Assessing the influence of pharmaceutical care on therapeutic optimisation outcomes in chronic patients in a real cohort

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ABSTRACT

Background: To compare in real clinical practise the application of Capacity-Motivation-Opportunity (CMO) methodology Pharmaceutical Care (PhC) against the usual PhC in people living with HIV (PLWH) vs. non-HIV patients for the optimisation of pharmacotherapy.

Methods: A cross-sectional study was conducted between December 2022 and January 2023. PLWH were compared with a group of patients with chronic conditions who attended the outpatient hospital pharmacy service. Descriptive and multivariate analyses were performed to study the association between the PhC model and criteria associated with therapeutic optimisation, such as the PIMDINAC and 3-HIT criteria.

Results: The study involved 145 patients, 75 PLWH, and 70 patients without HIV. The median age was 40 versus 39 years, respectively (p=0.22). The prevalence of the total criteria for PIMDINAC (12 vs. 20%, p=0.27) and 3-HIT (18.7 vs 48.6%, p<0.01) criteria was higher in patients without HIV. Regarding inappropriate medications, non-HIV patients were observed with a higher proportion (29 vs 55.7%, p=0.03). Differences were found in polypharmacy rates (62.7 vs 74.3%, p=0.04) and major polypharmacy (20 vs 38.6%, p=0.02) with higher rates in patients without HIV infection.

Conclusions: The PIMDINAC and 3-HIT criteria exhibited a high prevalence among non-HIV patients with chronic diseases. HIV infection was identified as a risk factor for nonadherence, inappropriate potent medication use, and the development of 3-HIT criteria. Considering the high prevalence observed in the group of patients without HIV who receive regular pharmaceutical care, it is imperative to implement a capacity-motivation-opportunity pharmaceutical care model within clinical routines.

Keywords: **HIV Infections, Quality of Health Care, Pharmaceutical care.**

Evaluación de la influencia de la atención farmacéutica en los resultados de optimización terapéutica en pacientes crónicos en una cohorte real

RESUMEN

Objetivos: comparar en la práctica clínica real la aplicación de la metodología de atención farmacéutica (AF) Capacidad-Motivación-Oportunidad (CMO) frente a la AF habitual en personas que viven con VIH (PVVIH) frente a pacientes no VIH para la optimización de la farmacoterapia.

Metodología: se llevó a cabo un estudio transversal entre diciembre de 2022 y enero de 2023. Se compararon PVVIH con un grupo de pacientes seronegativos con enfermedades crónicas que acudieron al servicio de pacientes externos de farmacia hospitalaria. Se realizaron análisis multivariantes para estudiar la asociación entre el modelo de AF y los criterios asociados con la optimización terapéutica, como los criterios PIMDINAC y 3-HIT.

Resultados: se incluyeron 145 pacientes, 75 PVVIH y 70 pacientes seronegativos con patologías crónicas. La mediana de edad fue de 40 años para PVVIH y 39 años para pacientes con enfermedades crónicas, respectivamente (p=0,22). La prevalencia de los criterios totales para PIMDINAC (12 vs. 20%, p=0,27) y criterios 3-HIT (18,7 vs. 48,6%, p<0,01) fue mayor en pacientes seronegativos. En cuanto a medicamentos inapropiados, se observó una proporción más alta en pacientes seronegativos (29 vs. 55,7%, p=0,03). Se encontraron diferencias en las tasas de polifarmacia (62,7 vs. 74,3%, p=0,04) y polifarmacia mayor (20 vs. 38,6%, p=0,02) con tasas más altas en pacientes seronegativos.

Conclusiones: los criterios PIMDINAC y 3-HIT exhibieron una alta prevalencia entre pacientes seronegativos con enfermedades crónicas. La infección por VIH se identificó como un factor de riesgo para la falta de adherencia, el uso inapropiado de medicamentos potentes y el desarrollo de criterios 3-HIT. Considerando la alta prevalencia observada en el grupo de pacientes seronegativos que reciben atención farmacéutica regular, es fundamental implementar el modelo de AF CMO dentro de la práctica clínica.

Palabras clave: **infección por VIH, Atención farmacéutica, Calidad Asistencial.**

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INTRODUCTION

In recent years, there has been a growing trend in the number of patients with chronic diseases, which has become a significant challenge for the care of these patients to optimise therapy to obtain positive health results. On the one hand, the implementation of effective antiretroviral therapy (ARV) has contributed to a notable increase in life expectancy for people living with HIV (PLWH), in some cases equivalent to non-HIV patients[1]. HIV infection has become a chronic disease and PLWH are now surviving, ageing, and requiring lifelong care and treatment[2]. On the other hand, immune-mediated pathologies in the field of rheumatology or digestive are becoming more prevalent and have become a significant challenge for the care of these patients[3].

Multimorbidity and polypharmacy are highly prevalent throughout the world, particularly among the elderly population[4]. Additionally, the ageing process presents new challenges for the health system, since it must meet its specific requirements.

Studies are already showing the importance of a collaborative and coordinated approach in the care of PLWH to provide patient-centred care. The benefits of this approach are highlighted, including better disease management, greater adherence to treatment, improved quality of life, and positive health outcomes for PLWH[5]. In addition, there are systematic reviews that underline the need for comprehensive and personalised medical care for older PLWH, considering the specific challenges they face in terms of therapeutic optimisation[6].

Pharmaceutical care (PhC) plays an essential role in multidisciplinary teams devoted to chronic patients to improve health outcomes. There are multiple studies that show the benefit it brings in clinical aspects and other fundamental aspects of the patient, such as quality of life[7].

In recent years, the concept of PhC has been redefined so that it is consistent with current times and the needs of patients[8]. This redefinition occurred in the context of a change in the central axis of the PhC model, which according to the traditional model was the medication. However, the development of the Capacity-Motivation-Opportunity (CMO) PhC model and the health results obtained in the different studies when applying this model revealed the need for a change in the centre of the model, which became patient[9,10].

The CMO is a model whose cornerstones are capacity, understood as providing individualised PhC adapted to each patient, through stratification; motivation, to achieve goals with drug therapy, replacing the traditional clinical interview with a motivational interview; and finally, opportunity, providing follow-up beyond personal consultation, through information, communication and learning technologies[11].

The application of this model has promoted the development of tools that aim to identify patients at risk of negative health outcomes related to their medication to optimise their treatment. Among these tools are the PIMDINAC criteria, which include three components such as potentially inappropriate medication (PIM), drug interactions (DI) and non-adherence to concomitant treatment (NAC), and the 3-HIT concept that a combined variable which includes high pharmacotherapeutic complexity, DI and NAC, applied in PLWH[12,13]. Furthermore, the PIMDINAC criteria have already been applied in patients without HIV infection[14].

Patient-centred PhC is essential in the pharmacotherapeutic optimisation of patient therapeutic regimens that allow us to achieve adequate health outcomes for patients. Above all, it is relevant for those patients with chronic diseases where polypharmacy and high complexity may be more prevalent. Therefore, we are faced with a population with a higher risk of developing negative effects associated with treatment, such as lack of adherence, drug-drug interactions, or potentially inappropriate medication that may compromise the achievement of therapeutic objectives, all of which have been studied and designed strategies for their prevention in PLWH[15].

The aim of the study was to compare in real clinical practise the application of the PhC CMO methodology with the usual PhC in PLWH versus non-HIV for the optimisation of pharmacotherapy.

METHODS

Study design, participants and ethics issues.

We conducted a single-centre cross-sectional analysis of PLWH patients between December 2022 and January 2023. Patients ≥ 18 years of age with active ARV and stability of hospital treatment for at least 6 months were selected at the time of a pharmacotherapeutic follow-up visit in the pharmacy services of the outpatient hospital. PLWH was followed according to a PhC CMO model. Patients were excluded if they participated in a clinical trial, did not give their written informed consent, or did not have the ability to respond to questionnaires.

To establish a comparable control group, non-HIV patients with chronic disease were selected. These patients were chosen from those who visited the outpatient pharmacy of a hospital located in the same health district. The chronic diseases considered were predominantly immune-mediated chronic, as well as other age-related chronic conditions such as Crohn's disease or rheumatoid arthritis. All non-HIV patients with chronic diseases were followed using the usual PhC model.

It is, therefore, two consultations in the pharmacy services of the outpatient hospital in routine clinical practice with two different PhC methodologies.

The study fulfilled all the ethical requirements and was approved by the Clinical Research Ethics Committee of Sevilla-Sur (C.I. 0042-N-23). This study was carried out according to the Declaration of Helsinki guidelines for biomedical research.

VARIABLES

Variables were collected during hospital pharmacy outpatient visits. The main variable measured was the number of patients with optimised therapy according to the absence of PIMDINAC and 3-HIT criteria. The secondary variables included were demographic (age, sex and date of diagnosis), comorbidities, and variables related to drug treatment. Variables considered in PLWH included CD4 cell counts and viral load of plasma HIV RNA. Only patients with all completed variables were included in the analysis.

To describe patterns of multimorbidities, we employed the categorization proposed by Prados-Torres et al who classi¬fied the patterns depending on the type of disease they were diagnosed including: cardiometabolic,

geriatric-depressive, thyroid mechanic and mixed[16].

Polypharmacy was defined as the use of 6 or more different drugs, including antiretroviral medication; major polypharmacy was restricted to the use of ≥11 different drugs. To describe the patterns of polypharmacy, we employed the categorization proposed by Calderón-Larrañaga et al.[17] who classified the patterns depending on the type of disease.

The MRCI index is a validated tool consisting of 65 items that has been validated to evaluate the complexity of a treatment regimen. This index assesses the complexity based on the number of medications, the dosage form, the frequency of the dose and any additional or special instructions required. The index score ranges from 1.5, which represents a single tablet or capsule taken once daily, to an undefined maximum score that increases with the number of medications taken[18]. Higher scores on the MRCI index indicate higher levels of complexity. Furthermore, in accordance with Morillo-Verdugo et al, we utilized a cut-off value of 11.25 for the MRCI index score to identify patients with complex treatment regimens[19].

DATA ANALYSIS

Discrete variables were presented as numbers (percentage), and continuous variables were presented as median (IQR). Differences in categorical variables were evaluated using a two-tailed likelihood ratio $\chi 2$ test or Fisher's exact test, while the t test or the Mann-Whitney U test was used for continuous variables as appropriate. Additionally, a logistic regression analysis was conducted to identify factors independently associated with compliance with both the PIMDINAC and 3-HIT criteria. Furthermore, an explanatory logistic model was developed to assess whether HIV infection predicted compliance with both criteria, along with other adjustment variables. A p-value <0.05 was considered statistically significant for bivariate comparisons. Data analysis was carried out using the IBM SPSS 28.0 statistical software package.

RESULTS

A total of 145 patients were included in the study (75 PLWH in CMO PhC group and 70 non-HIV patients with chronic disease in usual PhC group). Globally, 54.5% were male, with a median age of 56 years (IQR 46-64). The median number of comorbidities was 2 (IQR: 1-4), with the majority having a thyroid/mechanic pattern (81.4%). Among PLWH, 68 patients (90.7%) had an undetectable viral load, with a CD4 count >200 cells in 92 %. The most common disease among HIV non-infected patients attending the outpatient pharmacy was rheumatoid arthritis (34.7%), followed by psoriatic arthritis (15.3%), ankylosing spondylitis (11.1%) and severe asthma (11.1%). The most frequently used therapeutic groups for patients with chronic diseases other than HIV infection were anti-TNF therapy (60%) and interleukin inhibitors (25.7%).

Baseline characteristics were compared between PLWH and patients with chronic diseases but without HIV. Differences were observed in the morbidity patterns, with patients with chronic diseases showing a higher prevalence of the Thyroid/mechanic pattern (78.9% vs. 4.4%), while PLWH had a higher proportion of the metabolic/cardiac (73.9% vs. 19.3%) and psycho/geriatric patterns (21.7% vs. 1.8%). No differences were observed in the rates of polypharmacy (>6 drugs) or major polypharmacy (≥11 drugs) between the two groups in relation to pharmacotherapeutic variables. Demographic and clinical characteristics of both PLWH and non-HIV patients with chronic diseases are presented in Table 1.

Table 1. Baseline features and bivariate comparison of PLWH and non-HIV with chronic conditions

Characteristics	Overall population (n=145)	PLWH (n=75)	Non-HIV patients with chronic diseases (n=70)	P-value
Age (years)	56 (46-64)	55 (46-63)	57 (48-65)	0.22
Age at diagnosis (years)	46 (35-54)	43 (32-54)	47 (37-54)	0.47
Gender (male)	79 (54.5)	40 (53.3)	39 (55.7)	0.77
Comorbidities (n)	2 (1-4)	1 (0-3)	3 (2-5)	**<0.01**
Morbidity pattern	Overall population (n=132)	PLWH (n=23)	Non-HIV patients with chronic diseases (n=57)	0.09
Metabolic/Cardiac	13 (9.8)	17 (73.9)	11 (19.3)	
Thyroid/mechanic	118 (81.4)	1 (4.4)	45 (78.9)	
Psycho/geriatric	1 (0.8)	5 (21.7)	1 (1.8)	
Polypharmacy (>6)	99 (68.3)	47 (62.7)	52 (74.3)	**0.04**
Polypharmacy (>11)	42 (29)	15 (20)	27 (38.6)	**0.02**
Polypharmacy pattern	Overall population (n=74)	PLWH (n=23)	Non-HIV patients with chronic diseases (n=51)	**<0.01**
Depression/Anxiety	16 (21.6)	3 (4)	13 (25.5)	
COPD	20 (27)	3 (4)	17 (33.3)	
CVD	20 (27)	14 (18.7)	6 (11.8)	
Mixed	18 (24.4)	3 (4)	15 (29.4)	
Potentially inappropriate medications	42 (28.9)	18 (29)	39 (55.7)	**0.03**
Drug-Drug Interactions	76 (52.4)	39 (62.9)	37 (52.9)	0.12
Non-adherence	84 (57.9)	31 (41.3)	53 (75.7)	**<0.01**
Overall MRCI* ≥11.25	127 (87.6)	66 (88)	61 (87.1)	0.09

Values are median (IQR) or n (%); *MRCI, Medication Regimen Complexity index.

Regarding the 3-HIT criteria between groups, differences were found with a higher proportion in non-HIV patients with chronic diseases (18.7% vs. 48.6%; p <0.01). However, no differences were found when applying the PIMDINAC criteria, which presented a higher proportion of non-HIV patients with chronic conditions (12.0% vs 20.0%; p=0.27).

If the partial criteria that are part of both the PIMDINAC and 3-HIT criteria are analyzed separately, significant differences were observed in NAC among patients without HIV infection (41.3% vs. 75.7%; p <0.01). In relation to the partial criteria that are part of the PIMDINAC criteria, significant differences were observed in the prescription of potentially inappropriate medication that had a higher proportion of non-HIV patients with chronic disease (29% vs. 55.7%; p=0.03). Finally, analyzing the patients with an MRCI value >11.25 points, a criterion included in the 3-HIT concept, no differences were found between both groups of patients. Patients with optimized therapy and the presence of negative health outcomes such as appearance of PIMDINAC and 3-HIT criteria are presented in Table 2.

In multivariate logistic regression analysis adjusted for age, gender and group (PLWH/ non-HIV patients with chronic diseases), non-HIV patients with chronic conditions was found to be a higher probability of 3-HIT (OR 4.00, 95% CI 1.88 to 8.52, p<0.01). No differences were found were analyzed PIMDINAC criteria (p=0.17).

In the regression model, considering independently the factors involved in PIMDINAC and 3-HIT criteria, patients without HIV had an increased risk for a greater probability of NAC (OR 4.43, 95% CI 2.16 to 9.04, p<0.01) and PIM (OR 3.97, 95% CI 1.94 to 8.13, p<0.01). In contrast, when considering DI as a dependent variable, HIV infection was found to be a protective factor (OR 0.26, 95% CI 0.13 to 0.53, p <0.01).

DISCUSSION

Our findings indicate that the implementation of the CMO model resulted in a higher number of patients receiving optimised therapy, compared to those following the usual model. We found a high prevalence of the PIMDINAC and 3-HIT criteria in the general population, which is higher in both criteria for non-HIV patients with chronic diseases. To our knowledge, this is the first study to compare the prevalence of PIMDINAC and 3-HIT criteria between PLWH and patients without HIV, observing that there was a difference in 3-HIT criteria. The largest difference between the groups was in NAC and PIM. Contrary to expectations, there is a higher proportion of NAC in patients without HIV. However, we still see a problem with PIM, and it is essential to address the reduction of PIM by promoting deprescribing strategies. To achieve this objective, multidisciplinary patient management is essential, involving the different health professionals involved in their care.

We found that non-HIV patients with chronic diseases were at increased risk for the development of the 3-HIT factor phenomenon. Furthermore, Furthermore, if we analyze the independent criteria separately, we find that these patients without HIV infection also present a higher risk for the development of both PIM and NAC. Even though PLWH due to ARV have a higher risk of developing these factors, the existence of a greater risk in the non-HIV patients with chronic diseases can be explained by the intensive interventions that PLWH received by applying the CMO PhC model compared to usual PhC applied in patients without HIV.

Considering that polypharmacy was similar in both groups considering the difference in the proportion of patients who meet some criteria to include it in the different patterns of multimorbidity, these results highlight the need to continue deepening the development of strategies that allow pharmacotherapeutic optimisation reducing negative effects such as PIM, DI, or NAC.

The prevalence of PIM in PLWH patients in our study differs from that of other studies, ranging from 54% using the STOPP criteria to 60% with both the STOPP and LESS-CHRON criteria[20,21]. However, our results in non-HIV patients are in line with what was observed in a Spanish study of patients without HIV with multimorbidity and polypharmacy[22].

We observed a higher frequency of potential DI in PLWH compared to noninfected patients. Interestingly, we also discovered that the group of non-HIV patients had a significantly higher number of comorbidities. There are studies that indicate that the risk of DI increases in correlation with the number of comorbidities and medications prescribed[23]. In our case, we can explain that the risk of interactions is greater. This could be because the evaluation of potential DI may overestimate the rates of actual DI causing harm to the patient, as not all potential DIs necessarily translate into actual harm[24].

The difference in comorbidity patterns is explained by the underlying pathology of the patients included in the study, since patients with immune-mediated pathologies in the rheumatological field are included in the thyroid/ mechanical pattern. In the case of PLWH, there are studies that evaluate the relationship between polypharmacy and comorbid conditions among PLWH aged ≥65 years compared to HIV-negative people of the same age group, PLWH had an increased risk of cardiovascular disease[25].

Our results have implications both from a clinical and an organisational standpoint. Hospital pharmacy services' multidisciplinary care teams for chronic patients should consider the risks faced by patients with chronic pathologies, particularly those who are polymedicated due to the potential negative effects on their health goals. Therefore, they should focus on increasing the activation patient to mitigate the risk factors associated with polypharmacy

Table 2. Comparison of negative health outcomes and patients with optimized therapy

Characteristics	Overall population (n=145)	PLWH (n=75)	Non-HIV patients with chronic diseases (n=70)	P-value
Patients with optimized therapy	89 (61.4)	57 (76)	32 (45.7)	**<0.01**
PIMDINAC Criteria	23 (15.9)	9 (12)	14 (20)	0.27
3-HIT Criteria	48 (33.1)	14 (18.7)	34 (48.6)	**<0.01**

and its harmful effects[26]. This paper highlights the significant impact of patient pharmacotherapy factors on the risk of developing negative consequences such as DIs from an organisational perspective. Many of the behavioural risk factors associated with patient attitudes and beliefs in NAC may be beyond the direct influence of providers and are not related to quality of care. However, the use of construction tools combined with patient-centred PhC models, such as the CMO PhC model, could be helpful in identifying people at higher risk and developing interventions and preventive strategies to mitigate these harmful effects. Furthermore, this information could facilitate a more personalised approach to improve health outcomes.

One of the strengths of this study is that we employed two methods to determine NAC, which was assessed using two methods: the Morisky-Green questionnaire and electronic pharmacy dispensing records[27]. Although there is no perfect method to determine whether patients adhere to their prescribed medications, the combination of adherence measurements in this study improved the validity of the results obtained. Furthermore, we specifically evaluated the drug interactions between comedication and ARV. Another positive aspect of our study is the similarity in baseline characteristics, which allows us to gather valuable information. CMO PhC model presents a series of strengths compared to the traditional model, allowing the individualisation of interventions according to the specific taxonomy developed and the participation of the patient in the shared decision-making to achieve the proposed objectives and health results[28]. Therefore, we can consider that there is no intervention bias since we are applying two different models of PhC that are already being used in care practice in different hospitals.

The study had certain limitations that need to be acknowledged. First, due to its cross-sectional observational design, it only establishes associations and cannot establish causal relationships. Secondly, the sample size was relatively small, which warrants caution when interpreting the findings. Patients without HIV infection have a greater number of comorbidities and were not subjected to a PhC model that develops intensive interventions such as the CMO model. However, efforts were made to ensure comparability between the two groups in terms of baseline characteristics and demographics. Therefore, it would be valuable to replicate this analysis on a larger scale, encompassing a more diverse range of hospitals, to strengthen the reliability of these results. Furthermore, another limitation that we found, given the cross-sectional nature of the study and the absence of a validated taxonomy for the traditional pharmaceutical care model, was that it was not possible to compare the interventions carried out.

One of the most important pending challenges for the future is adapting a multidisciplinary methodology to the needs of the multidimensional approach that is needed in patients with chronic diseases, especially those who may be at increased risk of worse health outcomes. Other possible future research lines include the cost-effectiveness assessment of pharmaceutical care with the benefit obtained and comparing both satisfaction and patient experience between both models of pharmaceutical care.

CONCLUSION

The results of our study showed that the PIMDINAC and 3-HIT criteria were prevalent in both studied groups. Non-HIV patients with chronic diseases were associated with a higher risk of developing 3-HIT, PIM, and NAC, as well as a protective factor for the development of DI. The prevalence was higher in the group of patients without HIV infection with chronic diseases who were treated according to the traditional model of pharmaceutical care and, therefore, were not subjected to the intensive interventions of the CMO PhC model. Therefore, the crucial role of pharmacists should be the implementation of pharmaceutical care interventions based on the CMO model, as an important way to improve health outcomes for patients with chronic diseases.

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