Prevalence of compliance with PIMDINAC criteria among elderly people living with HIV and in non-infected outpatients with other chronic diseases

Maria Dolores Cantudo-Cuenca, Antonio Gutiérrez-Pizarraya, Patricia García-Lloret, Estefanía Gabella-Bazarot, Ramón Morillo-Verdugo

Pharmacy, Hospital Universitario de Valme, Sevilla, Spain

Correspondence to
Maria Dolores Cantudo-Cuenca, Pharmacy, Hospital Universitario de Valme, Sevilla, 41014, Spain; loli_cantudo@hotmail.com

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ABSTRACT

Background There is a high prevalence of multimorbidity and polypharmacy among older people, especially in people living with HIV (PLWH) with an increased life expectancy due to effective antiretroviral therapy (ART). Consequently, there is a higher risk of potentially inappropriate medications (PIM), potential drug-drug interactions (DI), and problems of non-adherence to treatment (NAC) in older PLWH. PIMDINAC criteria (potentially inappropriate medications (PIM), drug–drug interactions (DI), and non-adherence to treatment (NAC)) purport to jointly analyse these problems. The purpose of the study was to compare the prevalence of PIMDINAC criteria among elderly PLWH and non-infected patients with chronic diseases, and to determine whether HIV infection constitutes a predictor of the presence of PIMDINAC criteria, totally or partially.

Methods A cross sectional study was conducted between February and June 2020. HIV positive patients aged ≥65 years were compared with a group of patients with chronic conditions attending the outpatient hospital pharmacy service.

Results The study involved 140 patients: 47 HIV positive and 93 HIV negative, and mean age was 69 versus 73 years, respectively (p=0.062). The prevalence of total PIMDINAC criteria was similar between the groups (12.5 vs 10.8%, p=0.505). In relation to inappropriate medication, no differences were observed between groups (48.9 vs 55.9%, p=0434). Drug–drug interactions were higher in patients with chronic conditions (52.7 vs 25.5%, p=0.002) compared with non-adherence, which was higher in people with HIV (22.6 vs 65.6%, p<0.001). No differences in polypharmacy (≥6 and 11 drugs) rates were observed.

Conclusions PIMDINAC criteria were highly prevalent in older PLWH, similar to non-infected patients. HIV infection in older people was associated with a lower risk of drug–drug interactions. However, non-adherence was a risk factor compared with age matched controls. Deprescribing strategies, including a capability–motivation–opportunity pharmaceutical care model based intervention should be implemented in clinical routines.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is higher risk of PIMDINAC criteria (potentially inappropriate medication (PIM), drug-drug interactions (DI), and non-adherence to treatment (NAC)) in elderly people living with HIV. Few studies have analysed the extent of these, and the studies did not include a comparable non-infected control group.

WHAT THIS STUDY ADDS

⇒ PIMDINAC criteria were highly prevalent in older people living with HIV, similar to non-infected patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Pharmacists have a crucial role in improving adherence and health outcomes for HIV positive patients.

INTRODUCTION

Globally, there is a high prevalence of multimorbidity and polypharmacy, especially among older people.[1] Also, ageing creates new challenges for the healthcare system due to their special needs. In recent decades, effective antiretroviral therapy (ART) has resulted in an increased life expectancy for people living with HIV (PLWH), in some cases equivalent to people without HIV.[2]

As PLWH age and more patients are diagnosed at an older age, the burden on non-HIV comorbidities increases[3]. Multimorbidity is more common in geriatric PLWH than in non-infected ageing patients.[4] These older PLWH develop the same comorbidities as the general population but at an earlier age, possibly due to HIV infection and the adverse effects of ART.[5] This does not occur in younger PLWH.[6]

According to the Centers for Disease Control and Prevention, in 2018 more than half (51%) of people in the US and dependent areas with diagnosed HIV were >50 years of age.[7] In Spain, after reaching its peak of reported cases in the mid-1990s, this metric has experienced a progressive decline from 1996 (the year before ART was widely available) to 2019, and also showed an increase in the rates of new diagnoses in the age group 25–29 years between 2010 and 2017 and in the age group 30–34 years in the same period, followed by stabilisation. In the other age groups, no statistically significant changes were observed. Regarding the new diagnoses made in 2021 in Spain, 18.1% corresponded to people aged >50 years.[8]

In the coming years, according to a mathematical model from the national Dutch ATHENA cohort, it is estimated that 73% of PLWH will be older than 50 years by 2030.[9] However, the pharmaceutical management of older PLWH must face

the challenge caused by polypharmacy in these patients. Various studies have shown that polypharmacy is more common in PLWH aged 50–64 years than in the general population of a similar age. Recent research suggests that long term HIV infection is more important than the age of patients.[10 11]

All of these concurrent factors in this group of patients lead to an increase in pharmacotherapeutic complexity. Consequently, there is a higher risk of potentially inappropriate medications (PIM), potential drug–drug interactions (DI), and problems of non-adherence to treatment (NAC) in older PLWH.[12] Previous research[13] defined the prevalence of these three circumstances (PIMDINAC criteria, potentially inappropriate medications (PIM), drug-drug interactions (DI), and non-adherence to treatment (NAC)) in an older PLWH. However, there are no studies that have analysed the extent of these in PLWH aged ≥65 years compared with a non-infected control group. Thus given the importance of this trend, it is necessary to deepen our knowledge to provide the best clinical care and improve health outcomes.

The aim of this study was to compare the prevalence of PIMDINAC criteria among elderly PLWH with non-infected patients with chronic conditions, as well as to investigate whether HIV infection constitutes a predictor of the presence of PIMDINAC criteria, totally or partially.

METHODS

We conducted a multicentre cross sectional analysis of PLWH patients between February and June 2020. PLWH were selected at the time of a pharmacotherapeutic follow-up visit in the outpatient hospital pharmacy services. The analysis included patients aged ≥65 years receiving ART. Patients were excluded if they participated in a clinical trial, did not give written informed consent or did not have the ability to answer the adherence questionnaire.

As a comparable control group, HIV non-infected geriatric patients with a chronic disease were recruited from those attending the outpatient clinic of a single hospital pharmacy located in the same sanitary area. Chronic diseases were mainly chronic kidney disease or immune mediated inflammatory diseases, such as asthma, Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, and other age related chronic diseases.

Demographic variables (age, sex, and date of diagnosis), comorbidities and variables related to drug treatment were collected from the electronic medical record. Variables considered in PLWH included CD4 cell counts, CD4/CD8 ratio and viral load of plasma HIV RNA.

Definitions

Patterns of multimorbidity

We used the categorisation proposed by Prados-Torres *et al*[14] who classified patterns of multimorbidity according to the type of disease they were diagnosed with, including cardiometabolic, geriatric–depressive, thyroid mechanic, and mixed. Patients were classified into a specific pattern when they had been diagnosed with at least two diseases included in the pattern.

Medication Regimen Complexity Index (MRCI)

MRCI is a numeric dichotomous variable, with a value of 11.25 considered high and a value of <11.25 low.[15]

Polypharmacy

Polypharmacy was defined as the concomitant prescription of six or more active drugs, including ART and non-ART, and major polypharmacy as 11 or more active drugs, including ART and non-ART. To describe the patterns of polypharmacy, we used the categorisation proposed by Calderón-Larrañaga *et al*[16] who classified the patterns depending on the type of disease they were intended to treat: cardiovascular, depression–anxiety, acute respiratory infection, chronic pulmonary disease, rhinitis–asthma, pain and menopause. Patients were classified according to a specific pattern when prescribed at least three drugs in the pattern.

PIMDINAC criteria

The prevalence of PIMDINAC criteria was grouped into two categories: total (presence of PIM+DI+NAC criteria) or partial (isolated presence of some criteria).

Potentially inappropriate medications (PIM)

PIM was measured using the STOPP/START criteria.[17]

Drug–drug interactions (DI)

For PLWH, the University of Liverpool database was used to identify DI between ART and the concomitant medication.[18] Contraindicated interactions and potential interactions were considered as clinically relevant. The Micromedex database was used to check interactions between non-ART and ART and concomitant medications in patients with chronic diseases, considering moderate, major and contraindicated interactions.

Non-adherence criteria (NAC)

NAC was measured with the Morisky–Green questionnaire and electronic pharmacy dispensing records.[19] Patients had to meet both criteria for adherence to be considered adequate. Patients were considered NAC if, according to the distribution records, the proportion of days covered was <90% in the 6 months previously. For the Morisky–Green questionnaire, patients were considered NAC if they did not respond correctly to one of the four questions.

Statistical methods

Discrete variables were expressed as number (percentage) and continuous variables as median (IQR). Differences in categorical variables were calculated using a two sided likelihood ratio χ^2 test or Fisher's exact test, and the t test or the Mann–Whitney U test were used for continuous variables, when appropriate. Furthermore, a logistic regression analysis was performed to assess factors independently related to compliance with PIMDINAC criteria, completely or partially. Additionally, to assess if HIV infection is a predictor of compliance with PIMDINAC criteria, an explanatory logistic model was built with this variable as the independent variable along with other adjustment variables. A p value <0.05 was considered to be the statistical significance threshold in bivariate comparisons. Data analysis was performed with the IBM SPSS 20.0 statistical package.

RESULTS

During the study period, 140 patients were analysed, 52 (37.1%) were men, with a median age of 71 years (IQR 68–77). The median number of comorbidities was 3 (IQR 1–4), mostly of a metabolic/cardiac pattern (67 patients (47.9%)). In PLWH, 42 patients (93.3%) had an undetectable viral load, with a CD4 count >200 cells in 95.3% and a CD4/CD8 ratio >0.4 in 83.7%. The most frequent disease in HIV non-infected geriatric patients attending the outpatient pharmacy was chronic kidney disease

Table 1 Baseline features and bivariate comparison of patients with HIV and chronic conditions

Characteristics	Overall population (n=140)	HIV patients (n=47)	Non-HIV patients with chronic diseases (n=93)	P value
Age (years)	71 (68–77)	69 (68–75)	73 (68–79)	0.062
Gender (male)	52 (37.1)	38 (80.9)	50 (53.8)	0.002
Age at diagnosis (years)	60 (51–68)	52 (46–58)	63 (55–70)	<0.001
Comorbidities (n)	3 (1–4)	2 (1–3)	3 (2–5)	<0.001
Morbidity pattern				
Metabolic/cardiac	67 (47.9)	10 (21.3)	57 (61.3)	
Thyroid/mechanic	13 (9.3)	0	13 (14)	<0.001
Psycho/geriatric	5 (3.6)	2 (4.3)	3 (3.2)	
Liver disease	16 (11.4)	12 (25.5)	4 (4.3)	0.001
CRF	44 (31.4)	17 (36.2)	27 (29)	0.390
CVD	112 (80)	29 (61.7)	83 (89.2)	<0.001
CNS	48 (34.3)	14 (29.8)	34 (36.3)	0.425
Asthma/COPD	24 (17.1)	7 (14.9)	17 (18.3)	0.616
MRCI	–	10(7-16)	19(12-25)	–
Overall MRCI >11.25	99 (70.7)	20 (42.6)	79 (84.9)	<0.001
Polypharmacy (>6)	114 (81.4)	36 (76.6)	78 (83.9)	0.358
Polypharmacy (>11)	47 (33.6)	12 (25.5)	35 (37.6)	0.152
Polypharmacy pattern (n=101)				
Depression/anxiety	25 (17.9)	4 (8.5)	21 (22.6)	
COPD	14 (10)	0	14 (15.1)	<0.001
CVD	62 (44.3)	18 (38.3)	44 (47.3)	
PIMDINAC total	14 (11.2)	4 (12.5)	10 (10.8)	0.505
Inadequate medication	75 (53.6)	23 (48.9)	52 (55.9)	0.434
Drug–drug interactions	61 (43.6)	12 (25.5)	49 (52.7)	0.002
Lack of adherence	42 (33.6)	21 (65.6)	21 (22.6)	<0.001

Values are median (IQR) or n (%).
CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVD, cardiovascular disease; MRCI, Medication Regimen Complexity index; PIMDINAC, potentially inappropriate medication (PIM), drug–drug interactions (DI), and non-adherence to treatment (NAC).

(20.4%), followed by rheumatoid arthritis (18.3%), psoriatic arthritis (16.1%) and ankylosing spondylitis (7.5%).

When comparing baseline characteristics between PLWH with patients with chronic diseases without HIV infection, differences were observed in the rate of liver diseases (12 (25%) vs 4 (4.3%)) and cardiovascular diseases (29 (61.7%) vs 83 (89.2%)). In relation to pharmacotherapeutic complexity, 99 patients had an index >11.25 points (70.7%), with a higher proportion observed in the group of patients with chronic diseases compared with PLWH (20 (42.6%) vs 79 (84.9%)). Furthermore, no differences in polypharmacy rates were observed, considering these rates as >6 drugs, or for major polypharmacy (≥11 drugs). Demographic and clinical characteristics related to PLWH and patients with chronic diseases are shown in table 1.

Regarding PIMDINAC criteria between groups, no differences were observed in the presence of PIMDINAC total criteria, with a higher proportion in PLWH (4 (12.5%) vs 10 (10.8%), p=0505). However, in relation to partial criteria, such as the presence of DI and NAC, significant differences were observed, with a higher proportion of DI in the group of patients with chronic diseases (49 (52.7%) vs 12 (25.5%), p=0.002) as well as a lower lack of adherence compared with PLWH (21 (22.6%) vs 21 (65.6%), p<0.001). The most common PIM in patients with chronic diseases were prolonged use of proton pump inhibitors for more than 8 weeks (34, 44.2%) and benzodiazepine intake for more than 4 weeks (21, 27.3%). For PLWH, benzodiazepine intake for more than 4 weeks was 14 (58.3%). The most frequent DI detected in PLWH was metformin–dolutegravir interaction (3, 21.4%), and methotrexate–proton pump inhibitors interaction (11, 15.1%) in patients with chronic diseases.

In multivariate logistic regression analysis adjusted for age, gender and group (PLWH/patients with chronic diseases), factors related to partial fulfilment of some PIMDINAC criterion or total fulfilment were studied. In the regression model considering partial PIMDINAC criteria, regarding the presence of DI as a dependent variable, HIV infection was observed as a protective factor (OR 0.30, 95% CI 0.14 to 0.66, p=0.003). In contrast, when considering adherence as a dependent variable, HIV infection was found to be a risk factor for a higher probability of NAC (OR 6.54, 95% CI 2.72 to 15.72, p<0.001).

DISCUSSION

We found a high prevalence of PIMDINAC criteria in older PLWH, similar to non-infected patients. To our knowledge, this is the first study to compare the prevalence of PIMDINAC criteria among elderly PLWH and non-infected patients, observing that there were no differences in total PIMDINAC criteria and in the partial criterion of PIM. The largest difference between the groups was in non-adherence and DI. Contrary to expectations, we have highlighted the lower number of DI found in elderly PLWH. However, we continue to observe a problem of adherence in PLWH compared with the group of older patients with chronic diseases; in principle, they could only be considered different in the presence of HIV infection. The reduction of PIM should be adequately addressed in older people by promoting prescribing strategies. These interventions minimise 'the iatrogenic triad', polypharmacy, DI, and PIM. Multidisciplinary patient management and enhanced collaboration and involvement between HIV specialists, pharmacists, geriatricians, and primary care must be developed.

We found that HIV infection in older adults was a protective factor in developing DI, but a risk factor for NAC compared with controls in the general population of older adults of similar age. Furthermore, these PLWH did not have a significantly higher prevalence of PIMDINAC criteria, also in terms of PIM. Understanding the factors associated with these criteria can better inform clinical decision making towards NAC, deprescribing PIM and DI for individuals ageing with HIV, improving their management as well as quality and life expectancy.

If we analyse the criteria in isolation, the prevalence of NAC was significantly higher in older PLWH. Considering that polypharmacy was similar in both groups despite multimorbidity being lower in HIV patients, these results highlight the need to continue to deepen strategies to improve adherence and health outcomes for older PLWH.

Long acting drug delivery can be considered a key option, but we must keep in mind that there is a risk of non-adherence to concomitant chronic medications, which is of special importance in the older population.[20] The goal of maximum adherence remains important because this population is ageing and experiencing an increased risk of frailty, increasing multimorbidity and mortality.

Despite the initially more complex medication attributable to patients with HIV infection, this fact was observed both with the MRCI and the two definitions of polypharmacy used in our study. When analysing the PIM criterion in isolation, the rate was similar compared with HIV-non-infected participants (49% of elderly PLWH and 56% of non-infected individuals). Greene *et al*[21] showed a similar comparison, but contrary to our work, they concluded that PLWH aged ≥60 years may be at increased risk of PIM. Our result could be related to the

evolution of multidisciplinary and multidimensional PLWH management according to capacity–motivation–opportunity model,[22] as well as specialists who are more familiar with geriatric care emphasising the relevance of thinking about medication related problems in this population and that older PLWH may benefit from strategies employed in the general elderly population.[21]

The prevalence of PIM in our study is in line with other studies, ranging from 52% based on Beers criteria[21] to 54% using STOPP criteria,[23] or 60% with both STOPP and LESS-CHRON criteria.[24] Our results have also been observed in a Spanish study of non-infected patients aged 65–75 years with multimorbidity and polypharmacy. Moreover, the most frequently observed PIM were the same; prolonged use of proton pump inhibitors for >8 weeks and benzodiazepine intake for >4 weeks.[25] In our study, the number of elderly patients who were exposed to polypharmacy was high. In the literature,[5 10 21 21] the reported prevalence varied widely because they used different numerical thresholds, study population and methodology. In recent years there has been a trend towards a qualitative approach according to MRCI.

Regarding DI, we recorded a higher frequency of potential DI in elderly HIV non-infected patients compared with PLWH. This result could be explained because HIV clinicians are very involved in the DI potential of ART and, as a consequence, prescribe comedications without potential interactions, particularly in older polymedicated patients. Our results in the general population of the elderly coincide with the prevalence of DI reported in the literature for comparable populations.[26] However, evaluating potential DI could overestimate DI rates because not every potential DI translates into a real DI that causes patient harm.[27]

Interestingly, we also found that the number of comorbidities was significantly higher in the older group of non-HIV patients, consistent with several studies showing that the risk of DI increases with the number of comorbidities and number of prescribed drugs.[28]

The cardiovascular metabolic pattern of multimorbidity and cardiovascular disease were the most prevalent in both groups, significantly higher in non-infected patients compared with PLWH. This result can probably be explained by the higher cardiovascular risk of patients with immune mediated diseases[29] and the frequent consumption of non-steroidal anti-inflammatory drugs in this group.[30] Furthermore, according to another study,[5] evaluating the relationship between polypharmacy and comorbid conditions among PLWH aged ≥65 years compared with HIV negative individuals of the same age group, PLWH had a higher risk of cardiovascular diseases, although this trend decreased, possibly due to strategies to reduce cardiovascular risk factors, ART agents without related lipid disorders, reduction of immunodeficiency state and HIV positive patients with HIV exposure >10 years.[10]

A strength of this study is that we determined NAC using two methods. There is no ideal method to determine whether patients take their medications as prescribed, but this combination of adherence measurement increased the validity of the results obtained. Furthermore, unlike other studies, we evaluated DI between comedication and ART. Moreover, our study provides valuable information because both groups were comparable in age, polypharmacy and comorbidities.

The study had several limitations. Firstly, due to the cross sectional observational design, it cannot be used to demonstrate causality, only associations. Secondly, the sample size was small in the group of older HIV patients, requiring caution in the interpretation of the results, although both groups appeared balanced in terms of baseline and demographic variables. For this reason, it would be interesting to extend this analysis to a larger population, including more hospitals, to support these results. Further investigation could include information on quality of life, frailty and other geriatric syndromes. We should also look for areas for improvement in the follow-up of these patients and to launch more powerful studies, including multidisciplinary but also multidimensional interventions.

In conclusion, the results of our study showed that PIMDINAC criteria were highly prevalent in older PLWH and similar to non-infected patients. HIV infection in older people was associated with a lower risk of DI. However, after adjusting for baseline variables, we observed that having HIV infection was related to lack of adherence in these patients. The crucial role of pharmacists should be the implementation of the capacity–motivation–opportunity model based pharmaceutical care intervention as an important way to improve adherence and health outcomes for HIV positive patients.

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ORCID iD
Maria Dolores Cantudo-Cuenca http://orcid.org/0000-0002-6904-6184

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