT+3 TC (62.7%). The most frequent combinations with AZT +3TC was with EFZ (28.1%) and NVP (13.3%). The most prevalent of PI scheme with AZT +3TC medications was LPV/r (9.5%).

## DISCUSSION

According to Brazilian government, in 2011, the national population ratio was of 1.7, narrowing over the years (Szwarcwald et al., 2000; Dhaliya et al., 2000 Ribeirão Preto, considering cases from 1985 to 2011, ratios were 2.12 and 1.57, respectively. One factor that may explain the decrease in the proportion of HIV cases between men and women is the increased rates of heterosexual transmission to women (84.6%) (Brasil, 2011). In Ribeirão Preto, the higher exposure category of the 5628 cases from

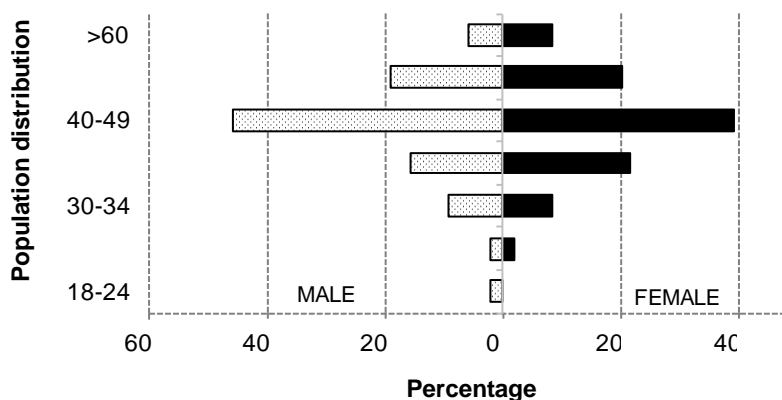
**Table 1.** Descriptive analyses of the population studied.

Data	Population		
	Total	Male	Female
Localization	Ribeirão Preto (state of São Paulo), Brazil		
N	295	152	143
<b>Age (years)</b>			
Mean	44.6	44.3	44.9
Standard deviation	9.1	8.9	9.2
Minimum	18	18	28
Maximum	75	75	71
Median	44	45	44
Percentile 25	39	39	38
Percentile 75	50	49.5	51

**Table 2.** Correlation between parameters related to the use of ARVs on the Basic Healthcare Unit.

Population	Total (n=295)			Male (n=152)			Female (n=143)		
	Dropout	Age	Scheme change	Dropout	Age	Scheme change	Dropout	Age	Scheme change
Age	-0.196*	-	-	-0.157	-	-	-0.240**	-	-
Scheme change	0.132*	-0.003	-	0.010	0.059	-	0.245**	-0.072	-
Regularity	-0.558**	0.224**	-0.115*	-0.534**	0.137	0.009	-0.585**	0.331*	-0.237**

\*P&lt;0.05; \*\*P&lt;0.01

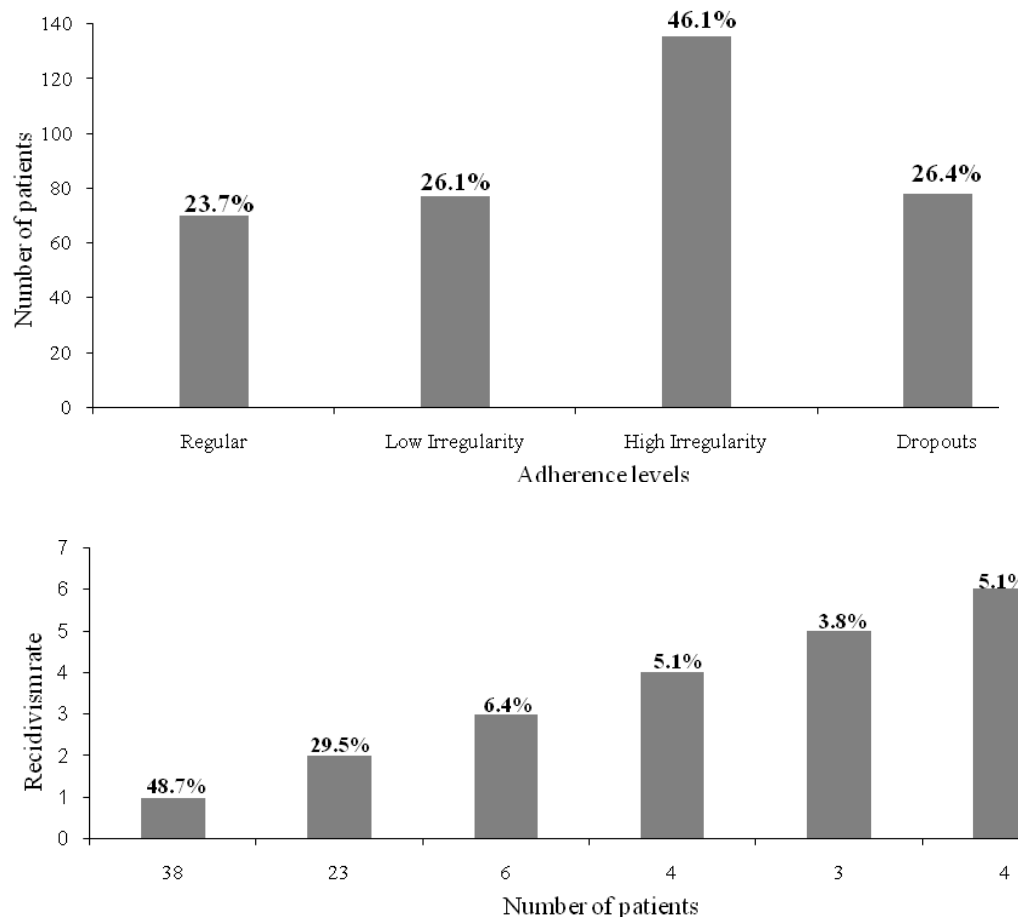
**Figure 1.** Distribution of the population studied regarding age range (n total=295, n males= 152, n females= 143).

from 1985 to 2011, is heterosexual (43.8%) followed by injecting drug users (IDU) (29.35%) (Ribeirão, 2013).

The studied population had the lowest ratio male/female, this is an expressive female predomination, and considering heterosexual category as high risk, the PUMed should pay attention to this scenario. Santos et al. (2009) suggested, after analyzing the vulnerability to HIV among Brazilian women, the need to think about prevention strategies focused on women and not just

focus on their individual behaviors.

Regarding the percentage of AIDS cases in this population, there are many differences when comparing to São Paulo state, which prevails in the range between 30 and 39 years (38.4%), followed by the range of 40 to 49 years (20,2%) (São Paulo, 2011). In Ribeirão Preto, the most prevalent age group according to the first diagnosis is 30 to 39 (2120 from 5637 patients, 37.6%) and 20 to 29 years (1855 from 5637 patients, 32.9%)



**Figure 2.** Adherence levels (A) and recidivism rate (B) of related patients in the study (n=295).

years. A projection from the first diagnosis to today for patients in Ribeirão Preto shows that the largest proportion of age groups are 40 to 49 (2360 of 5616, 42.02%) and 50 to 59 (1349 of 5616; 24.02%), the same age groups presented by the studied population. Therefore, we observe that age in this study is more pronounced than in the state of São Paulo. Due to increasing of life expectancy, it is necessary to develop special actions for control and prevention of HIV infection in patients older than 40 years.

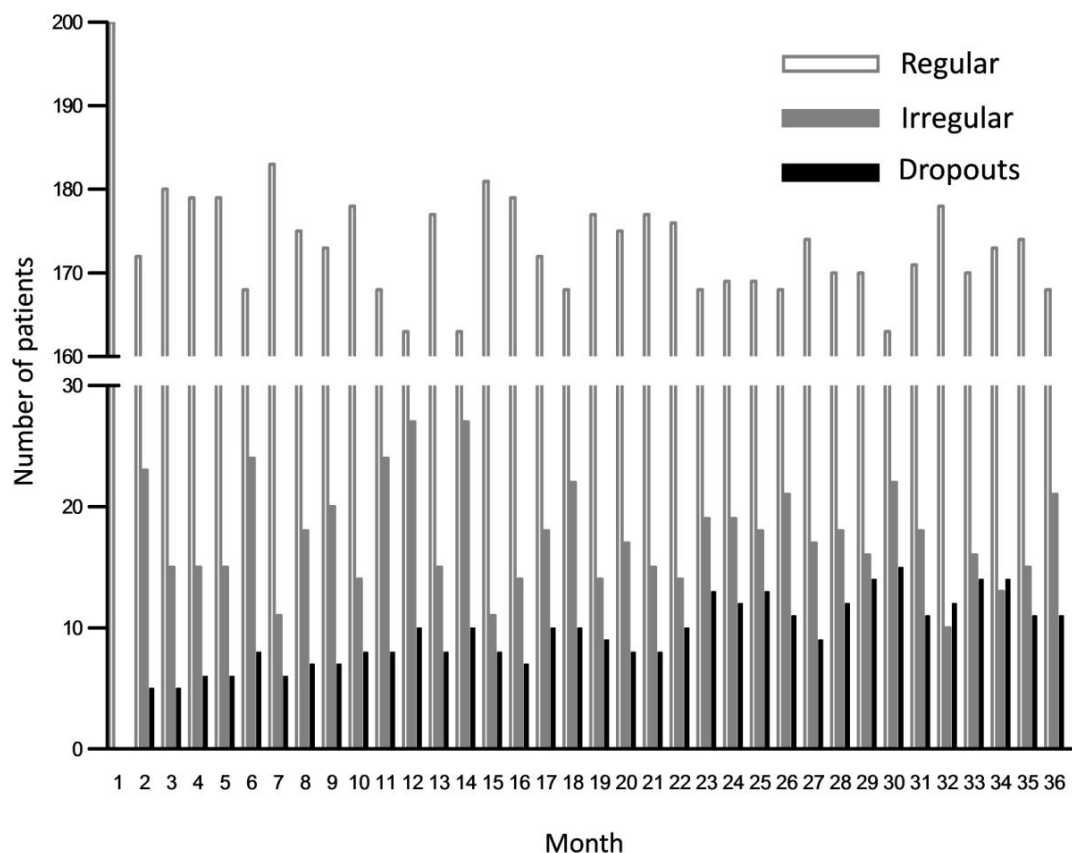
### Evaluation of adherence

In their studies performed in Philadelphia (USA), Grossberg et al. (2004) concluded that, despite the self-reports indicate that patients would be 100% adherent to treatment, only 41% were considered adherent by the pharmacy dispensing records. According to Bedell et al. (2000), only one third of patients from an academic center in Boston (USA) used their medications as prescribed and despite they understand the risks of the nonadherence, the level of adequately compliance to

medication used was lower than recommended. Here it was noticed that the chronic HAART users had low adherence (Figure 3). According to Jordan et al. (2000), for chronic diseases there are decreases in adherence with the time of treatment because, in general, patients feel asymptomatic, become comfortable and opt out of the treatment.

According to Paterson et al. (2000), to decrease the viral load is necessary ingestion of 95% of the prescribed medications. When analyzing patients at high irregularity period without pickup, the value added up 46.1% (Figure 2A). Hence, actions such as residence visits, educational campaigns and supervised medication use should be encouraged to inhibit this practice of patients. According to Safren et al. (2001), another way to increase HAART adherence could be the self monitoring condition (using daily report, recording the number of pills prescribed and the number of pills taken) and life step condition (utilizing cognitive-behavioral, problem-solving and motivational interviewing techniques).

The percentage of individuals considered regular and irregular in our findings were not similar to previous studies (11.8 and 57.9%; 55.9 and 44.1%; 64.1 and 35.9%,



**Figure 3.** Regularities, irregularities, and dropouts of patients in HAART from BHDU from January 2009 (1st month) to December 2011 (36<sup>th</sup> month). n=200: patients who pickup ARVs from month 1 to 36.

respectively) (Gomes et al., 2009; Brito et al., 2006; Nogueira et al., 2007). Data from WHO (2003) reported that only about 1/3 of individuals use the medication as prescribed. Furthermore, Rocha et al. (2011) found that 19.4% of patients which were considered adequately compliant by self-report had, according to the pharmacy records, dropped out of the treatment. Hence, a comparison between all studies is very important to establish methodological standardization to estimate the adherence. These differences observed between the several studies may be due to the difficulty of classifying adherence to HAART. The studies usually establish different cut off points. For instance, Bonolo et al. (2007) compared adherence studies found in cut off points ranging from 80 to 100% of adherence for achieving the treatment efficacy. In addition, other variables may influence the evaluation of treatment adherence, such as access and services with high quality, physical structure of the BHDU and inter-relations between the multidisciplinary equip.

Special attention should be directed to patients who dropout the HAART. In this study, these individuals totaled 78 (26.4%). Brito et al. (2006) reported 35.9% of dropouts, while Gomes et al. (2009) 30.3%. Despite

these high values, we should also consider the recidivism rate of these individuals. Here we observed that 78.2% of patients dropout and returned to treatment once or twice and 20.4% did it from 3 to 6 times.

The effectiveness of HAART is strictly associated to treatment adherence. Raffa et al. (2006) determined the viral level and the genotype resistance by analyzing plasma of patients in HAART. They reported that adherence between 80 to 90% increased the viral genotypic mutations at a higher rate of those who adhered in a lower or higher range. They concluded that ingestion of HAART in this interval can cause virologic resistance and treatment failure. Therefore, adherence studies are extremely important since we can identify the characteristics of patients, those at low adherence, using strategic tools to improve this parameter. In this context, it is worth mentioning that pharmaceutical care (Foisy and Akai, 2004), pharmacotherapy monitoring and health promotion activities (ongoing education) (Rueda et al., 2006) are very important for patients diagnosed as HIV positive. These actions can improve the adherence to treatment and, for more vulnerable groups such as children and elderly people, the contamination and side effects by HIV.

### Correlations between the parameters related to the use of antiretrovirals

We observed that the higher regularity, lower dropouts in the studied population. In relation to age, its negative value correlated with dropouts. In contrast, change in the treatment scheme is positively correlated with dropouts and negatively associated with regularity. This implies to say more changes in treatment scheme of the individual is associated with a higher dropout rate. Concerning only males, there were no statistically significant influence on these correlations, except regarding regularity and dropout rate, as expected. Females strongly influenced the correlations in general population, particularly for dropouts and changes in treatment scheme. Finally, we did not observe any correlation between age and changes in treatment scheme for general population or genders.

This study demonstrates that there are relevant tendencies to dropouts in relation to age and gender. Multidisciplinary should be direct efforts in order to improve the regularity of these patients. Thus, knowing the particularities in adherence of a population through simple statistical studies, actions can be promoted such as coherent use of drugs specifically targeted to groups as a way to increase adherence at levels higher than 95% with subsequent increase of treatment efficacy.

### Characterization of changes in treatment schemes

The combinations of HAART medical prescriptions were schemes associating two NRTIs, with a NNRTI being the most common medication AZT + 3TC (62.7%). The most frequent combinations with AZT + 3TC was with EFZ (28.1%) and NVP (13.3%). The most prevalent of PI scheme with AZT + 3TC medication was LPV/r (9.5%). In studies that also evaluated the therapy used, the more prescribed schemes were also schemes combining two NRTIs and one NNRTI, with values similar to the scheme AZT + 3TC + EFV (30.7, 26.9 and 34.1%) (Gomes et al., 2009; Blatt et al., 2009; Fonseca et al., 2012).

### Conclusion

Therefore, a well-studied data associated to precise statistical analysis can contribute significantly within particular characteristics of population and thus be able to use this information to develop actions to improve the treatment. For this reason, it is a necessary knowledge of the multidisciplinary staff to use this information properly in an interdisciplinary way, acting to serve the population in health promotion and continuous education in a humanistic way, thus increasing adherence.

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