ORIGINAL ARTICLE

HIV pharmaceutical care in primary healthcare: Improvement in CD4 count and reduction in drug-related problems

C.G.R.C. Molino [a], Renata Cavalcanti Carnevale [a], Aline Teotonio Rodrigues [a], Patricia Moriel [b], Priscila Gava Mazzola [b],*

[a] *Department of Clinical Pathology, School of Medical Sciences (FCM), University of Campinas (UNICAMP), Rua Tessália Vieira de Camargo, 126, Campinas, São Paulo 13083-970, Brazil*
[b] *Faculty of Pharmaceutical Sciences (FCF), University of Campinas (UNICAMP), Department of Clinical Pathology, School of Medical Sciences (FCM), University of Campinas (UNICAMP), Rua Sérgio Buarque de Holanda, 250, CB-II – sala E06 – 2° Piso, Campinas, São Paulo 13083-859, Brazil*

Abstract *Background:* Highly active antiretroviral therapy (HAART) is complex and many factors contribute to a patient's response to initial therapy including adherence, drug effectiveness, and tolerance. Close HAART follow-up is needed, particularly when there are concurrent therapies such as prophylactic antibiotics and medications for the treatment of comorbidities. *Objective:* To assess the effectiveness of pharmacist intervention in reducing drug related problems in HIV/AIDS outpatients (intervention group) and in improving clinical parameters in the intervention group compared to the control group. *Methods:* We conducted a prospective controlled intervention study with patients paired by gender and initial T CD4+ lymphocyte (CD4) count. HIV-infected patients of a public outpatient service were enrolled for the study by consecutive and convenience sampling. Patients selected for the study were divided into a control group and an intervention group. Both groups were followed for one year; however, only the intervention group received pharmaceutical care. The primary outcome was the drug related problem (DRP) analysis for the intervention group. Secondary outcomes were CD4 count and viral load evaluation for both groups. *Results:* There was a total of 143 patients enrolled in this study, with 53 (37.06%) patients in the control group and 90 (62.94%) patients in the intervention group. A total of 202 pharmacist interventions with 193 pharmacist-patient and 9 pharmacist-physician interventions were proposed. After one year of pharmaceutical care, a reduction of 38.43% between the initial and final DRP was found

* Corresponding author.
  E-mail address: pmazzola@fcf.unicamp.br (P.G. Mazzola).

($p = 0.0001$). The most common DRPs found were related to medication safety. The intervention group showed a mean increase of 84% for the CD4 count in comparison with that observed in the control group. The viral load was not significantly different between the final and initial mean values for both groups. *Conclusion:* Pharmacist appointments enabled identification, prevention, and solving of drug related problems, especially those related to drug safety. Also, pharmacist interventions improved adherence and increased HAART effectiveness as suggested by the higher elevation in the CD4 count seen in the intervention group in comparison with the control group.

1. Introduction

In Brazil, from 1980 to June 2014, 757,042 cases of Acquired Immunodeficiency Syndrome (AIDS) were reported, of which 411,800 (54.4%) of the cases were reported in the southeast of Brazil (Brazil. Ministry of Health., 2014). Among those, 15,768 were new AIDS cases in 2014, with a national incidence rate of 20.4/100,000 individuals with AIDS reported in 2013 (Brazil. Ministry of Health., 2014). Although Brazil provides free therapy to treat against Human Immunodeficiency Virus (HIV), access to pharmaceutical care for people living with HIV/AIDS is a major challenge for public health systems, especially in developing countries (Oliveira et al., 2002; Remondi et al., 2014).

The goal of highly active antiretroviral therapy (HAART) is to achieve maximum suppression of HIV replication, resulting in an increased immune response. However, HAART is not effective unless patients are committed and able to adhere to the treatment regimen. In addition, health care professionals must be able to manage the therapy. Non-adherence or partial adherence to HAART can lead to virologic failure, development of viral resistance to antiretroviral drugs, and death (Bezabhe et al., 2016).

HAART is complex and many factors contribute to a patient's response to initial therapy including adherence, drug effectiveness, and tolerance (Bolsewicz et al., 2015; Henderson et al., 2011; Verdugo et al., 2007). Furthermore, drug related problems (DRPs) are frequently found in HIV/AIDS patients. DPRs mainly occur due to drug-drug and drug-food interactions, adverse drug reactions, drug omission or unnecessary prescribed drug, no dosage adjustment in patients with renal or hepatic impairment, errors in drug indication, dosing, regimen and scheduling (Carcelero et al., 2011; Li and Foisy, 2014; Molino et al., 2014; Ojeh et al., 2015).

Drug interaction is commonly found between HAART, HAART and other drugs used to treat comorbidities, and HAART and food (Hughes et al., 2015; Ojeh et al., 2015; Rathbun and Liedtke, 2011). Antiretroviral drugs that function as protease inhibitors are extensively metabolized by the cytochrome P450. The concomitant use of these drugs and others also metabolized by CYP P450 can result in drug interaction (Hughes et al., 2015; Rathbun and Liedtke, 2011). Drugs with narrow therapeutic index and metabolized by CYP450, such as warfarin, require close monitoring when used with HAART (Esterly et al., 2013).

Besides some of the well-known mechanisms of drug interactions causing side effects, medications often present adverse effects leading to treatment discontinuation (Hughes et al., 2015; Rathbun and Liedtke, 2011; Verdugo et al., 2007, 2010). A multi-center study conducted in Spain found that a quarter of HIV patients had discontinued tenofovir treatment due to adverse drug effects (Verdugo et al., 2007). Also, the risk of virologic failure commonly associated with antiretroviral resistance increases when compliance decreases (Bezabhe et al., 2016; Pirkle et al., 2009). Close HAART follow-up is needed, particularly when there are concurrent therapies such as prophylactic antibiotics and medications for the treatment of comorbidities. Studies have shown a significant decrease in medication errors in institutions where pharmacists perform interventions with a team of clinicians. These studies support the fact that pharmacist intervention can reduce the number of adverse events, improve quality of health care, and minimize hospital costs (Carnevale et al., 2015; Chisholm-Burns et al., 2010; De Rijdt et al., 2008; Kaboli et al., 2006; Kopp et al., 2007; Stark et al., 2011).

1.1. Aim of the study

Pharmaceutical care encourages patients to be familiar with their own regimens, making it easier to understand the importance of drug adherence, as well as increasing therapy adherence, effectiveness, and tolerance. The aim of this study was to evaluate the effectiveness of pharmacist intervention in reducing drug related problems in the HIV/AIDS outpatients (intervention group) and in improving clinical parameters in the intervention group compared to the control group.

2. Methods

2.1. Design and setting

This study was performed at the Hospital Dia-University of Campinas Teaching Hospital, Campinas, Brazil, from January 2009 to June 2012.

We conducted a prospective controlled intervention study with patients paired by gender and initial T CD4+ lymphocyte (CD4) count. First, the clinical pharmacy staff analyzed all medical charts available during medical appointments in Hospital Dia to check whether patients fit the study criteria. Then, those who fit these criteria were assigned to Control/Intervention Group through a convenience sample. Both groups were followed for one year; however, only the intervention group received pharmaceutical care.

Each patient from the control group was matched with a patient from the intervention group according to their baseline CD4 count, considering a maximum variation range of 10% between their CD4 counts. Since the control group consisted

of replaced patients, we could pair each intervention patient with a control patient and compare the outcomes.

Laboratory specimens were collected in the morning and subsequent analysis was carried out by a laboratory at the University of Campinas Teaching Hospital.

2.2. Subjects

HIV/AIDS outpatients from the Hospital Dia were eligible to participate in our study if they were between 18 and 65 years of age, with a body mass index of $< 30 \, kg/m^2$ and were undergoing HAART. Elderly patients (> 65 years old) were excluded since it is known that elderly individuals present with more comorbidities; thus, their pharmacotherapy is more complex and associated with a greater number of drug interactions, adverse reactions, and toxicity (Hasse et al., 2011). Furthermore, previous data have shown that higher HIV infection progression and mortality rates have been identified among older patients compared with younger patients (Nguyen and Holodniy, 2008). Obese patients were also excluded since they present with higher incidences of hyperlipidemia and the fact that some HIV medications, such as protease inhibitors, are associated with weight gain and fat accumulation (Bavinger et al., 2013; Crum-Cianflone et al., 2010; Dube, 2000; Friis-Møller et al., 2003; Hasse et al., 2011).

Patients were excluded if they were homeless or prisoners, had severe psychiatric disease that limited their comprehension, did not follow up on previously scheduled appointments, refused to participate in the study, got pregnant, attended fewer than two pharmacist appointments, had pharmacist appointments at an interval greater than 6 months, did not complete one year of pharmaceutical care, were switched to another health service, or missed their appointments with their physician.

2.3. Pharmaceutical care service

A clinical pharmacy team analyzed patients' medical charts to ensure they fit with the study criteria. Those who were eligible were assigned to an intervention or control group depending on the clinical pharmacist's appointment schedule.

After undergoing their routine physician appointments, patients in the intervention group received pharmaceutical care appointments during the one-year follow-up. Control group patients continued with their usual care without pharmaceutical care service.

Patients in the intervention group had at least three pharmaceutical care appointments of 30–60 min each. The maximum interval between returns proposed to all patients from the Hospital Dia was four months.

The pharmaceutical care service provided for the intervention group was based on the pharmacotherapy workup. The definition of the pharmacotherapy workup employed was: a process in which pharmacists use rational decision-making to assess a patient's drug-related needs, identify drug therapy problems, develop a care plan, conduct follow-up evaluations, and avoid safety and efficacy problems (Cipolle et al., 2004).

Pharmaceutical care activities comprised data collection through patient interview and medical history. The clinical pharmacist team used a standard form to collect data and guide appointments. The team consisted of two pharmacists trained in pharmaceutical care and four undergraduate pharmacist students.

The primary outcome was the drug related problem (DRP) analysis for the intervention group, considering all drugs in use by the patient: HAART, over the counter, and others to treat comorbidities. DRP analysis was not performed for the control group because these patients did not receive pharmaceutical care. Two pharmacists identified and classified individually the DRPs into four categories: (1) Indication: unnecessary drug therapy or additional drug therapy was required to treat or prevent a medical condition; (2) Efficacy: a drug was ineffective or the dosage was too low to produce the desired response; (3) Safety: the drug caused an adverse reaction or the dosage was too high which resulted in undesirable effects; (4) Adherence: the patient was not able or willing to take the drug regimen appropriately (Cipolle et al., 2004). Laboratory tests and patient's symptoms were used to identify and monitor DRPs. Micromedex was used to check theoretical adverse drug reaction. Adverse drug reaction was considered when a patient reported a symptom or when there was an abnormality in laboratory tests which could not be explained by anything else other than adverse drug reaction.

Secondary outcomes were CD4 count and viral load evaluation for both groups. To analyze the influence of pharmaceutical care service on these parameters, we considered their results before and after one year of pharmaceutical care service in the intervention group. In the control group, initial CD4 count and viral load were compared to the final values.

After the clinical pharmacists identified the DRPs, they developed a care plan that comprised measures to be taken by the patient and the medical team. The care planning was checked by two pharmacists before initiation of the intervention. The pharmacist interventions were performed both orally and with standardized written form methods. Interventions were classified into 2 major categories: pharmacist-physician interventions or pharmacist-patient interventions. Then, interventions were divided into 4 categories: resolve DRP, prevent DRP, health promotion or quality of life. "Resolve DRP": when there was a real problem, such as lack of adherence or presence of adverse drug reactions; "prevent DRP": when there was a potential problem, such as a potential drug interaction; "health promotion": patient education related to hygiene habits, disease, laboratory tests, drug storage orientation and condom use; "quality of life": interventions related to lifestyle (proper eating and sedentarism), drug use (illicit drugs, tobacco and excessive intake of alcohol), and specialist referral, when necessary.

The clinical pharmacists were trained to properly classify the DRP and intervention categories. Once a week the clinical pharmacist team discussed all patient cases and solved issues regarding the DRP intervention classification. If no consensus was reached, a third pharmacist was consulted.

Antiretroviral drugs were provided to the patients by a specialized community pharmacy, also located at the University of Campinas.

2.4. Statistical analysis

Primary and secondary outcomes were analyzed using a paired t-test to compare the baseline values to the results found after

the pharmacist interventions, considering a two-sided $p < 0.05$ as statistically significant. Graphics were made using Origin 6.0® and Microsoft Office Excel® software.

2.5. Ethical approval

This study was approved by the Research Ethics Committee at the School of Medical Sciences, University of Campinas, Brazil, (protocol number 727/2009). Each patient signed a consent form.

3. Results

There was a total of 143 patients enrolled in this study, with 53 (37.06%) patients in the control group and 90 (62.94%) patients in the intervention group. Among them, 57 (39.86%) were excluded with 10 (17.54%) of the patients excluded from the control group and 47 (82.46%) from the intervention group. At the end, 43 patients were eligible in every arm (Fig. 1). Both groups were followed for 12 months.
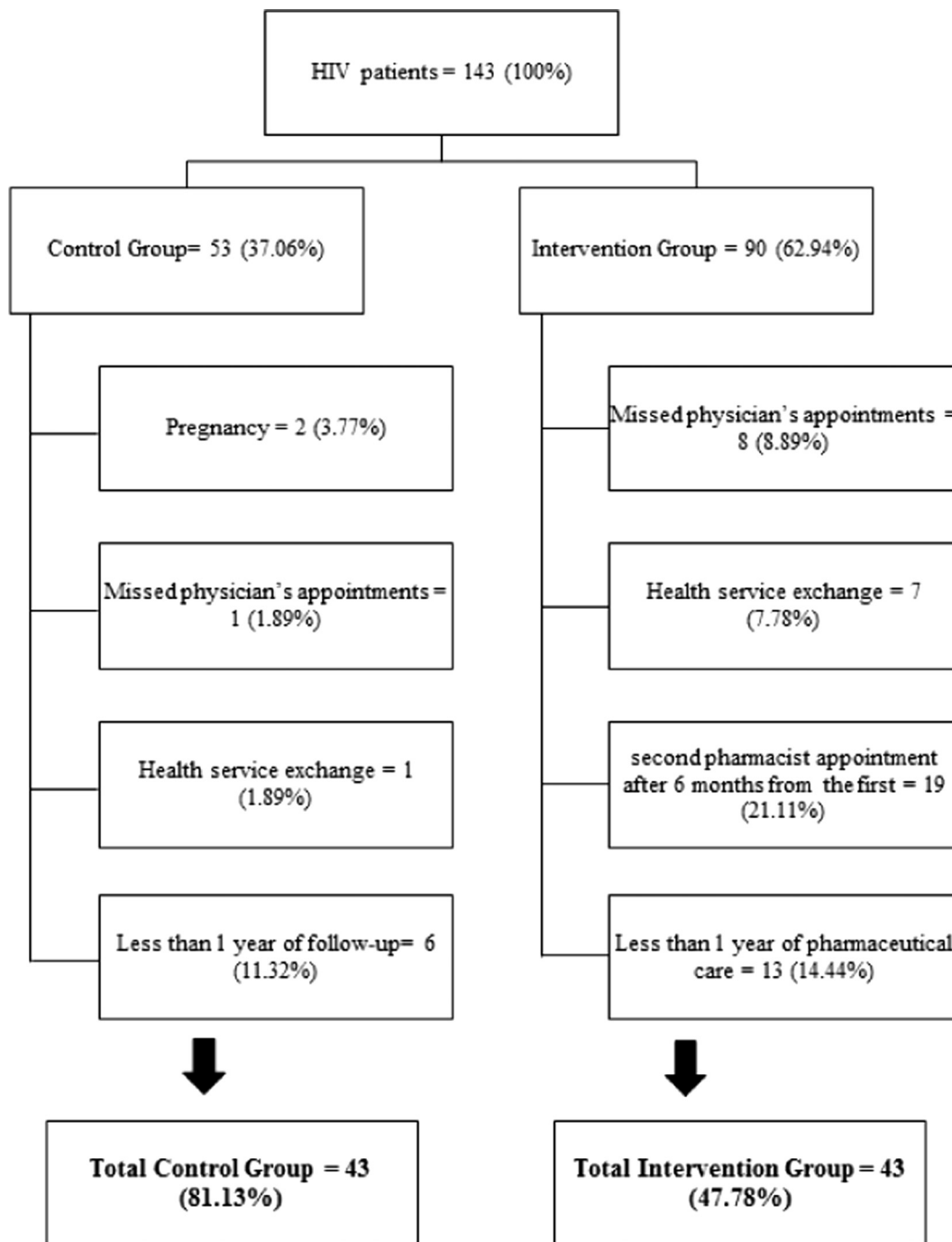

Figure 1 Total initially selected for the study and the reasons for discontinuing patients.

Each patient's baseline characteristics are shown in Table 1. Since the patients were paired according to their gender and CD4 count, we found equal numbers of men ($n = 28$, 65.12%) and women ($n = 15$, 34.88%) between the groups and similar mean basal CD4 counts, where the control group presented with 291.09 [210.34–371.84] cells/mm^3 and the intervention group presented with 297.72 [208.30–387.14] cells/mm^3. The groups were similar in regard to their age, ethnicity, and time of HIV diagnosis and treatment. Most prescribed HAART was tenofovir, lamivudine and efavirenz in the control group (20%), and zidovudine, lamivudine and efavirenz in the intervention group (20%). Hepatitis C was the most frequent comorbidity in both groups with a 20% ($n = 8.6$) occurrence in each group.

The clinical pharmacists team performed 194 appointments in the intervention group (mean of 4.51 [4.08–4.94] appointments per patient). A total of 202 pharmacist interventions with 193 (95.54%) pharmacist-patient and 9 (4.46%) pharmacist-physician interventions were proposed. A mean of 4.7 pharmacist interventions per patient and 1.04 pharmacist interventions per appointment was performed.

All pharmacist-physician interventions were accepted and aimed to resolve an identified DRP such as an additional drug therapy required (5/9, 55.56%), unnecessary drug therapy (2/9, 22.22%), and different drug required (2/9, 22.22%).

Pharmacist-patient interventions consisted of health education (19/193, 9.84%) and quality of life (50/193, 25.91%), to prevent (50/193, 25.91%) and resolve DRP (74/193, 38.34%). Pharmacist-patient interventions to prevent DRP were mostly related to a non-adherence problem (32/50, 64%). Most pharmacist-patient interventions aimed to resolve DRP adjusted dosing schedules in accordance with patient's meal patterns (31/74, 41.89%). Fig. 2 shows how often pharmacist interventions were performed in regard to health education, quality of life, resolution, and prevention of DRPs.

Fig. 3 shows DRPs from the first pharmacist appointment and after one year. Initially, 216 DRPs were identified with 5.02 [4.02–6.03] DRPs per patient. After one year of pharmaceutical care, 133 DRPs were found with 3.09 [2.43–3.75] DRPs per patient. A reduction of 38.43% between the initial and final DRPs was found and was statistically significant at $p = 0.0001$.

The most common DRPs found were related to medication safety with 138 (3.21 [2.60–3.82] DRPs per patient) found initially and 86 (2.00 [1.58–2.42] DRP per patient) one year later. Indication DRP was the second most frequent with 50 (1.16 [0.77–1.56] DRP per patient) and 24 (0.56 [0.27–0.84] DRP per patient) initially and after one year, respectively (Fig. 3).

Fig. 4 shows CD4 count dispersion for both groups. The CD4 count mean presented with a significant increase in both the intervention ($p = 0.00003$) and the control group ($p = 0.0078$). However, the intervention group showed a mean increase of 84% for the CD4 count in comparison with that observed in the control group; the CD4 mean variation found was 154.66 and 83.80 in the intervention and control group, respectively ($p = 0.4$).

At baseline, both groups had a statistically similar viral load ($p = 0.10$). The viral load was not significantly different between the final and initial mean values for both groups ($p = 0.5$ for the control group and $p = 0.2$ for the intervention

Table 1 Baseline characteristics of the control and intervention group.

Characteristics	Control group[a]	Intervention group
Age (Mean $\pm$ SD; years)	41.49 $\pm$ 9.33	41.74 $\pm$ 7.93
Gender		
Men n (%)	28 (65.12)	28 (65.12)
Women n (%)	15 (34.88%)	15 (34.88%)
Ethnicity n (%)		
Caucasian	31 (72.09)	26 (60.47)
Mulatto	10 (23.26)	13 (30.23)
Asian	–	1 (2.33)
Black	2 (4.65)	3 (6.98)
HIV diagnosis (Mean [CI]; years)	7.05 [5.32–8.78]	8.02 [6.06–9.98]
HIV treatment duration (Mean [CI]; years)	5.98 [4.41–7.55]	6.35 [4.70–7.99]
Number of comorbidities (Mean $\pm$ SD)	2.70 $\pm$ 1.70	2.80 $\pm$ 1.90
Number of tablets per day (Mean $\pm$ SD)	9.55 $\pm$ 4.70	10.25 $\pm$ 4.21
Initial CD4 mean count ([CI]; cells/mm^3)	291.09 [210.34–371.84]	297.72 [208.30–387.14]
Initial viral load mean count ([CI]; copies/ml)	19×10^3 [50–42×10^3]	40×10^3 [6×10^3–75×10^3]
Most prescribed HAART n (%)[b]		
AZT + 3TC + EFV	7 (17.50)	8 (20.00)
AZT + 3TC + LPV/r + TDF	2 (5.00)	7 (17.50)
TDF + 3TC + EFV	8 (20.00)	6 (15.00)
TDF + 3TC + LPV/r	5 (12.50)	6 (15.00)
AZT + 3TC + LPV/r	4 (10,00)	4 (10.00)
ABC + 3TC + EFV	0	3 (7.50)
Other	14 (35.00)	6 (15.00)

[a] Data from three patients in the control group were not considered to HIV diagnosis, treatment time, tablets per day and comorbidities ($n = 40$).
[b] Most prescribed HAART was related to $n = 40$ in control and intervention group. 3TC: lamivudine. ABC: abacavir. AZT: zidovudine. EFV: efavirenz. LPV/r: lopinavir/ritonavir. TDF: tenofovir.

group). Although the final control group viral load mean was lower than that presented by the intervention group (12×10^3 and 17×10^3 copies/mL, respectively), an approximate 4-fold viral load reduction was found in the intervention group when compared to the control group (23×10^3 for the intervention group and 6×10^3 for the control group).

Regarding the viral load limit of detection (viral load < 50 copies/mL), 51.16% ($n = 22$) of individuals in the control group and 60.47% ($n = 26$) in the intervention group began and ended the study with a viral load < 50. In addition, 9.3% ($n = 4$) of the patients in the control group and 2.33% ($n = 1$) of patients in the intervention group began the study with a viral load < 50 and after one year they presented with a viral load > 50. Finally, 3 (6.98%) patients in the intervention group presented with a clinically significant increase in their viral load compared with 11 (25.58%) patients in the control group.

4. Discussion

According to Brazilian epidemiological data, the prevalence of people living with HIV/AIDS in Brazil is 0.4% (Brazil. Ministry of Health., 2014). Of all cases from 1980 to June 2014, the highest concentration of those affected is among individuals aged 25–39, which comprises 54% and 50.3% of men and women, respectively (Brazil. Ministry of Health., 2014). Similarly, we found an age average of 41.63 [39.29–43.96] and 41.60 [38.41–44.79] years for all men and women enrolled in this study.

Viktil and Blix (2008) showed that a clinical pharmacist is able to identify, resolve, and prevent a clinically significant DRP (Viktil and Blix, 2008). Furthermore, they found evidence that pharmacist interventions positively influence clinical outcomes, such as improvement of drug and disease surrogate markers, reduction of hospitalization length of stay and re-admissions, and rates of disease events (Viktil and Blix, 2008). Likewise, studies have shown that clinical outcomes in HIV patients, as viral load reduction and CD4 increase, can be improved by pharmacist interventions, (Abah et al., 2014; Nevo et al., 2015; Reis et al., 2016; Saberi et al., 2012).

During the one-year of pharmaceutical care, most interventions (95.54%) were pharmacist-patient interventions, which resulted in a significant DRP reduction of 38.43% after one year of pharmaceutical care. Other studies had shown that pharmacist interventions are able to reduce DRPs, especially problems related to medication safety, such as the presence of adverse drug reactions for example (Blix et al., 2006; Chisholm-Burns et al., 2010; de Maat et al., 2004; Granas et al., 2010; Verdugo et al., 2010; Viktil and Blix, 2008). In our study, 46 interventions intended to solve an adverse drug reaction including a DRP drug-food interaction ($n = 31$) and/or drug-drug ($n = 15$) interaction. After those interventions, problems in regard to safety decreased from 138 to 86, a reduction of 37.68%, indicating that the pharmacist interventions influenced the reduction of adverse reactions.

A previous study showed that 50–80% of all DRPs are predictable (Viktil and Blix, 2008) and thus pharmacist interventions might resolve and prevent DRPs leading to a
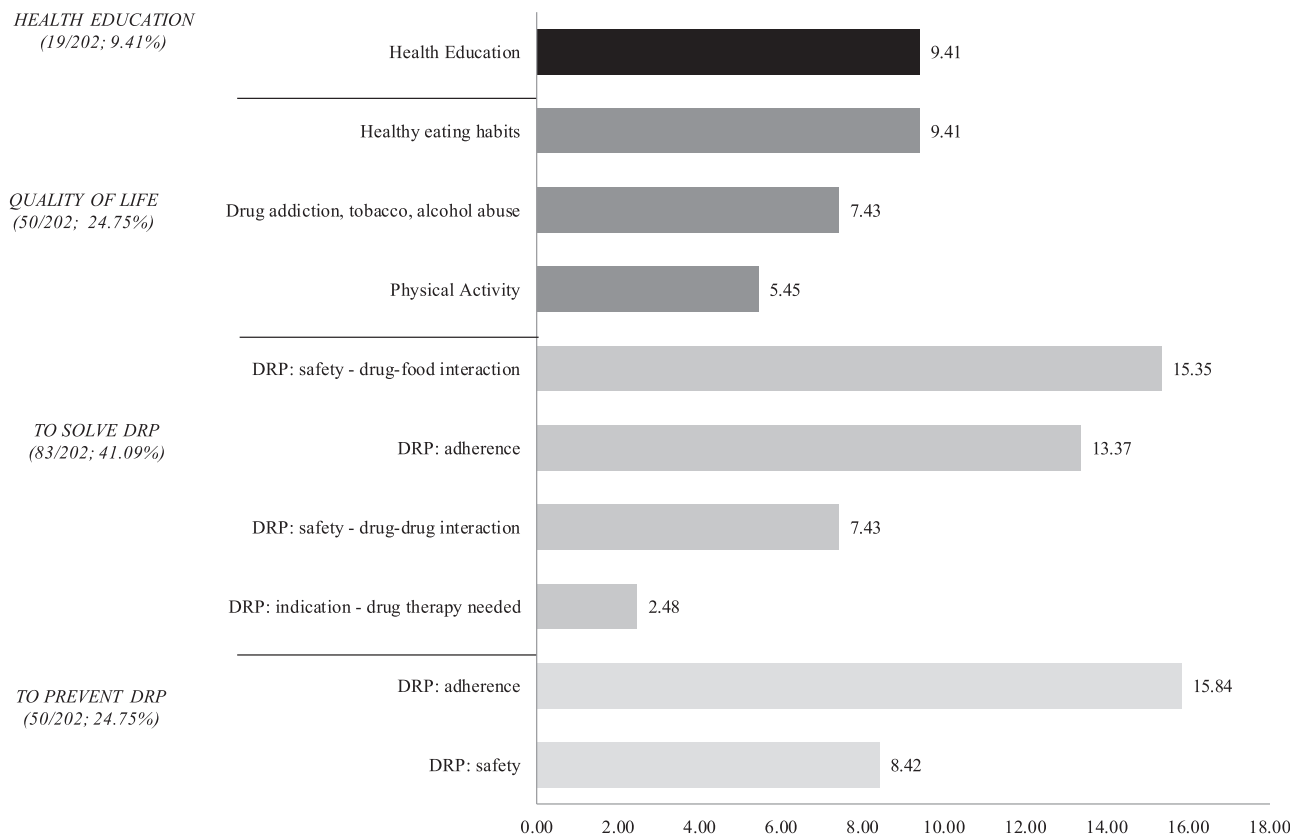
Figure 2 Percentage of pharmacist interventions commonly performed during the study. DRPs, Drug-related problems.
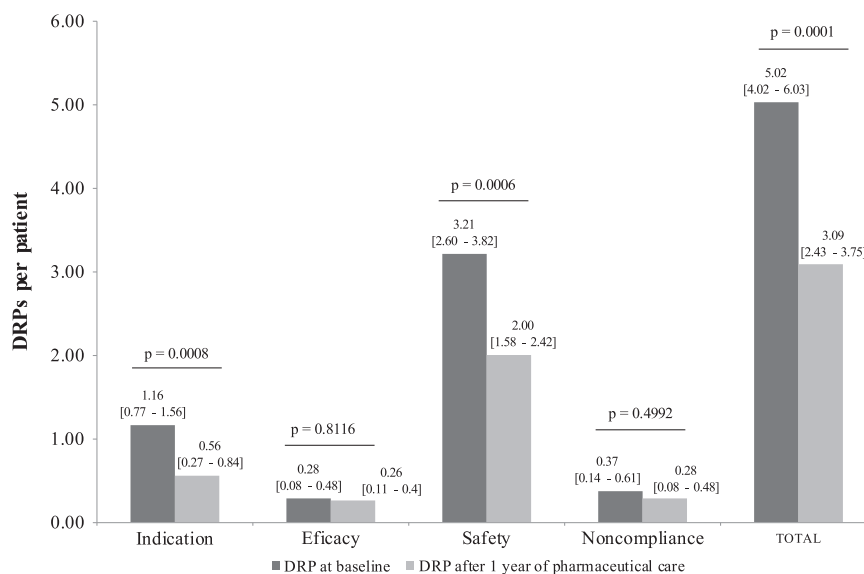
Figure 3 Mean drug related problems per patient identified in first appointment and after 1 year of pharmaceutical care. DRPs, Drug-related problems.
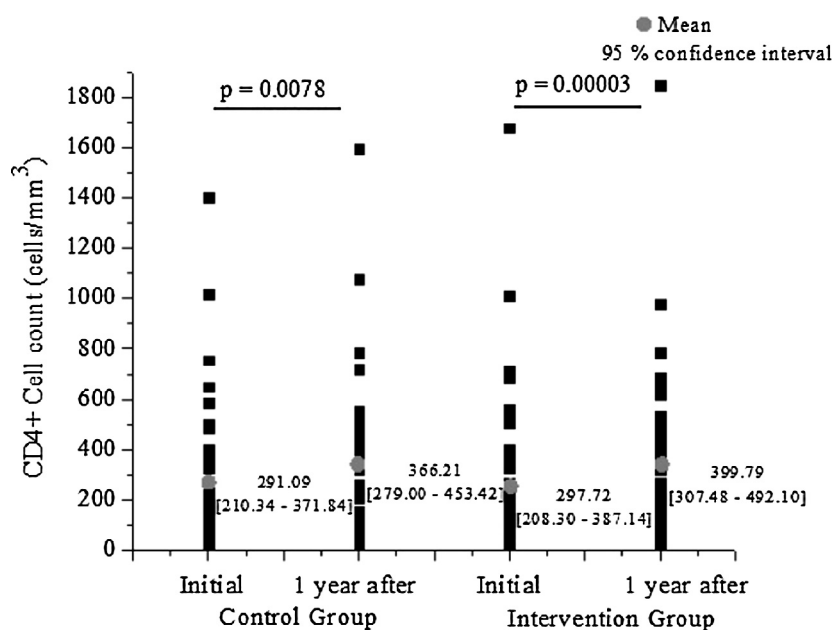
Figure 4 CD4 count dispersion initially and after 1 year for intervention and control group.

significant impact in DRP reduction; however, they were not enough to address all problems identified. Regarding other DRPs (indication, effectiveness, and adherence) no expressive reduction was observed as that presented for safety DRPs. These aspects might happen due to few pharmacist-physician interventions conducted ($n = 9$; 4.46%). Health team interventions were proposed to reduce indication and effectiveness DRPs, though these are the most complex interventions to be implemented for the pharmacy staff because many patients do not want a new drug added to their therapy regimen since they already take a large amount of tablets daily.

Although it is well known that a clinical pharmacist must be present at prescription time and actively participate in clin-ical case discussions in regard to the pharmacist-physician interventions (Blix et al., 2006; Kucukarslan et al., 2003; Viktil and Blix, 2008), our interventions were performed by medical record entries and a verbal approach. Nonetheless, our study had 100% of the pharmacist-physician interventions accepted suggesting that this combined method could also be effective and should be explored in the future.

As our data show, pharmacists should intercede with clin-ician teams in cases of HAART intolerance and with patients to instruct them on how to adequately take antiretroviral drugs, encouraging therapy adherence. Knowing that barriers to treatment adherence are complex and diverse but could also be related to patients' cultural attitudes and beliefs

(Bolsewicz et al., 2015) and it increases when patients have a greater understanding about their own health (Blix et al., 2004; de Lyra et al., 2007; de Oliveira, 2011; Strand et al., 2004), we performed interventions to enhance patient knowledge in relation to HIV/AIDS, HAART, and laboratory tests.

In the present study, we observed a significant increase in CD4 counts for both groups. However, the intervention group presented with a mean CD4 increase of 154.66 cells/mm^3 while the control group had an increase of 83.8 cells/mm^3 ($p = 0.401$) by the end of one year. Additionally, after one year of follow-up there were 9 (20.93%) patients in the intervention group and 6 (13.95%) in the control group with CD4 counts > 500 cells/mm^3 and an undetectable viral load. These data demonstrate the clinical relevance of the pharmacist interventions in the intervention group.

The viral load parameter did not demonstrate a statistical difference; however, the viral load reduction was greater in the intervention group, resulting in a mean reduction of 23.52×10^3 RNA copies/mL, while in the control group there was 6.23×10^3 RNA copies/mL. Viral load quantification is an important marker of HAART adherence (Bonner et al., 2013). Previous studies had shown that the pharmacist, through pharmaceutical care and interventions, could improve adherence which would help with reducing the viral load (Henderson et al., 2011; Nevo et al., 2015; Reis et al., 2016; Saberi et al., 2012).

4.1. Strength and limitations

This study had some limitations. For instance, the pharmacist appointments had to follow the physician's schedule, and therefore some data could not be analyzed due to a lack of information in the medical charts, such as laboratory tests, medications dose, and over-the-counter DRPs. Thus, certain cases were not considered for analyses such as DRPs. Furthermore, due to the lack of information we could not find out the control DRP rate. Although there was no randomization due to the healthcare facility routine, pharmacists selected any patients that accepted to participate in this study. After that, the pharmacist checked whether the patient satisfied the inclusion/exclusion criteria. Thus, future studies should assess whether pharmacist interventions would have an influence on adverse drug reaction outcomes and confirm and quantify them by the use of specific laboratory tests.

5. Conclusion

The results of this study indicate that pharmacist interventions positively influenced the patients' clinical outcomes. Pharmacist appointments enabled identification, prevention, and solving of drug related problems, especially those related to drug safety. Lastly, pharmacist interventions improved adherence and increased HAART effectiveness as suggested by the higher elevation in the CD4 count and the viral load reduction seen in the intervention group in comparison with the control group.

We suggest governments and healthcare managers should encourage the use of pharmaceutical care as a public health service, particularly by HIV patient assistance programs.

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