Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/070.2022

Patricia García-Lloret[1]
Yolanda Borrego-Izquierdo[2]
Mercedes Manzano-García[3]
María G. Cantillana-Suárez[4]
Antonio Gutiérrez-Pizarraya[1]
Ramón Morillo-Verdugo[1]

Potentially inappropriate medications according to Marc, STOPP and PRISCUS criteria in a cohort of elderly HIV+ patients. The COMMPI project

[1]Pharmacy Department, Valme University Hospital. Seville (Spain)
[2]Pharmacy Department, Gerencia de Atención Primaria. Cantabria (Spain)
[3]Pharmacy Department, Mérida Hospital. Badajoz (Spain)
[4]Pharmacy Department, San Agustín University Hospital. Linares (Spain)

Article history
Received: 15 July 2022; Revision Requested: 16 August 2022; Revision Received: 1 September 2022;
Accepted: 29 September 2022; Published: 23 November 2022

ABSTRACT

Introduction. The objective is to determine the prevalence of potentially inappropriate drugs according to the Marc, STOPP, and PRISCUS lists in elderly HIV patients.

Patients and methods. It was an observational, retrospective, and multicenter study. People living with HIV 65 years or older who underwent chronic concomitant treatment were included. Descriptive and multivariate analyzes were performed to study the association between polypharmacy and potentially inappropriate medication compliance.

Results. A total of 55 patients were included, 81.8% men and a median age of 69 years (IQR: 67-73). The median number of comorbidities was 3 (IQR: 2-5) and the most frequent pattern of multimorbidity was cardiometabolic (62.9%). The predominant antiretroviral treatment was triple therapy (65.5%). Polypharmacy was present in 70.9% of the patients and 25.5% had major polypharmacy. The most frequent polypharmacy pattern was cardiovascular (69.2%). The percentage of potentially inappropriate medications according to the Marc, STOPP and PRISCUS lists was 65.5%, 30.9% and 14.5%, respectively (p<0.001). Adjusted for age and sex, polypharmacy was not independently associated with potentially inappropriate medication compliance in any of the lists.

Conclusion. Polypharmacy and potentially inappropriate medications have a high prevalence. There is great variability in the percentage according to the list applied. Age, sex, and presence of polypharmacy are not predisposing factors to the presence of potentially inappropriate medications.

Keywords: HIV, polypharmacy, potentially inappropriate medication list

Correspondence:
Yolanda Borrego Izquierdo
Pharmacy Department, Gerencia de Atención Primaria. Cantabria (Spain).
E-mail: yolanda.borrego@scsalud.es

Prevalencia de medicamentos potencialmente inapropiados según criterios Marc, STOPP y PRISCUS en una cohorte de pacientes VIH+ de edad avanzada. Proyecto COMMPI

RESUMEN

Introducción. El objetivo de este estudio es determinar la prevalencia de medicamentos potencialmente inapropiados según los listados Marc, STOPP y Priscus en pacientes VIH+ de edad avanzada.

Pacientes y métodos. Estudio observacional, transversal y multicéntrico. Se incluyeron aquellos pacientes VIH+ mayores de 65 años en tratamiento antirretroviral y tratamiento concomitante crónico. Para conocer la asociación entre polifarmacia y presencia de medicación potencialmente inapropiada se llevaron a cabo análisis descriptivos y multivariante.

Resultados. Se incluyeron 55 pacientes (81.8% hombres); mediana de edad 69 años (RIQ 67-73). Todos presentaban alguna comorbilidad (mediana 3, RIQ 2-5). El patrón de multimorbilidad más frecuente fue cardio-metabólico (62.9%). La triple terapia fue el esquema de tratamiento antiretroviral predominante (65.5%) y el patrón de polifarmacia más frecuente fue el cardiovascular (69.2%). Se identificó presencia de polifarmacia en un 70,9% y un 25,5% polifarmacia mayor. El cumplimiento de algún criterio según el listado Marc, STOPP y PRISCUS observó en 65,5%, 30,9% y 14,5% de los pacientes (p<0.001). Según análisis multivariante se observa que la edad, sexo o presencia de polifarmacia no son factores determinantes de presencia de medicamentos inapropiados en los listados.

Conclusión. La prevalencia de medicación potencialmente inapropiada según los listados utilizados fue alta, existiendo una gran variabilidad en la identificación entre las diferentes herramientas. Edad, sexo y polifarmacia no son factores predictivos de presencia de medicamentos potencialmente inapropiados.

Palabras clave: VIH, polifarmacia, lista de medicación potencialmente inapropiada

INTRODUCTION

HIV infection has changed a deadly condition to a chronic disease due to potent antiretroviral treatments (ART) [1]. As a consequence, the life expectancy of people living with HIV (PLWH) has increased with time, and this population is aging with a high burden of age-related chronic comorbidities and no-HIV prescriptions with ART concomitantly [2,3]. This fact was already predicted by the statistical model developed by Smit et al. [4], which estimated that in 2030, 73% of PLWH will be over the age of 50, 28% will have three comorbidities, and 20% of patients will receive three co-medications. The combination between antiretroviral therapy, which consists of at least two or three drugs, and medications needed to treat comorbidities leads this population to complex polypharmacy.

Some studies described that polypharmacy has been associated with a series of consequences such as drug-drug interactions, risks of falls or fractures, and a greater presence of adverse drug events and hospitalizations [5-7]. The concept of polypharmacy is related to other concepts such as pharmacotherapeutic complexity or potentially inappropriate medication (PIM) [8,9].

In recent years, an arsenal of tools has emerged that have a purpose to optimize pharmacological treatments in older patients by detecting drugs or families of drugs that are considered inappropriate in these patients. Some of these are Beers criteria, Screening Tool of Older Persons' Prescriptions (STOPP)/ Screeaning Tool to Alert doctors To Right Treatment (START) criteria, PRISCUS list and Marc list among others [10-13]. Available studies have reported an extensive prevalence of benzodiazepines and high anticholinergic burden drugs among the HIV population [14,15]. Furthermore, elderly people living with HIV (EPLWH) are at increased risk of having PIM and are substantially higher than HIV-uninfected people [16-18].

At present, to our knowledge, no work has been published on the identification of PIM in EPLWH based on these three lists (STOPP/START criteria, PRISCUS list and Marc list), making a comparison between the percentage of PIM according to the different tools.

The aim of this study was to determine the prevalence of PIM according to the Marc, STOPP, and PRISCUS lists in EPLWH in pharmacotherapeutic follow-up in outpatient consultations of several Pharmacy Services.

PATIENTS AND METHODS

Design and study population. An observational, retrospective, and multicenter study has been carried out in three hospitals in Spain. PLWH aged 65 years-old and older on active ART and with chronic concomitant treatment attending at Pharmaceutical Care Consultation of the Hospital Pharmacies from March 2021 until May 2021 were included. Patients in clinical trials, treated for pre and post-exposure prophylaxis, as well as with a short life expectancy, were excluded.

Demographic characteristics, immunological and virological laboratory data, as well as pharmacotherapeutic variables were collected. Data were obtained from the patient clinical records.

Definitions.

- **Polypharmacy**. It was defined as the use of six or more different drugs, including antiretroviral medications [19,20].
- **Major polypharmacy**. It was restricted to the use of ≥11 different drugs.
- **Polypharmacy patterns**. To describe them, we used the categorization proposed by Calderón-Larra**ñ**aga et al. [21] who classified the patterns according to the type of disease they were intended to treat cardiovascular, depression-anxiety, acute respiratory infection, chronic pulmonary disease, rhinitis-asthma, pain, and menopause. To establish the corresponding polypharmacy patterns for each patient, active drugs are classified according to the anatomical therapeutic chemical classification (ATC) [22] using only the first three levels of classification and a patient was classified into a specific pattern when at least three drugs included in the pattern were dispensed.
- **Pharmacotherapeutic complexity**. It was measured by the *Medication Regimen Complexity Index* (MRCI). The MRCI index is a validated 65-item tool that evaluates the complexity of the treatment regimen based on the number of medications, the dosage form, the frequency of the dosage and additional or special instructions. This index score ranges from 1.5 (for someone taking a single tablet or capsule taken once a day) to an undefined maximum since the score increases with the number of medications; higher scores indicate higher complexity [23]. Furthermore, according to Morillo-Verdugo et al. [20] a cut off value of 11.25 was used for the MRCI index score to consider a complex patient.
- **Multimorbidity patterns**. To describe them, we used the categorization proposed by Prados-Torres et al. [24] who classified the patterns according to the type of disease they were diagnosed (cardiometabolic, geriatric-depressive, thyroid disease, and mixed). Patients were classified according to a specific pattern when they had been diagnosed with at least two diseases included in the pattern.
- **Anticholinergic risk**. To determine the anticholinergic risk, we use the *Drug Burden Index* (DBI) [25]. According to this scale, each drug is assigned an anticholinergic load value. The anticholinergic load will be the sum of the values of the prescribed drugs. Patients are classified into patients with low anticholinergic load when they have a value ≤0.5 and high when the value is >0.5.

Statistical analysis. Discrete variables were expressed as counts (percentage) and continuous variables as means and SD or medians and interquartile ranges (IQR) as appropriate. Differences in categorical variables were calculated using a two-sided likelihood ratio Chi square test or Fisher's exact test, and the t test or the Mann–Whitney U test was used for continuous variables, when appropriate.

Table 1 Baseline and pharmacotherapeutics features of patients (n=55).

Characteristics	N	%	Median	IQ range
Age (years)	-	-	69	67-73
Sex				
Male	45	81.8	-	-
Female	10	18.2	-	-
Undetectable viral load (<50 copies/mL)	55	100	-	-
CD4 level >200 cells/mL	48	87.3	552	368-763
CD4/CD8 ratio >0.4	47	85.5	-	-
Number of comorbidities	-	-	3	2-5
Multimorbidities patterns (35 patients)				
Cardiometabolic	22	62.9	-	-
Geriatric depressive	4	11.4	-	-
Thyroid disease	1	2.8	-	-
Mixed	8	22.9	-	-
ART type				
NRTI + INI	29	52.7	-	-
NRTI + NNRTI	5	9.2	-	-
NRTI + IP	2	3.6	-	-
Others	19	34.5	-	-
Polypharmacy	39	70.9	-	-
Major polypharmacy	14	25.5	-	-
Polypharmacy patterns (26 patients)				
Cardiovascular	18	69.2	-	-
Anxious-depressive	4	15.4	-	-
COPD	2	7.7	-	-
Mixed	2	7.7	-	-
MRCI (points)	-	-	11	7-18
High MRCI index (>11.25 points)	24	43.6	-	-
High anticholinergic load (>0.5 points)	14	25.5	-	-

ART: Antiretroviral therapy; NRTI: Nucleoside reverse transcriptase inhibitors; INI: Integrase inhibitors; NNRTI: Nonnucleoside reverse transcriptase inhibitors; IP: protease inhibitor; COPD: Chronic obstructive pulmonary disease; MRCI: medication regimen complexity index.

A logistic regression model was performed for each of the three lists, in order to assess the association between polypharmacy and PIM according to each list, adjusting for age and sex. The threshold for statistical significance was defined as $p<0.05$. Data analysis was performed with SPSS v20.0.

Ethics approval. The study was approved by the ethics committee "Comité Ético de Investigación del Sur de Sevilla" (Seville, Spain) (reference 1006-N-21).

RESULTS

A total of 55 patients were included in this study and 81.8% (n=45) were male. The median age was 69 years (IQR: 67-73). The baseline characteristics of the patients are summarized in Table 1.

All study participants presented undetectable viral load, 87.3% had a CD4 level >200 cells/mL (median 552; IQR: 368-763) and CD4/CD8 ratio >0.4 in 85.5%. Globally, the median

Table 2 Distribution of the STOPP, Marc and PRISCUS criteria in the study population

STOPP CRITERIA	N	%
Anxiolytics lasting more than 4 weeks	10	18.2
Antiulcer drug not indicated	3	5.5
Inadequate antithrombotic	2	3.6
Antipsychotic used for more than 4 weeks	2	3.6
NSAIDs and long-term antirheumatics	2	3.6
Beta blockers	2	3.6
Oral hypoglycemic agents excluding insulin	1	1.8
Antidepressants	1	1.8
MARC LIST	N	%
THERAPEUTIC GROUPS		
Beta-adrenergic blockers	15	27.3
Benzodiazepines and analogs	14	25.5
Platelet antiaggregant	14	25.5
Oral hypoglycemic agents	13	23.6
Insulins	5	9.1
Opioids	5	9.1
Loop diuretics	3	5.5
NSAIDs	3	5.5
Oral anticoagulants	2	3.6
Antipsychotics	2	3.6
Immunosuppressants	1	1.8
SPECIFIC MEDICINES		
Spironolactone/eplerenone	3	5.5
PRISCUS LIST	N	(%)
DRUGS		
Sedative-hypnotic	4	7.3
Anxiolytics	2	3.6
Antidepressants	1	1.8
NSAIDs and antirheumatics	1	1.8

NSAIDs: Non-steroidal anti-inflammatory drugs

number of comorbidities was 3 (IQR: 2-5). The multicomorbidity pattern was obtained in 35 patients, cardiometabolic pattern in 62.9%, mixed in 22.9%, geriatric depressive in 11.4%, and thyroid disease in 2.8%.

Overall, 70.9% (n=39) of the patients presented polypharmacy, 25.5% (n=14) had major polypharmacy, obtaining the polypharmacy pattern in 26 of them. The most common polypharmacy pattern was cardiovascular (69.2%), followed by anxiuos-depressive (15.4%) and 7.7% for both chronic obstructive pulmonary disease and mixed pattern. The median MRCI index was 11.0 (IQR: 7.0-18.0), 43.6% (n=24) had a high pharmacotherapeutic complexity. Additionally, we found a high anticolinergic load in 25.5% of patients.

The percentage of PIM according to the Marc, STOPP, and PRISCUS lists was 65.5%, 30.9% and 14.5%, respectively (p<0.001). The most identified PIM were anxiolytics (18.2%) with STOPP criteria, sedative-hypnotics (7.3%) with the PRISCUS list and beta-blockers (27.3%), antiplatelet agents (25.5%), anxiolytics (25.5%) and hypoglycemic agents (23.6%) with the Marc list. The distribution of the criteria for each list is collected in Table 2.

A univariate analysis was performed to determine the association between the presence of PIM by any of the three listed with the following qualitative variables: polypharmacy, major polypharmacy, polypharmacy pattern, and multimorbidity pattern. The results are shown in Table 3.

When analyzing the association between polypharmacy and STOPP list, a higher frequency is observed in those patients who comply with the list (14; 82.4% vs. 25; 65.8%; p=0.067). On the contrary, statistical significance is reached in major polypharmacy, in favor of a higher proportion of polypharmacy in patients with compliance with list (8; 47.1% vs. 6; 15.8%; p=0.021). Regarding the patterns, there is a higher frequency in patients who presented both a polypharmacy pattern (11; 64.7% vs 15; 39.5%; p=0.003) and a multimorbidity pattern (13; 76.5% vs 22; 57.9%; p=0.335), compared to those who do not meet any criteria, being only statistically significant in the case of polypharmacy pattern.

Acording to polypharmacy and compliance with the Marc list, we again observed a higher proportion of patients with polypharmacy (28; 77.85% vs 11; 57.9%; p=0.067). Nevertheless, statistically significant differences were observed in major polypharmacy (14; 38.9% vs 0; 0%; p=0.001) and both a polypharmacy pattern (24; 66,7% vs 2; 10,5%; p=0.003) and a multimorbidity pattern (29; 80,6% vs 6; 31,6%; p=0.003).

Finally, when observing the association between polypharmacy and the PRISCUS list, we again found a higher prevalence in patients who comply with the list (7; 87.5% vs 32; 68.1%; p=0.414). The same occurs with the presence of major polypharmacy (3; 37,5% vs 11; 23,4%; p=0.405). In the case of polypharmacy pattern (5; 62.5% vs 21; 44.7%; p=0.510) and multimorbidity pattern (7; 87.5% vs 28; 59; 6%; p=0.064), both are present in a greater proportion in patients with compliance with the PRISCUS list, however no statistical significance is observed in any case.

Pharmacotherapeutic complexity were also compared for the three lists. Statistical significance was only found in the Marc list, being 17.5 for the compliant versus 6.9 for the non-compliant (p=0.001).

In the multivariate analysis, we analyzed the association of PIM compliance and polypharmacy for the three lists adjusted by age and sex, and polypharmacy; it turned out to be independent in the Marc, PRISCUS, and STOPP lists, with OR=3.14 (IC95% 0.82-11.96), OR=2.93 (IC95% 0.28-30.77) and OR=0.60 (IC95% 0.10-3.57) respectively. Given the low in-

Table 3 Univariate analysis of the presence of potentially inappropriate medication and pharmacotherapeutic variables

Pharmacotherapeutic characteristics	STOPP Compliant n (%) vs. non-compliant n (%) p-value	Marc Compliant n (%) vs. non-compliant n (%) p-value	PRISCUS Compliant n (%) vs. non-compliant n (%) p-value
Polypharmacy (n=39)	14 (82.4%) vs 25 (65.8%) p=0.067	28 (77.8%) vs 11 (57.9%) p=0.067	7 (87.5%) vs 32 (68.1%) p=0.414
Major polypharmacy (n=14)	8 (47.1%) vs 6 (15.8%) p=0.021	14 (38.9%) vs 0 (0%) p=0.001	3 (37.5%) vs 11 (23.4%) p=0.405
Polypharmacy pattern (n=26)	11 (64.7%) vs 15 (39.5%) p=0.003	24 (66.7%) vs 2 (10.5%) p=0.003	5 (62.5%) vs 21 (44.7%) p=0.510
Multimorbidity pattern (n=35)	13 (76.5%) vs 22 (57.9%) p=0.335	29 (80.6%) vs 6 (31.6%) p=0.003	7 (87.5%) vs 28 (59.6%) p=0.064

cidence of the event and the small number of patients in the study, it was not possible to adjust for more variables.

DISCUSSION

Our study shows a high prevalence of PIM according to the lists used in the cohort analyzed, with great variability in the identification of this concept among the different tools. We found the highest proportion of PIM when using the Marc list and the lowest one with the PRISCUS list.

Our work includes patients with a high percentage of polypharmacy. The high prevalence of polypharmacy in PLWH has been widely described in international studies [26,27] and national studies [28,29]. Furthermore, some studies reported that polypharmacy is more widespread in the EPLWH population than in the general population without HIV infection [3,30].

Specifically, the multicenter study by Gimeno-Gracia et al. [28], with a slightly higher cohort of patients of the same age group, presented a polypharmacy result very similar to our study.

In addition, many authors have described which concomitant medications were prescribed most frequently prescribed; cardiovascular drugs and central disorders of the nervous system are the most prevalent [31,32]. This fact is reflected in the present study. The most observed polypharmacy pattern in our cohort is the cardiovascular pattern, followed by the depressive-anxious pattern. Consistent with this, the most identified multimorbidity pattern is cardiometabolic.

Concomitant medication is known to be the cause of complexity pharmacotherapeutic in EPLWH. ART contributes to a lesser extent due to the simplification of dosage guidelines in recent years [33]. In our study, almost half of the patients present a high complexity index, with a median of 11.0 points. There are other published studies, such as the one by Contreras et al. [34], where a lower mean complexity index (6.9 points), with 20.6% of patients with a high complexity index. This difference may be due to the fact that the study was carried out in HIV patients older than 18 years. Younger patients usually present a lower pharmacotherapeutic complexity than older people due to the absence of comorbidities.

As already mentioned, some authors have described a high prevalence of PIM in PLWH. Among these PIM they found benzodiazepines and drugs with anticholinergic properties [15]. In this study, there is also evidence of a widespread prescription of benzodiazepines; it is the group of drugs most identified as PIM by all three tools. However, due to the low value that benzodiazepines contributes to the anticholinergic load, we only observed 25.5% of patients with a high anticholinergic load. This result is not insignificant, since there are other studies of a similar population with lower percentages of high anticholinergic load, 15% [15].

Polypharmacy, major polypharmacy and polypharmacy and multimorbidity patterns were found to be more common in patients whose compliance with any of the three lists was high. It seems logical to think that presenting different drugs for different comorbidities will allow them to be included within the same pattern of polypharmacy and diseases within the pattern of multimorbidity. Additionally, this means that the specific clinical characteristics that define any of the criteria collected by the three tools are more likely to be met.

On the other hand, multivariate analysis shows that this compliance is not affected by the variables age, sex and polypharmacy.

Regarding the variability in the identification of PIM by the different lists, we might think that the criteria included in them do not quite fit the PLWH. Similarly, other authors have evaluated the concordance of criteria for four lists for the

identification of PIM in the older population, obtaining great variability of them [35].

It is important to note that the characteristics of each of the tools used in this study differ from each other, and maybe because of this, we have found variability in the identification of PIM. In the case of the Marc list, it only takes into account the prescription of drugs belonging to different groups of therapeutics that are considered high-risk for chronic patients. This list does not describe the clinical situation in which that drug is used or the duration of treatment. In contrast, the STOPP criteria and PRISCUS lists are more specific and demanding lists. These lists detail the use of PIM in specific clinical situations or mention the duration of treatment, making it more difficult for the patient to meet some criteria. Despite this, Aguiar et al have described the limitations of the STOPP criteria [36].

We recognize some limitations. First, the underestimation of PIM prescription, not including medications not considered chronic (less than 90 days of prescription) or OTC (over-the-counter medication) or recommended in the community pharmacy for minor illness or minor symptoms. However, they are considered to not have a relevant effect because they are used sporadically or for less than three months. Another possible limitation could be the small number of patients who meet the inclusion criteria. This can lead to inconsistent results and limits us in the multivariate analysis that adjusts only for sex, age, and polypharmacy. However, this limitation could be overcome with increasing sample size. Thus, it does not invalidate the results obtained, which can serve as hypotheses for future lines of research.

Given the design of the study that does not contemplate patient follow-up, it is unknown whether the PIMs detected may have had any negative effect on the study population.

The results obtained in this study can provide guidance on which tool may be more sensitive to detect the use of PIM. Additionally, seeing the variability of the data, another possible line of research would be the development and validation of a PIM list for the elderly HIV population.

There is great variability in the prevalence of potentially inappropriate medications depending on the tool used. This finding should lead to the design of a tool more sensitive to detect PIM in the elderly HIV-infected population.

FUNDING

None to declare.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. National Plan on AIDS; Spanish Society of Geriatrics and Gerontology; Metabolic Alterations and Comorbidities Study Group. Consensus document on aging in people with infection by thehuman immunodeficiency virus (2021 Update) May 2021. [cited 25 June 2022] Available from: https://www.sanidad.gob.es/gl/ciudadanos/enfLesiones/enfTransmisibles/sida/documentos/110521_Doc_CONSENSO_ENVEJECIMIENTO_Y_VIH.pdf
2. Gimeno-Gracia M, Crusells-Canales MJ, Javier Armesto-Gómez F, Rabanaque-Hernández MJ. Prevalence of concomitant medications in older HIV+ patients and comparison with general population. HIV Clin Trials. 2015;16(3):117-124. doi:10.1179/1528433614Z.0000000012
3. Gimeno-Gracia M, Crusells-Canales MJ, Armesto-Gómez FJ, Compaired-Turlán V, Rabanaque-Hernández MJ. Polypharmacy in older adults with human immunodeficiency virus infection compared with the general population. Clin Interv Aging. 2016;11:1149-1157. doi:10.2147/CIA.S108072
4. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Sighem Av, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis. 2015;15(7):810-8. doi: 10.1016/S1473-3099(15)00056-0.
5. Holtzman C, Armon C, Tedaldi E, Chmiel JS, Buchacz K, Wood K et al. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. J Gen Intern Med. 2013;28(10):1302-1310. doi:10.1007/s11606-013-2449-6
6. Gleason LJ, Luque AE, Shah K. Polypharmacy in the HIV-infected older adult population. Clin Interv Aging. 2013;8:749-763. doi:10.2147/CIA.S37738
7. Edelman EJ, Gordon KS, Glover J, McNicholl IR, Fiellin DA, Justice AC. The next therapeutic challenge in HIV: polypharmacy. Drugs Aging. 2013;30(8):613-628. doi:10.1007/s40266-013-0093-9
8. Morillo-Verdugo R, Blanco Ramos JR, Abdel-Kader Martín L, Álvarez de Sotomayor M. El reto del envejecimiento y la complejidad farmacoterapéutica en el paciente VIH [The challenge of aging and pharmacoterapeutic complexity in the HIV + patient]. Farm Hosp. 2018;42(3):120-127. doi:10.7399/fh.10931
9. Courlet P, Livio F, Guidi M, Cavassini M, Battegay M, Stoeckle M et al. Polypharmacy, Drug-Drug Interactions, and Inappropriate Drugs: New Challenges in the Aging Population With HIV. Open Forum Infect Dis. 2019;6(12):ofz531. doi:10.1093/ofid/ofz531
10. American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019; 67(4):674-694. doi: 10.1111/jgs.15767.
11. Delgado Silveira E, Montero Errasquín B, Muñoz García M, Vélez-Díaz-Pallarés M, Lozano Montoya I, Sánchez-Castellano C et al. Mejorando la prescripción de medicamentos en las personas mayores: una nueva edición de los criterios STOPP-START [Improving drug prescribing in the elderly: a new edition of STOPP/START criteria]. Rev Esp Geriatr Gerontol. 2015;50(2):89-96. doi:10.1016/j.regg.2014.10.005
12. Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int. 2010;107(31-32):543-551. doi:10.3238/arztebl.2010.0543

13. MARC PROJECT. Preparation of a List of High-Risk Medications for Chronic Patients. Madrid: Ministry of Health, Social Services and Equality; Report 2014 . [cited 25 June 2022]. Available from: https://seguridaddelpaciente.es/resources/documentos/2014/Proyecto_MARC_2014.pdf

14. López-Centeno B, Badenes-Olmedo C, Mataix-Sanjuan A, Bellón JM, Pérez-Latorre L, López JC et al. Potentially inappropriate medications in older adults living with HIV. HIV Med. 2020;21(8):541-546. doi:10.1111/hiv.12883

15. Mazzitelli M, Milinkovic A, Pereira B, Palmer J, Tong T, Asboe D et al. Polypharmacy and evaluation of anticholinergic risk in a cohort of elderly people living with HIV. AIDS. 2019;33(15):2439-2441. doi:10.1097/QAD.0000000000002403

16. Greene M, Steinman MA, McNicholl IR, Valcour V. Polypharmacy, drug-drug interactions, and potentially inappropriate medications in older adults with human immunodeficiency virus infection. J Am Geriatr Soc. 2014;62(3):447-453. doi:10.1111/jgs.12695

17. McNicholl IR, Gandhi M, Hare CB, Greene M, Pierluissi E. A Pharmacist-Led Program to Evaluate and Reduce Polypharmacy and Potentially Inappropriate Prescribing in Older HIV-Positive Patients. Pharmacotherapy. 2017;37(12):1498-1506. doi:10.1002/phar.2043

18. Livio F, Deutschmann E, Moffa G, Rrustemi F, Stader F, Elzi L et al. Analysis of inappropriate prescribing in elderly patients of the Swiss HIV Cohort Study reveals gender inequity. J Antimicrob Chemother. 2021;76(3):758-764. doi:10.1093/jac/dkaa505

19. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230. doi: 10.1186/s12877-017-0621-2.

20. Morillo-Verdugo R, Robustillo-Cortés MA, Abdel-Kader Martín L, Álvarez de Sotomayor Paz M, Lozano de León Naranjo F, Almeida González CV. Determination of a cutoff value for medication regimen complexity index to predict polypharmacy in HIV+ older patient. Rev Esp Quimioter. 2019;32(5):458-464. PMID: 31528986

21. Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F, Poblador-Plou B, Lairla-San José M, Abad-Díez JM et al. Polypharmacy patterns: unravelling systematic associations between prescribed medications. PLoS One. 2013;8(12):e84967. doi:10.1371/journal.pone.0084967

22. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2022. [cited 25 June 2022]. Available from: https://www.whocc.no/atc_ddd_index/

23. Alves-Conceição V, Rocha KSS, Silva FVN, Silva ROS, Cerqueira-Santos S et al. Are Clinical Outcomes Associated With Medication Regimen Complexity? A Systematic Review and Meta-analysis. Ann Pharmacother. 2020;54(4):301-313. doi:10.1177/1060028019886846

24. Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. J Clin Epidemiol. 2014;67(3):254-266. doi:10.1016/j.jclinepi.2013.09.021

25. Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med. 2007 Apr 23;167(8):781–787

26. Ruzicka DJ, Imai K, Takahashi K, Naito T. Greater burden of chronic comorbidities and co-medications among people living with HIV versus people without HIV in Japan: A hospital claims database study. J Infect Chemother. 2019;25(2):89-95. doi:10.1016/j.jiac.2018.10.006

27. Harmon JL, McGee KS. Addressing Polypharmacy in Older Adults Living With HIV. *J* Assoc Nurses AIDS Care. 2019;30(1):73-79. doi:10.1097/JNC.0000000000000028

28. Gimeno-Gracia M, Sánchez-Rubio-Ferrández J, Robustillo-Cortés MLA, Morillo-Verdugo R. Prevalencia de polifarmacia y complejidad farmacoterapéutica en personas mayores con VIH en España. Estudio POINT [Prevalence of polypharmacy and pharmacotherapy complexity in elderly people living with HIV in Spain. POINT study]. Farm Hosp. 2020;44(4):127-134. doi:10.7399/fh.11367

29. López-Centeno B, Badenes-Olmedo C, Mataix-Sanjuan Á, McAllister K, Bellón JM, Gibbons S et al. Polypharmacy and Drug-Drug Interactions in People Living With Human Immunodeficiency Virus in the Region of Madrid, Spain: A Population-Based Study. Clin Infect Dis. 2020;71(2):353-362. doi:10.1093/cid/ciz811

30. Kong AM, Pozen A, Anastos K, Kelvin EA, Nash D. Non-HIV Comorbid Conditions and Polypharmacy Among People Living with HIV Age 65 or Older Compared with HIV-Negative Individuals Age 65 or Older in the United States: A Retrospective Claims-Based Analysis. AIDS Patient Care STDS. 2019;33(3):93-103. doi:10.1089/apc.2018.0190

31. Guaraldi G, Malagoli A, Calcagno A, Mussi C, Celesia BM, Carli F et al. The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: a cross sectional study of people aged 65 - 74 years and more than 75 years. BMC Geriatr. 2018;18(1):99. doi:10.1186/s12877-018-0789-0

32. Siefried KJ, Mao L, Cysique LA, Rule J, Giles ML, Smith DE et al. Concomitant medication polypharmacy, interactions and imperfect adherence are common in Australian adults on suppressive antiretroviral therapy. AIDS. 2018;32(1):35-48. doi:10.1097/QAD.0000000000001685

33. Manzano-García M, Robustillo-Cortés A, Almeida-González CV, Morillo-Verdugo R. Evolución del índice de complejidad de la terapia antirretroviral en paciente VIH en una cohorte de práctica clínica real [Evolution of the Complexity Index of the antiretroviral therapy in HIV+ patients in a real life clinical practice]. Rev Esp Quimioter. 2017;30(6):429-435. PMID: 29115368

34. Contreras-Macías E, Gutiérrez-Pizarraya A, RobustilloCortés MA, Morillo-Verdugo R. High level of medication regimen complexity index correlate with worse quality of life in people living with HIV. Rev Esp Quimioter. 2021;34(2):93-99. doi:10.37201/req/097.2020

35. Ma X, Yin X, Li M, Wang Y, Xin H, Liu W. Appropriate use of essential medicines in the elderly: a comparison of the WHO essential medicines list and PIM criteria. Eur J Clin Pharmacol. 2021;77(4):509-516. doi:10.1007/s00228-020-03038-0

36. Aguiar JP, Gama Marques J, Alves da Costa F. Utility and limitations of a screening tool of older person's prescription among psychiatric elder patients: A comprehensive review. Aging and Health Research. 2021; 1(3): 100031. https://doi.org/10.1016/j.ahr.2021.100031.