

# The management of polypharmacy in people living with HIV

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## Abstract

*Antiretroviral therapy (ART) has modified the prognosis of HIV which has evolved into a chronic condition. People living with HIV (PLWH) are living longer presenting an increased number of comorbidities leading to polypharmacy. Literature on the prevalence, associated factors, drug-drug interactions (DDIs), effects on ART-outcomes, geriatric conditions, and nutritional status together with health-interventions aimed to reduce it is presented in this review. A literature search was conducted on the MEDLINE database for all relevant English- and Spanish-language studies since 2006. Studies providing data of interest were identified and ordered in groups: (i) prevalence and associated factors (n = 37), (ii) DDIs (n = 19), (iii) Effects on ART-outcomes (n = 12), (iv) Effects on health conditions (n = 13), and (V) Health-interventions to assess and/or reduce it (n = 9). Polypharmacy occurs in 9-91% of PLWH (2.6-19.5% affected by severe polypharmacy). Main factors associated with polypharmacy are older age, a higher number of comorbidities, frailty, deteriorated renal function, and previous hospitalizations. DDIs were present in 19.15-84% of cases (1.3-12.2% for the most severe types). Mainly involved non-ART drugs were antihypertensives, statins, antithrombotic agents, corticosteroids, divalent cations, and antiacids. Polypharmacy can affect ART selection, adherence, and outcomes and has been related to some geriatric conditions such as falls, frailty, and poor nutritional status. Potentially prescribing issues are present in up to 87.9% of cases according to the STOPP-START and Beers criteria and some pharmacist-led interventions have been shown to reduce it. Considering these findings, polypharmacy should be considered a clinical concern in this population and treatment-optimization programs are needed to reduce its burden.*

## Keywords

*Antiretroviral agents. HIV. Polypharmacy. Drug interactions. Aging. Treatment outcome. Treatment adherence and compliance. Malnutrition. Sarcopenia.*

## Introduction

Antiretroviral therapy (ART) has modified the prognosis of HIV during the last decades chronicizing the

disease<sup>1</sup>. People living with HIV (PLWH) are living longer presenting an increased risk of developing comorbidities as well as needing to take multiple medications<sup>2</sup>. One of the main challenges of HIV health providers is to improve the quality of life of

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PLWH by achieving the best health outcomes. In this context, newer, more active and less toxic HIV drug classes of antiretrovirals have improved the efficacy and tolerability of ART being of high value those which improve tolerability and simplify treatment regimens<sup>3</sup>. Moreover, ART simplification strategies aimed to improve adherence and facilitate regimen compliance and tolerability have emerged during the last decades such as dual ART (those based on the treatment with two antiretroviral agents as an initial or maintenance treatment), less-pill regimens, or the recent emergence of novel long-acting antiretrovirals<sup>4</sup>. The chronification of ART linked to a best life expectancy, along with the need for rigorous adherence, the long-term toxicities of ART, the complexity of some regimens, and their impact on health-care costs, make necessary the simplification of treatment regimens<sup>5</sup>.

Besides ART complexity, the use of multiple non-ART medications can be a common concern among older PLWH due to impaired patients' health and the risk of worsening adherence. Polypharmacy, commonly defined as the use of five or more multiple medications has been related to multiple adverse clinical outcomes among older people. In the case of PLWH, polypharmacy and its negative effects could appear earlier due to the risk of decreased adherence to ART, the risk for drug-drug interactions (DDIs) between ART and non-ART medications and increased susceptibility to medication adverse effects in this population<sup>6,7</sup>.

In this context, literature aimed to elucidate the main characteristics of polypharmacy in elder PLWH as well as its association with common geriatric syndromes such as frailty, falls, cognitive impairment, malnutrition, or frailty is of interest to HIV health providers. Furthermore, literature on health interventions aimed to prevent or avoid polypharmacy and its complications in this population is emerging and there is a need for studies collecting all this evidence. We hypothesize that the prevalence of polypharmacy in PLWH is high, that this condition is associated with some demographic, socioeconomic, and health factors, can compromise. ART-selection and ART-outcomes, along with the risk for a higher number of relevant DDIs, are associated with some geriatric syndromes, can play a role on impaired nutritional status and frailty and can be reduced by some health-interventions aimed to detect and reduce it. The present work is therefore aimed to assess and present available literature related to four main aspects: the prevalence and the factors associated

with polypharmacy in PLWH, the prevalence and characteristics of DDIs in populations of PLWH suffering higher prevalences of polypharmacy, the effects of polypharmacy on ART-selection,-outcomes, ageing health conditions such as cognitive and nutritional worsening, and the health-interventions that may have a role by detecting and reducing the burden of polypharmacy and/or its consequences in PLWH.

## Methods

We conducted a review of the literature on this topic. A literature search was conducted on MEDLINE using PubMed for all relevant English- and Spanish-language studies since 2006 and up to January 31, 2022. 2006 was determined as the onset date to present currently relevant literature since this is considered the beginning date of the modern ART era<sup>8</sup>. The following combination of MeSH and search terms were used in the articles search: ("ART, Highly Active" [Mesh] OR "HIV Infections" [Mesh] OR "HIV" [Mesh] OR "Anti-Retroviral Agents" [Mesh] OR "HIV Long-Term Survivors" [Mesh] OR HIV [tiab] OR "antiretroviral therap\*" [tiab] OR ART[tiab]) AND ("Polypharmacy" [Mesh] OR "Drug Interactions/prevention and control" [Mesh] OR "Drug Interactions/therapy" [Mesh] OR "Inappropriate Prescribing" [Mesh] OR "Deprescriptions" [Mesh] OR "Medication Reconciliation" [Mesh] OR "Potentially Inappropriate Medication List" [Mesh] OR polypharm\* [tiab] OR "many drug\*" [tiab] OR "many medic\*" [tiab] OR "multiple medic\*" [tiab] OR deprescript\* [tiab]). A subsequent reference check was done to find additional eligible studies. Original peer-reviewed articles reporting randomized and observational studies were included in the study. Abstracts, posters, protocols, book chapters, and literature published as a preprint were not included in the study. Those studies providing relevant data for more than one covered point for this review were prioritized to reach a final set of studies. Identified studies were ordered in four groups: (i) studies on the prevalence and factors associated with polypharmacy, (ii) studies on the prevalence and characteristics of DDIs, (iii) studies on the effects of polypharmacy on ART-selection, outcomes and ageing health conditions, nutritional status and frailty, and (iv) studies that assessed health-interventions aimed to assess and reduce polypharmacy and its consequences. Studies were presented in narrative form and tables were used to sum information on polypharmacy prevalence and associated factors (Table S1), and DDIs (Table S2).

## Results

We found 37 studies reporting information on prevalence and factors associated with polypharmacy, 19 on DDIs, 12 on effects on ART outcomes, 13 on ageing-health-conditions, nutritional status and frailty, and 9 on health interventions aimed to assess and/or reduce it.

### **Prevalence and factors associated with polypharmacy in PLWH**

The prevalence of polypharmacy in PLWH has been assessed in multiple observational studies mostly reporting data from outpatient cohorts<sup>9-44</sup>. These studies were performed in Canada<sup>9</sup>, the United States<sup>10,12,14,18,25,35,44</sup>, the United Kingdom<sup>11,19,41</sup>, Italy<sup>13,24</sup>, Spain<sup>16,21,22,26,28,30,32,42,43,46</sup>, Switzerland<sup>17</sup>, Germany<sup>20,38</sup>, Belgium<sup>23</sup>, Australia<sup>27</sup>, Switzerland<sup>29,40</sup>, Thailand<sup>31</sup>, Japan<sup>33</sup>, Brazil<sup>34</sup>, Uganda<sup>36</sup>, China<sup>37</sup>, and France<sup>39</sup>. Moreover, one multinational study reported data from 24 countries<sup>15</sup>. Most of these studies defined polypharmacy as the presence of  $\geq 5$  concomitant drugs (slight definitions changes through studies:  $\geq 4-5$  non-ART, pills per day, health conditions treated or non-ART/non-antitubercular drugs) and some of them also assessed the prevalence of severe polypharmacy ( $\geq 10$  non-ART drugs). Moreover, some studies assessed the prevalence of polypharmacy in different age groups, compared it between PLWH and non-PLWH or assessed its evolution considering long follow-up periods or in those patients who were diagnosed earlier or who have been treated longer. Table S1 presents the prevalence of polypharmacy reported in the studies found through literature search together with the main studies' information and characteristics.

Polypharmacy was identified in the 9-91% of cases (defined as taking  $\geq 5$  non-ART medications)<sup>9-14,16-23,25,27-29,31,33,35,40,41,44</sup>, in the 23.3-96% (defined as taking  $\geq 5$  medications including ART)<sup>30,32,34,43,44</sup>, and in the 42.1% (defined as taking  $\geq 5$  pills per day or taking medicines for  $\geq 5$  health conditions)<sup>15</sup>. Severe polypharmacy was identified in 7.9-19.5% of cases (taking  $\geq 10$  non-ART medications)<sup>17,19,22</sup> in the 2.6% of patients (taking  $\geq 10$  non-ART/non-antitubercular medications)<sup>24</sup> and in the 30% of cases (when defined as taking  $\geq 10$  medications)<sup>32</sup>. The mean number of concurred medications per patient in the cohorts reported in these studies ranged from 2.7 to 7.0<sup>14-16,19,20,23,24,27,30,32</sup> and from 1 to 8 in those studies that reported median values<sup>10,11,14,17,18,25,29,33,44</sup>. Mean age of included cohorts ranged from 46.0 to 72.1 years<sup>13,14,16,19,20,23,24,27,28,30</sup>, and from 31 to 78 years when reported as median values<sup>10,11,17,18,21,29,31-33,40</sup>.

Some studies reported the percentage of patients affected by polypharmacy comparing populations of PLWH and non-PLWH. For instance, the prospective study performed by Ware et al. (2018) in the United States reported a higher prevalence of patients with polypharmacy in PLWH when compared to non-PLWH after adjusting for age, race/ethnicity, medication insurance and enrollment period (25.3% vs. 18.7%,  $p < 0.0001$ )<sup>18</sup>. Moreover, the cross-sectional study performed by Guaraldi et al. in Italy in 1573 geriatric patients of whom 1258 were PLWH also found multimorbidity and polypharmacy more prevalent in geriatric PLWH (37% vs. 24% in PLWH and non-PLWH, respectively)<sup>13</sup>. The retrospective study performed by Calcagno et al. in Italy in 2432 patients (1158 PLWH) found a higher prevalence of polypharmacy and a major number of concomitant medications for those non-HIV infected (21.8% vs. 26.1%,  $p = 0.015$  and 2.6 vs. 3.1,  $p < 0.001$ ; in PLWH and non-PLWH, respectively). However, multivariate binary logistic analysis found HIV-positive serostatus as an independent predictor for polypharmacy<sup>24</sup>.

Multiple studies found higher prevalences of polypharmacy in older age groups<sup>9,11-13,15,18,20,22-25,29,36</sup>. Moreover, some studies reported data comparing non-ART burden between different elder age groups of PLWH and non-PLWH. For instance, in one study that reported data on the mean non-ART medications in different elder age groups of PLWH and non-PLWH, a higher mean of non-ART medications for those PLWH who were older was observed (3.58 vs. 3.88 in those patients with 65-69 years and 70-74 years, respectively) and that these mean values were comparable between the older groups of non-PLWH and younger groups of PLWH (3.58 vs. 3.62, 65-69 years PLWH and 70-74 years non-PLWH, respectively, and 3.88 vs. 3.83 70-74 years PLWH and 80-84 years non-PLWH)<sup>14</sup>. The high prevalence of polypharmacy among the PLWH cohorts could be explained by the presence of a greater number of comorbidities and the increasing prevalence of some of them during recent decades such as those of cardiovascular origin. Among assessed studies, we found hypertension, diabetes mellitus, dyslipidemia, or coronary arterial disease as some of the major chronic clinical concerns in this population<sup>12,14-17,20,25,30-32,45</sup>. In addition, the emergence over time of other chronic clinical conditions such as anxiety and depressive symptoms, chronic kidney disease, chronic obstructive pulmonary diseases, and metabolic bone diseases also comprises a significant increase in the medication load of those patients

ts<sup>10,13,15–17,25,27,28,30,32,45</sup>. Then, some of the most common taken non-ART medications found in the cohorts assessed by these studies were anti-hypertensive and lipid-lowering agents, oral glucose-lowering agents, antithrombotic agents, anti-infective agents, and central nervous system agents such as antidepressants and proton pump inhibitors<sup>11,13,14,16,17,18–21,25,27,29,31,33,45</sup>.

In addition, some studies with long follow-up periods have made it possible to evaluate the evolution of polypharmacy in PLWH over time. The study performed by Moore et al. found a higher increase in polypharmacy (defined as taking  $\geq 5$  non-ART medications) in PLWH compared with non-PLWH through the study period (5-year period, 16–35% in PLWH vs. 24–32% in non-PLWH)<sup>12</sup> although other studies such as the prospective study performed by Ware et al. (2018) did not find a higher increase on the prevalence of polypharmacy in those PLWH through the 12-year study period and analyzing different age groups<sup>18</sup>. Moreover, in the cross-sectional study performed by Okoli et al. published in 2020 including 2112 PLWH taking ART in 24 countries significantly higher prevalences of polypharmacy were found for those patients with an earlier HIV diagnosis year (50.3% before 2010, 38.9% between 2010 and 2016, and 33.5% between 2017 and 2019,  $p < 0.001$ )<sup>15</sup> and, in the retrospective study performed by Livio et al. including 175 PLWH  $\geq 75$  years in Switzerland patients with a longer HIV-infection duration tended to be taken a higher median number of non-ART drugs (4 < 10 years, 5 between 10 and 20 years and 7 more than 20 years)<sup>17</sup>. Furthermore, the cross-sectional study performed by Lopes et al. in Germany in 2680 PLWH found that those groups of patients with longer ART duration had higher prevalences of polypharmacy ( $\leq 1$  year: 35.8%, 1–5 years: 43.1%, and  $\geq 5$  years: 48.9%)<sup>20</sup>.

From a gender perspective, some studies found comparable percentages of polypharmacy between male and female PLWH. The prospective study performed by Justice et al. in the United States found male PLWH as likely as female PLWH to have polypharmacy (34.1% and 35.7%, male and female, respectively) and a higher percentage of polypharmacy between included male non-PLWH when it was compared with female non-PLWH (39.4% and 35.5%, male and female, respectively)<sup>25</sup>. Some studies found higher percentages of polypharmacy in male patients such as the observational study performed by Krentz HB and Gill MJ in Canada (34.1% and 26.1% in men and women, respectively)<sup>9</sup>. Other studies such as the retrospective study

performed by Livio et al. in Switzerland in 175 PLWH  $\geq 75$  years found a higher risk of polypharmacy in female patients (63.2% vs. 72.0% in men and women, respectively)<sup>17</sup>. In addition, the retrospective study performed by Calcagno et al. in Italy found female gender as an independent predictor for polypharmacy in PLWH<sup>24</sup>.

Considering the high prevalence of polypharmacy in this population, some studies have been designed to investigate whether some demographic, socio-economic, and/or clinical factors could be independently associated with polypharmacy among PLWH and if these factors differed from the non-HIV population. We found eight studies that reported factors independently associated with polypharmacy among PLWH. Through the different studies explored, older age was the factor most commonly related to polypharmacy<sup>12,13,18,24,35</sup>. Other factors closely related to age such as frailty<sup>36</sup>, the number of comorbidities<sup>46</sup>, an estimated glomerular filtration rate  $< 60$  mL/min per  $1.73\text{m}^2$ <sup>27</sup>, or having been hospitalized one or more times in the previous year<sup>36</sup> have also been associated with polypharmacy in PLWH. Regarding concomitant drugs, use for conditions different to HIV, cardiovascular, antiulcer, or antipsychotic drugs use has been associated with polypharmacy in PLWH<sup>44</sup>. For instance, multiple drugs are often required to treat mental health conditions leading to drug adverse effects which contribute to prescription cascade. Similarly, antiulcer drugs have been also associated with polypharmacy, as one of the reasons for prescribing them is high medication burden presence.

In the case of the presence of medication insurance coverage among PLWH, a multicenter study performed in the United States aimed to investigate the prevalence and trends of polypharmacy among 3160 patients of the Multicenter AIDS Cohort Study over 12 years period showed that having medication insurance coverage was an independent risk factor for polypharmacy after adjusting for confounders, among others<sup>18</sup>. Moreover, a subsequent study assessing the same cohort of patients grouped according to observed patterns of polypharmacy over time, non-polypharmacy, slow increasing polypharmacy, rapidly increasing polypharmacy, and sustained polypharmacy found that being HIV positive, being  $\geq 50$  years, presence of medication insurance coverage, having a college degree or higher and having increased health care use were positively associated with being in groups with sustained or increasing polypharmacy<sup>35</sup>. Furthermore, other conditions such as being enrolled in a clinical trial (especially in the earlier enrollment period)<sup>18,35</sup>, HIV infection duration<sup>13</sup>, having an internist's

prescription<sup>36</sup>, and managing HIV in a general practice or by a hospital-based clinic<sup>27</sup> have been associated with polypharmacy in PLWH. Factors associated with polypharmacy reported in these studies together with adjusted association measures are presented in Table S1.

## **DDIs and polypharmacy in PLWH**

### **DDIs**

Due to the presence of ART, PLWH could be at a greater risk for harm from polypharmacy than uninfected individuals. For instance, a major increase in the number of DDIs for each additional non-ART medication has been observed when comparing PLWH and HIV-uninfected individuals<sup>6</sup>. Then, the study of DDIs is of special interest to this population. Both pharmacokinetic and pharmacodynamic DDIs have been described between ART and non-ART medication and this fact has been analyzed in multiple cohorts of PLWH. We found a total of 19 studies reporting quantitative data on the presence of DDIs (at least one DDI between ART and non-ART medications or categorized according to severity) in PLWH in which the presence of polypharmacy was also assessed.<sup>11,16,22,23,26,30,33,34,37-44,45,47,48</sup>. These studies assessed DDIs using different databases. The Liverpool Drug Database was the most used in these studies and only 3 out of 19 studies used other databases such as the Lexicomp or DRUGS.COM databases<sup>33,42,44</sup>. Seven out of 16 studies that used The Liverpool Drug Database reported the severity of DDIs by Flags (red, amber, yellow, and green flags)<sup>16,22,23,37,39,40,48</sup>, and the other nine studies reported DDIs severity by grades (contraindication, potential, weak, and no interaction)<sup>11,26,30,34,38,41,43,45,47</sup>. In addition, four studies reported information on DDIs mechanisms according to whether they were pharmacokinetic or pharmacodynamic<sup>26,30,43,47</sup>.

Among the populations assessed in these studies, variable percentages of patients in polypharmacy were found (between 14% and 59.6%, and up to 93% if defined as taking  $\geq 5$  drugs)<sup>16,22,23,33,34,37,39-41,43</sup>. The percentage of patients in whom at least one DDI between ART and non-ART medications was identified in some studies and ranged from 19.15% to 84%<sup>11,16,22,23,26,30,33,34,37-43,45,47</sup>. The median number of DDIs between ART and non-ART was also variable and ranged from 0 to 15<sup>41,44,47</sup>. However, when grading DDIs by severity, the majority of studies reported low rates of the most severe types of DDIs (red flags and contraindicated DDIs). In the case

of those studies that reported DDIs severity using the flags classification provided by the Liverpool Drug Database, the most frequent type of DDI severity reported was the amber flag (56.9-94% of total amber, yellow, and red DDIs)<sup>22,23,37,39,40</sup> that were present in the 18.27-62%<sup>22,23,40</sup> of patients. By contrast, the most severe DDIs (red-flag DDIs) were less commonly reported through studies (1.8-31.9%) of total amber, yellow, and red DDIs<sup>16,22,23,37,39,40</sup> and have been reported in the 2-7.1% of the patients affected by DDIs<sup>16,22,23,39,40</sup>. In the case of those studies which classified DDIs by grades similar data were reported. The most frequently reported DDI was the potential DDI (88.2-97.3% of total described DDIs)<sup>26,30,34,41</sup> that were found in the 33.0-93.1% of patients<sup>11,26,38,47</sup>. By contrast, DDIs that supposed contraindications to drug combinations were less commonly reported (2-11.8% of total described DDIs)<sup>26,30,34,41,45</sup> and were detected only in the 1.3-12.2% of patients<sup>11,26,38</sup> those studies that considered the DDIs mechanism, pharmacokinetic DDIs were more commonly reported than pharmacodynamic ones<sup>26,30,43,47</sup>.

From a qualitative perspective, although these DDIs have been specially reported for some therapeutic drug classes, there were described important differences across found studies. The non-ART therapeutic classes that have been most commonly reported as a cause of DDIs in those studies that included PLWH on polypharmacy were: cardiovascular system drugs such as calcium antagonists or lipid-lowering agents, central nervous system drugs such as benzodiazepines and antidepressants, proton-pump inhibitors, corticosteroids, divalent cations, antidiabetics, bronchodilators, and dietary supplements<sup>23,30,37,45</sup>. The case of the lipid-lowering agents statins is of special interest since it is frequently prescribed medication in the elderly. Statins such as rosuvastatin, pravastatin, or atorvastatin cause DDIs through cytochrome 3A4 with some antiretrovirals such as protease inhibitors<sup>11,26,34,39-41</sup>, being a cause of DDIs in up to 22.7% of cases<sup>26</sup>, and supposing up to 24% of the most severe DDIs<sup>42</sup>. Another type of DDI highly described in the literature is the DDI between integrase strand transfer inhibitors and divalent cations that affected the 6.4-22.7% of reviewed studies' population<sup>26,30,40</sup>. Central nervous system drugs are also described in some studies as a cause of around 20% of described DDIs<sup>30</sup>. Of them, benzodiazepines (described as the cause of 15.7-25.8% of total DDIs), antidepressants (up to 22% of total amber-flag DDIs), and quetiapine (up to 22% of total red-flag DDIs) have been described as major causes of DDIs<sup>22</sup>.

The experience reported by some observational studies is helpful to understand the complexity of DDIs

in this population. For instance, the cross-sectional study performed by Zheng et al. in 2022 in China in a sample of 185 PLWH found that the antihypertensives were the concomitant medications more commonly present in potential DDIs with ART. Moreover, this study found that ART regimens containing efavirenz were present in 71% of detected DDIs<sup>37</sup>. The study performed by Chen et al. in China found the DDIs between antiretrovirals and calcium antagonists the most common, and the most potential DDIs involving regimens containing lopinavir plus ritonavir<sup>45</sup>. In the case of the cross-sectional study performed by Kunimoto et al. in Japan in 2021 in 71 PLWH, investigators found calcium, magnesium, and iron agents involved in 90.9% of cases of non-ART involved in potential DDIs and the integrase strand transfer inhibitors as the antiretrovirals more commonly involved in potential DDIs<sup>33</sup>. By contrast, the retrospective study performed by El Moussaoui et al. in Belgium in 2020 found the protease inhibitors as the antiretrovirals most commonly involved both in the case of orange- and red-flag interactions and in the two reported study periods followed by the non-nucleoside reverse transcriptase inhibitors<sup>23</sup>. The study performed by Loste et al. in Spain showed cobicistat as the drug most commonly involved in potential DDIs (42.2% of cases), followed by dolutegravir (9.9% of cases) and that most commonly involved non-ART medications were metformin and mineral supplements<sup>16</sup>. In the case of the cross-sectional study performed by Ruellan et al. in 239 PLWH in France, authors found ritonavir and cobicistat as the drugs most commonly involved in DDIs, followed by non-nucleoside reverse transcriptase inhibitors (34.7% and 27.8%, respectively) and lipid-modifying agents, antithrombotic agents and calcium channel blockers as the non-ART medications involved in a major number of DDIs (18%, 13.9%, and 8.3%, respectively)<sup>39</sup>. In the study performed in Spain by Gimeno-Gracia et al. in 74 PLWH, the non-nucleoside reverse transcriptase inhibitors and the protease inhibitors were involved in most cases of DDIs (40.7% and 29.6%, respectively), and the lipid modifying drugs statins, the oral antidiabetics, the urological agents and the mineral supplements in the case of non-ART drugs (22.7%, 9.1%, 7.3%, and 6.4%, respectively)<sup>26</sup>. In the case of the population-based cross-sectional study performed by López-Centeno et al. in Spain, authors found corticosteroids such as budesonide, mometasone, fluticasone, and triamcinolone, the antipsychotic drug quetiapine, the antithrombotic agents clopidogrel and ticagrelor, imidazole and triazole antifungals,

domperidone, and simvastatin as the non-ART medications and boosted darunavir as the antiretroviral most commonly involved in red-flag DDIs<sup>22</sup>. Another study that presented relevant data on this field was the observational study performed by Deutschmann et al. in Switzerland. This study that included 9298 PLWH showed that the use of unboosted integrase strand transfer inhibitors reduced the prevalence of potential DDIs in patients of the Swiss HIV Cohort Study compared to 10 years before despite an increase in the non-ART medications use in this cohort over these years (combined amber and yellow-flag DDI prevalence was 43%, 59 in the previous period, with a 24% reduction of boosted antiretrovirals, and 13% reduction of non-nucleoside reverse transcriptase inhibitors). Moreover, this study showed the combination of boosted antiretrovirals and corticosteroids or quetiapine as the main cause of red-flag DDIs followed by the combination of atazanavir or rilpivirine and proton pump inhibitors<sup>40</sup>. A summary of studies reporting data on the prevalence of DDIs between ART and non-ART medication in PLWH and polypharmacy data on these studies is presented in Table S2.

### ***Effects of polypharmacy on treatment selection, health outcomes, and geriatric conditions***

#### **Effect of polypharmacy on treatment selection**

Taking multiple concomitant medications increases treatment complexities such as the risk for drug adverse effects or relevant DDIs leading to prefer ART regimens that allow pill burden, prescribing cascade, and toxicities minimization.

In this context, the cross-sectional analysis performed by Guaraldi et al. in 2944 PLWH treated with ART using electronic data from the prospective Modena HIV Metabolic Clinic Cohort Study found that single-tablet regimens (464 out of 2944 patients treated with efavirenz plus emtricitabine plus tenofovir, rilpivirine plus emtricitabine plus tenofovir, or elvitegravir plus cobicistat plus tenofovir) were less likely to be prescribed in cases of patients with polypharmacy (negative association with a relative risk reduction of 0.48, 95% confidence interval [CI]: 0.28-0.81). Authors discussed that these findings could be explained by minor flexibility of these regimens in case of multimorbidity (e.g., the risk of bone, renal or cardiovascular adverse effects) or potential DDIs. By contrast, fewer drug

regimens were associated with older age, longer HIV duration and the moment when ART was initiated suggesting greater flexibility in cases of multimorbidity or polypharmacy<sup>49</sup>. These findings differ from those found later in a multicenter study performed in Spain by Gimeno-Gracia et al. In this study, investigators performed a cross-sectional study aimed to assess the prevalence of polypharmacy in 74 PLWH treated with ART aged  $\geq 65$  years. This study showed a 71.6% prevalence of polypharmacy (defined as the prescription of at least 6 active ingredients and including antiretrovirals), 81.1% of patients treated with triple ART, and 48.6% of patients receiving a single tablet regimen (being the most common combination abacavir plus lamivudine plus dolutegravir). Of note, this study showed a population with an elevated prevalence of polypharmacy in which a high percentage of patients were treated with a single tablet regimen when compared with previous ones. These results could be explained by differences in the available ART pill combinations between different contexts<sup>26</sup>.

From the patient perspective, the cross-sectional study performed by Okoli et al. in 24 countries assessed the relation between polypharmacy (defined as taking  $\geq 5$  pills per day or being treated with medicines for  $\geq 5$  health conditions) and self-rated overall health and perceptions of treatment necessities in 2112 PLWH treated with ART using data from the 2019 Positive Perspectives survey. This study assessed two different proxies of polypharmacy, one related to patients' overmedication perception and a behavioral proxy based on patients' intention to reduce medication. This study showed a 42.1% prevalence of polypharmacy, 45.7% of patients perceiving overmedication, and 43.7% responded positively to behavioral proxy on medication cut-down attempts. Moreover, worse measures for overall well-being were detected among patients receiving polypharmacy such as minor treatment satisfaction (69.7% vs. 75.0%,  $p = 0.007$ ). Treatment priorities were compared between ART initiation time and the moment when the survey was performed among participants who were  $\geq 2$  years after HIV diagnosis ( $n = 1624$ ). After adjusting for confounders, PLWH reporting polypharmacy had significant and independent higher odds of having new concerns for risk of DDIs (adjusted odds ratio [OR] 1.32, 95% CI: 1.02-1.71), and drug side effects (adjusted OR 1.31, 95% CI: 1.02-1.68). In the case of PLWH who perceived themselves as overmedicated, they had significant and independent higher odds of having new concerns for the number of medications in their ART and the need

to keep them at a minimum (adjusted OR = 1.54, 95% CI: 1.22-1.95), the risk of DDIs (adjusted OR = 1.38, 95% CI: 1.08-1.77), the flexibility of dosing (adjusted OR = 1.41, 95% CI: 1.10-1.82), and availability of ART (adjusted OR = 1.39, 95% CI: 1.05-1.85). Moreover, 73.1% of participants reported being ready to switch to an ART containing less medications as long as their viral load was controlled<sup>15</sup>. Polypharmacy has been associated with a higher proportion of treatment discontinuations and switches. For instance, the study performed by Krentz and Gill in 1329 PLWH using the Southern Alberta clinic Cohort, (Calgary, Canada) categorized patients as having continuous ART or those who stopped their ART for  $> 30$  days, or who switched one or more drugs within their regimen. One-third (32.2%) of included patients discontinued or switched their ART during follow-up. Patients on polypharmacy were more likely to stop or change ART than patients without polypharmacy (36.8% vs. 30.0%, respectively,  $p < 0.01$ ). Moreover, the proportion of patients categorized as non-continuous ART increased with the number of daily antiretroviral pills taken from 24.8% for patients on one or two pills a day to 42.1% for patients taking more than two antiretroviral pills daily showing an strong association between polypharmacy and non-continuous ART<sup>9</sup>.

In the case of the cross-sectional study performed by Lopes et al. in 2680 PLWH (mean age 46 years, 7.0 mean non-ART medications prescribed and 10.2 among PLWH  $\geq 50$  years) in Germany aimed to estimate the rate of potential DDIs or/and contraindications for first-line ART, authors found that ART regimens with a lower potential for DDIs were those including unboosted integrase-strand transfer inhibitors, non-tenofovir disoproxil fumarate based regimens including raltegravir plus emtricitabine plus tenofovir alafenamide, followed by three dolutegravir-based regimens (dolutegravir plus lamivudine, dolutegravir plus abacavir plus lamivudine, and dolutegravir plus emtricitabine plus tenofovir alafenamide) and bictegravir plus emtricitabine plus tenofovir alafenamide while the higher potential for DDIs was observed when using boosted- and efavirenz-based regimens<sup>20</sup>.

## Effects of polypharmacy on treatment outcomes

### *Virological control*

Some studies have analyzed the effect of polypharmacy on virological outcomes in PLWH. The study

performed by Khawcharoenporn et al. in Thailand assessed the association between virological suppression (defined as < 20 HIV RNA copies/ml at 12 months after ART beginning) and polypharmacy. The results of this study showed non-significant differences in virological suppression between patients with and without polypharmacy (96% vs. 92%, respectively,  $p = 0.704$ ) although a significantly higher increase in the mean CD4 cell count was observed in the non-polypharmacy group (+ 207 vs. + 403 cells/mm<sup>3</sup>,  $p < 0.001$ )<sup>31</sup>. A recent cross-sectional study performed by Murray et al. examined viral load in 621 PLWH aged  $\geq 50$  years treated with ART. This study showed a higher significant rate of patients receiving  $\leq 15$  medications who had undetectable plasma HIV RNA (defined as < 20 HIV RNA copies/ml) compared with patients receiving > 15 medications (80.6% vs. 67.8%, respectively;  $p = 0.03$ ) and that receiving > 15 medication decreased significantly the odds of having undetectable plasma HIV RNA viral load (OR 0.49, 95% CI: 0.26-0.96,  $p = 0.0322$ )<sup>47</sup>. Through a different methodology, the previously described study performed by Okoli et al. assessed the relation between polypharmacy (defined as taking  $\geq 5$  pills per day or being treated with medicines for  $\geq 5$  health conditions) and self-reported virological control in 2 112 PLWH. This study found significantly worse measures for overall well-being for those patients receiving polypharmacy. Self-reported virologic control was minor among those patients who were on polypharmacy (69.7% vs. 75.0%;  $p = 0.007$ ). Moreover, after adjusting for confounders a significant and independent lower odds for self-reporting virological control was also found (adjusted OR 0.54, 95% CI: 0.42-0.70)<sup>15</sup>.

### *Hospitalization and mortality*

The relationship between hospitalization or mortality and polypharmacy among PLWH has been little studied and only a few studies provide information on this. Justice et al. performed a prospective study that examined the relationship between polypharmacy and hospitalization and mortality in 9473 virologically suppressed PLWH receiving ART and 39 812 uninfected individuals using data from the United States Veterans Health Administration. This study found that, following adjusted analysis, taking > 2 non-ART medications were associated with a 20% and a 49% increased risk of mortality among PLWH and HIV-uninfected individuals, respectively, and that taking  $\geq 5$  non-ART medications concurred a 43% increased risk of mortality in

both groups. After adjusting for demographic factors and severity of illness, hospitalization was independently associated with polypharmacy (> 2 non-ART medications: hazard ratio 1.51, 95% CI: 1.47-1.55;  $\geq 5$  non-ART medications: hazard ratio 1.52, 95% CI: 1.49-1.56) being the risk of hospitalization similar by HIV status. Moreover, a dose-response association between non-ART medication and hospitalization was found (8% increased risk of hospitalization for any additional non-ART medication) both in PLWH and uninfected individuals and between non-ART medication and mortality (5% increased risk of mortality for any additional non-ART medication) among PLWH<sup>25</sup>. A subsequent prospective study performed by Justice et al. examined the association between known pairwise drug interactions (KDPIs) and medication count (including ART and non-ART medication), the effect of KDPIs on the association between non-ART medication count and hospitalization in patients with and without HIV, and the association between non-ART medication count and hospitalization after adjusting for physiological frailty and KDPIs. This study included 9186 suppressed-RNA viral load PLWH receiving ART from the Veterans Aging Cohort Study and 37 930 uninfected individuals receiving at least one non-ART medication. Investigators found a major increase in the number of KDPIs for each additional non-ART medication in PLWH than in HIV-uninfected individuals (2.94 vs. 2.67 additional KDPIs) and an association between non-ART medication count and hospitalization risk that remained significant after adjusting for demographics and physiological frailty in both people with and without HIV (Hazard ratio [HR] 1.07, 95% CI: 1.06-1.08 and HR 1.07, 95% CI: 1.06-1.07, respectively) and also after adjusting for KDPI Index (HR 1.06, 95% CI: 1.05-1.07 and HR 1.04, 95% CI: 1.03-1.05, respectively)<sup>6</sup>. In the case of those patients who attended an urban clinic in Uganda, the study performed by Ssonko et al. mentioned above also assessed the association between polypharmacy and hospitalization. Participants were asked about the number of hospitalizations in the previous year. The results of the multivariate-adjusted analysis showed that the presence of polypharmacy was associated with one or more hospitalization episodes in the previous year (prevalence ratio = 1.8, 95% CI: 1.1-3.1;  $p = 0.02$ )<sup>36</sup>.

### *Adherence to ART*

Polypharmacy can impair adherence to treatments including ART leading to worse clinical outcomes in

PLWH<sup>8</sup>. Some studies have assessed the relationship between polypharmacy and adherence to ART in different settings and using different methodologies.

For instance, Cantudo-Cuenca et al. performed a prospective study aimed to assess the effects of comorbidities and comedications on adherence to ART in 594 treated HIV-infected patients. Patients were assessed at 12-month follow-up after inclusion. Polypharmacy was defined as taking  $\geq 5$  non-ART medications, and correct adherence to ART was considered if dispensing records were  $> 90\%$  and the Morisky Medication Adherence Scale score was 4. This study showed polypharmacy as an independent predictor for non-adherence to ART following multivariate analysis (OR 0.36, 95% CI: 0.21-0.61)<sup>50</sup>. In addition, the recent cross-sectional study performed by Zheng et al. examined the relationship between concomitant medication-related burden and ART adherence in 185 PLWH  $\geq 50$  years. ART adherence was assessed using the self-reported 3-item measure of the Center for Adherence Support Evaluation (CASE) Adherence Index score (considering a score of  $\geq 11$  as good adherence, and a score  $< 10$  as poor adherence), and medication burden using the Chinese version of LMQ-3. This study showed a negative and significant association between adherence to ART and medication-related burden ( $r_s = -0.250$ ,  $p = 0.001$ ) suggesting the need for special attention to concomitant polypharmacy in PLWH<sup>37</sup>. Similarly, the multicentric study performed by Gimeno-Gracia et al. explained above observed adherence to ART of 85.1% when calculated from the dispensation records of the last 6 months (correct adherence to ART was considered if dispensing records were  $> 95\%$ ), and 68.5% when the Simplified Medication Adherence Questionnaire was used. These results reflect low rates of adherence in PLWH treated with multiple drugs and the need for new strategies to optimize polypharmacy management in this population<sup>26</sup>. The prospective study performed by Khawcharoenporn et al. mentioned above also addressed this issue. The study involved 248 PLWH that initiated ART. After inclusion, patients were assessed at 12-month follow-up. Polypharmacy was defined as taking  $\geq 5$  non-ART medications continuously for at least 1 year since ART began, and adherence to ART was measured by scheduled and unannounced pill recount at follow-up visits and the 3-item CASE score, meaning a higher score a better adherence. In contrast with the previous studies, this study showed no significant differences in ART adherence between those patients who received or did not polypharmacy (100% ARV adherence: 12 out of 23 patients on polypharmacy [52%] vs. 129 out of 225

non-polypharmacy patients [57%]; median [IQR] 3-item CASE score: 16 [15-16] vs. 16 [15-16], in patients with and without polypharmacy, respectively,  $p = 0.856$ )<sup>31</sup>. Polypharmacy can also be common among African older PLWH. The cross-sectional study performed by Ssonko et al. in Uganda assessed the prevalence, associated factors and adverse effects of polypharmacy among older ( $\geq 50$  years) PLWH treated with ART. This study included 411 PLWH of whom 63 were on polypharmacy (defined as taking  $\geq 4$  non-ART medications). Adherence to ART was established on self-report and pill recount. Study authors found no association between polypharmacy and ART adherence but also a possible relation with the setting and the need to further explore this issue<sup>36</sup>.

## The effect of polypharmacy in geriatric conditions in PLWH

### *Neurological, cognitive and anticholinergic burden*

Despite considerable advances in ART, neurocognitive impairment remains an important clinical concern among elder PLWH. Medication with anticholinergic activity has been previously associated with dementia and neurocognitive impairment in the older population so studies considering this fact on elder PLWH affected by polypharmacy are of interest for this study.<sup>51,52</sup>

Jakeman et al. performed a prospective study aimed to assess the prevalence of prescribed medications with anticholinergic activity and if this was associated with self-reported neurocognitive impairment in 1019 PLWH  $\geq 65$  years treated with ART ( $n = 1007$ , 99%). Self-reported neurocognitive impairment assessment included questions related to memory loss, attention difficulties, and slowing in reasoning. This study found a 50% prevalence of polypharmacy, and that 20% of patients took one or more medications with anticholinergic activity. After adjusting for confounding factors including polypharmacy, a trend relationship between the use of one or more anticholinergic medications and self-reported neurocognitive impairment was observed (OR: 1.69; 95% CI = 0.97-2.95,  $p = 0.06$ ) and, although a strongest association was found with depression (OR: 4.60; 95% CI = 2.62-8.09), self-reported neurocognitive impairment was associated with the use of 1 ACH medication in a sub-group analysis of 911 patients without depressive symptoms (OR: 2.51; 95% CI: 1.31-4.80)<sup>51</sup>. The retrospective study by Mazzitelli et al. aimed to assess anticholinergic risk in 790 HIV-treated

PLWH > 50 years found that, 44.7% were on polypharmacy (defined as taking  $\geq 5$  drugs), 7.9% were on severe polypharmacy (defined as taking  $\geq 10$  drugs), 14.9%-17.6% of patients took at least one anticholinergic drug, and 26.9%-27.8% had high anticholinergic risk (assessed by anticholinergic risk score and anticholinergic burden scale, respectively). In addition, authors found that 12.2% of patients who were on drugs with anticholinergic activity were osteoporotic, an important consideration taking into account the risk of falls and fractures discussed below<sup>19</sup>.

### *Falls and fractures*

Falls are considered an important issue in PLWH due to their high incidence and their relation with negative healthcare outcomes such as fractures. Falls occurred earlier in PLWH with fall rates among middle-aged PLWH (45 to 55 years) similar to > 65 years HIV-uninfected individuals<sup>52</sup>. In this context, some authors have reported data on the effect that polypharmacy could have on these geriatric concerns among PLWH. Some studies have found associations between the number of medications HIV patients take and the risk of falls. To start, the retrospective study performed by Erlandson et al. collected data on fall history during the previous 12 months, medical diagnoses and functional assessments in 359 treated HIV-infected patients (aged 45-65 years). This study found an association between polypharmacy and falls. Odds of falling increased by 1.4 (95% CI: 1.3-1.6,  $p < 0.001$ ) for each additional prescribed medication and an independent association was found between falls and beta-blockers, antidepressants, antipsychotics, sedatives, opiates, and didanosine after adjusting for the comorbidity being treated<sup>52</sup>. The retrospective study performed by Ruiz et al. assessed the incidence and risk factors associated with falls during the previous year using data from a register of 2000 HIV-infected patients. Investigators found that 32 patients suffered falls (mean age 48.19 years) and that taking more than 5 medications was related to falls ( $p < 0.005$ )<sup>53</sup>. Moreover, a posterior study performed by Erlandson et al. in 303 HIV-infected and 233 HIV-uninfected individuals found that a higher number of recent medications was an independent predictor for a greater frequency of falls among HIV-infected patients<sup>54</sup>. Furthermore, a study aimed to assess if polypharmacy was associated with falls and fractures among 250 PLWH and DSM-IV substance dependence during the past year of injection drug use and performed by Kim et al. found that the odds of falls that required medical

attention were higher with each additional medication overall (OR 1.12; 95% CI: 1.05-1.18), each additional non-antiretroviral medication (OR 1.13; 95% CI: 1.06-1.20), each additional sedating medication (OR 1.36; 95% CI: 1.14-1.62), and non-opioid sedating medication (OR 2.89; 95% CI: 1.06-7.85), but not with non-sedating or non-opioid medication and that 8 or more overall medication and 2 or more sedating medications were fall predictors. In the case of fractures, odds were (OR 1.05; 95% CI: 0.97-1.13) for each additional medication overall and (OR 1.11; 95% CI: 0.89-1.13) for each additional sedating medication<sup>55</sup>. Finally, the results of a nested case-control study performed by Womack et al. in 13 530 cases of individuals who fell and 67 060 controls matched by age, race, sex, HIV status, observation duration, and baseline date found that benzodiazepine and muscle relaxant use was associated with serious falls among PLWH (OR 1.24 95% CI 1.08-1.40 and OR 1.29 95% CI 1.08-1.46, respectively) and that non-ART medication taken was associated with increased risk of serious falls among HIV-infected and uninfected individuals (OR 1.20 95% CI 1.17-1.23, per 5 medications)<sup>56</sup>.

### *Nutritional status and frailty*

HIV infection increases energy requirements, decreases food intake, impairs nutrient absorption, and metabolism and produces gastrointestinal symptoms such as diarrhea. The prevalence of risk or malnutrition is high among PLWH. Moreover, the number of individuals with nutritional risks is higher among PLWH when compared with HIV-uninfected individuals, suggesting that regular screening and monitoring of the nutrition status in PLWH could lead to better health outcomes in this population<sup>57,58</sup>. Taking into account these considerations, the effect that polypharmacy could have on nutrition status in this population is of special interest. In this context, the prospective study performed by Thet et al. explored changes in nutritional status and related factors during 4 years in 250 PLWH  $\geq 50$  years treated with ART (67.6% receiving more than 3 medications and 14.6% more than 6). Nutritional status was assessed using the Mini Nutritional Assessment (MNA). This study found that 1.4% of patients were malnourished and 16.8% were at risk of malnutrition at baseline and 20.4% of patients deteriorated nutritional status during the follow-up period (decline in the mean MNA score 25.8 vs. 24.8  $p < 0.001$ ). Moreover, the presence of polypharmacy was independently associated with nutritional status deterioration in multivariate analysis (OR: 1.35; 95% CI: 1.10-1.65)<sup>58</sup>.

Frailty phenotypes have been related to poorer health-care outcomes both in PLWH and non-PLWH. Prevalence among PLWH is variable but it seems that it occurs earlier and with higher incidences than in the HIV-uninfected population. Furthermore, a relation between the presence of polypharmacy and frailty has been reported in PLWH. For instance, Blanco et al. performed a cross-sectional study aimed to assess the prevalence of frailty (defined using Fried's criteria) and pre-frailty as well as their risk factors and quality of life in 248 HIV-treated patients (mean age 49 years). This study found a prevalence of pre-frailty and frailty of 39.1% and 4.4%, respectively, and that taking > 5 drug non-HIV-related drugs were more frequent in frail patients ( $p = 0.004$ )<sup>28</sup>. Moreover, a cross-sectional study performed by McMillan et al. aimed to assess factors associated with frailty and to determine frailty subtypes among 389 PLWH > 50 years (mean age 61.1 years) with controlled HIV-infection found a heterogeneous presentation of frailty in this population and that polypharmacy was associated with frailty<sup>59</sup>. Later, the study performed by Beanland et al. assessed three short frailty tests in 84 HIV-affected outpatients > 40 years. This study found a prevalence of positive frailty test of 19%, 33%, and 20% (gait speed, timed-up-and-go test, and self-reported health questionnaire tests, respectively), and that presence of polypharmacy was significantly associated with polypharmacy according to gait speed and timed-up-and-go test scores<sup>60</sup>. Finally, the cross-sectional study performed by Sung et al. in 1762 PLWH and 2679 non-infected HIV patients aimed to determine the association between polypharmacy and an adapted frailty-related phenotype (studying 4 different domains: Shrinking, exhaustion, slowness, and low physical activity) found a higher odds of having any frailty phenotype for patients with HIV versus without for each additional chronic non-ART medication (11% vs. 4%, OR: 1.11; 95% CI: 1.08-1.14 vs. OR: 1.04; 95% CI: 1.03-1.04)<sup>61</sup>.

### **Quality of life**

Simplification of medication regimens could lead to increased adherence and quality of life in PLWH. The study performed by Okoli et al. previously mentioned was consistent with this affirmation. After adjusting for confounder (including comorbidities), a significant and independent association between polypharmacy (overall prevalence of 42.1%) and poorer health-related outcomes (adjusted OR 0.73; 95% CI, 0.59-0.91 and 0.64; 95% CI, 0.53-0.78, for treatment satisfaction and optimal overall health, respectively) was found<sup>15</sup>.

### **Health interventions aimed to assess and reduce polypharmacy**

The assessment of potentially inappropriate prescriptions (PIPs) that can be a cause of harm or no longer provide health benefits has gained increasing attention as a means to reduce unnecessary/inappropriate polypharmacy in elderly PLWH. To this end, some tools such as the screening tool for older people's prescriptions and screening tool to alert to right treatment (STOPP-START) criteria and/or the Beers criteria have been tested to minimize PIPs in PLWH.

For instance, Loste et al. performed a cross-sectional study in 91 PLWH aged  $\geq 65$  years (mean age 72.1 years and taking a mean of 5.7 non-ART medications) in Spain aimed to assess the prevalence and the drugs more commonly involved in potential prescribing issues according to the STOPP-START criteria and the concordance between STOPP-START and Beers criteria. Potential prescribing issues were identified in 87.9% of cases according to the STOPP-START and the Beers criteria (inappropriate prescriptions according to STOPP-START criteria: 71.4% and Beers criteria: 45.1%) being the drug type more commonly involved in potential prescribing issues the benzodiazepines<sup>16</sup>. These results were comparable to those found by Greene et al. in the United States following a retrospective chart review in 89 PLWH aged  $\geq 60$  (median age of 64 years and taking a median of 13 medications including ART). In this study, at least one potentially inappropriate medication was found in 52% of PLWH according to the modified Beers criteria. Moreover, this study found that older PLWH concurred a higher number of medication-related problems when compared with non-HIV older participants and that these problems were mostly due to those medications aimed to treat comorbidities<sup>44</sup>. Two studies also assessed the prevalence of inappropriate prescribing medications in those PLWH enrolled in the Swiss HIV Cohort Study. The first was the 2-centre prospective study performed by Courlet et al. that included 122 PLWH  $\geq 65$  years (taking a median of 4 non-ART medications) and that found 31% of participants in this group having at least one inappropriate prescribed medication, being the more common medications involved the benzodiazepine and the hypnotic ones<sup>29</sup>. The second was the retrospective study performed by Livio et al. in 175 elder PLWH aged  $\geq 75$  years (median age of 78 years and taking a median number of 5 medications). Inappropriate prescriptions were identified in 67% of cases according to the STOPP/START and the Beers

criteria, most of them were identified in non-ART prescriptions, and the more common were inappropriate dosing, the lack of indication, prescription omission, prescription not appropriate in older and DDIs<sup>17</sup>. The cross-sectional study performed by López-Centeno et al. in the region of Madrid in 1292 PLWH  $\geq 65$  years (median age of 69 years) also found 37.3% of participants having at least one potentially inappropriate medication according to the 2019 Beers criteria. These studies also found polypharmacy and female gender as factors independently associated with potentially inappropriate medication and the benzodiazepines, the non-steroidal anti-inflammatory ibuprofen, metoclopramide, and zolpidem as the most involved drugs<sup>21</sup>. Finally, the observational study performed by Vinuesa-Hernando et al. in 30 PLWH  $> 65$  years (median age of 71 years and taking a mean number of 6.6 concomitant medications) assessed the prevalence of PIPs according to the STOPP and the List of Evidence-based prescribing for CHRONIC patients (LESS-CHRON) criteria. This study found that according to STOPP criteria, at least one drug was a candidate for deprescribing in 63.3% of cases, and in 60% according to the LESS-CHRON model. The proportion of patients eligible for deprescribing since they met criteria with one or another method was 70%<sup>32</sup>.

Other studies also assessed health interventions aimed to reduce polypharmacy. For instance, the pharmacist-led randomized interventional trial performed by McNicholl et al. in the United States aimed to use the Beers criteria and the STOPP criteria to assess PIPs and pharmacists' interventions to reduce polypharmacy in 248 PLWH  $\geq 50$  years (mean age 58 years) taking a mean of 11.6 non-ART medications found that PIPs were identified in the 54% and 63% of participants using the STOPP and the Beers criteria, respectively. Moreover, this study found that 69% of included participants had at least one medication discontinuation (and near to 10% had 6 or more medication discontinuations) following pharmacist intervention and that more than 40% of participants had at least one STOPP or Beers criteria requiring immediate intervention<sup>62</sup>. A second study providing important data on this field was the observational study performed by Waters et al. that reported the 2-year multidisciplinary experience of a clinic dedicated to PLWH aged  $> 50$  years in which patients received full medication, adherence, polypharmacy, and DDIs review. 150 patients were attended (median age of 58 years and 38% taking  $\geq 3$  non-ART drugs) over 2 years. This study reported that 21% of the assessed patients received an intervention such as dose adjustment or change of ART or non-ART medication<sup>63</sup>. Finally,

the cross-sectional study performed by Kara et al. included 181 PLWH (mean age of  $> 40.4$  years) that took ART for at least 3 months and were interviewed by a clinical pharmacist. This study used the Pharmaceutical Care Network Europe classification V 7.0 to classify incident drug-related problems. 58 interventions were performed in 45 out of 181 participants (19% drug change, 10.3% dose change, 5.2% drug interruption, and 29.3% new drug introduction). Moreover, this study found that a significantly higher number of interventions were performed in those patients with polypharmacy compared with patients without polypharmacy (38.9% vs. 18.9% of patients, respectively,  $p < 0.001$ )<sup>64</sup>.

## Discussion and conclusions

Despite the simplification of ART and the emergence of new more active and safer HIV drug classes improved survival of PLWH that has increased the long-term complexity of their medical care<sup>1,4</sup>. The increased longevity of these populations comprises an increased risk of developing comorbidities which may lead to an increased need to take multiple medications, increased pill burden and risk for medication adverse effects<sup>7,8</sup>. In this context, a need to analyze the presence and the healthcare burden of polypharmacy among PLWH has emerged during recent decades. Polypharmacy, mostly defined as taking  $\geq 5$  non-ART drugs, is very common in this population. Its prevalence can be up to 91% and up to 19.5% for severe polypharmacy (taking  $\geq 10$  non-ART drugs)<sup>10,17</sup>. Higher prevalences have been observed in older PLWH groups and further investigation is needed to elucidate if gender differences are present though some studies reported a higher risk for female PLWH after adjusting for confounders. Some factors have been associated with polypharmacy in PLWH such as older age<sup>12,13,18,24,35</sup>, the number of comorbidities<sup>46</sup>, the frailty<sup>36</sup>, having a deteriorated renal function<sup>27</sup>, or having been hospitalized one or more times in the previous year<sup>36</sup>. Moreover, PLWH are at a greater risk for medication harm due to DDIs between ART and non-ART medication and a major increase in the number of DDIs for each additional non-ART medication has been observed among that PLWH<sup>6</sup>. Some studies assessed the prevalence of DDIs between ART and non-ART among PLWH populations with variable prevalences of polypharmacy (17-40%). These studies found 19.15-84% of patients affected by at least one DDI between ART and non-ART medications and 1.3-12.2% of patients affected by the most severe types of DDIs (red flag/contraindicated DDIs). From a qualitative perspective, the ART-drug classes mostly involved in

these severe types of DDIs were those that can interact with some medication used for other common conditions such as antihypertensives, statins divalent cations, anti-thrombotic agents, and corticosteroids<sup>22,33,37,39</sup>. Up to date, only few studies have assessed the influence of polypharmacy on antiretroviral drug selection and adherence or clinical outcomes such as virological control, need for hospitalization or mortality. Some of these studies observed that PLWH taking a higher number of medications (> 15) were less likely to have undetectable HIV-RNA<sup>47</sup>, and a negative effect on adherence in those PLWH taking multiple medications<sup>26,37,50</sup>, though further investigation is needed to elucidate the effects of polypharmacy on these clinical outcomes through different settings. Polypharmacy could comprise a higher risk for some geriatric conditions development and neurocognitive impairment and dementia remains an important clinical concern among elder PLWH. Moreover, concomitant use of drugs with anticholinergic effect, previously associated with dementia and neurocognitive impairment occurrence in older populations, have been described in up to 17.6% to 20% of cases in this population<sup>19,51</sup>. Falls, considered an important concern among elder populations have been described as occurring earlier in those PLWH<sup>52</sup> and have been related to polypharmacy in some studies including older PLWH<sup>52,53</sup>. Nutritional status and frailty development are also two important concerns in the elder population. PLWH are at a higher risk for poorer nutritional status, and polypharmacy was found to be independently associated with nutritional status deterioration<sup>58</sup>. In addition, it seems that frailty development could occur earlier and more often in PLWH compared with non-PLWH, and some studies have revealed a possible association between polypharmacy and the need to take more non-ART medications and frailty occurrence in this population<sup>28,60,61</sup>. In this context, some tools aimed to assess PIPs and the need for further intervention such as medication discontinuations have been analyzed in PLWH. The number of PIPs identified using the STOPP-START and the Beers criteria can be up to 87.9% in older PLWH, higher than when comparing with non-HIV populations, pointing to the imperative need for treatment-optimization strategies led by multidisciplinary teams including clinical pharmacists<sup>16,44</sup>. Considering these findings, polypharmacy should be considered a clinical concern in this population and treatment-optimization programs are needed to define specific health interventions to reduce its burden. However, some knowledge gaps remain unanswered in this field and further investigation is needed to improve knowledge of the clinical consequences of polypharmacy in this population and

the health-care interventions needed to reduce its clinical consequences.

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## Supplementary data

Supplementary data are available at *Aids Reviews* online (10.24875/AIDSRev.M23000059). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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