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Outcomes Beyond Infection Management in Comprehensive Medication Management Services for People Living with HIV

Resultados além do gerenciamento da infecção em um serviço de Gerenciamento da Terapia Medicamentos para pessoas vivendo com HIV

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ABSTRACT
To assess the clinical outcomes of comprehensive medication management (CMM) services offered to people living with HIV (PLHIV) at a Brazilian Antiretroviral Medication Dispensing Unit. The study was divided into a cross-sectional stage (stage I), to evaluate associated factor with the identification of two or more drug therapy problems (DTP) in the initial assessment; and a quasi-experimental stage (stage II), conducted with a single group of PLHIV to evaluate clinical outcomes.**:** A total of 52 PLHIV, with 60±11.3 years of age were followed up. In stage I, the presence of dyslipidemia (OR=5.38; 95%CI=1.61-17.97) and the use of seven or more medications (OR=4.28; 95% CI=1.32-13.88) were factors associated with the identification of DTP. In stage II, a significant difference was demonstrated between the initial and final values of systolic blood pressure, triglycerides, HIV viral load and CD4+T-cells count (p<0,05). The CMM service favored positive clinical outcomes.

Keywords: HIV. Medication therapy management. Pharmaceutical services. Patient outcome assessment

RESUMO
Avaliar os resultados clínicos de serviços de gerenciamento da terapia medicamentosa (GTM) oferecidos a pessoas vivendo com HIV (PVHIV) em uma unidade de dispensação de medicamentos brasileira. O estudo foi dividido em uma etapa transversal (etapa I), que avaliou o fator associado à identificação de dois ou mais problemas relacionados ao uso de medicamentos (PRM) na avaliação inicial; e uma etapa *quasi- experimental* (etapa II), realizada com um único grupo de pacientes para avaliar desfechos clínicos. Foram acompanhadas 52 PVHIV. A média de idade foi de 60±11,3 anos (min. = 29; máx. =78). A presença de dislipidemia (OR=5,38; IC 95%=1,61-17,97; p=0,006) e o uso de sete ou mais medicamentos (OR=4,28; IC 95%=1,32-13,88; p=0,015) foram fatores associados a identificação de dois ou mais PRM. Foi demonstrada uma diferença significativa entre os valores iniciais e finais de pressão arterial sistólica, carga viral do HIV, contagem de células T CD4+ e triglicerídeos (p<0,05). O serviço de GTM favoreceu os desfechos clínicos positivos.

Palavras-chave: Avaliação de resultados da assistência ao paciente. Gerenciamento de terapia medicamentosa. HIV. Serviços farmacêuticos.

INTRODUCTION

HIV infection (human immunodeficiency virus) is still a global public health problem, even with the advances in its treatment and prophylaxis.[1] From 2007 to June 2022, 434.803 were notified cases of HIV infection in Brazil.[2] Since the discovery of the HIV virus, collective responses and public health policies have emerged to control the infection, since it can progress to a more advanced stage of infection, aids (acquired immunodeficiency syndrome).[1] Moreover, new scientific studies on the treatment and forms of prevention have emerged. The result of this effort was the improvement in the life expectancy and quality of life of people living with HIV (PLHIV).[3]

The antiretroviral therapy (ART), which is considered one of the major advances in the control of HIV infection, consists of the combination of antiretroviral drugs (ARVs) to suppress the virus and stop the progression of the disease.[1] Despite the advantages of ART, some factors can hinder the continuity of treatment, such as: the complexity of pharmacotherapy, drug interactions, adverse effects, and treatment failures.[1,4,5]In addition, the non-acceptance of the diagnosis, the fear of discrimination and social exclusion may reflect in the difficulty to achieve satisfactory results with the treatment. [4-6] Regard-less of the potential problems related to ART, access to it has considerably improved the prognosis of PLHIV, causing the HIV infection, which was considered of high lethality, to be characterized as a chronic condition. [4]

Due to all these advances, PLHIV are undergoing an aging process, and, therefore, the health demands are growing, involving not only the management of HIV infection, but also of other chronic noncommunicable diseases, increasing the complexity of their pharmacotherapy.[7] In addition, PLHIV may present other health conditions related to the infection itself, such as opportunistic infections, coinfections and non-infectious comorbidities associated with HIV, which, if not properly assessed and monitored, worsen the clinical picture of PLHIV.[4]

Given this scenario, the practice of Pharmaceutical Care can contribute considerably to the therapeutic success of ART and control of other health problems of PLHIV, though the provision of global assessment and optimization of pharmacotherapy. Through this, the pharmacist assumes coresponsibility for caring through a holistic and patient-centered practice, which allows individualizing interventions related to the prevention, identification and resolution of drug therapy problems (DTP).[8] According to Cipolle, Strand and Morley (2012), the care process methodology adopted in Pharmaceutical Care provides a logical reasoning for decision making that standardizes the pharmacist's clinical practice and allows its high applicability and reproducibility. This process enables the monitoring and assessment of

patients relationship with their medications in daily life and their effects on their health. Moreover, it involves the construction of care plans in order to achieve therapeutic goals and guarantee the most appropriate, effective, safe and convenient pharmacotherapy for each patient. [8,9]

Currently called comprehensive medication management (CMM) services, clinical services based on the theoretical and methodological framework of Pharmaceutical Care have shown positive clinical, economic and humanistic results, which justify their expansion and consolidation in health systems.[10-14] However, to the best of our knowledge, there are no studies that assessed the clinical impact of CMM services to PLHIV, including elderly individuals and/or followed-up outside the hospital/outpatient setting. In addition, no studies were found with the global assessment of all health problems and medicines used by PLHIV. Thus, the present study aimed to assess the clinical outcomes of the CMM service offered to PLHIV followed up in an Antiretroviral Medication Dispensing Unit in a large Brazilian city.

METHODOLOGY

STUDY DESIGN

This study was divided into two distinct stages, with an analytical cross-sectional component (Stage I) and a quasi-experimental longitudinal component (Stage II). Stage I was conducted in order to identify the associated factors with the identification of DTP in the first assessment.

Stage II was performed through a quasi-experimental study, with a single group of patients inserted into CMM services, using a pre-test/post-test design and without a control group to describe the service data and assess selected clinical outcomes. The use of quasi-experimental study design is encouraged by the World Health Organization to assess outcomes in "real world" services provided in health systems, as is the case of the CMM services offered in the present study.[15] The study was drafted according to the Standards for Reporting Implementation Studies (StaRI) statement.[16]

LOCATION OF THE STUDY

The study was conducted at a public Antiretroviral Medication Dispensing Unit of Belo Horizonte, Minas Gerais. This city is a large Brazilian capital and has about 2.5 million

inhabitants, being the most populous and urbanized municipality in the state and with the highest incidence of HIV infection case.[17]

The Antiretroviral Medication Dispensing Unit is a pharmacy specialized in the ART dispensing. It is a part of the Brazilian universal public health system, which is called Unified Health System (*Sistema Único de Saúde - SUS*). In Brazil, antiretroviral agents are dispensed free of any charge only in the SUS. During antiretroviral treatment, PLHIV are assisted by pharmacists, that provide health education consultations for initiation, modification and maintenance of ART. However, in order to expand the care provided to PLHIV, the CMM services began to be offered in the Antiretroviral Medication Dispensing Unit, in addition to the health education consultations. The present study focuses specifically on the CMM services.

THE CMM SERVICES IN THE ANTIRETROVIRAL MEDICATION DISPENSING UNIT

The CMM services was implemented in the Antiretroviral Medication Dispensing Unit in August 2018 and was offered by three pharmacists, previously trained in the Pharmaceutical Care theoretical-methodological framework, proposed by Cipolle, Strand & Morley (2012). Two of these pharmacists had a workload of 40 hours per week and one pharmacist works 20 hours per week in the Antiretroviral Medication Dispensing Unit. Their working hours are divided between patient care (CMM provision, antiretroviral dispensing and health education consultations) and the administrative part of the dispensing unit (eg. managing medication supply and other health workers).

Before the initiation of the provision of the CMM services, pharmacists held meetings with the board of the Antiretroviral Medication Dispensing Unit in order to present the services and describe its potential benefits for PLHIV. In addition, a communication was sent via email to physicians and other health care professionals from the public and private health system, informing them about the services. The pharmacists suggested some groups of patients who could benefit from the CMM services (such as patients in the use of multiple medications, nonadherent to ART and/or patients who were not reaching the ART goals) and asked physicians to refer patients to them. In addition, some PLHIV were invited to receive CMM services during the health education consultation or at the time of ART dispensing. In these circumstances, initially, PLHIV aged 60 years or more were invited. Subsequently, PLHIV of any age group who had more than one chronic disease were invited.

In the CMM services, the consultations occurred in an individualized manner and were carried out in a private environment in two consultation rooms available for that purpose. The

first consultation, called initial assessment, lasted, in general, about an hour; and the subsequent consultations had a variable time according to the therapeutic needs of each PLHIV. Referrals to other professionals were made by the pharmacists when necessary.

The CMM services offered at the Antiretroviral Medication Dispensing Unit was fully based on the theoretical-methodological framework of the Pharmaceutical Care practice, proposed by Cipolle, Strand & Morley (2012). Thus, the care process adopted was the pharmacotherapy workup (PW), by which pharmacists assess all medications used by patients (prescribed and non-prescribed) for all their health problems (for HIV infection and all other health problems), with the aim of identifying, resolving and preventing DTP in order to achieve favorable clinical outcomes.[8]

Decision making by PW involves a rational and systematic process, in which all medications used by PLHIV are assessed to assure that they are appropriate, effective, safe and convenient. Thus, according to PW, seven types of DTP can be identified: the DTP1, when the medication is unnecessary; the DTP2, in cases of need for additional drug therapy; the DTP3, in cases of the need of a different drug product; the DTP4, when dosage is too low to be effective; the DTP5, in case of adverse drug reaction; the DTP6, when the dosage is too high; and, finally, the DTP7 of non-adherence, when the pharmacotherapy is not convenient for the patient.12 The entire care process and patient outcomes were documented in a CMM record structured in the Microsoft Office Excel Software (2016 version).

STUDY POPULATION AND DATA COLLECTION

All adult (18 years of age or older) PLHIV inserted in the CMM service offered at the Antiretroviral Medication Dispensing Unit from August 2018 to April 2020 with at least one CMM consultation were included in the present study (n=52). Therefore, the total population of the service was evaluated.

All data used in the cross-sectional and longitudinal stages were collected directly from the CMM services records. Data were collected and transferred to Stata® software, version 12, where all analyses were performed.

Data regarding the CMM service were collected (consultations, identified DTP and implemented interventions), as well as demographic data and data regarding health problems and medications used by the patients (prescribed and non-prescribed). Data regarding clinical and laboratory parameters for HIV infection and for the most frequent diseases and adverse drug reactions were also collected: HIV viral load (VL – in ´number of copies/mL´), CD4+ T

lymphocytes cells count (CD4+ T – in ´number of cells/mm3´), glycated hemoglobin (HbA1c - in 'percent'), systolic blood pressure (SBP - in 'mmHg'), diastolic blood pressure (DBP - in 'mmHg'), low density lipoprotein cholesterol (LDLc - in 'mg/dL'), high density lipoprotein cholesterol (HDLc - in 'mg/dL'), triglycerides (TG - in 'mg/dL'), total cholesterol (TC - in 'mg/dL'), serum glutamic-oxaloacetic transaminase (GOT - in ´U/L´), serum glutamic-pyruvic transaminase (GPT - in ´U/L´), serum creatinine (Cr - in ´mg/dL´).

STUDY VARIABLES AND DATA ANALYSIS

For the purpose of population characterization, the following variables were described: gender; age (years completed at the initial assessment); number and types of documented health problems; number and types of medications used (prescribed and non-prescribed); and health system use profile (followed up exclusively in the SUS vs followed up in the SUS and private health system).

To characterize the CMM service provided, the total number of CMM consultations was described. In addition, the number of DTP identified in the first CMM consultation (initial assessment) and in the total of all consultations was described. The DTP were characterized according to their resolution status (resolved vs unresolved) and their types, classified according to PW previously cited (DTP 1 to 7). The interventions performed by the pharmacists were also quantified and characterized if whether they were accepted or not.

The descriptive analysis of data was performed by determining the absolute and relative frequencies of qualitative variables; and mean, standard deviation, minimum (min) and maximum (max) of quantitative variables.

In Stage I (crosssectional component), univariate and multivariate analyses were performed to identify associated factors with the identification of multiple DTPs in the initial assessment, and therefore, patients who should be prioritized for inclusion in CMM services. To this end, the variable "number of initial DTPs" was dichotomized according to its third quartile (75%) and defined as the dependent variable. The independent variables investigated, dichotomized according to their median, were: age, number of medications used in the initial assessment, and types of health problems identified in the initial assessment. The dichotomization was performed to facilitate the adoption of the associated factors as potential inclusion criteria for the CMM services.

Univariate analyses were performed using Pearson's chisquare test or Fisher's exact test. Independent variables with p-value < 0.15 in the univariate analysis were included in the

multivariate model performed by stepwise logistic regression. To assess the goodness of fit of the multivariate model, the Hosmer-Lemeshow test was used. The univariate and multivariate analyses were based on the odds ratio (OR) results and their respective 95% confidence intervals (95% CI) estimated by logistic regression. A statistical significance level of 5% was the criterion adopted to identify the characteristics independently associated with the dependent variable.

In Stage II (quasi-experimental component), to assess the selected clinical outcomes of the CMM services, a linear regression model was built from the difference between the initial and final values of clinical and laboratory parameters (lymphocytes cells count, glycated hemoglobin, systolic blood pressure, diastolic blood pressure, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, total cholesterol, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, serum creatinine) and cardiovascular risk (calculated according to the American Heart Association – AHA).[22] Those specific clinical outcomes were selected according to its relevance to monitor PLHIV, as well as the most frequent comorbidities. The p-value for the linear regression model was considered statistically significant if lower than 5%. Regardless of the distribution of the variables (parametric or non-parametric), the model was considered valid if the residuals showed normal distribution according to the Shapiro-Wilk test, and homoscedasticity according to the Breusch-Pagan/Cook-Weisberg test.

For all the analyses of Stage II, patients were included only if they had more than one CMM consultation and documented values for the assessed clinical and laboratory parameters. The time between the initial and final values of the parameters varied from patient to patient, since the number of consultations and follow-up periods are individualized according to the therapeutic needs of each patient.

ETHICAL ASPECTS

This study is a part of the project "Clinical and economic results, humanistic, cultural and educational aspects of CMM services in the Unified Health System", approved by the research ethics committee on May 28, 2014 number 664.354 under registration CAAE-25780314.4.0000.5149.

RESULTS

A total of 52 PLHIV were assessed, with a mean age of 60 ± 11.3 years (min = 29; max=78), and most of them were male (n= 41; 78.85%). Most of the people included in the study received medical care and follow-ups in the private health system (n= 45; 88.24%).

The mean number of health problems identified at the beginning of the assessment was 5.2 + 1.6 (minimum = 2; maximum = 8). The most prevalent diseases were hypertension (65.38%; n = 34), dyslipidemia (55, 76%; n = 29) and central nervous system diseases, among them major depressive disorder, anxiety and insomnia (40.38%; n = 21).

In the initial assessment, 82.76% of patients (n= 43) were using five or more medications, with a mean of 7.4 ± 2.3 medications per patient (min = 3; max = 12). In total, 385 medications were used at the initial assessment. Of these, 165 drugs were part of ART (42.9% of total drugs), configuring a mean of 3.2 ± 0.4 (min = 3; max = 5).

In the first assessment, 128 DTP were identified, and 92.31% of patients (n = 48) had at least one DTP identified in their pharmacotherapy. The total number of consultations performed was 177 (mean = 2.4 ± 1.5 consultations; min =1; max = 8) (Table 1).

Table 1. Demographic, health and medication use profile of the People Living with HIV inserted in the Comprehensive Medication Management service (CMM) at the Antiretroviral Medication Dispensing Unit. Belo Horizonte - MG. 2018-2020

Characteristics	n (%)
Gender	
Female	11 (21.1)
Male	41 (78.9)
Age (complete years)	
29 - 60	35 (67.3)
≥ 60	17 (32.7)
Number of consultations	
1 - 3	40 (79.6)
≥ 3	12 (20.4)
Number of medications at initial assessment*	
3 - 6	20 (38.5)
≥ 7	32 (61.5)
Number of health problems at initial assessment*	
2 - 5	32 (61.5)
≥ 5	20 (38.5)
Number of DTP identified in the initial assessment*	
0 - 4	46 (88.5)
≥ 4	6 (11.5)

*Initial assessment: first consultation of CMM; DTP = Drug Therapy Problem.

Throughout all the CMM consultations, a total of 171 DTP was identified, and 38 of them involved patients who only had one consultation. Among the DTP, most of them were

related to the need for additional drug therapy (DTP2) (24.6%; n = 42), and then the DTP of unnecessary medication, being 20.5% (n = 35). Regarding the identification of DTP by disease, 40 were related to HIV, 24 to hypertension, 18 to dyslipidemia and 13 to major depressive disorder. For the DTP involving HIV, the DTP of ineffective drug (n =20; 50.0%), mainly related to efavirenz, stands out. Of the identified DTPs, 69 (40.4%) were resolved and for 54 (31.6%) it was not possible to assess their resolution (Table 2).

Table 2 - Frequency of the types of Drug Therapy Problems (DTP) related or not to HIV identified in the consultations of the comprehensive medication management (CNM) service of the Antiretroviral Medication Dispensing Unit. Belo Horizonte - MG. 2018-2020

Type of DTP	Total n (%)	HIV n (%)	Other diseases n (%)
1. Unnecessary medication	35 (20.5)	1 (2.5)	34 (25.9)
2. Need for additional medication	42 (24.6)	0 (0. 0)	42 (32.1)
3. Ineffective medication	34 (19.9)	20 (50.0)	14 (10.7)
4. Low dose	18 (10.5)	0 (0.0)	18 (13.7)
5. Adverse Reaction	17 (9.9)	11 (27.5)	6 (4.6)
6. High dose	2 (1.2)	0 (0.0)	2 (1.5)
7. Non-adherence	23 (13.5)	8 (20.0)	15 (11.5)
Total	**171 (100.0)**	**40 (100.0)**	**131 (100.0)**

Table 3 shows the results of the univariate and multivariate analyses. The presence of dyslipidemia, central nervous system diseases and the use of seven or more medications at the initial assessment (independent variables) were statistically significantly associated with the identification of two or more DTP at the initial assessment (dependent variable).

Table 3. Univariate and multivariate analyses of factors associated with the dependent variable - identification of two or more Drug Therapy Problems (DTP) at the first consultation to the comprehensive medication management (CMM) service of the Antiretroviral Medication Dispensing Unit (ADMU). Belo Horizonte - MG. 2018-2020

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI) *	p-value**	OR (95% CI) *	p-value**
Number of medications used in the initial assessment				
0-6	1.00			
≥7	5.16 (1.27 -20.96)	0.02	4.28 (1.32-13.88)	0.015
Dyslipidemia				
No	1.00			
Yes	4.79 (1.23 -18.69)	0.02	5.38 (1.61-17.97)	0.006
Central nervous system diseases				
No	1.00			
Yes	5.28 (1.28-21.88)	0.02	3.64(1.13-11.69)	0.030
Age				

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI) *	p-value**	OR (95% CI) *	p-value**
No	1.00			
Yes	0.79 (0.45 – 1.37)	0.91	-	-
Hypertension				
No	1.00			
Yes	1.89 (1.06 – 3.34)	0.29	-	-
Diabetes mellitus				
No	1.00			
Yes	0.3 (0.15 – 1.57)	0.64	-	-

** OR (95% CI) = Odds ratio and 95% Confidence Interval estimated by logistic regression; ** Calculated by logistic regression and significant when p <0.05.

In addition, a statistically significant difference was demonstrated between the initial and final values of SBP, VL, CD4+ T and triglycerides. Cardiovascular risk, TC, Cr, GOT and GPT showed a reduction compared to the initial values, but the difference was not statistically significant (Table 4).

Table 4. Comparison of the initial and final values of clinical and laboratory parameters identified in the comprehensive medication management (CMM) service of the Antiretroviral Medication Dispensing Unit (ADMU). Belo Horizonte - MG. 2018-2020., Belo Horizonte, Brazil (2018-2020)

Parameter	Initial mean ± standard deviation	Final mean ± standard deviation	p-value
VL	26116.4 ± 21118.0	59.2 ± 65.8	0.0001*
CD4+ T	474.6 ± 331.7	656.6 ± 387.1	0.0283**
SBP	129.0 ± 17.9	119.7 ± 19.9	0.0409*
TG	214.1 ± 133.1	171.8 ± 91.3	0.0390*
TC	177.4 ± 44.7	170.5 ± 48.5	0.2684**
Cr	1.5 ± 1.5	1.2 ± 0.6	0.5033*
GOT	34.1 ± 18.8	29.9± 18.8	0.2233*
GPT	31.6 ± 19.4	25.7± 21.6	0.1159*
CVR	15.5 ± 10.6	14.5 ± 11.6	0.0904**

Label: CD4+ T = CD4+ T lym-phocytes cells count; Cr = serum creatinine; CVR = cardiovascular risk; GOT = oxalacetic transaminase; GPT = pyruvic transaminase; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; VL = HIV viral load. Analyses: *Wilcoxon signrank test ** t Test.

DISCUSSION

This study allowed assessing the clinical outcomes of CMM services offered to PLHIV, both in the parameters of HIV effectiveness and in those of other comorbidities presented by them. Although there are studies that assess outcomes of pharmaceutical services other than CMM in this population [18,19], this one is the first to assess the outcomes of interventions performed by pharmacists related to all health problems and all medications used by PLHIV

using a rational decision making process. In addition, most patients who were included in the CMM service are elderly, making it possible to identify the main pharmacotherapeutic needs of this growing group among PLHIV, something that, to our knowledge, has not yet been described in the literature.

As a result of the criteria suggested to physicians and adopted in the invitation to join the CMM service, the population of the service had a high average age (60 ± 11.3 years), being very different from the average age of PLHIV in Brazil, which is between 25 and 39 years in both genders.[2] However, it is necessary to point out that demographic transition added to improved access to ART over the years is causing chronic and degenerative diseases to begin to gain greater representation among PLHIV.[20] Even with the aging trend of the population living with HIV, it is important to highlight that the increase in HIV prevalence in the elderly has not been accompanied by the formulation of guidelines or specific therapeutic recommendations for this population.[3]

This characteristic of the study population reflects a greater complexity of the pharmacotherapy of PLHIV and the service offered, since the elderly living with HIV have higher chances of having more comorbidities and, consequently, use more medications than younger patients.[21] This could be observed in the percentage of patients in polypharmacy (82.8%) and the average number of health problems (5.2 ± 1.6) identified in the initial assessment. This complex profile in a population of PLHIV with increasing life expectancy reinforces the need for implementation and qualification of CMM services aimed at these people. Additionally, the use of antiretroviral agents requires a continuous monitoring of the patient in the health care system by a multidisciplinary team, including the pharmacist.[4] This professional, by offering CMM services, in addition to improving the pharmacotherapeutic outcomes of PLHIV, can strengthen their bond in the health system, given the transition in which this population is inserted.

As for the type of diseases, we observed a considerable prevalence of hypertension (65.38%) and dyslipidemia (55,76%) among the investigated PLHIV, which are well-established risk factors for cardiovascular diseases.[22] It is known that rates of hypertension in PLHIV are higher than in patients not living with the infection and the prevalence of dyslipidemia is also high among PLHIV due to metabolic changes often caused by HIV. [22] Among adult PLHIV in Brazil, the multimorbidity of chronic noncommunicable diseases increased, some national and international studies, which analyze the presence of these comorbidities, have shown similar prevalence to the one identified in the present study. [20,23]

The number of identified DTPs (n = 128; mean of 2.5 per patient) is another data that reinforces the relevance of offering the CMM service in this type of scenario. The similar study realized by Neves et al (2019) offering the CMM service in primary care, demonstrated an average of 3.5 MRP, higher than that found in the present study, for patients who received follow-up with the pharmacist.[14] Another study that evaluated the factors associated with the identification of DRP among elderly patients in primary health care demonstrated that 73.60% of elderly people had at least one DTPs, a percentage that was as high as that demonstrated in this study (93.36%).[24] It also highlights the fact that during the consultations following the initial one, a considerable number of DTP were identified (n = 171), which suggests the need for the professional to monitor the PLHIV continuously and to know in depth their clinical history, especially more complex patients. In this sense, these results suggest that health education consultations can be an important means for screening patients who have more pharmacotherapeutic needs and who might benefit more from the CMM service.

The most frequent types of DTP were those involving the need for additional medication (n = 42; 24.6%) and the use of unnecessary medication (n = 35; 20.5%). Other studies that assessed the clinical outcomes of CMM services also pointed out similar rates of these DTP.[12,14,25] A study conducted in primary care in Belo Horizonte, which assessed a CMM service provided to a population with a similar mean age to the present study, also identified a frequency of DTP related to the need for additional medication around 20% (21.8%).[14] Another cross-sectional study with 81 patients co-infected with tuberculosis and HIV/AIDS and followed up in a reference hospital for infectious diseases in Minas Gerais showed that 80% of patients had at least one DTP and, among them, the most prevalent cause was related to the need for additional medication (57%), as in the present study.[26] The "need for additional medication" as the most prevalent type of DTP, may suggest an underutilization of medicines, which is often a problem neglected by health services and professionals, including pharmacists.[27] This characterizes an obstacle to access a more effective pharmacotherapy, compromising clinical outcomes. Thus, it is necessary to establish the clinical reasoning proposed by the PW, to assess each medication used by the patient in terms of its appropriateness, effectiveness and safety, and finally assess the patient's behavior in terms of being adherent or not.

Among the types of DTP related to ART, a relevant prevalence of ineffective medication use (n= 20; 50.00%) and adverse reaction (n=11; 27.50) was observed. The main parameter of ART effectiveness is the undetectable viral load, and the achievement of this therapeutic goal can be influenced by clinical, behavioral, and ART related factors.[28] Efavirenz was the drug

that was most related to DTP regarding treatment ineffectiveness, which can be explained by the fact that this first-generation non-nucleotide reverse transcriptase inhibitor has a low barrier to viral resistance.[8] In addition, efavirenz has toxicity to the central nervous system and its effects usually include vivid dreams, confusion and dizziness, which can interfere with the user's daily life activities and impair its use, causing ineffectiveness.[4] Currently, in the Brazilian protocol for the management of adult PLHIV, dolutegravir is the therapeutic alternative that has the best response to achieve undetectable viral load with better tolerability.

Tenofovir was the antiretroviral drug most frequently involved in the identification of DTP of adverse reaction. The renal and bone toxicity resulting from the use of this medication are of clinical relevance, especially considering the high mean age identified in this study, which is related to a higher frequency of renal dysfunction and osteoporosis.[4] Abacavir and zidovudine are therapeutic alternatives that can be implemented in the patient's pharmacotherapy in cases of tenofovir related renal toxicity. In addition to these two alternatives, the use of dual therapy (lamivudine associated with a second antiretroviral drug) when abacavir and zidovudine are contraindicated for the patient is currently recommended.[4] In this context, it is up to the pharmacist, the CMM service provider, to assess together with the medical team which is the best therapeutic alternative for the patient to achieve the parameters of effectiveness and safety with lower risk of failure, viral resistance and adverse reaction.

Although adherence is a widely discussed issue when it comes to ART, the adherence related DTPs involving these medications were not so frequent (n = 8; 20.0%). This finding can be explained by the fact that the selected patients already had good adherence to ART and were continuously monitored by the specialized service regarding the use of medications, both through medical and pharmacist consultations. On the other hand, the number of DTPs was higher for the other drugs that are not components of ART (n=15; 11.45%). This strengthens the argument that continuous monitoring through a holistic and global view of pharmacotherapy is essential to achieve adequate clinical outcomes for diseases other than HIV, since the patient's clinical stability interconnects all comorbidities. Above all, when assessing adherence, it should be considered that it involves several factors related to the patient, the health system, the health care team, the disease, and the medications being used. [22] The PW decision making method allows for the assessment of adherence to ART, a subject that is widely discussed in the literature when it comes to pharmaceutical services offered to PLHIV.[14,25]

Multivariate analyses demonstrate that the use of seven or more medications (OR=4.28; 95%CI), and the presence of dyslipidemia (OR=5.38; 95%CI) and central nervous system diseases (OR=3.64; 95%CI) are factors independently associated with the identification of two

or more DTPs at the initial patient assessment. The studie by Damazio et al. (2019) also identified a positive association between polypharmacy and identification of multiple DTP. This finding suggests that patients who have one or more of these characteristics are the most likely to need the CMM service, and can be used as a prioritization criterion in the inclusion of patients in the services. Practice management is one of the pillars for the implementation of the CMM, which makes these results important for the organization of the demand and definition of inclusion.[9] The criteria that existed before were defined according to the pharmacists' experience, these data can help them to redefine and guide the priorities for care so that new patients can also benefit from the service.

In the analyses of the outcomes of the service, a statistically significant reduction was observed in some clinical and laboratory parameters (VL, CD4+ T, SBP, TG) at the end of the period assessed in this study. These results demonstrate a positive clinical impact of this service offered to PLHIV in the parameters of effectiveness of ART and other comorbidities, i.e., the CMM service has potential not only in meeting the pharmacotherapeutic needs of patients related to HIV, but also other associated diseases. The fact that the study population was mostly composed of elderly people demonstrates the importance of offering this service, since they are more likely to present multiple comorbidities and, consequently, more problems related to the use of medicines. In addition, advanced age is a risk factor for hypertension and dyslipidemia, diseases whose effectiveness parameters were positively impacted by the CMM service.

Regarding the improvement in TG, it is known that PLHIV have a higher risk of presenting changes in the lipid profile when the HIV viral load is not controlled and depending on the ART in place, as is the case of protease inhibitors and non-nucleoside reverse transcriptase inhibitors.[22] Changes in serum lipid levels directly impact the elevation of the patient's cardiovascular risk.[22] Although this data was assessed in the present study, it did not present a statistically significant difference ($p= 0.09$) due to the lack of some clinical parameters and the number of patients included. Other studies that evaluated CMM services offered to PLHIV did not access TG results or other clinical parameters not directly related to HIV. This fact makes the present results unique in the literature and demonstrates the importance of the holistic approach in CMM.

The achievement of undetectable viral load and CD4+ T lymphocyte cells count, are the main therapeutic goals in HIV. The results of the present study suggest that pharmacists' interventions were able to improve VL ($p<0.05$) and CD4+ T ($p=0.03$). Even in continuous follow-up with the infectious disease specialist, some of them had problems related to the effectiveness of ART, which directly impacts the achievement of the therapeutic goal for HIV.

Drawing a parallel with the descriptive data presented,[15] of the DTPs (50.0%) related to ART were type 3 (use of ineffective medication), and efavirenz was more related to this type of DTP. The assessment of alternative therapies that can replace efavirenz in cases of ineffectiveness or adverse effects, as mentioned above, becomes necessary. Currently, dolutegravir is a drug that can replace regimens containing non-nucleoside reverse transcriptase inhibitor, such as efavirenz and also those containing protease inhibitors associated with ritonavir.[4] In this context, the relevant pharmacists' interventions to change the regimen according to what is recommended in the protocol for the management of HIV infection can improve patients' clinical outcomes. It should also be considered that not reaching the viral load and CD4+ T lymphocyte count can increase the risk of HIV transmission and the susceptibility of PLHIV to opportunistic infections.[4]

Therefore, maintaining the CMM service in the public dispensing unit can provide benefits to patients and should be considered as a pharmaceutical service to be implemented in secondary care as it has proven clinical impact in this population. In comparison, an intervention study by Molino et al. 2016, demonstrated that the group of PLHIV who received the PW guided service in an outpatient service showed a statistically significant increase in CD4+ T count of the group that received the pharmacists' interventions (p=0.01), but not for VL (p=0.20). However, different from what was proposed in the present study, Molino et al. 2016 did not assess the parameters of effectiveness and safety associated with other comorbidities, which has special relevance since CMM services aim to assess the patient's pharmacotherapeutic needs globally. Other studies also detected a statistically significant reduction in SBP)[14,]. No other studies evaluating CMM services offered to PLHIV was identified in the literature.

This study presents some limitations. First, only one of the pharmacists had previous experience in providing CMM services in other scenarios, although all three of them had been properly trained according to the theoretical-methodological framework of Pharmaceutical Care. The lack of experience of the two pharmacists may have impaired the service documentation and the quality of data necessary for assessing clinical outcomes. The process of care and documentation require mastery of practice and professional experience, being improved over time, and this can directly affect the quality of the data collected.[9,12] Despite this limitation, it is important to emphasize that only one practice model was implemented, which ensured that all patients received the same level of quality care.

Another point of limitation is the fact that most patients included receive medical care in private health services, besides the Antiretroviral Medication Dispensing Unit under study

being a unit where there is no presence of physicians from the public health system. The interaction of the pharmacist with the prescribers and the multiprofessional team is essential for building partnerships, facilitating the acceptance of the proposed interventions and the understanding, by other professionals, of the pharmacist's role as caregiver and coresponsible for the results of the patient's pharmacotherapy.[30] Thus, the service profile may have hindered the implementation of interventions with physicians, although the acceptability of interventions was intermediate (35.4%). However, in the study by Detoni et al. (2016), the CMM service provided in a specialty medication dispensing unit without the presence of physicians, for COPD patients cared primarily in the private health care system, provided a higher acceptability of pharmacists' interventions (60.0%). Therefore, the mechanisms of communication with prescribers and with the health care team should be improved in order to increase the acceptability of the interventions in this challenging scenario.

The workload of clinical pharmacists inserted in the CMM provision was also a limiting factor, as it reduced the number of assessments and, consequently, the ability to include new patients in the service and solve DTP. This may also have limited the number of patients with multiple consultations and may have underestimated the impact of the service. However, at the beginning of the implementation of a clinical service, as is the case of this study, the care of a sufficient number of patients to ensure the quality of clinical practice should be prioritized, in order to generate indicators that stimulate the development of the service, so that it can be subsequently expanded.[29]

It is important to emphasize that this study has a quasi-experimental design, as it is an assessment of an already implemented service. Therefore, the participants were not randomly selected, and it was not possible to define a control group. In contrast, this type of study is a viable alternative to assess clinical outcomes of *"real world*" services, being encouraged by the World Health Organization[15], especially for services that already have proven positive impacts in other settings, as is the case of the CMM. [11,13,14,25] Taking this study design into consideration, another limitation of the study is the fact that it was carried out in a small population in a unique practice setting. Therefore, direct comparison with other services is not appropriate due to the impossibility of extrapolating data to other realities.

Despite the limitations, the results obtained described a population with high pharmacotherapeutic complexity and a considerable number of DTP, highlighting the relevance of offering CMM services for PLHIV. In addition, it is noteworthy that, despite being a newly implemented service in a challenging and unusual scenario for the pharmacist, the CMM showed a positive and statistically significant impact on relevant clinical parameters for PLHIV,

which reinforces its potential. We cannot, however, affirm that there is external validity beyond the particular scenario described in the present study. In the future, however, further research assessing clinical outcomes of CMM provided to PLHIV for a larger group of patients may better elucidate its potential.

The results of this study show the relevance of this service in clinical practice, since the global management of pharmacotherapy favors the achievement of parameters of effectiveness and safety of treatments for all patient comorbidities. By optimizing pharmacotherapy for PLHIV with a high average age and polypharmacy, a safe aging process is promoted, as these people have their pharmacotherapeutic needs met. Especially among PLHIV, continuous monitoring ensures the achievement and maintenance of viral suppression and immunological effectiveness, which are essential to promote the interruption of HIV transmission. In addition to the impact on individual health, this type of service can also have economic impacts on the health service. The importance of multidisciplinary monitoring is also highlighted, since the perspective of another non-medical professional through a clinical service with a well-consolidated theoretical-methodological framework, as demonstrated in this study, promotes the achievement of positive results with the treatment.

CONCLUSION

In conclusion, the present study indicates that the CMM services favored the optimization of pharmacotherapy, assisting in obtaining positive clinical outcomes, since statistically significant improvement was demonstrated in SBP, VL and CD4+ T among PLHIV. The high prevalence of identified and resolved DTP confirms how this service is relevant and can improve the effectiveness and safety of the pharmacotherapy of PLHIV. In addition, the present study suggests that the use of seven or more medications, dyslipidemia and diseases of the central nervous system can be used as criteria for prioritizing patients to be referred to CMM services at the Antiretroviral Medication Dispensing Unit.

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