**Potentially Inappropriate Medications** **in Older Adults living with HIV**

**Short title:** PIMs in older PLWH

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**Abstract**

**Objective:** We assessed the prevalence of potentially inappropriate medication (PIM) among older (≥ 65 years) people living with HIV (O-PLWH) in the region of Madrid.

**Design:** cross-sectional population-based study

**Methods:** We analyzed the dispensation registry of community and hospital pharmacies from the Madrid Regional Health Service (SERMAS) between January 1 and June 30, 2017, looking specifically at PIMs according to the 2019 Beers Criteria. Co-medications were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System.

**Results:** A total of 6,636,451 individuals received medications. Among them, 22,945 were receiving antiretrovirals (ARVs), and of those 1,292 were O-PLWH. Overall, 1,135 (87.8%) O-PLWH were taking at least one co-medication and polypharmacy (≥ 5 co-medications) was observed in 852 (65.9%). A PIM was identified in 482 (37.3%) O-PLWH. Factors independently associated with PIM were polypharmacy (aOR 7.08 [95%CI: 5.16-9.72]) and female sex (aOR 1.75 [95%CI: 1.30–2.35]). The distribution of PIMs according to ATC drug classes were nervous system drugs (N=369 [28.6%]), musculoskeletal system drugs (N=140 [10.8%]), gastrointestinal and metabolism drugs (N=72 [5.6%]), cardiovascular drugs (N=61 [4.7%]), respiratory system drugs (N=13 [1.0%]), antineoplastic and immunomodulating drugs (N=10 [0.8%]), and systemic anti-infectives (N=2 [0.2%]). Five drugs accounted for 84.8% of the 482 O-PLWH with PIMs: lorazepam (38.2%), ibuprofen (18.0%), diazepam (10.2%), metoclopramide (9.9%), and zolpidem (8.5%).

**Conclusions:** Prescription of PIMs is highly prevalent in O-PLWH. Consistent with data in uninfected elderly, the most frequently observed PIMs were benzodiazepines and NSAIDs. Targeted interventions are warranted to reduce inappropriate prescribing and polypharmacy in this vulnerable population.

**Key words:** HIV; Aging; Potentially inappropriate medication; Polypharmacy; Antiretroviral drugs; Comorbidity; Epidemiology.

**Introduction**

Potentially inappropriate medication (PIM) is a term used to describe the use of a medicine for which the associated risks outweigh the potential benefits, especially when more effective alternatives are available [1]. Elderly patients living with HIV (PLWH) are more likely to be exposed to PIMs because they often suffer from multiple chronic diseases and therefore use a high number of drugs; and because they experience age-related physiological changes, which can impact drug pharmacokinetics and pharmacodynamics and thereby predispose elderly PLWH to adverse drug reactions [2].

Common tools to detect inappropriate prescribing in elderly individuals include the Beers criteria [3] and the Screening Tool of Older Persons’ Prescriptions (STOPP)/Screening Tool to Alert doctors to Right Treatment (START) criteria [4]. These tools list instances of inappropriate drug dosing, indication, treatment duration, treatment omission as well as inappropriate drugs for use in elderly.

The advances in antiretroviral therapy (ART) has increased the live expectancy of PLWH and is leading to a growing HIV cohort that is exposed to the risks of age-related comorbidities, age-related physiological changes, and care by multiple providers [5, 6]. All these factors could increase the risk of PIM among this population group; however, little is known about the subject. Consequently, we designed this study to assess the prevalence of PIMs among older PLWH.

**Materials and Methods**

Ours was a cross-sectional population-based study carried out in the region of Madrid (Spain) between January 1 to June 30, 2017. We analyzed the dispensation registry of community and hospital pharmacies from the Madrid Regional Health Service (SERMAS), looking specifically at PIMs among older PLWH according to the 2019 AGS Beers Criteria [3]. Older PLWH were defined as those ≥ 65 years. The SERMAS registry permits access to demographics and all prescription drugs (antiretrovirals [ARVs] and non-antiretroviral medications [co-medications]). ARVs were categorized according to class. Co-medications were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System. Non-antiretroviral polypharmacy (polypharmacy hereafter) was defined as the intake of ≥ 5 co-medications.

For the descriptive study, values were expressed as absolute numbers and percentages, and as medians and interquartile ranges (IQRs). Logistic regression analysis was used to investigate factors associated with PIMs. The variables analyzed included age, gender, and polypharmacy. IBM SPSS Statistics for Windows version 21.0 was used for all calculations. All statistical tests were 2-sided, and a P-value of <.05 was considered statistically significant.

**Results**

During the study period, 6,636,451 different individuals received medications in the region of Madrid; among them, 22,945 were receiving ARVs; and of those, 1,292 (5.6%) were older PLWH. The median (IQR) age was 69 (67-73) years, and 1,027 (79.5%) were males. Overall, 1,135 (87.8%) older PLWH were taking at least one co-medication, and polypharmacy was observed in 852 (65.9%).

A full description of ARVs use in older PLWH is shown in **Supplementary Table 1.** The distribution of anchor ARVs per patient was integrase strand transfer inhibitors (INSTIs) 645 (49.9%), non-nucleoside reverse transcriptase inhibitors (nnRTIs) 566 (43.8%), and ritonavir or cobicistat boosted protease inhibitors (PIs) 328 (25.4%). The most frequently prescribed anchor ARVs were dolutegravir (29.6%), boosted darunavir (18.8%), and rilpivirine (15.9%). Overall, 1,023 (79.2%) older PLWH were treated with at least one nRTI. The most frequently used nRTI combinations were abacavir/lamivudine (44.7%), tenofovir disoproxil fumarate/emtricitabine (23.6%), and tenofovir alafenamide/emtricitabine (8.0%).

A full description of the co-medications among older PLWH classified by the ATC therapeutic subgroup is shown in **Supplementary Table 2.** The most frequent co-medications were cardiovascular drugs (C) 900 (69.7%), gastrointestinal and metabolism drugs (A) 881 (68.2%), nervous system drugs (N) 788 (61.0%), blood drugs (B) 504 (39.0%), and systemic anti-infectives (J) 435 (33.7%).

At least one PIM was identified in 482 (37.3%) older PLWH; among these, the most frequent ATC classes involved in PIMs were nervous system drugs (N) (28.6%), musculoskeletal system drugs (M) (10.8%), gastrointestinal and metabolism drugs (A) (5.6%), and cardiovascular drugs (C)(4.7%) (see **Figure 1** for a full description). Thirty-one different co-medications caused 667 PIMs among 482 older PLWH; of these PIMs, 293 (60.8) involved benzodiazepines, 131 (27.2%) involved non-steroidal anti-inflammatory drugs (NSAIDs) (see **Table1** for a detailed description). Five comedications accounted for 84.8% PIMs: lorazepam (38.2%), ibuprofen (18.0%), diazepam (10.2%), metoclopramide (9.9%), and zolpidem (8.5%).

A total of 72 (14.9%) PIMs involved anticholinergic drugs, the most frequent of which were amitriptyline (1.3%), butylscopolamine (1.3%), dexchlorpheniramine (1.0%), hydroxyzine (0.7%), and cyclobenzaprine (0.5%).

Factors independently associated with PIM were polypharmacy (aOR 7.08 [95%CI: 5.16-9.72]) and female sex (aOR 1.75 [95%CI: 1.30–2.35]).

**Discussion**

In this population-based study with 1,292 older PLWH, two-thirds of which experienced polypharmacy, a PIM according to the 2019 AGS Beers criteria, was identified in 37% of study participants. Benzodiazepines and NSAIDs were the most common inappropriate drugs prescribed, and female sex and polypharmacy increased the risk of having a PIM.

Inappropriate prescribing is frequent in older individuals and has been associated to adverse health outcomes [7-13]. The literature in older PLWH has focused mainly on drug-drug interactions (DDIs) involving ARVs, but only a few studies have focused explicitly on prescribing issues. In a retrospective study of 89 PLWH aged 60 and older, mostly male Caucasians, 52% had at least one PIM based on 2012 AGS Beers criteria [14]. In this study, the main drugs involved in PIMs were testosterone, ibuprofen, zolpidem, and lorazepam; and 17% of PLWH received anticholinergic drugs. In a prospective study involving 248 PLWH aged 50 and older, two-thirds of whom were males [15], PIMs were identified in 63% and 54% individuals according to the 2012 AGS Beers and the STOPP/START Criteria, respectively. Benzodiazepines, NSAIDs, 1st generation antihistamines, tricyclic antidepressants, and non-benzodiazepine hypnotics were the most common PIMs, according to the 2012 AGS Beers Criteria [15]. In a retrospective study of the Swiss HIV Cohort, two-thirds of 111 PLWH aged 75 and older, mostly males, had at least one potentially inappropriate prescribing issue according to the 2012 AGS Beers and STOPP/START Criteria [16]. Potential prescribing errors in this last study included unadjusted dosage, no indication, medication omission, medication not appropriate in older individuals, deleterious DDIs, and treatment duration exceeding recommendations; of note, the proportion of patients with more than one prescribing issue was significantly higher in those with polypharmacy.

The prevalence of PIM in our study is lower than what has been reported in similar studies [14-16], a discrepancy that is most likely explained by the fact we focused exclusively on the prescription of inappropriate drugs and not in other issues such as medication omission, inappropriate dosing, or no indication. Consistent with data from studies in elderly individuals with and without HIV, the most frequently observed PIMs were benzodiazepines and NSAIDs [2, 14, 15]. Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase the risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults. On the other hand, NSAIDs increase the risk of gastrointestinal bleeding or peptic ulcer disease in high-risk adults and can increase blood pressure and induce kidney injury [3].

In our study, 15% of older PLWH received anticholinergic drugs, medications to be avoided in older people because they are associated with a wide variety of adverse effects, both peripheral (constipation, oral and ocular dryness, tachycardia and urinary retention) and central (agitation, confusion, delirium, falls, hallucinations and cognitive disorders) to which this population is particularly susceptible [3].

Factors independently associated with increased risk of PIM in our study included polypharmacy, something frequently found in other studies, and female sex. Gender-related differences in polypharmacy could explain the increased risk of having a PIM in women. Some of these differences may be explained by the more frequent contact with the healthcare system among women, which may provide them with extra opportunity for detecting diseases and receiving prescriptions; and also gender-related biological differences in the occurrence of specific comorbidities associated with a chronic need for medication [17, 18].

Our study is limited by the absence of information about comorbidities by the lack of information about the medical management of patients, including potential dosage adjustments, and by the absence of information about clinical outcomes of patients with PIMs. The strengths of our study include its population-based design, the large sample size, and the automatic retrieval of both ARVs and co-medications from an official comprehensive prescription database.

In conclusion, we found that in the region of Madrid, PIM is highly prevalent in older PLWH, particularly among women and individuals with polypharmacy and involve mainly benzodiazepines and NSAIDs. Our data highlight the need for education on prescribing principles in elderly as well as interventions to prevent unnecessary polypharmacy and harmful medications for reducing inappropriate prescribing in this vulnerable, growing population [12, 19].

**Contributions**

BLC and JB conceived the study. CM and SK made substantial contributions to the conception and design. BLC, CBO, and JM analyzed the data. AMS, LPL, JCL, JB, and MJC made substantial contributions to the acquisition of data. BLC and JB drafted the manuscript, and all authors revised it critically and approved the final version.

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**Conflicts of interest**

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