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REVIEW
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The challenge of aging and pharmacoterapeutic complexity in the HIV+patient

El reto del envejecimiento y la complejidad farmacoterapéutica en el paciente VIH+

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Abstract

Objective: To describe the current knowledge and management of aging and pharmacotherapeutic complexity in HIV+ patients.

Method: A review of literature was carried out, including articles, originals or reviews, published in English or Spanish, from 2007 to 2017, which analysed the aging and pharmacotherapeutic complexity in HIV+ patients. The terms «Polypharmacy»/«Polifarmacia», «Aging»/«Envejecimiento», «Frailty»/«Fragilidad», «Complejidad Farmacoterapéutica»/«Medication Regimen Complexity» and «HIV»/«VIH» were combined. The review was carried out independently by two authors. The degree of agreement, according to the Kappa index, was analysed.

Results: A total of 208 references were analysed, including, finally, only 68. An aging of the population and an increase in associated comorbidities have been identified, especially over 50 years-old. Immunological changes similar to those that are generated in a non-infected elderly population have been described. These conditions influencing the prescription of antiretroviral treatment, according to studies identified. In parallel, polypharmacy is increasingly present, being defined exclusively by the concomitant use of five drugs. Pharmacotherapeutic complexity, through the Medication Regimen Complexity Index, has begun to analyse and relate to health outcomes. There has been a need to know and apply concepts already known in non-HIV-aged population, such as deprescription, potentially inappropriate medication, cholinergic risk, although few results are available.

Conclusions: There is a growing interest to know about the relationship between HIV and aging. Pharmacotherapeutic complexity is beginning to be used as a pharmacotherapeutic follow-up criterion due to its

Resumen

Objetivo: Describir el conocimiento actual y el manejo del envejecimiento y la complejidad farmacoterapéutica en pacientes VIH+.

Método: Se realizó una revisión bibliográfica, incluyéndose artículos, originales o revisiones, publicados en lengua inglesa o española, desde 2007 al 2017, que analizaron el envejecimiento y la complejidad farmacoterapéutica en pacientes VIH≥. Se combinaron los términos: "Polypharmacy"/"Polifarmacia", "Aging"/"Envejecimiento", "Frailty"/"Fragilidad", "Complejidad Farmacoterapéutica"/"Medication Regimen Complexity" y "HIV"/"VIH". La revisión se realizó de forma independiente por dos autores. Se analizó el grado de concordancia según el índice Kappa.

Resultados: Se analizaron 208 referencias bibliográficas, incluyéndose finalmente 68. Se ha identificado un envejecimiento de la población y un incremento de las comorbilidades asociadas, especialmente a partir de los 50 años. Se han descrito cambios inmunológicos similares a los que se generan en la población anciana no infectada. Esto condiciona, según estudios identificados, la prescripción del tratamiento antirretroviral. Paralelamente, el concepto de polifarmacia está cada vez más presente, definiéndose exclusivamente por el uso concomitante de cinco fármacos. La complejidad farmacoterapéutica, a través del *Medication Regimen Complexity Index*, se ha empezado a analizar y a relacionar con resultados en salud. Se ha evidenciado una necesidad de profundizar y aplicar conceptos ya conocidos en la población no VIH envejecida, como desprescripción, medicación potencialmente inapropiada, riesgo colinérgico, etc., aunque existen pocos resultados disponibles.

Conclusiones: Existe un interés creciente en profundizar en la relación VIH y envejecimiento. La complejidad farmacoterapéutica está empezando a uti-

influence on health outcomes. It is necessary to manage and incorporate new concepts that help pharmacotherapeutic optimization in this population.

lizarse como criterio de seguimiento farmacoterapéutico por su influencia en los resultados en salud. Es necesario manejar e incorporar nuevos conceptos que ayuden a la optimización farmacoterapéutica en esta población.

Introduction

Human immunodeficiency virus (HIV) infection is now considered to be a chronic disease thanks to the striking decrease in mortality following the introduction of highly active antiretroviral therapy (HAART) and the subsequent arrival of new more potent drugs with better dosage regimens[1]. Increased survival has led to the parallel ageing of the HIV-positive population. In fact, data on different cohorts of HIV-positive patients have already been published in international studies, showing that more than 50% of the individuals in treatment were already more than 50 years old. It has been suggested that by 2030 this percentage will have increased[2].

The aging of the population has led to an increase in a range of comorbidities. It is also known that these comorbidities have a greater prevalence and occur earlier in HIV-positive patients than in the general population. It has been estimated that aging will accelerate over the next 10 years[3-6]. Simultaneous with the increase in comorbidity, the concept of polypharmacy has gained increasing exposure in the setting of the increased prevalence of HIV-positive patients[7], although, according to most authors, there is no consensus on its definition[8]. With the aim of providing a more accurate picture of pharmacotherapy, rather than a simply quantitative one, the term medication regimen complexity has been coined. Different tools are available for its measurement, and its relationship with different health outcomes is already known[9-12].

The experience and scientific evidence obtained with the general population are already serving as a starting point for the assessment and management of elderly patients with HIV[13-16]. However, knowledge and consensus on many key factors is needed within the multidisciplinary teams caring for these patients, which would help to reorientate and improve healthcare in this population.

The objective of this review was to describe the current state of knowledge and the management of aging and medication regimen complexity in HIV-positive patients.

Methods

A literature search was conducted using the following databases: Medline (via Pubmed), Scopus, Web of Science, the Cochrane Library, and Google Scholar.

Inclusion criteria were: all English- or Spanish-language original or review articles published between 2007 and 2017 which analysed the management of aging and medication regimen complexity in HIV-positive patients older than 50 years.

The Medline database was searched using Medical Subject Headings (MeSH), which is a thesaurus created by the US National Library of Medicine. The following English and Spanish terms were used in combination: "Polypharmacy"/"Polifarmacia", "Aging"/"Envejecimiento", "Frailty"/"Fragilidad", "Complejidad Farmacoterapeutica"/"Medication Regimen Complexity", and "HIV"/"VIH".

The articles were independently reviewed by two of the authors of this article. Disagreements were resolved by consensus. Inter-rater agreement on the inclusion of the selected articles was assessed using the Kappa index (a cutoff value of 0.80 was used to indicate good correlation).

Subsequently, we analysed and combined the data extracted from the articles that met the inclusion criteria.

Results

A total of 208 bibliographic references related to the study objectives were identified and analysed. Figure 1 shows the flowchart of the revised bibliography according to the inclusion and exclusion criteria used. Table 1 shows the selected studies, which include data relevant to the setting of HIV-positive patients.

In general, polypharmacy has been defined as the concomitant and simultaneous use of multiple medications. However, the term has many definitions, which include aspects such as the use of potentially inappropriate
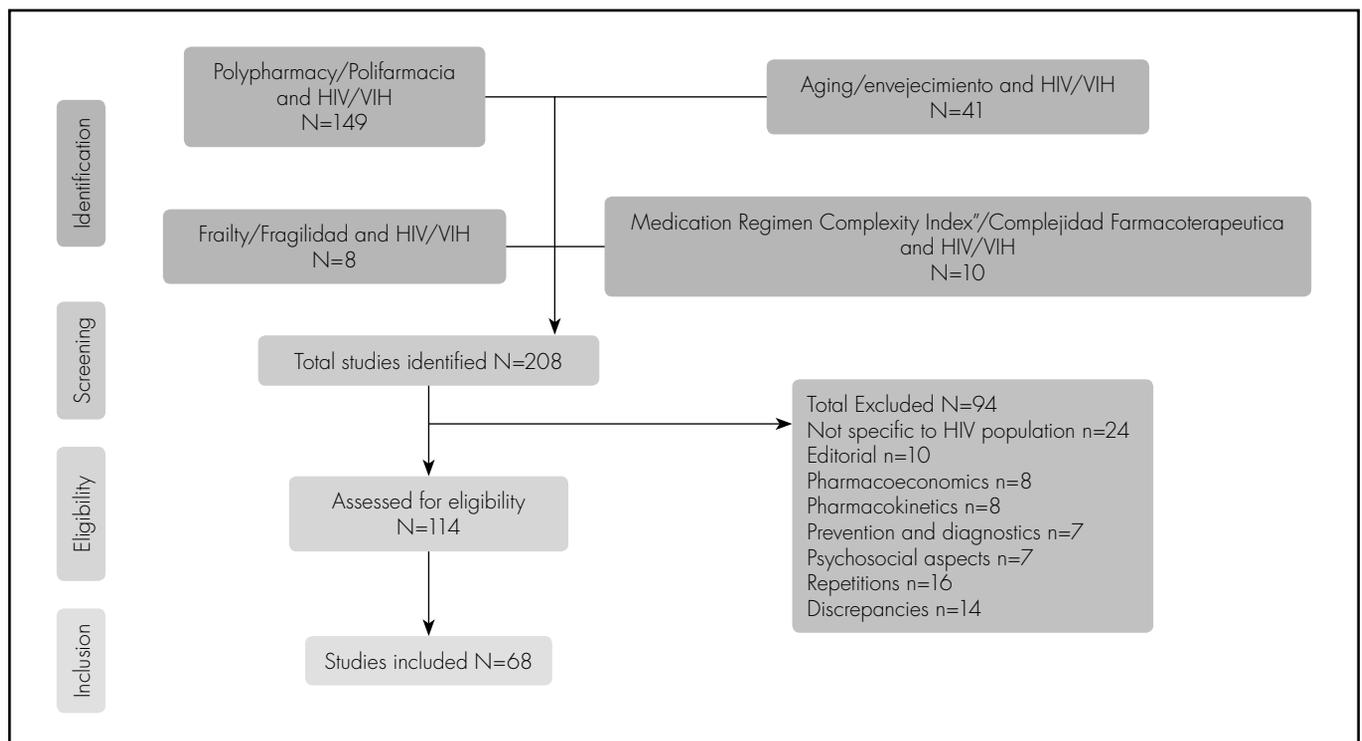

Figure 1. *Flow Diagram of the Literature Review and Inclusion/Exclusion Process of the Studies Analysed.*

TABLE 1. Main Conclusions of the Original Articles on HIV+ Patients Included in the Review

AUTHORS-YEAR (REFERENCE)	MAIN CONTRIBUTIONS
AGING AND FRAILTY	
Deeks et al. 2009[3]	Although mortality in HIV-positive patients continues to decrease, it is still higher than in the non-HIV population. The risk of non-AIDS-based comorbidities, including cardiovascular disease, liver disease, and cancer, is higher in the HIV population than in the general population.
Blanco JR et al. 2010[4]	In the absence of specific guidelines on the management of elderly HIV-positive patients, specific strategies need to be designed to optimize therapies in these types of patients. Clinical trials and pharmacodynamic and pharmacokinetic studies are needed.
Guaraldi G et al. 2011[20]	The prevalence of polypharmacy among HIV-positive patients aged 41 to 50 years was similar to that among the non-HIV population aged 51 to 60 years. A low nadir CD4 count and prolonged exposure to ART is associated with increased comorbidity.
Schouten J et al. 2014[21]	Age-associated comorbidities (i.e., mainly cardiovascular, renal, and mental disease) are more prevalent in the HIV-positive patient. In these patients, permanent and residual inflammation are factors that contribute to these comorbidities.
Smit M et al. 2015[22]	In 2030, the percentage of patients older than 50 years will be much higher than at present. There will be a significant increase in the number of associated comorbidities and, in parallel, the prescription of associated drugs.
Choi AI et al. 2007[41]	Black patients with HIV and diabetes have a 4- to 5-fold higher risk of decreased kidney function than that of the rest of the population.
Hasse B et al. 2011[47]	This was one of the largest worldwide cohort studies. It confirmed that multimorbidity is a problem of the first magnitude in HIV-positive patients. Multimorbidity particularly includes diabetes mellitus, cardiovascular diseases non-AIDS malignancies, and osteoporosis. Their risk increased with older age in HIV-positive elderly patients.
POLYPHARMACY AND NEW ASSOCIATED CONCEPTS	
Gimeno-Gracia M et al. 2016[6]	The amount of medication prescribed for comorbidities is higher in the elderly HIV-positive population than in the non-HIV+ population. In this population, the most frequently prescribed drugs are ACEIs, statins, antidiabetics, antithrombotic agents, and calcium channel blockers.
Edelman EJ et al. 2013[7]	This study provides an algorithm for the optimization of pharmacotherapy in HIV-positive patients with polypharmacy. It provides a deeper perspective on reconciliation, toxicity, and the benefit-risk balance of prescriptions, and on prioritizing and planning in each patient.
Krentz HB et al. 2012[8]	This study investigated pill burden in HIV-positive patients over an extended period of follow-up. It describes the concomitant use of families of drugs and the more commonly prescribed drugs.
Nozza S et al. 2017[16]	There are a high number of "unconventional" prescriptions for antiretroviral treatment in elderly HIV-positive patients, due to the need for individualization caused by the concomitant prescription of drugs and the need to avoid relevant interactions.
Gleason LJ et al. 2013[18]	Currently, the key factors in managing the HIV-positive patient are: to reduce therapeutic burden, adjust doses, raise awareness of the influence of interactions on therapeutic success, and establish methodologies for a systematic review of all prescribed medication.
Marzolini C et al. 2011[23]	Increased comorbidities and comedication in these patients increases the risk of relevant drug interactions.
Holtzman C et al. 2011[24]	Of a total of 3800 patients analysed during a 5-year observation period, 7.0% had at least 1 contraindicated interaction: the main problems were the use of proton pump inhibitors, statins, and benzodiazepines. 30.0% of patients more than 50 years of age had prescriptions for medicinal herbs and vitamin supplements.
Cuzin L et al. 2017[26]	The highest prevalence of comorbidities, and the highest number of concomitant prescriptions, appears in long-term HIV-positive patients.
Guaraldi G et al. 2017[27]	The choice and prescription of ART is influenced by concomitantly prescribed drugs. Potential interactions decrease the use of single-tablet-regimen co-formulations in the older HIV-positive population.
Cantudo-Cuenca MR et al. 2014[35]	Patients with more prescribed drugs have lower adherence to antiretroviral treatment.
Nachega JB et al. 2012[36]	New approaches are needed to improve the measurement and assessment of adherence in older HIV-positive patients with co-morbidities and simultaneous prescriptions for ART.
Littlewood RA et al. 2008[38]	Despite the success of ART, a large percentage of HIV+ patients continue to use alternative medicines (medicinal herbs, vitamin supplements, etc), which significantly interfere with therapeutic success.

TABLE 1 *(cont.).* Main Conclusions of the Original Articles on HIV+ Patients Included in the Review

AUTHORS-YEAR (REFERENCE)	MAIN CONTRIBUTIONS
Barry DT *et al.* 2011[40]	The nonmedical use of opioids in HIV-positive patients in the USA was associated with being Hispanic, aged 40 to 44 years, alcohol use disorders associated with drug use, smoking, co-infection with hepatitis C, and chronic pain.
McNicholl IR *et al.* 2017[51]	PIP was identified in 54% and 63.0% of HIV+ patients more than 50 years of age using the STOPP and Beers criteria, respectively.
Casajús-Navasal A *et al.* 2018[53]	The percentage of HIV-positive patients aged 50 years or more who take anticholinergic drugs was significantly higher on the ACB scale than on the ARS scale.
TREATMENT REGIMEN COMPLEXITY	
Martin S *et al.* 2007[9]	This study presents an antiretroviral regimen complexity index scoring system. This comprehensive system includes aspects such as treatment scheme, administration methods, special instructions, and required preparations.
Metz KR *et al.* 2014[11]	In a cohort of HIV+ patients in real-life treatment, the Patient-level Medication Regimen Complexity Index (pMRCI) score ranged from 2 to 67.5. Antiretroviral treatment contributed around 25% to the pMRCI.
Zhou S *et al.* 2014[25]	This study was the first to discuss and assess pill burden in HIV+ patients. The median number of medications per participant was 8 and the median individual daily pill burden was 8 pills. Duration of ART and having more than 3 comorbidities was associated with high pill burden.
Monje Agudo P *et al.* 2014[30]	A complexity index greater than 5 identifies patients at high risk of ART discontinuation.
Jiménez Galán R *et al.* 2016[31]	Treatment complexity is a key factor in achieving health goals in HIV+ patients receiving treatment for dyslipidaemia. The complexity index was significantly higher in patients who did not reach the target values for hyperlipidaemia.
Calvo-Cidoncha E *et al.* 2015[32]	The addition of antihepatitis C therapy to antiretroviral treatment in HIV+ patients significantly increases treatment complexity and the incidence of blips in HIV viral load. After introducing anti-HCV therapy in HIV+ patients, adherence to ART decreased.

medications (PIMs), the underuse of medication, or therapeutic duplication. Different numerical cutoff points have been used in published studies, although most have defined polypharmacy as the use of 5 concomitantly prescribed drugs[17,18]. However, since the publication of the document on HIV and advanced age by the National AIDS Plan and the Spanish Society of Geriatrics and Gerontology in 2015, which included this definition, a consensus has emerged in Spain that patients are polymedicated if they simultaneously use 6 or more active principles. This definition will be used to correlate and compare future studies[19].

Different studies have already demonstrated the relevance of the problem from a qualitative perspective. Guaraldi *et al.* (2011) were the first authors to show that more than 2 chronic comorbidities were more common in HIV-positive patients older than 50 years than in non-HIV-infected participants of the same age[20]. These data were confirmed by Schouten *et al.* in 2014[21]. Furthermore, a modelling study by Smit *et al.* suggested that 84% of HIV-infected patients would have more than 2 comorbidities by 2030[22]. Marzolini *et al.* published the first study to show that 50 years is the age at which HIV-positive patients need significantly more medication prescriptions, and that 20% of these patients are prescribed more than 4 medications[23]. A cross-sectional analysis of American patients within the HIV Outpatient Study (HOPS) cohort showed that 95% of the patients older than 60 years were polymedicated, which was due to concomitant medication in 73% of these patients[24].

A recently introduced analogous concept is pill burden, which includes the number of medications and the number of pills. Zhou *et al.* were the first authors to discuss pill burden in HIV-positive patients[25]. The results showed that the median number of medications per participant was 8 (interquartile range [IQR]: 6-11). The median individual daily pill burden was 8 pills (IQR: 5–15), which comprised 3 antiretrovirals (ARVs) (IQR: 2-5) and 6 non-ARVs (IQR: 3-12.5). The duration of antiretroviral treatment (ART) (for every 2 years in treatment) and more than 3 comorbidities was significantly associated with high pill burden (more than 10 pills per day). In a similar analysis in a French cohort, Cuzin *et al.* found that 62% of HIV patients older than 50 years had comorbidities and 71% were receiving comedication[26]. In a

Spanish study, Gimeno-Gracia *et al.* investigated the use of concomitant medication in HIV-positive patients compared to the general population. In descending order of frequency, the most commonly prescribed families of medications were angiotensin-converting enzyme inhibitors, antidiabetics, statins, antithrombotic agents, and calcium channel blockers[6]. It has been found that antiretroviral therapy (ART) strategies are also affected by polypharmacy. Guaraldi *et al.* suggested that single-tablet-regimens strategies are less likely to be prescribed in patients with simultaneous prescriptions for concomitant drugs because of the risk of drug-drug interactions, among other factors[27]. The Italian GEPPO cohort study also confirmed that ARV regimens in elderly HIV patients are tailored according to polypharmacy[16].

Recently, attempts have been made to pass from the analysis of the qualitative aspects of polypharmacy, particularly in HIV patients, to its quantitative aspects by analysing numeric data that can subsequently be used to measure healthcare outcomes. This aspect was analysed in the Pharmacy Practice Model Summit 2011 document published by the American Society of Hospital Pharmacy (ASHP), which recommended that the pharmacotherapeutic follow-up of patients should be conducted based on a patient medication complexity index (CI). The CI should include factors such as the severity of the disease, number of medications, and comorbidities[28]. Up to this point in time, Martin *et al.* (2007) had published the only CI, which was designed to assess ARVs[9]. This CI provided a score based on the weighting of 15 variables grouped into four main blocks: dosing schedules, administration methods, special instructions, and required preparations. Since then, the University of Colorado has continued to develop the tool to simplify its calculation and extrapolate it to any other pathology. This project led to the development of the *Patient-level Medication Regimen Complexity Index* (pMRCI) and the *Antiretroviral Medication Regimen Complexity Index* (ARCI)[10,11,29], which include scores ranging from 0.75 to infinity depending on the prescribed medication.

In a HIV-positive cohort, Metz *et al.* found that the pMRCI scores ranged from 2 to 67.5 (ARVs contributed approximately 25% to the total value)[11]. Several authors have analysed the relationship between CIs and different

health outcomes. Monje-Agudo *et al.* found that a CI score of 5 marked the threshold above which patients had a higher risk of ART discontinuation[30]. Jiménez-Galán *et al.* analysed the relationship between medication complexity and adherence with therapeutic objectives in HIV-positive patients with dyslipidaemia. They found that although most patients met the objectives for ART, almost half of them did not meet the therapeutic objectives of dyslipidaemia treatment, especially those with a higher CI[31]. Calvo-Cidoncha *et al.* confirmed that the addition of antihepatitis C therapy to ART in HIV-hepatitis C virus (HCV) co-infected patients led to an increase in medication regimen complexity and the risk of blips, and a decrease in adherence to ART[32].

Clearly, patient treatment adherence is one of the main aspects to consider regarding the repercussions of medication regimen complexity. Adherence has already been investigated in general population studies, whose results are of interest because of their possible relevance to the HIV-positive population[33]. A recent systematic review showed that a lack of adherence was associated with polypharmacy[12]. Although some of these studies suggested that adherence rates tend to be better in older HIV-positive patients than in younger individuals, it has been observed that cognitive deterioration can hinder this objective. In addition, polypharmacy can contribute to regimen fatigue[34]. The study conducted by Cantudo-Cuenca *et al.* in the HIV-positive population showed that the concomitant use of medication decreases adherence to ARVs[35].

Another factor highlighted in the literature is the risk of drug interactions, which can be seen to increase in older HIV-positive patients due to treatments for multiple comorbidities that appear in this population (36-38). Furthermore, it is already known that most ARVs and other commonly used medications share a metabolic pathway at the level of cytochrome P450 and P-glycoprotein[39].

Polypharmacy and its impact on interactions have been described in studies such as that by Holtzman *et al.* in an American cohort of HIV-infected outpatients[24]. Slightly more than 3800 patients were analysed over a 5-year observation period. Of these patients, 7% were prescribed at least 1 contraindicated ARV/non-ARV combination. The main contraindicated non-ARVs were proton pump inhibitors, statins, and benzodiazepines. Another key finding of this study was that almost 30% of HIV patients older than 50 years were using medicinal herbs, vitamins, and other supplements that can interact with ARVs, as shown in other studies[40-44].

In clinical terms, a basic issue has been to identify how the medication combinations used to treat chronic diseases and ART in older HIV-infected adults increases the risk of clinically relevant interactions which can lead to the loss of drug efficacy, virological failure, and toxicity. It has been found that older patients are more susceptible to interactions than younger individuals[19]. Firstly, older patients have more age-related comorbidities. Secondly, age-related physiological changes affect the pharmacokinetic and pharmacodynamic properties of medications. These physiological changes, which are also seen in HIV-positive patients, can be explained by a set of factors that include the patient's genetics, lifestyle, and specific environment. Age-related pharmacokinetic changes are due to changes in the body mass index and in the functioning of organs that eliminate medications. Older age is associated with decreased hepatic volume and hepatic blood flow[19], as well as creatinine clearance, leading to the decreased elimination of medications and thus their accumulation. The glomerular filtration rate decreases by about 1% per year as age increases. Current methods to estimate renal function may lead to it being overestimated in older adults if low muscle mass is not taken into account[45-46]. This problem is further complicated in HIV-infected adults because they typically have less muscle mass than non-HIV-positive adults. Another aspect to consider is that renal function can also be decreased by other pathologies or factors that act as confounders, such as diabetes mellitus, hypertension, low CD4 cell count, race, and the use of ARVs[47-48]. Thus, the estimation of renal function is more difficult in HIV-infected older adults, and affects the dosage and prescription of drugs excreted by the kidneys[19].

Frailty is another key concept of increasing relevance in the management of HIV patients. It is an emerging syndrome which has been shown to be a good predictor of worse health status and adverse events in the general population[13,14]. Frailty embodies a biological syndrome of diminished functional reserves, altered homeostatic capacity, and reduced resistance to external stressors. It is the result of an accumulation of deficiencies in physiological systems and increases vulnerability to various adverse outcomes, including falls, delirium, hospitalization, disability, and death[15]. It is known that HIV-positive patients experience immune changes similar to those caused by aging in the uninfected elderly population. These changes occur as a result of a baseline state of immune activation and persistent inflammation that gradually lead to the premature aging of the immune system known as immunosenescence[48]. Chronic activation of the immune system is marked by persistent viral replication in reservoirs, coinfections with other viruses, and particularly by bacterial translocation due to persistent alteration of the intestinal barrier[48].

These aspects have led to the new concept of "potentially inappropriate medications" (PIMs)[49]. Their use involves the risk of patients experiencing adverse events which outweigh the clinical benefits of the PIMs, particularly in settings in which there are safer and more effective therapeutic alternatives. PIMs also include medications that are used more frequently or for a longer duration than indicated, the use of medications with a high risk of drug-drug interactions, the duplication of medications of the same class, the incorrect selection of the drug or dose, and the non-use or underuse of beneficial medications that are clinically indicated.

In the last decade, there has been growing interest in developing criteria to define the appropriateness of pharmacological treatment in the elderly. Different groups of criteria have been developed for the detection of PIMs in elderly patients, such as the Beers criteria and the Screening Tool of Older Person's Prescriptions/Screening Tool to Alert doctors to Right Treatment (STOPP/START) criteria[50]. The application of these criteria to improve the use of medicines and avoid the use of PIMs in the HIV-positive population has been investigated and validated in several studies. McNicholl *et al.* recently identified potentially inadequate prescribing (PIP) in 54% and 63% of HIV-positive patients older than 50 years, using the STOPP and Beers criteria, respectively[51]. Although the study by Greene *et al.*[52] used a smaller sample than the previous study, it provided the first hints of aspects such as PIMs. PIMs were assessed by applying the Beers criteria, which includes a guide list of medication and classes of medications that should be avoided in patients older than 65 years. Likewise, so-called anticholinergic risk was assessed using the validated anticholinergic risk scale (ARS) scale. This instrument is scored on a scale ranging from 0 to 3, where 3 indicates high risk and 0 indicates no risk. The highest scores predicted a high risk of falls and mental disorders in the elderly population. The study found that 52% of patients were receiving PIMs and 17% had an anticholinergic risk score of 3. In real-world clinical practice, Casajús-Navasal *et al.* used the anticholinergic burden (ACB) scale and ARS scale to measure anticholinergic risk in a cohort of Spanish patients older than 50 years old. In total, 43.3% and 36.4% of patients had high anticholinergic risk on the ACB and ARS scales, respectively[53].

Deprescribing is a concept that is well known in the setting of the HIV-negative elderly population[54-57]. Scott *et al.*[58] defined it as the systematic process of identifying and discontinuing medications in cases in which current or potential harm outweighs current or potential benefit within the setting of individualized healthcare that takes into account the patient's current level of functioning, life expectancy, values, and preferences. This process of drug withdrawal has the potential benefit of reducing the harmful effects associated with polypharmacy, while ensuring the ability of the patient to continue receiving the most appropriate therapy[59]. Studies have identified several barriers to reducing the number of medications and to facilitating deprescribing[60,61]. Currently, there is a wealth of information on when to start a therapy, including in the HIV-positive patient, but there is very little on how and when to stop it. Despite a lack of evidence in support of therapy being continued, the literature typically describes the continuation of the prescribed treatments[60,61].

These new approaches to the management of medication derive from the concept of optimization of pharmacotherapy and the inclusion and application of these new concepts. This has led to a consensus on the need to review all prescribed medications at least every 6 months in elderly HIV-positive patients who have been prescribed 4 or more medications, and at least once a year in the remaining patients[19]. An emerging priority is to identify and establish strategies to reduce medication regimen complexity and avoid polypharmacy in elderly HIV-positive patients to the greatest ex-

tent possible. It is recommended that the review of prescribed medications should be conducted in a systematic manner using a sequential and structured methodology. Tables 2 and 3 show recommendations extracted from the literature on optimizing prescription strategies and introducing a review of polypharmacy in daily clinical practice.

Discussion

The management of HIV-positive patients, especially elderly ones, is of growing concern, as shown by the increasing number of articles addressing this problem in recent years. However, we need to deepen our understanding of the new concepts and to confirm the results based on them, given that the definitions used, particularly those of polypharmacy and medication regimen complexity, and the comparative analysis methodology applied have not yet been standardised. Additionally, these new concepts, which have been identified as challenges by the professionals that serve this population, require a refocusing on care management in all professional settings. A priority issue is to avoid an exclusive focus on the treatment of the infection and the management of ARVs (adherence, interactions, and adverse effects). The literature analysed shows an increasing number of emerging problems associated with aging, such as the management of comorbidities and functional and cognitive impairment. Furthermore, the physiological changes associated with aging must be taken into account in order to optimize pharmacotherapy and the clinical monitoring of these types of patients. According to the literature, such changes are not linear or consistent. Therefore, a global approach is needed that can identify elderly HIV-positive individuals, who are at risk of aging with a worse state of health or, equivalently, who are at risk of having a worse quality of life. The first available data on the application of these concepts in the older non-HIV population confirm a high rate of PIPs and elevated severe anticholinergic risk.

No study has addressed deprescribing in this population, but given the results published by various authors, a strategy is needed to implement this strategy and to measure its usefulness.

The main limitations found in the analysis were the use of different populations, age thresholds, and study methodologies. Similarly, the different definitions used and their lack of standardization make it difficult to compare different studies that have addressed similar concepts, especially polypharmacy and medication regimen complexity.

Future studies will confirm how the approach proposed by some authors will lead to a new vision of these patients and their management. Evidence is already urgently needed that would demonstrate that this new way of understanding the pathology leads to improvements in the health setting and in the patients themselves, given that such evidence is not currently available.

In conclusion, there is a growing interest in deepening our understanding of the relationship between HIV infection and aging. Medication regimen complexity is beginning to be used as a criterion for pharmacotherapeutic follow-up because of its influence on health outcomes. New concepts have to be incorporated and applied that will improve pharmacotherapeutic optimization in this population.

Conflict of interests

No conflict of interests

Table 2. Ten Key Recommendations to Improve Pharmacological Prescription in HIV+ Patients

10 Key Recommendations
1. Review the medication periodically. Discuss and agree on changes with patients. Inform patients of the pharmacotherapeutic treatment aims.
2. Suspend all non-indicated medications.
3. Prescribe medication only if there is a clear indication.
4. Avoid potentially dangerous drugs in older patients.
5. Review and adjust the recommended doses according to liver and kidney function.
6. Simplify the treatment regimen and reduce treatment complexity.
7. Avoid or eliminate unnecessary pharmacological treatments.
8. As far as possible, limit the number of prescribers.
9. Identify, prevent, and manage adverse reactions.
10. Avoid prescription cascades.

Table 3. Recommendations on Introducing Medication Review in Daily Clinical Practice

Recommendations
1. Prioritize and establish medication review in selected patients with several clinical problems, polypharmacy, or high treatment complexity.
2. Implement a program and strategy of continuous and complete medication review for all patients, with greater focus on patients with greater complexity.
3. Include institutionalized patients.
4. Start the treatment process review in multidisciplinary meetings.
5. Define and agree on functions within the healthcare team in order to conduct a complete treatment review with permanent communication.
6. Periodically repeat the polypharmacy and treatment regimen complexity review according to the characteristics of each type of patient.
7. Apply, know, and, when appropriate, share the criteria for de-prescribing based on the Beers or STOP-START recommendations, anticholinergic risk, and potentially inappropriate medication.

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