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ORIGINAL RESEARCH

# Impact of a CMO-Based Pharmaceutical Care Model on 3-HIT Criteria in Older People Living with HIV: The DIS3HIT Project

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**Background:** People living with HIV (PLWH) are increasingly affected by ageing-related issues, including multimorbidity and polypharmacy, which heighten the risk of drug-related problems. The 3-HIT phenomenon— defined as the simultaneous presence of high pharmacotherapeutic complexity, clinically relevant drug–drug interactions, and poor adherence to concomitant medication—represents a significant challenge in the care of older PLWH.

**Objective:** To evaluate the impact of a Capacity-Motivation-Opportunity (CMO) pharmaceutical care model on reducing the prevalence of the 3-HIT criteria in PLWH aged ≥50 years and to assess pharmacotherapeutic goal achievement according to patient stratification.

**Methods:** A prospective, multicentre intervention study was conducted in nine Spanish hospitals (March 2023–March 2024), including PLWH aged ≥50 on antiretroviral and concomitant therapy. Participants were stratified into three levels of pharmaceutical care according to the CMO model (Capacity, Motivation, Opportunity). Clinical, virological, and pharmacotherapeutic data were collected at baseline and week 24. Interventions were tailored to individual needs and stratification level.

**Results:** Among 154 participants (mean age 62.6 years (SD: 7.47); 75.3% male), the predominance of male participants was consistent with the demographic profile of ageing PLWH cohorts in Spain. Polypharmacy was highly prevalent (96.1%), and 17.5% of participants simultaneously met all three 3-HIT criteria at baseline. After 24 weeks, 3-HIT prevalence decreased significantly to 9.4% ($p<0.05$), with marked improvements in adherence to concomitant medication (from 50% to 76.6%). The proportion of individuals achieving at least one pharmacotherapeutic goal increased from 58.4% at baseline to 73.8% at follow-up. The intervention was associated with sustained pharmaceutical actions, particularly regarding adherence support, treatment validation, and care coordination.

**Conclusion:** Implementation of a structured, stratified pharmaceutical care model based on the CMO methodology significantly reduces 3-HIT prevalence in older PLWH, primarily through improved adherence to concomitant medication, while maintaining virological control. These findings support the inclusion of CMO-based approaches in clinical practice to optimise pharmacotherapy and improve outcomes in ageing HIV populations.

**Keywords:** pharmaceutical care, HIV, medication adherence, polypharmacy, outcome assessment

## Introduction

HIV infection has evolved into a chronic condition thanks to the remarkable reduction in mortality following the introduction of antiretroviral therapy (ART) and the development of new, more effective antiretroviral drugs with improved dosing regimens.[1]

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The increase in survival has been accompanied by a progressive ageing of people living with HIV (PLWH). In fact, since 2015, it is known that more than 50% of the cohorts of HIV-infected patients in both the US and Europe have an average age of over 50 years, an aspect that will become more marked in the next decade.[2,3]

The ageing of PLWH is associated with a higher prevalence of chronic comorbidities[4,5] leading to an increase in medication for these participants. Recent studies indicate that polypharmacy prevalence among PLWH over 50 years old is significant.[5–8] Additionally, the complexity of treatment regimens may compromise adherence, a crucial factor for maintaining viral suppression and preventing disease progression.[9,10]

The simultaneous presence of multiple comorbidities and associated polypharmacy negatively impacts health outcomes, increasing the risk of drug-drug interactions,[11,12] potentially affecting the efficacy of ART and increasing the occurrence of adverse effects,[13] hospitalizations,[14] risks of falls and/or fractures[15] and mortality.[16] Not less important is the difficulty in managing the benefit/risk balance of medication concomitant to ART and the greater risk of the presence of potentially inappropriate medication than in the non-HIV population, particularly anticholinergic drugs.[17,18]

All these new needs that appear in PLWH have introduced new challenges in healthcare and have opened a new scene in the hospital pharmacy practices that care for these individuals. A comprehensive, personalized approach is crucial to optimise health outcomes and improve the quality of life in this population. To this end, a model of pharmaceutical care (PC) was developed based on the CMO[19] methodology, together with a series of tools to help to improve the care of these participants, including the inclusion of stratification systems that allow for the optimisation of time and resources, enabling PC focused on the needs of each patient.[20]

Some authors in the field of HIV research, such as Guaraldi et al[21] defined the so-called "iatrogenic triad" which includes, in older HIV patients, the presence of: polypharmacy, potentially inappropriate medication prescription and relevant drug interactions.[22]

However, for all this to be real, a component of medication adherence is necessary, which is often not present, as the literature indicates. In this context, the concept of "3-HIT" emerges, referring to the elements that are considered key in the management of polypharmacy in PLWH. Such elements that define the 3-HIT phenomenon are high pharmacotherapeutic complexity, the presence of drug-drug interactions and low adherence to concomitant medication.

A recent study has assessed the presence of this phenomenon in PLWH, detecting it in 6.3% of the participants analysed. The risk of 3-HIT has been related to the number of drugs prescribed.[23] Some authors have identified how these elements will mark the optimisation of pharmacotherapy in this population in the next decade, therefore, in addition to identifying their presence, it is necessary to establish appropriate strategies for their management in a multidisciplinary and multidimensional manner, among which deprescribing is a particularly useful tool in the process of development.

The present analysis builds on the DIS3HIT Project, which originally described the coexistence of pharmacotherapeutic complexity, drug–drug interactions and poor adherence in ageing PLWH.

The aims of this study are to determine whether pharmaceutical intervention based on the CMO methodology can contribute to the reduction of the prevalence of the 3-HIT criteria in PLWH aged 50 years old and above who undergo pharmacotherapeutic follow-up in outpatient pharmacy clinics of participating hospitals and to analyse the degree of compliance with pharmacotherapeutic objectives according to stratification level based on the CMO methodology.

# Materials and Methods

## Study Design and Participants

We conducted a prospective, multicentre intervention study (March 2023–March 2024) across nine Spanish hospitals, enrolling PLWH aged ≥50 years. Participants were on active antiretroviral treatment, with concomitant medication prescribed for at least three months prior to inclusion in the study, attending PC visits in a participating hospital pharmaceutical department for ≥1 year before the beginning of the study, and eligible to sign the informed consent. Participants were excluded if they were unable to complete the study questionnaires or were included in clinical trials during the study period.

## Outcomes

Baseline demographic data (gender and age), HIV infection control variables (plasma viral load (copies/mL) CD4 count at the time of inclusion (cells/μL), CD4/CD8 ratio, comorbidities (multimorbidity pattern and Charlson Index) and pharmacotherapeutic (type of ART, single-tablet regimen, Medication Regimen Complexity Index (MRCI), adherence to ART (SMAQ questionnaire), adherence to concomitant medication (Morisky-Green questionnaire) and presence of clinically relevant interactions) variables were recorded at the initial clinical evaluation. Virologic control was defined as plasma HIV-RNA <50 copies/mL, in line with national clinical guidelines and uniformly applied across all participating centres.

The comorbidity patterns used are those described by Prados-Torres et al[24] and are classified into three groups: cardio-metabolic, mechanical-obese-thyroid and psycho-geriatric.

MRCI is an index, developed by George et al,[25] which is calculated by considering the following three items: dosage form, posology and additional administration instructions. In a recently published article, a complex patient is defined as a patient with a complexity index value of 11.25 or higher.[26]

The primary outcome of the study was the change in the total (all three criteria present) or partial (any of the three criteria present) 3-HIT phenomenon between baseline and week 24.

## Interventions

Participants received pharmaceutical care following the CMO model, a structured methodology designed to guide personalised pharmacotherapeutic follow-up.[19,20] Interventions were planned and recorded according to the three CMO stratification levels: level 1 for participants with the highest clinical and pharmacotherapeutic complexity, level 2 for intermediate priority, and level 3 for individuals with stable conditions and lower intervention needs. Pharmaceutical interventions were documented at baseline, week 12 and week 24 in order to monitor the evolution of care needs over time, while the impact on the total or partial 3-HIT phenomenon was evaluated at baseline and week 24.

At each interview, achievement of pharmacotherapeutic objectives (including adherence, glycaemic and blood pressure control, management of comorbidities, anxiety, insomnia and reduction of unnecessary medication, among others) was assessed according to the participant's CMO priority level, comparing outcomes at week 24 with those at baseline.

Pharmaceutical interventions were recorded at baseline, week 12 and week 24, whereas clinical, virological and pharmacotherapeutic outcomes were assessed at baseline and week 24.

## Polypharmacy

Although no cut-off point for polypharmacy is optimal for predicting the development of adverse events that contribute to worsening adherence, we considered that, according to the common definition of polypharmacy, the use of five or more different drugs, including ART.[27] Major polypharmacy was restricted to the use of 11 or more different drugs. To describe the patterns of polypharmacy, we use the categorization proposed by Calderón-Larrañaga et al[28] who classified those patterns according to the type of disease they were intended to treat (depression-anxiety; cardiovascular; chronic obstructive pulmonary disease). After categorizing a drug according to the anatomical therapeutic chemical classification system up to the first three levels, a patient was classified into a specific pattern when he received at least three drugs included in the pattern.

## Statistical Analysis

Data analysis was performed using IBM SPSS Statistics (version 29.0).

## Sample Size

The sample size was determined based on feasibility, given the real-world multicentre nature of the study and the finite pool of eligible participants across the nine hospitals involved. No formal hypothesis-driven sample-size calculation was performed; therefore, no prespecified type I error, expected effect size or statistical assumptions were applied. The final

cohort of 154 participants exceeded the anticipated recruitment target and provided sufficient precision to estimate changes in the primary outcome (total or partial 3-HIT prevalence) using within-participant comparisons over time.

### Descriptive Analysis

Quantitative variables were summarised using means and standard deviations (SD), as all continuous variables followed approximately symmetric distributions in this dataset. Qualitative variables were expressed as frequencies and percentages.

### Comparative Analysis

Comparisons between baseline and week 24 were performed using repeated measures within the same participants. Quantitative variables were analysed using the paired *t*-test. The Wilcoxon signed-rank test was predefined for variables not meeting normality assumptions, although it was not required for the variables reported. Only participants with measurements available at both timepoints (complete cases) were included in paired analyses; no imputation of missing data was performed. For categorical paired data, the McNemar test was used.

### Statistical Significance

For all statistical tests, a two-sided $\alpha$ level of 0.05 was considered statistically significant.

### Ethics

The study was carried out according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the Declaration of Helsinki. The study protocol and any other information that required prior approval was reviewed and approved by the ethics committee of the research center Comité de Ética de Investigación Sevilla Sur (Study Code: 0397-N-23).

## Results

A total of 154 participants were included at baseline (Figure 1). Of these, 145 attended the week-12 intervention visit and completed week-24 follow-up. Nine participants did not complete follow-up: five missed scheduled visits, three were transferred to another centre, and one died due to comorbidity-related causes. These participants did not differ meaningfully from the retained cohort in baseline age, comorbidity burden, number of medications or pharmacotherapeutic complexity. Characteristics of the study population are summarized in Table 1.

Most of them were male (75.3%), with a mean age of 62.6 years (SD: 7.47). In terms of virological status, 90.9% had an undetectable viral load, 95.5% had a CD4 cell count higher than 200 cells/μL and 24% had a CD4/CD8 ratio below 0.4 at baseline.

At baseline, the most commonly prescribed ART regimen among participants was a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) plus an integrase inhibitor, used by 35.1% of individuals. This was followed by two NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) (7.1%) and two NRTIs plus boosted protease inhibitor (PI/b) (3.2%). Other regimens were used in 54.5%. Additionally, the use of Single Tablet Regimens (STR) was high across the cohort, 81.2% were on STRs at baseline.

At week 24, the distribution remained similar, with the two NRTIs plus an integrase inhibitor regimen still being the most prevalent (34.4%). At week 24, 80.5% of individuals continued on STRs.

Virologic control was maintained throughout follow-up. At baseline, 90.9% of participants (140/154) had HIV-RNA <50 copies/mL, compared with 96.6% (140/145) at week 24. No episodes of virologic rebound were detected among participants who completed follow-up. Participants were stratified according to the CMO model into three levels of PC priority, based on clinical complexity, therapeutic needs, and the potential impact of pharmaceutical intervention: 17.5% of participants were at priority level 1 (high priority), 42.9% at the priority level 2 (medium priority) and the remaining (39.6%) were at level 3.

The individuals had a mean Charlson comorbidity Index of 4.28 (SD: 3.64). The most prevalent comorbidity pattern was cardiometabolic, affecting 66.9% of participants. A total of 31.2% presented a geriatric–depressive comorbidity

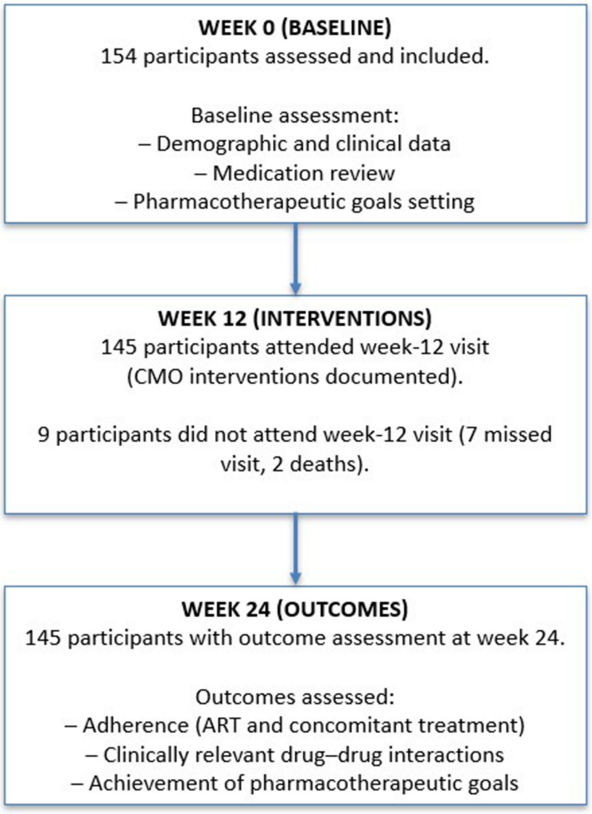


**Figure 1** Study flow chart.

pattern compatible with neuropsychiatric or age-related syndromes. Thyroid–mechanical comorbidities were presented in 22.7%.

The mean number of concomitant drugs prescribed at baseline was 8.46 (SD: 3.64) and the mean pharmacotherapeutic complexity was 19.04 (SD: 11.78). From a therapeutic point of view, 96.1% of participants met polypharmacy criteria, and 39.6% had major polypharmacy. Most individuals (62.3%) had a pattern of polypharmacy related to

**Table 1** Baseline Characteristics of the Study Population Vs week 24

| Variable | Value | |
|---|---|---|
| | Week 0 | Week 24 |
| Total cohort (N) | 154 | 145 |
| Male gender (n, %) | 116 (75.3) | – |
| Age in years (mean, SD) | 62.60 (7.5) | – |
| Charlson comorbidity index (mean, SD) | 4.28 (3.6) | – |
| Number of concomitant medications (mean, SD) | 8.46 (4.2) | 8.29 (4.0) |
| Pharmacotherapeutic complexity index (mean, SD) | 19.04 (11.8) | 18.94 (11.1) |
| CD4 count ≥ 200 cells/μL (n, %) | 147 (95.5) | – |

(*Continued*)


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**Table 1** (Continued).

| Variable | | Value | |
|---|---|---|---|
| | | Week 0 | Week 24 |
| CD4/CD8 ratio < 0.4 (n, %) | | 37 (24.0) | – |
| Polypharmacy (n, %) | | 148 (96.1) | 138 (92.6) |
| Major polypharmacy (n, %) | | 61 (39.6) | 58 (38.9) |
| Polypharmacy pattern | Depression/anxiety (n, %) | 48 (31.2) | 48 (32.2) |
| | Cardiovascular (n, %) | 96 (62.3) | 96 (64.4) |
| | Chronic Obstructive Pulmonary Disease (n, %) | 19 (12.3) | 15 (10.1) |
| Anticholinergic burden (moderate/high) (n, %) | | 24 (15.6) | 26 (17.9) |
| Adherence to ART (n, %) | | 119 (77.3) | 125 (89.3) |
| Adherence to concomitant medication (n, %) | | 77 (50.0) | 108 (76.6) |
| Clinically relevant drug–drug interactions (n, %) | | 60 (39.0) | 42 (28.2) |
| Virologic control* (n, %) | | 140 (90.9) | 140 (96.6) |
| Stratification | Level 1 (n, %) | 27 (17.5) | 21 (14.8) |
| | Level 2 (n, %) | 66 (42.9) | 55 (38.7) |
| | Level 3 (n, %) | 61 (39.6) | 66 (46.5) |

**Note**: *Virologic control was defined as HIV-RNA <50 copies/mL. Outcomes at week 24 are reported for participants with available follow-up data (N = 145).
**Abbreviations**: SD, Standard Deviation; ART, Antiretroviral Therapy.

cardiovascular pathology, 31.2% related to depression or anxiety and 9.7% to Chronic Obstructive Pulmonary Disease. Furthermore, 15.6% had a medium or high anticholinergic load.

In terms of adherence, 77.3% were adherent to ART and only 50% were adherent to concomitant medication. Thirty-nine percent of participants had clinically relevant interactions.

As specified in the Methods, only pharmaceutical interventions were documented at week 12, while outcome measures were analysed at baseline and week 24.

After 24 weeks of follow-up, an improvement in clinical outcomes was observed (Table 2). The proportion of individuals who achieved at least one pharmacotherapeutic goal increased significantly, from 58.4% (n=90) at baseline to

**Table 2** Pharmacotherapeutic Objectives (Baseline vs Week 24)

| Objective | Baseline, n (%) | Week 24, n (%) | p value |
|---|---|---|---|
| HIV control | 6 (3.9) | 3 (2.1) | 0.825 |
| Adherence improvement | 14 (9.1) | 8 (5.5) | 0.884 |
| Blood glucose control | 10 (6.5) | 6 (4.1) | 0.819 |
| Blood pressure control | 11 (7.1) | 7 (4.8) | 0.802 |
| Dyslipidemia control | 13 (8.4) | 6 (4.1) | 0.939 |
| Respiratory disease control | 4 (2.6) | 2 (1.4) | 0.776 |

(*Continued*)

**Table 2** (Continued).

| Objective | Baseline, n (%) | Week 24, n (%) | p value |
|---|---|---|---|
| Quality of life/Pain management | 14 (9.1) | 11 (7.6) | 0.681 |
| Anxiety management | 20 (12.9) | 14 (9.6) | 0.819 |
| Insomnia management | 4 (2.6) | 1 (0.7) | 0.905 |
| Obesity management | 4 (2.6) | 3 (2.1) | 0.619 |
| Toxicity management | 3 (1.9) | 2 (1.4) | 0.650 |
| Social issues | 4 (2.6) | 3 (2.1) | 0.619 |
| Smoking/Alcohol management | 5 (3.2) | 3 (2.1) | 0.737 |

**Note**: All analyses include only participants with available measurements at both baseline and week 24 (N = 145).

73.8% (n=107) at week 24 (p=0.000). These clinical benefits were observed across all stratification levels. In each group: in level 1 from 25% to 54.2% (p=0.016), in level 2 from 56.3% to 70.3% (p=0.012) and in level 3 from 76.8% to 85.7% (p=0.000).

Throughout the 24-week follow-up, a wide range of pharmaceutical interventions were carried out, aligned with the three pillars of the CMO model: Capacity, Motivation and Opportunity. These interventions were tailored to each patient's stratification level and clinical needs. They are summarized in Table 3.

These interventions were sustained across the study period (baseline, week 12 and week 24), with some increasing in frequency as clinical needs evolved; particularly those related to adherence, education and coordination.

Regarding the 3-HIT phenomenon (Table 4), at the beginning of the study, 17.5% of PLWH (n=27) met the criteria for the 3-HIT phenomenon. At the end of follow-up, prevalence was reduced to 9.4% (n=14). In terms of partial 3-HIT components, there were statistically significant differences in improved adherence to concomitant medication (p=0.000).

**Table 3** Pharmaceutical Interventions Carried Out According to the CMO Model During Follow-Up

| Intervention Category | Total (N)* | Participants (%) | Basal (n) | Week 12 (n) | Week 24 (n) |
|---|---|---|---|---|---|
| ***Capacity Interventions*** | | | | | |
| ART review and validation | 374 | 81.0 | 147 | 106 | 121 |
| Concomitant medication review and validation | 426 | 92.2 | 152 | 133 | 141 |
| Review of therapeutic objectives | 347 | 75.1 | 129 | 97 | 121 |
| Coordination with other healthcare professionals | 120 | 26.0 | 50 | 36 | 34 |
| Referral to other services | 45 | 9.7 | 19 | 10 | 16 |
| Treatment planning | 258 | 55.8 | 109 | 73 | 76 |
| Medication reconciliation | 137 | 29.7 | 60 | 17 | 60 |
| ***Motivational Interventions*** | | | | | |
| Safety-related interventions | 211 | 45.7 | 76 | 68 | 67 |
| Special follow-up | 127 | 27.5 | 46 | 38 | 43 |
| Adherence support | 359 | 77.7 | 132 | 103 | 124 |

(*Continued*)


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**Table 3** (Continued).

| Intervention Category | Total (N)* | Participants (%) | Basal (n) | Week 12 (n) | Week 24 (n) |
|---|---|---|---|---|---|
| Patient commitment | 177 | 38.3 | 77 | 42 | 58 |
| Co-responsibility | 161 | 34.8 | 72 | 37 | 52 |
| Patient education/information | 257 | 55.6 | 105 | 64 | 88 |
| Self-care promotion | 97 | 21.0 | 37 | 25 | 35 |
| ***Opportunity Interventions*** | | | | | |
| Fast communication | 276 | 59.7 | 84 | 98 | 94 |
| Transversal follow-up | 75 | 16.2 | 30 | 20 | 25 |
| Transversal training | 33 | 7.1 | 17 | 5 | 11 |
| Social coordination | 19 | 4.1 | 11 | 4 | 4 |
| Active coordination | 13 | 2.8 | 5 | 2 | 6 |

**Notes**: *N value reflects the total number of that intervention performed; n values indicate how many were performed in week 0, week 12 and week 24. Percentages indicate the proportion of participants who received at least one intervention of each category during follow-up. The total N reflects the cumulative number of interventions performed; repeated interventions in the same participant were counted separately.
**Abbreviation**: ART, Antiretroviral Therapy.

**Table 4** Prevalence of Total and Partial 3-HIT Criteria Throughout the Study

| 3-HIT Criteria | Baseline (n, %) | Week 24 (n, %) | p value |
|---|---|---|---|
| Global 3-HIT | 27 (18) | 14 (9.4) | 0.013 |
| Partial 3-HIT | | | |
| High pharmacotherapeutic complexity | 80 (52) | 87 (58.4) | 0.210 |
| Clinically relevant drug–drug interactions | 27 (18) | 27 (18.1) | 1.000 |
| Poor adherence to concomitant medication | 47 (31) | 21 (14.3) | 0.000 |

**Notes**: Among the 27 participants who met total 3-HIT criteria at baseline, 14 no longer fulfilled all three criteria at week 24, with no new cases identified. This corresponds to an absolute paired reduction of 9.4% (95% CI: 4.7–14.1), as estimated from discordant pairs in the paired analysis.

## Discussion

This multicentre study demonstrates that implementing a structured, CMO-based PC model reduces the prevalence of the 3-HIT phenomenon in older PLWH, primarily through improved adherence to concomitant medication, while maintaining virological control throughout follow-up.

These findings should be interpreted in the context of the limited evidence available on the 3-HIT phenomenon. The only study to date evaluating its prevalence in PLWH reported a rate of 6.3%, substantially lower than the 17.5% observed in our cohort. This difference is clinically plausible, as our population was older, presented a higher comorbidity burden and had greater pharmacotherapeutic complexity—all factors that favour the coexistence of the three 3-HIT components. Furthermore, the multicentre real-world nature of our study likely captured a broader spectrum of frailty and treatment intensity. Together, these elements highlight the importance of early identification and proactive management of 3-HIT in ageing PLWH. Beyond statistical significance, the observed reduction in total 3-HIT prevalence represents a clinically meaningful improvement, given the well-established association of the 3-HIT phenomenon with medication-related harm, including non-adherence, drug–drug interactions and adverse clinical outcomes in ageing PLWH.

The results of our study clearly reflect the impact of ageing in PLWH, with a high prevalence of comorbidities and polypharmacy, as pointed out by Deeks et al, who emphasise that PLWH are living longer, but with a higher burden of age-related comorbidities, requiring an approach to care that goes beyond traditional virological control.[29] Patel et al found that medication burden in this population is associated with lower adherence highlighting the importance of individualised pharmaceutical monitoring strategies.[30] This trend has been confirmed by Marzolini et al who reported that more than 90% of people with HIV over the age of 50 are receiving five or more drugs, with a parallel increase in the burden of treated comorbidities and the risk of potential interactions.[31] These findings reinforce the need to incorporate pharmacotherapeutic assessment tools to detect risk situations and promote treatment appropriateness. This perspective is consistent with the vision proposed by Justice et al using the Veterans Aging Cohort Study (VACS) Index, a tool designed to predict mortality in people living with HIV that goes beyond classical virological and immunological parameters such as viral load or CD4 count. This index is a clear example of this multidimensional perspective, integrating variables related to non-HIV comorbidities, biomarkers and demographic data, underlining the importance of assessing the patient's overall health beyond virological control.[32]

Within this framework of increasing complexity, it is also essential to incorporate a systematic assessment of the risk of iatrogenesis. Guaraldi et al introduced the concept of the "iatrogenic triad", which encompasses the coexistence of polypharmacy, potentially inappropriate medication (PIM) use and clinically relevant drug interactions in ageing people with HIV, identifying this phenomenon as a key factor of morbidity in this population.[33] Tools such as the PIMDINAC criteria, specifically developed and validated in PLWH, allow for the structured detection of inappropriate drugs, taking into account both the peculiarities of ageing and the risks associated with antiretroviral treatment. Díaz-Acedo et al demonstrated their usefulness in older people with HIV, where PIMs were significantly associated with polypharmacy, neuropsychiatric comorbidities and psychotropic use.[34] Recently, these criteria have also been validated in individuals with multiple sclerosis, which supports their applicability in other contexts of complex chronicity.[35]

In our cohort, the high rate of comorbidities, together with the high prevalence of polypharmacy and anticholinergic burden, illustrates the clinical complexity of this ageing population, and supports the need to use integrative approaches to optimise risk stratification and therapeutic decision-making. Several studies have shown that multidimensional pharmaceutical interventions based on the CMO model are effective in the integrated management of older people with HIV. Both the PIMDINAC study and the 3-HIT project have shown that this approach can identify individuals at risk, optimise pharmacotherapy and reduce iatrogenic phenomena, positioning the clinical pharmacist as a key agent in the management of therapeutic complexity in this population. Taken together, both our results and the data available in the literature support a change in the way we approach the follow-up of people with older HIV. This not only improves health outcomes, but also contributes to preserving quality of life in an ageing population with a chronic disease that is highly manageable but not without additional risks.

The results observed in our study can be explained by the synergistic action of two fundamental mechanisms: the implementation of the CMO model as a structured PC strategy and the improvement in adherence to concomitant medication. On the one hand, the CMO methodology incorporates complementary tools such as clinical stratification systems, the pharmacotherapeutic complexity index (MRCI) and patient-centred scales (PROMs/PREMs) that facilitate personalised, proactive and efficient care,[36,37] allowing optimisation of resources and targeting of pharmaceutical interventions. On the other hand, adherence to treatment is a crucial determinant of treatment effectiveness, especially in people with polypharmacy. Interventions focused on health education, motivational reinforcement and the use of validated questionnaires (SMAQ, Morisky-Green) can identify barriers and improve adherence.[38] In the context of PLWH, non-adherence to antiretroviral therapy has been shown to be associated with faster progression to AIDS,[39] and self-reported adherence levels correlate with objective measures such as electronic monitoring.[40] Thus, a considerable part of the improvement observed in the prevalence of the 3-HIT phenomenon seems to be driven by the enhancement of adherence to concomitant treatment. This finding may be explained by the fact that pharmacists have extensive experience in addressing medication adherence, which allows us to achieve more consistent results in this domain. In contrast, tackling the other two components of the phenomenon may be more challenging, as it involves PLWH who are already highly polymedicated and burdened with complex clinical conditions. In such cases, simplifying treatment complexity or reducing drug–drug interactions is inherently more difficult.

In this context, the clinical pharmacist assumes a key role in the review of ART and concomitant medication, by validating interaction profiles and identifying potentially inappropriate drugs.[22,34] This role should be coordinated with other healthcare professionals, reinforcing the "Opportunity" component of the CMO model, which has proven to be a pillar for improving continuity of care and clinical problem solving in PLWH.[41] Furthermore, systematic review of PIMs, especially with adapted criteria such as PIMDINAC, and structured deprescribing strategies, have demonstrated efficacy in reducing iatrogenesis in older people with HIV.[42,43]

Taken together, the evidence supports the move towards proactive, multidimensional, patient-centred pharmaceutical models, with the CMO model providing a robust and reproducible basis for addressing the therapeutic challenges of an increasingly ageing and clinically complex population.

The strengths of this study include its prospective, multicentre design conducted across nine hospitals, and the standardised 24-week follow-up using validated tools such as the MRCI, Charlson Index and multimorbidity patterns. These features reinforce the methodological soundness and clinical applicability of the findings. However, several limitations must be acknowledged.

First, the absence of a control group limits the ability to establish a definitive causal relationship between the intervention and the observed outcomes. Although this limitation is inherent to real-world pre–post designs, it could be partially mitigated through alternative analytical approaches—such as repeated-measures pre–post analyses, mixed-effects models or interrupted time-series frameworks—that allow within-subject comparisons and enhance causal inference. Second, potential selection bias may be present, as only participants with ≥1 year of previous pharmaceutical follow-up were included, which may enrich the sample with more adherent or engaged individuals. Third, adherence was measured through validated questionnaires, which are known to overestimate real adherence levels.

Fourth, some degree of heterogeneity across participating centres—related to differences in patient profiles, workflow organisation and local implementation of the CMO model—may have introduced variability in the intensity and type of interventions delivered. Finally, although the 24-week duration was adequate to evaluate intermediate pharmacotherapeutic outcomes, it limits the assessment of long-term sustainability and its impact on hard outcomes such as hospitalisations or mortality.

The choice of a 24-week observation period reflects routine HIV outpatient care, where structured clinical and pharmacotherapeutic reviews are typically scheduled every 4–6 months. This timeframe is considered sufficient to detect meaningful changes in adherence, pharmacotherapeutic complexity and drug-related problems after implementing a pharmaceutical care intervention. However, several quality-of-life domains in ageing PLWH—such as functional status, frailty progression or psychosocial well-being—evolve more gradually and are unlikely to change substantially within 24 weeks. Longer follow-up periods would therefore be required to determine whether improvements in pharmacotherapy translate into sustained benefits in these broader patient-centred outcomes.

As future lines of action, randomised clinical trials are warranted to confirm the efficacy of the CMO model and establish causal relationships. Additionally, the model should be externally validated in non-HIV populations, particularly those with high therapeutic complexity—such as individuals with multimorbidity, chronic psychiatric disorders, or neurodegenerative diseases—where medication-related harm is also prevalent. Exploring its adaptation to other vulnerable groups would allow its usefulness in specialised PC to be extended. Integration into primary care settings could also be considered and assessing its cost-effectiveness could further support its scalability and inclusion in healthcare policy and clinical practice guidelines. Finally although paired comparisons were appropriate for this real-world multicentre design, future studies could benefit from more sophisticated longitudinal modelling (eg, mixed-effects models) to analyse trajectories over time and compare intervention strategies.

## Conclusion

In conclusion, a tailored CMO-driven PC approach effectively mitigates polypharmacy-related risks in older PLWH—reducing the prevalence of the 3-HIT phenomenon without compromising virologic control. The main driver of this improvement was the enhancement of adherence to concomitant medication, underscoring the pivotal role of adherence-focused interventions within the CMO framework. These findings support the incorporation of structured, stratified PC

models, such as the CMO model, into clinical guidelines and health policy frameworks to ensure safer and more sustainable management of ageing populations PLWH with increasing complexity.

## Disclosure

The authors report no conflicts of interest in this work.

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