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REVIEW

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Prescribing issues in elderly individuals living with HIV

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ABSTRACT

Introduction: Combined antiretroviral therapy has transformed HIV infection into a chronic disease thus people living with HIV (PLWH) live longer. As a result, the management of HIV infection is becoming more challenging as elderly experience age-related comorbidities leading to complex polypharmacy and a higher risk for drug-drug or drug–disease interactions. Furthermore, age-related physiological changes affect pharmacokinetics and pharmacodynamics thereby predisposing elderly PLWH to incorrect dosing or inappropriate prescribing and consequently to adverse drug reactions and the subsequent risk of starting a prescribing cascade.

Areas covered: This review discusses the demographics of the aging HIV population, physiological changes and their impact on drug response as well as comorbidities. Particular emphasis is placed on common prescribing issues in elderly PLWH including drug–drug interactions with antiretroviral drugs. A PubMed search was used to compile relevant publications until February 2019.

Expert opinion: Prescribing issues are highly prevalent in elderly PLWH thus highlighting the need for education on geriatric prescribing principles. Adverse health outcomes potentially associated with polypharmacy and inappropriate prescribing should promote interventions to prevent harm including medication reconciliation, medication review, and medication prioritization according to the risks/benefits for a given patient. A multidisciplinary team approach is recommended for the care of elderly PLWH.

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1. The 'graying' of the HIV epidemic

Due to effective antiretroviral treatments, HIV infection has evolved from a deadly to a chronic disease. As a result, the persons living with HIV (PLWH) are aging and have a life expectancy close to the general population [1–3], although differences in estimates are observed depending on HIV transmission risk group, race, gender, lifestyle and CD4 cell counts at antiretroviral treatment initiation [4]. The growing proportion of elderly PLWH is diverse and includes patients diagnosed several years ago and who are aging with HIV infection as well as patients infected at an older age [5]. A mathematical model using data from the Dutch HIV cohort ATHENA projected that the median age of patients on antiretroviral treatment will increase from 43.9 years in 2010 to 56.6 in 2030. PLWH aged ≥60 years will represent 40% of the HIV population with 28% having ≥3 comorbidities. Consequently, it is estimated that 54% of PLWH will be prescribed co-medications by 2030, compared with 13% in 2010, with 20% taking ≥3 co-medications [6]. Similar projections are observed when modeling Italian and American HIV population data [7].

The 'graying' of the HIV epidemic brings new challenges as elderly experience more age-related comorbidities leading to complex polypharmacy and a higher risk for drug–drug interactions (DDIs). In addition, age-related physiological changes affect pharmacokinetics and pharmacodynamics thereby predisposing elderly PLWH to incorrect dosing and inappropriate prescribing.

This review covers age-related physiological changes and their impact on drug response with particular emphasis on common prescribing issues in elderly PLWH. A PubMed search was used to compile all relevant publications until February 2019.

In the following sections, the term elderly refers as being ≥65 years in accordance with the World Health Organization definition of elderly or older individuals [8].

2. Age-related changes in pharmacokinetics and pharmacodynamics

Advanced age is characterized by anatomical, physiological and biological changes that can alter drug pharmacokinetics as summarized in Table 1 [9,10]. These changes include a delayed gastric emptying time and a decreased acid gastric secretion, all of which can modify drug absorption although the effect of aging on drug absorption remains inconclusive due to contradictory findings, but it is generally considered to be of little clinical significance [10]. The distribution of drugs is affected due to a progressive reduction in total body water and lean body mass leading to a relative increase in body fat so that lipophilic drugs have a greater distribution.

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Table 1. Age-related physiological changes and impact on pharmacokinetics.

Physiological change	Pharmacokinetic effect
Drug absorption	
• ↓ Gastric emptying time, ↓ Acid gastric secretion[a]	Modification of drug absorption Note: Absorption may be affected by commonly prescribed drugs in elderly (antacids, proton pump inhibitors, H_2 blockers).
Drug distribution	
• ↓ Albumin (malnutrition)	↑ Free fraction of drugs.
• ↓ Lean muscle and total body water	↓ Vd for hydrophilic drugs tends to be balanced by ↓ renal clearance thus resulting in little effect on $t_{1/2.}$ Note: risk of toxicity if dose not adapted particularly in case of coexisting renal impairment.
• ↑ Body fat	↑ Vd and longer $t_{1/2}$ of lipophilic drugs, tendency to drug accumulation and lower threshold for adverse drug reactions.
Drug metabolism	
• ↓ Hepatic mass, ↓ Hepatic blood flow	↓ Reduced hepatic clearance and potential for higher drug concentrations.
Drug excretion	
• ↓ Kidney mass, ↓ Renal blood flow, ↓ GFR	↓ Reduced renal clearance requiring dose adjustment of drugs excreted mainly through the kidneys.

GFR, glomerular filtration rate; GI, gastrointestinal; $t_{1/2}$, elimination half-life; Vd, volume of distribution.
[a]Contradictory findings with some studies reporting differences in elderly compared to young individuals while other studies did not show any age-dependent effects.

Furthermore, serum albumin decreases with age leading to an increase in unbound drug, which is transported to peripheral tissue sites for uptake and is eliminated by the excretory organs. Aging has been associated with a decrease in hepatic clearance (30–40%); this effect is explained by the decline in both liver mass and blood flow rather than an alteration of the hepatic enzyme activity [11]. Of interest, the liver mass was shown to decrease by 10–15% and by 20% per age decade after the age of 65 years in women and men, respectively [10]. Finally, the most significant pharmacokinetic change with aging is the reduction in renal clearance due to a decrease in kidney weight caused by a loss of nephrons, a reduced renal blood flow and consequently a lower glomerular filtration rate. The latter declines progressively reaching 50% of the value of a young adult by the age of 90 years when considering the aging process only [10]. Overall, there is a progressive decline in several physiological parameters relevant to drug disposition with age.

Another issue relates to the fact that elderly individuals, including elderly PLWH, are often excluded from clinical trials resulting in limited knowledge about drug pharmacokinetics at older age. Available studies for antiretroviral drugs indicate that the concentrations of the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz and the integrase inhibitor (INI) raltegravir are not significantly changed in PLWH > 60 or 45–79 years whereas protease inhibitors (PI) are mostly increased [12–14]. Nucleoside reverse transcriptase inhibitors (NRTI)/nucleotide reverse transcriptase inhibitors (NtRTI) are affected differently as tenofovir exposure was shown to be decreased by 8–13% whereas emtricitabine exposure was increased by 19–73% in PLWH ≥ 55 years [15]. Finally, maximal concentrations of dolutegravir were increased by 25% in PLWH ≥ 60 years; this change did not have any negative consequences on sleep or daytime functioning [16]. All these studies have limitations as the number of PLWH above the age of 65 is small and patients with significant comorbidities or frailty were excluded, which could have mitigated the observed pharmacokinetic changes thus highlighting the need for more pharmacokinetic studies.

Age-dependent physiological changes can also modify drug pharmacodynamics resulting in a more or less pronounced drug effect, particularly for medications belonging to the cardiovascular or central nervous systems (CNS). Differences in drug response can be explained by changes in the affinity to receptor sites or in the number of receptors as well as changes in homeostatic processes with aging [17]. For instance, beta-blockers have a diminished effect in elderly possibly due to alterations in binding affinity or due to receptor downregulation [17,18]. Conversely, elderly are more sensitive to the effect of benzodiazepines. For instance, the dose of midazolam to reach sedation was shown to be half in individuals ≥65 years compared to young individuals [19], a similar effect is to be expected in elderly PLWH. On a general note, the long-term use of benzodiazepines should be avoided in elderly PLWH due to the increased sensitivity and related risk of cognitive impairment, balance problems, falls and consequently fractures [20,21]. The use of non-benzodiazepine sedative-hypnotics is also problematic and has been associated with an increased risk of falls in older adults (≥71 years) [22]. The risk/benefit balance of sedative hypnotics proved indeed to be unfavorable in elderly. The number needed to treat (NNT) for sleep improvement is 13 while the number needed to harm (NNH) for any adverse reaction is 6 indicating that the occurrence of an adverse event is more than twice likely compared to a gain in sleep quality [23]. Finally, due to a reduction in cholinergic receptors in the brain, elderly PLWH are also more likely to experience central anticholinergic adverse reactions (i.e. cognitive impairment, delirium) therefore drugs with anticholinergic properties should be avoided [24]. Of interest, HIV-infected women receiving more than one medication with anticholinergic properties were shown to have lower learning and executive performance compared to women not treated with such medications. When considering all women exposed to anticholinergic drugs, the cognitive performance was shown to be worse in HIV-infected compared to uninfected women suggesting that viral proteins may cause an additive effect to anticholinergic drugs [25]. Drug classes with potential different pharmacodynamics response in elderly PLWH are presented in Table 2 [9,17,18].

Altogether, physiological changes put elderly PLWH at risk to be treated with incorrect dosing and inappropriate drugs. These prescribing issues were shown to occur frequently in PLWH ≥ 75 years enrolled in the Swiss HIV Cohort Study (SHCS) [26].

Thus, knowledge of which drugs to adjust in case of renal function impairment is essential for safe prescribing. Although one limitation is that dosage recommendations in case of severe renal dysfunction (i.e. eGFR <30 mL/min/1.73 m^2 [27]) are not always available, particularly for older drugs. Of note, caution should be exercised when estimating the renal function using plasma creatinine or equations incorporating creatinine (e.g. creatinine clearance Cockcroft-Gault, eGFR CKD-EPI, and MDRD) as older adults have a lower production of creatinine due to a reduced muscle mass [28]. For drugs undergoing hepatic metabolism, one key principle is to start low, go slow and titrate, at least for chronic treatments such as antihypertensives, statins or

Table 2. Drug classes with potential different pharmacodynamic responses in elderly PLWH.

Drug class	Pharmacodynamic issue	Recommendation
Antihypertensives	Orthostatic hypotension	Start with lower dose and titrate dose
Beta blockers	↓ Beta-receptor function	May require higher dose beta-blocker
Diuretics	↑ Sensitivity to drug effect	Monitor blood pressure/electrolytes
Benzodiazepines	↑ Sensitivity (↑ sedation at lower doses and lower concentrations, postural sway)	Use at lowest dose and for a short duration
Opioids	↑ Sensitivity (↑ risk of respiratory depression)	Use with caution at the lowest efficient dose
Anticholinergic drugs	↑ Sensitivity (peripheral and central anticholinergic adverse reactions: constipation, dry mouth, urinary incontinence, cognitive impairment, delirium)	Avoid
Vitamin K antagonists	↑ Effect (↑ inhibition of synthesis of vitamin K dependent clotting factors)	Start with lower dose and adjustdose based on INR

antidepressants. As a rule of thumb, older individuals need about 50–75% of the optimal dose for younger individuals [29].

3. Age-related comorbidities in PLWH

With the advent of potent antiretroviral treatments, the HIV population is aging and experience age-related conditions, such as cardiovascular diseases, chronic kidney disease, hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease, cancer, osteoarthritis, osteoporosis, and neurocognitive impairment. As expected, the number of comorbidities increases with age: in the French Dat'AIDS cohort, 18.4% of PLWH aged ≥75 years had ≥4 comorbidities versus 4.3% of those aged 50–74 years [30]. Number of age-associated comorbidities was also significantly higher in PLWH aged ≥65 years compared to those aged 50 to 64 years in the SHCS [31]. In a cross-sectional study nested in the latter cohort, PLWH aged ≥75 years had a median of 7 comorbidities: the 10 most frequent in decreasing order of frequency were hypertension, chronic kidney disease, dyslipidemia, neurocognitive disorders, osteoporosis, polyneuropathy, cancer, coronary heart disease, arthrosis, and diabetes mellitus [26].

Several studies, mainly in the field of cardiovascular diseases and cancer, have found a higher prevalence of comorbidities in PLWH compared to HIV-uninfected age-matched controls [5,32–41]. Notably, age-associated comorbidities (≥1 including cardiovascular, metabolic, pulmonary, renal, bone and cancer) were significantly more prevalent in PLWH aged ≥45 years of the Dutch AGEhIV Cohort compared to HIV-uninfected controls, 69.4% versus 61.8%; P = 0.009, respectively [38]. Furthermore, multimorbidity defined by the concurrent presence of ≥2 noninfectious comorbidities was shown to be significantly higher in PLWH versus HIV-uninfected controls, and even more pronounced in those with a long history of HIV infection [5,32]. Cancer risk was found to be statistically significantly higher in PLWH ≥ 50 years versus HIV-uninfected controls, especially some cancers such as anal, lung, liver and oral cavity/pharyngeal cancers [35]. In another cohort study spanning from 1996 to 2009, cumulative incidence of cancer by age 75 in PLWH was statistically significantly higher for Kaposi sarcoma and non-Hodgkin's lymphoma as well as non-AIDS-defining cancers such as lung, anal, colorectal, liver, and Hodgkin lymphoma compared to HIV-uninfected controls [40].

Normal aging and HIV infection are characterized by interconnected immune-inflammatory processes, which may potentiate each other [42]. Consistent with this assumption, age-related co-morbidities tend to occur at an earlier age in PLWH compared to age-matched uninfected individuals. Besides chronic immune activation by HIV infection, the earlier onset of comorbidities in PLWH may also relate to behavioral, lifestyle factors (e.g. smoking, alcohol consumption, drug use) and viral co-infections (e.g. hepatitis, sexually transmitted diseases), all of which place them at higher risk of acquiring comorbidities [43]. In addition, chronic exposure to antiretroviral drugs, especially the first generation of PIs, NNRTIs, and NRTIs is associated with various toxicities leading for instance to metabolic disorders (e.g. dyslipidemia is frequently observed with the PIs fosamprenavir, indinavir, lopinavir, the NNRTI efavirenz, the NRTI stavudine; hyperlactatemia can occur with the NRTIs zidovudine, stavudine, didanosine) [44,45]. The NtRTI tenofovir disoproxil fumarate can cause renal toxicity [46], efavirenz can lead to CNS side effects (i.e. sleep disturbance, headache, depression, suicidal ideation) whereas hypersensitivity reactions have been reported for the NNRTI nevirapine [45].

4. Polypharmacy

Polypharmacy is commonly defined as being on ≥5 concomitant medications. This cutoff was selected, as it appears to best reflect the risk of having adverse health outcomes [47]. However, it is also important to mention that polypharmacy is often unavoidable when treating a patient with multiple comorbid conditions making the use of polypharmacy appropriate in this context whereas 'excessive' polypharmacy is deleterious and should be avoided [48]. In HIV medicine, polypharmacy refers usually to non-HIV drugs only, which are given in addition to HIV regimens consisting mostly of three combined antiretroviral drugs.

The prevalence of polypharmacy has been shown to be consistently higher in HIV-infected compared to age-matched HIV-uninfected individuals across different age categories in large cohort studies [49,50]. Differences in the extent of polypharmacy between HIV-infected and HIV-uninfected individuals tend to become less marked when considering older age categories (i.e. 65–74 years and ≥75 years referring to the young-old and old age groups as used previously [51]) [49]. This observation is likely explained by the natural occurrence of age-related chronic diseases regardless of HIV infection. The duration of HIV infection seems to affect the extent

of polypharmacy as a longer history of HIV infection was associated with a higher prevalence of dyslipidemia, chronic kidney disease, and diabetes mellitus and consequently increased polypharmacy. This association could partly be explained by metabolic toxicities related to the long-term exposure to certain antiretroviral drugs [51].

Analyses of HIV cohorts in different developed countries have reported a high prevalence of non-HIV polypharmacy in PLWH aged 50–75 years ranging from 43% up to 94% [26,51–57]. Of interest, the prevalence of polypharmacy in the Ugandan cohort of ≥50 years PLWH was shown to be lower (15%) [58] possibly due to limited access to medications. As expected, cohort studies have indicated that cardiovascular drugs, gastrointestinal agents, hormone replacement therapies or antiplatelet/anticoagulant medications are more often prescribed in ≥50 years as compared to younger PLWH [49,59].

Polypharmacy has some negative consequences. Some studies have suggested that a higher number of medications may decrease adherence; however, the findings have not been consistent [60–63]. This observation is likely due to the fact that adherence is a complex behavior involving drug-related factors (i.e. number of drugs, adverse effects, dosing regimens) as well as the psychological profile of a patient (i.e. cognitive ability, belief about the benefit or necessity of taking medications). Of interest, an analysis of the SHCS reported that PLWH (median age: 56 years) had a better adherence to antiretroviral therapy compared to their other co-administered treatments as the patients see the direct benefit of antiretroviral treatment (viral load suppression) and therefore are convinced about its necessity [64].

Studies performed in elderly HIV-uninfected individuals have linked polypharmacy to an increased risk of DDIs, drug–disease interactions and adverse drug reactions with the subsequent risk of starting a prescribing cascade (occurring when an adverse drug reaction is misinterpreted as a new medical condition resulting in further prescriptions, see section 5.2) [52–54,56,59]. Other adverse health outcomes associated with polypharmacy include functional physical decline, cognitive impairment, falls and related fractures, hospitalization and premature mortality [65–69]. However, causality assessment between polypharmacy and the aforementioned outcomes is challenging, as residual confounding factors linked to disease burden are difficult to eliminate in observational studies.

Considering the potential negative consequences of polypharmacy, efforts should be made to reduce unnecessary comedications. Future studies are needed to evaluate the impact of polypharmacy reduction on the prevention of harmful health outcomes.

5. Prescribing issues in elderly

The prescription of medicines is an essential component of the care of elderly PLWH. Several factors make prescribing a particular complex and challenging task in this population.

Age-related pharmacokinetic and pharmacodynamic changes predispose older PLWH to adverse drug reactions as discussed in section 2. Polypharmacy is often unavoidable in multimorbid patients and increases the potential for DDIs or drug–disease interactions as discussed in section 5.3.

The benefit–risk ratio of medication is difficult to assess in older people, as they are generally not included in clinical trials, especially if they have more than one morbidity and take medicines. In addition, the impact of medications on outcomes such as quality of life, which is of particular relevance for older persons, is not systematically evaluated in trials.

Prescribing guidelines, including guidelines for the treatment of PLWH (e.g. EACS, DHHS, BHIVA), generally focus on single diseases and fail to provide guidance on how to prioritize treatment in multimorbid patients for whom a more global approach is warranted.

Several providers are often involved in prescribing treatment for older PLWH, which increases the risk of inappropriate medication, especially if the role of the general practitioner as the coordinator of care is not well defined.

5.1. Inappropriate prescribing

Prescribing medications is a complex task, especially in older people who generally require complex regimens for multiple chronic conditions. Inappropriate prescribing has been defined as prescribing of medications that have more potential risks than potential benefits or prescribing that does not agree with accepted medical standards [70–74]. Inappropriate prescribing is highly prevalent in older individuals (≥65 years) and associated with negative health outcomes [75–79].

Several tools have been developed to assess appropriate/inappropriate prescribing in older people [80]. Of these, the Beers criteria and the STOPP (Screening Tool for Older Person's Prescriptions)/START (Screening Tool to Alert doctors to the Right Treatment) criteria are among the most widely used and can also be applied to elderly PLWH.

The Beers criteria was developed in 1991 by Mark H. Beers, an American geriatrician [70] and updated in 1997 [81], 2003, 2012, 2015 and 2019 [20]. The criteria are established from meta-analyses, systematic reviews, and expert consensus panel and include [20]:

- medications to avoid in most older adults (e.g. first-generation antihistamines due to their highly anticholinergic effects)
- medications to avoid in older adults with specific diseases or syndromes (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) in case of heart failure due to their potential to promote fluid retention and exacerbate heart failure)
- medications to be used with caution (e.g. dabigatran in patients ≥75 years or with creatinine clearance below 30 mL/min due to increased risk of bleeding)
- potentially severe DDIs (e.g. lithium and ACE inhibitors due to risk of lithium accumulation)
- medications to avoid or requiring dosage adjustments based on the patient's kidney function (e.g. pregabalin in case of creatinine clearance <60 mL/min due to increased risk of CNS adverse reactions)

The STOPP/START criteria were developed by Irish geriatricians and pharmacists. The first version was released in 2008 [82]

and the second updated version in 2015 [21]. The STOPP criteria are organized by physiological systems and have additional criteria than those listed in the Beers such as:

- medications prescribed without clinical indication
- medications prescribed beyond the recommended duration
- prescription of duplicate drug classes (e.g. two concurrent NSAIDs)
- medications that predictably increase the risk of falls (e.g. benzodiazepines)

Finally, the START criteria consist of evidence-based indicators of potential prescribing omission in older individuals with specific medical conditions (e.g. laxatives in patients receiving opioids regularly).

The Beers and STOPP criteria and ratings are not superimposable although there is some degree of overlap between these tools like for instance the major drug classes to avoid in older people (Table 3) [83,84]. STOPP/START performed better than Beers at detecting potentially inappropriate prescribing [85,86]. Furthermore, use of STOPP/START criteria was associated with some evidence of reduced falls, delirium episodes, hospital length of stay and primary or emergency care visits [87–91].

Only a few studies have specifically focused on prescribing issues beyond DDIs in older PLWH. In a retrospective study, 52% of PLWH aged ≥60 (n = 89) had at least one inappropriate prescription based on Beers criteria (2012) and 17% received a drug with anticholinergic properties. Medication issues were higher in PLWH compared to an age and sex-matched HIV-uninfected control group, although the latter had less comorbidity [52].

In a prospective study, 54% and 63% of PLWH aged ≥50 (n = 248) had inappropriate prescriptions using the STOPP (2008) and Beers criteria (2012), respectively. The number of medications was significantly associated with having a Beers or STOPP criteria identified. These prescription issues were corrected, but the impact of the intervention was not evaluated [56].

In a retrospective study of SHCS, 69% of PLWH aged ≥75 (n = 111) had at least one prescribing error. The analysis was performed using several tools: Beers and STOPP/START criteria, Anticholinergic Risk Scale [92], DDI checker (www.hiv-druginteractions.org), published DDIs studies and package inserts. Overall, 169 prescribing issues were detected and included: incorrect drug dosage (25%), absence of indication (21%), medication omission (19%), medication not appropriate in elderly (19%), deleterious DDIs (14%) and treatment duration exceeding recommendations (2%). The proportion of patients with more than one prescribing issue was significantly higher in those with polypharmacy [26].

Of interest, these studies show that prescribing issues in older PLWH are more frequently observed for non-HIV drugs and go beyond the well-known issue of DDIs with antiretroviral drugs suggesting the need for education on geriatric medicine principles. Furthermore, prescribing issues in older PLWH is at least as prevalent as in older HIV-uninfected people. As expected, polymedicated patients with high comorbidity burden are the most at risk. STOPP/START and Beers criteria may serve as an aid to prescribing in elderly PLWH, especially during medical training, but they should neither be a substitute for careful clinical judgment based on knowledge and experience, nor hinder a holistic individualized management of PLWH, as these tools are mostly disease/drug-oriented and do not address patients complexity and specificities.

5.2. Prescribing cascade

A prescribing cascade occurs when an adverse drug reaction is misinterpreted as a new medical condition, resulting in the initiation of a potentially unnecessary drug therapy, which in turn puts the patient at further risk of adverse reactions. The prescription of levofloxacin and codeine for an ACE inhibitor-induced cough misdiagnosed as a pneumonia, with subsequent *Clostridium difficile* diarrhea and confusion, is a typical example of deleterious prescription cascade. First described in 1995 [93], the concept of prescribing cascade has been later expanded to include over the counter medications as well as medical devices, for instance, pacemaker device insertion for a potentially reversible cholinesterase inhibitor-induced bradycardia [94,95]. Some well-established prescription cascades are listed in Table 4 [96–98].

Elderly PLWH are particularly at risk population for prescribing cascades, since they are often both polymedicated and particularly vulnerable to adverse drug reactions due to pharmacokinetic, pharmacodynamic and homeostatic processes changes with aging as discussed in section 2. In addition, adverse drug reactions are more likely to be misinterpreted as non-drug-related medical conditions in this population. For instance, a metoclopramide-induced movement disorder may be misdiagnosed as Parkinson's disease in an elderly PLWH, but less likely in a young patient as Parkinson's disease is less prevalent in younger people.

The very first step to prevent prescribing cascades lies in the avoidance of adverse drug reactions. Preventable adverse drug reactions, accounting for at least 30% of all adverse drug reactions [110], are mostly related to prescription issues. Thus, education and training in clinical pharmacology are of utmost importance to ensure good prescribing, especially in the complex and challenging field of geriatrics [111]. The second step is the early recognition of adverse drug reactions. Any new symptoms or signs should be considered as potentially drug-related until proven otherwise, particularly if the drug has been recently started or the dose increased [112]. Although obvious in theory, causality assessment can be time-consuming and challenging in elderly polymedicated PLWH with multiple health-care providers, as it mainly relies on the precise temporal relationship between drug exposures and adverse reactions [62].

In case of a suspected adverse reaction, the recommended strategies include: reconsidering the absolute need for the suspected offending drug; reducing the dosage of the suspected offending drug, as adverse-drug reactions are largely dose-dependent; considering alternative safer drugs. The

Table 3. Selected top 10 drug classes to avoid in elderly PLWH.

Drug class	Problems/alternatives
First generation antihistamines e.g. clemastine, diphenhydramine, doxylamine, hydroxyzine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: cetirizine, desloratadine, loratadine
Tricyclic antidepressants e.g. amitriptyline, clomipramine, doxepin, imipramine, trimipramine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: citalopram, escitalopram, mirtazapine, venlafaxine
Benzodiazepines Long and short acting benzodiazepines e.g. clonazepam, diazepam, midazolam Non-benzodiazepines hypnotics e.g. zolpidem, zopiclone	Elderly are more sensitive to their effect, risk of falls, fractures, delirium, cognitive impairment, drug dependency. Use with caution, at the lowest dose and for a short duration. Alternatives: non-pharmacological treatment of sleep disturbance/sleep hygiene
Atypical antipsychotics e.g. clozapine, olanzapine, quetiapine	Anticholinergic adverse reactions, increased risk of stroke and mortality (all antipsychotics). Alternatives: aripiprazole, ziprasidone
Urological spasmolytic agents e.g. oxybutynin, solifenacin, tolterodine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: non-pharmacological treatment (pelvic floor exercices)
Stimulant laxatives e.g. senna, bisacodyl	Long-term use may cause bowel dysfunction. Alternatives: fibers, hydration, osmotic laxatives
NSAIDs e.g. diclofenac, indomethacin, ketorolac, naproxen	Avoid regular, long-term use of NSAIDs due to risk of gastrointestinal bleeding, renal failure, worsening of heart failure. Alternatives: paracetamol, weak opioids
Digoxin Dosage > 0.125 mg/day	Avoid doses higher than 0.125 mg/day due to risk of toxicity. Alternatives for atrial fibrillation: beta-blockers
Long acting sulfonylureas e.g. glyburide, chlorpropamide	Can cause severe prolonged hypoglycemia. Alternatives: metformin or other antidiabetic classes
Cold medications Most of these products contain antihistamines (e.g. diphenhydramine) and decongestants (e.g. phenylephrine, pseudoephedrine)	First generation antihistamines can cause central and peripheral anticholinergic adverse reactions as described above. Oral decongestants can increase blood pressure. Avoid

NSAID = nonsteroidal anti-inflammatory drug. Refer to Beers criteria [20] for more exhaustive list.

Table 4. Common prescribing cascades in elderly individuals [99–109].

Initial treatment	Adverse drug reaction	Subsequent treatment
NSAID	Rise in blood pressure	Antihypertensive
ACE inhibitor	Cough	Cough suppressant; antibiotic
Thiazide diuretic	Hyperuricemia; gout	Allopurinol; colchicine
Amlodipine	Edema	Diuretic
Beta-blocker	Depression	Antidepressant
Antihypertensive	Dizziness	Prochlorperazine
Erythromycin	Arrhythmia	Antiarrhythmic
Quinolone	Delirium	Antipsychotic
Cholinesterase inhibitor	Incontinence	Anticholinergic
Cholinesterase inhibitor	Diarrhea	Bismuth subsalicylate
Cholinesterase inhibitor	Rhinorrhea	Diphenhydramine
SSRI; SNRI	Tremor	Benzodiazepine
Tricyclic antidepressant	Decreased cognition	Cholinesterase inhibitor
Tricyclic antidepressant	Constipation	Laxative
Meperidine	Delirium	Antipsychotic
Lithium	Tremor	Propranolol
Metoclopramide	Extrapyramidal effect	Antiparkinsonian agent
Antipsychotic	Extrapyramidal effect	Antiparkinsonian agent

ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

prescription of a new drug to treat an adverse drug reaction should be a last resort option, yet in some cases unavoidable.

5.3. Drug–drug interactions with antiretroviral drugs

An important prescribing issue in elderly PLWH relates to DDIs particularly with antiretroviral drugs. An analysis of the SHCS comparing PLWH aged ≥50 and <50 years showed that the frequency of DDIs was significantly higher in older compared to younger PLWH (51% versus 35%) [59], similar observations have been reported in other studies [52,53,113,114]. Antiretroviral drugs are recognized to be amongst the therapeutic agents with the highest potential for DDIs as these drugs can be both a victim and a perpetrator of DDIs leading to either a decreased or an increased exposure of the HIV drug or the co-medication and consequently to treatment failure or toxicity (Figure 1). The INIs raltegravir, dolutegravir, and bictegravir, the NNRTIs rilpivirine and doravirine as well as the entry inhibitor maraviroc undergo extensive hepatic metabolism but have no inhibitory effects on drug metabolizing enzymes and therefore have a low potential to cause DDIs. Conversely, the NNRTIs efavirenz, etravirine, nevirapine induce drug metabolizing enzymes, whereas ritonavir and cobicistat, used to boost levels of PIs and the INI elvitegravir, inhibit drug metabolizing enzymes and drug transporters. It is noteworthy to mention that ritonavir has also inducing properties whereas cobicistat has none thereby explaining differences in their interaction profiles [115]. For instance, the co-administration of ritonavir and dabigatran has no significant effect on dabigatran pharmacokinetics (mixed inducing and inhibitory effects on the intestinal transporter P-glycoprotein (P-gp) likely compensate each other) whereas cobicistat increases the anticoagulant exposure by 127% (only inhibitory effect on P-gp) [116] therefore co-administration is not recommended.

Pharmacokinetic DDIs with antiretroviral drugs can occur at the level of absorption, metabolism or elimination via several mechanisms including (Figure 1):

- *Changes in gastric pH*: e.g. acid neutralizing agents substantially reduce the absorption of atazanavir [117] and rilpivirine [118] as both antiretroviral drugs require a low

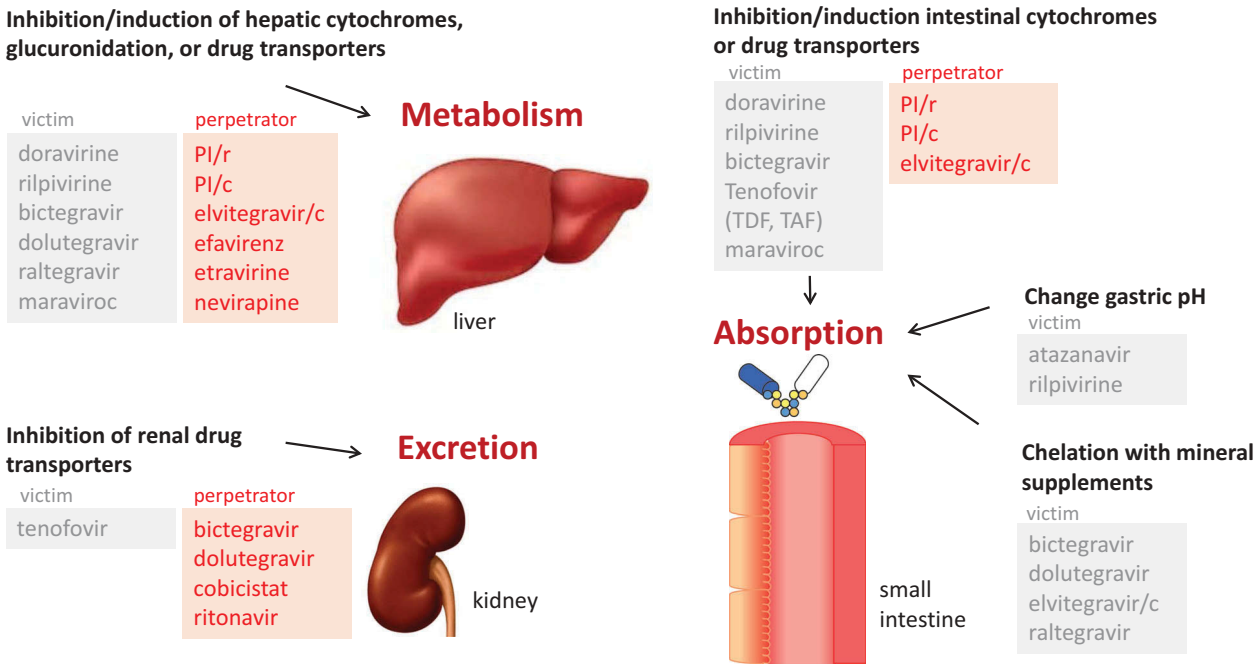

Figure 1. Mechanisms of drug–drug interactions with antiretroviral drugs. c = cobicistat; PI = protease inhibitor; r = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate. Victim = antiretroviral drugs victim (impacted) of DDIs; perpetrator = antiretrovirals drugs causing DDIs.

pH for optimal solubility which may compromise their efficacy.

- *Chelation*: e.g. divalent cations such as aluminum, calcium, magnesium present in antacids, supplements, or iron products form a complex with INIs, which may impair their absorption and efficacy [119–121]. All INIs contain an ion-chelating motif, which predispose them to chelation with cations [122].
- *Inhibition/induction of intestinal cytochrome P450 3A4 (CYP3A4) and/or intestinal transporters*: e.g. PIs boosted with cobicistat increase the absorption of dabigatran due to the inhibition of the intestinal efflux transporters P-gp. This results in higher systemic concentrations of dabigatran and consequently an increased risk of bleeding [116].
- *Inhibition/induction of hepatic CYPs and/or glucuronidation enzymes and/or hepatic transporters*: e.g. PIs boosted with ritonavir or cobicistat increase, for instance, the exposure of several statins via inhibition of CYP3A4 and/or hepatic transporters thereby increasing the risk of myopathy or rhabdomyolysis [123].
- *Inhibition of renal tubular transporters*: e.g. dolutegravir and bictegravir inhibit the uptake of metformin in the tubular cells via the organic cation transporter OCT2 whereas cobicistat and ritonavir inhibit the secretion of metformin in the urine via the multidrug and toxin extrusion protein MATE1 thereby increasing the exposure of the antidiabetic drug [124,125]. Thus, concomitant use of high doses of metformin is not recommended, also close monitoring is warranted in patients with renal impairment due to the risk of metformin-related lactic acidosis.

Pharmacodynamic DDIs, whereby the co-administration of drugs with similar toxicity profiles results in additive risk for drug-related adverse events, may also occur with antiretroviral drugs. For instance, TDF has been associated with both acute and chronic renal toxicity [46,126]. Thus, co-administration of nephrotoxic medications can increase the risk of nephrotoxicity in PLWH particularly in case of pre-existing renal dysfunction (as often observed in elderly PLWH) or in case of long treatment duration [127]. However, co-administration with nephrotoxic agents is unlikely to be of concern for TAF, as this second-generation prodrug achieves higher concentrations of the active moiety in the lymphocytes but results in 90% lower systemic levels of tenofovir compared to TDF [128].

Consistent with age-dependent comorbidities encountered in elderly PLWH, DDIs with antiretroviral therapy are frequently observed with cardiovascular drugs, psychotropic drugs or gastrointestinal drugs [49,53,59,113,114] particularly with boosted regimens. When possible, antiretroviral drugs with a lower potential for DDIs such as unboosted INIs, doravirine or rilpvirine should be favored (Figure 2). Selected DDIs between antiretroviral drugs and various co-medications commonly prescribed in elderly PLWH or DDIs of particular clinical relevance (i.e. anti-tuberculosis drugs) as well as recommendations on how to manage these DDIs are presented in Table 5. Additional DDIs or detailed information of the selected DDIs can be found in the HIV drug interactions database from the University of Liverpool [129]. Other freely available electronic resources to check DDIs with HIV drugs include the Toronto General Hospital immunodeficiency Clinic's drug therapy guide [130] and the University of California HIVInSite website [131]. DDIs between non-HIV drugs can be checked for instance in Micromedex [132] or Lexicomp [133].

A limited number of drug combinations are evaluated in clinical studies, thus guidance on the management of DDIs is mostly theoretical or is lacking, particularly when administering concomitantly several drugs, which may interact

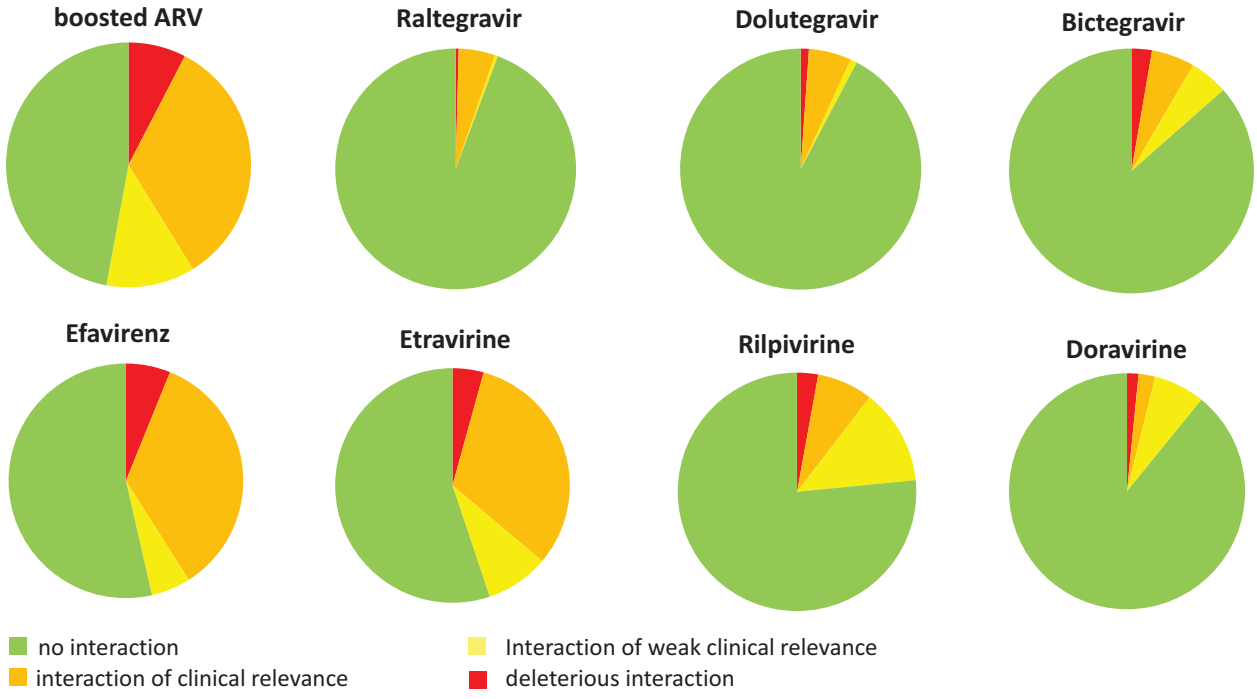

Figure 2. Drug–drug interactions profiles of several antiretroviral drugs[a]. a = the interaction profiles are based on 700 co-medications listed in the Liverpool HIV drug interactions website (www.hiv-druginteractions.org) [129]. Selected antiretroviral drugs undergo enzyme-mediated metabolism and some of these antiretroviral drugs have inhibitory/inducing properties. Note: interactions of weak clinical relevance do not require any particular action whereas interactions of clinical relevance may require a dose adjustment or clinical monitoring to manage the interaction. Boosted ARV = boosted antiretroviral drugs include protease inhibitors boosted with ritonavir (PI/r) or with cobicistat (PI/c) and elvitegravir/c.

mutually. Thus, the knowledge of the metabolic pathway of a given drug is essential to predict the likelihood of having a clinically significant interaction. DDIs of large magnitude are generally expected when the major metabolic pathway is inhibited or induced by strong inhibitors or inducers. Conversely, DDIs tend to be mitigated for drugs eliminated by multiple enzymes or pathways as metabolism and elimination can still occur through the unaffected pathways [163]. Another issue is that DDIs studies are mostly performed in healthy volunteers or PLWH with minimal or limited comorbid conditions so that available data may not apply to older PLWH with declining organ functions, multiple morbidities, medication intolerability, complex drug regimens, and frailty. In addition, it is unknown whether older age influences the extent of CYP mediated inhibition or induction. Induction of verapamil by rifampicin was shown to be similar in healthy elderly individuals (mean age of 67 years) compared to young controls [164] however it is unclear whether this observation applies to older frail PLWH thus highlighting the need for more studies.

The presence of age-related comorbidities increases not only the risk of DDIs between HIV drugs and co-medications or between co-medications but also the risk of drug–disease interactions whereby a medication recommended for one condition may adversely affect another coexisting condition [165]. For instance, the prescription of corticosteroids could aggravate an existing diabetes mellitus [166] or the use of TDF could worsen changes in bone mineral density in PLWH with osteoporosis [167]. Thus, the choice of antiretroviral drugs is limited in elderly PLWH by not only the co-medications in use but also the presence of comorbidities. TDF should be avoided in patients with existing kidney or bone diseases and abacavir in those at high risk for cardiovascular diseases [46,167,168]. Of interest, the presence of multimorbidity and polypharmacy in elderly PLWH was associated with a higher likelihood of prescribing mono- or dual antiretroviral therapies sparing NRTIs/NtRTIs, notably TDF suggesting that HIV clinicians are concerned about long-term toxicities and tailor antiretroviral treatments to prevent comorbidities [30,169]. However, it should be noted that dual HIV regimens can only be used in specific conditions (e.g. dolutegravir/rilpivirine in patients who are virologically suppressed on a stable antiretroviral regimen for at least six months with no history of virological failure and no pre-existing drug resistance) whereas monotherapies are not recommended by any guidelines.

In summary, DDIs are practically unavoidable in elderly PLWH given the life-long antiretroviral treatments and the higher prevalence of non-HIV polypharmacy related to more age-related comorbidities. Thus, the recognition, prevention, and management of DDIs remain a key priority in HIV care. The potential for DDIs needs to be considered systematically when selecting an antiretroviral regimen or when adding any new co-medication to an existing HIV treatment with particular attention to adjust dosage or perform clinical monitoring when needed. In this regard, searchable online drug interactions databases constitute valuable tools to recognize and manage unwanted DDIs in clinical practice. Furthermore, educational programs should be promoted to improve awareness on the issue of DDIs, and communication between prescribers

Table 5. Selected drug–drug interactions of interest in elderly PLWH.

Drug class	ARV	Comments/recommendations
Antacids H_2-receptor blockers Proton pump inhibitors	Atazanavir Rilpivirine	Solubility of ARV decreases as pH increases [117,118]. Administration recommendations: • Antacids: ATV: 2 h before or after antacid; RPV: 4 h before or 2 h after antacid • H_2-receptor blockers: ATV: simultaneous administration or >10 h after H_2-blocker. The dose of H_2-blocker should not exceed the equivalent of 40 mg famotidine twice daily (treatment-naïve patients) or the equivalent of 20 mg famotidine twice daily (treatment-experienced patients); RPV: 4 h before or 12 h after H_2-blocker • Proton pump inhibitors: contraindicated
Antacids Mineral supplements (iron,calcium, magnesium)	Bictegravir Dolutegravir Elvitegravir/c Raltegravir	Integrase inhibitors form a complex with divalent cations at the level of the gastrointestinal tract, thus reducing their absorption [119–121,134]. Administration recommendations: • BIC: 2 h before antacid (fasted); simultaneous with mineral supplements (fed) • DTG: 2 h before or 6 h after antacids or mineral supplements • EVG/c: separate by 4 h from antacids or mineral supplements • RAL: not recommended with aluminum and magnesium containing antacids. Co-administration possible with calcium carbonate-containing antacids but only with RAL BID. Separate by 4 h from mineral supplements, only administration of RAL BID possible.
Corticosteroids[a]	Boosted PI Elvitegravir/c	Inhibition of steroids metabolism increases the risk of Cushing syndrome (CS). Risk is not limited to oral administration but may also occur after topical, ocular, intra-articular or intrathecal administration of steroids [135,136]. A dose reduction of corticosteroid does not eliminate the risk of CS. Avoid boosted HIV drugs when possible or, if unavoidable, use a corticosteroid with a lower propensity to cause CS with periodic control of cortisol. • Budenoside, fluticasone, triamcinolone, mometasone: contraindicated • Beclomethasone, methylprednisolone, hydrocortisone: can be used with boosted regimens • Dexamethasone can reduce the exposure of boosted HIV drugs particularly if used at high doses and for a long duration. Use with caution
Antidepressants[a]	Boosted PI Elvitegravir/c	Increased exposure of tricyclic antidepressants due to inhibition of metabolism. Furthermore, tricyclic antidepressants are not recommended in elderly due to peripheral (constipation, orthostatic hypotension) and central (sedation, confusion, delirium) anticholinergic adverse reactions [20,21]. Avoid regardless of DDIs with boosted HIV drugs. • Selective serotonin reuptake inhibitors exposure can be increased [137]. Titrate to effect. Caution is needed when combining escitalopram or citalopram with ATV, LPV, or SQV due to the risk of QT interval prolongation associated with these drugs.
Benzodiazepines[a]	Boosted PI Elvitegravir/c	Increased exposure of benzodiazepines due to inhibition of metabolism. Furthermore, elderly have an increased sensitivity and consequently are at increased risk of cognitive impairment, delirium, falls; therefore, benzodiazepines should be avoided when possible [20,21]. • Midazolam, triazolam: contraindicated • Other benzodiazepines: use at the lowest dose and for a short duration.
Vitamine K antagonists[a]	Boosted PI Elvitegravir/c	DDIs are expected with boosted HIV drugs due to inhibition/induction of CYPs but can be managed by close INR monitoring [138–142]. • Dose adjustments may be needed when switching pharmacokinetic booster as ritonavir has inducing properties on cytochromes, whereas cobicistat does not [115].
Direct-acting anticoagulants[a]	Boosted PI Elvitegravir/c	Direct-acting anticoagulants are substrates of CYPs and/or transporters and therefore are subject to significant DDIs. Their anticoagulant effect cannot be measured routinely and data on management of DDIs are limited [116,143–145]. • Apixaban, rivaroxaban: avoid • Dabigatran: co-administration is possible with PI boosted with ritonavir but is not possible with cobicistat boosting • Edoxaban: consider a dose reduction from 60 to 30 mg
Antiplatelets[a]	Boosted PI Elvitegravir/c	• Aspirin: no DDIs • Clopidogrel: boosted HIV drugs alter antiplatelet effect. Coadministration with boosted regimens is not possible; use alternative antiplatelet agents or unboosted regimens [146–148]. • Prasugrel: boosted HIV drugs do not alter antiplatelet effect. Coadministration with boosted regimens is possible [148]. • Ticagrelor: contraindicated as boosted HIV drugs may substantially increase ticagrelor concentrations and the related risk of bleeding.
ACE inhibitors	Boosted PI Elvitegravir/c	ACE inhibitors undergo minimal metabolism and therefore do not interact with boosted HIV drugs.
Beta-blockers	Boosted PI Elvitegravir/c	• Limited pharmacokinetic interactions with boosted HIV drugs. However, PR interval monitoring may be warranted in patients with underlying block or those with atrioventricular nodal blocking agents [149] in case of coadministration with ATV, LPV, SQV due to a potential additive effect on PR interval.
Calcium channel inhibitors[a]	Boosted PI Elvitegravir/c	Inhibition of metabolism increases calcium channel inhibitors concentrations and thereby the hypotensive effect. • Start at a lower dose and titrate based on response to therapy. A 50% dose reduction may be considered for amlodipine and diltiazem [150,151]. • Lercanidipine: contraindicated

(*Continued*)

Table 5. (Continued).

Drug class	ARV	Comments/recommendations
Diuretics[a]	Boosted PI Elvitegravir/c	• Thiazide-type diuretics: no DDIs • Eplerenone: contraindicated with boosted HIV due to the increase in exposure and related risk of hyperkaliemia
Statins[a]	Boosted PI Elvitegravir/c	Can significantly increase the exposure of some statins and the related risk of myopathy or rhabdomyolysis [123]. • Simvastatin, lovastatin: contraindicated • Other statins: start with low dose and titrate to effect. Use of standard dose is possible with pitavastatin [152]. ATV is a strong inhibitor of the hepatic uptake transporter OATP1B1 resulting in large magnitude DDIs with statins. Atorvastatin and rosuvastatin doses should not exceed 10 mg daily with ATV.
Antidiabetics[a]	Boosted PI Bictegravir Elvitegravir/c Dolutegravir	• Sulfonylureas: potential increase in concentrations with boosted HIV drugs, monitor effect and reduce sulfonylureas dose if needed. • Metformin: DTG> BIC increase metformin exposure due to inhibition of renal transporter OCT2. Consider adjusting metformin dose when starting DTG. With BIC: no need to adjust dose in patients with normal renal function otherwise close monitoring is advised [124,125]. • Saxagliptin: maximal daily dose: 2.5 mg • Dapagliflozin, empagliflozin, exenatide, linagliptin, liraglutide, sitagliptin, vildagliptin: no clinically relevant DDIs
Cancer drugs[a]	Boosted PI Elvitegravir/c	Multiple cancer drugs are metabolized by cytochromes and therefore are subject to significant DDIs leading to toxicities. Limited data to guide DDIs management [153–155]. • Favor ARVs with a low potential for metabolic DDIs when possible (Figure 2)
Erectile dysfunction agents[a]	Boosted PI Elvitegravir/c	Can significantly increase the exposure and cause drop in blood pressure. Use with caution [156,157]. • Sildenafil: 25 mg every 48 h • Tadalafil: 10 mg every 72 h • Vardenafil: 2.5 mg every 72 h
Begnin prostatic hyeperplasia drugs[a]	Boosted PI Elvitegravir/c	Exposure increased due to inhibition of metabolism. • 5-Alpha reductase inhibitors: consider reduction in dutasteride dosing frequency if adverse reactions are noted; no dose adjustment needed for finasteride due to wide safety margin [158] • Alpha adrenergic antagonists: alfuzosin is contraindicated given the increased risk of orthostatic hypotension; doxazosin and prazosin: start at lowest dose and titrate until effect is reached; tamsulosin: start at 0.4 mg/day and monitor blood pressure [158]
Nonsteroidal anti-inflammatory drugs	TDF	Coadministration may increase the risk of nephrotoxicity [159]. • Avoid long-term use and perform close monitoring of renal function.
Rifampicin, rifabutin	PI/r PI/c Elvitegravir/c Bictegravir Dolutegravir Raltegravir Doravirine Etravirine Rilpivirine Efavirenz	• Contraindicated with rifampicin, alternative rifabutin 150 mg once daily • Contraindicated with rifampicin, alternative rifabutin 150 mg every other day • Contraindicated with rifampicin, alternative rifabutin 150 mg every other day • Contraindicated with rifampicin and rifabutin • Dolutegravir 50 mg twice daily with rifampicin, dolutegravir 50 mg once daily with rifabutin [160] • Raltegravir 400 or 800 mg twice daily with rifampicin [161], raltegravir 400 mg twice daily with rifabutin • Contraindicated with rifampicin, alternative doravirine 100 mg twice daily with rifabutin • Contraindicated with rifampicin, alternative rifabutin 300 mg once daily (if etravirine is administered without PI) • Contraindicated with rifampicin and rifabutin • Efavirenz 600 mg once daily with rifampicin [162], increase daily dose rifabutin by 50% in the presence of efavirenz

ARV = antiretroviral drug; ATV = atazanavir; BIC = bictegravir; c = cobicistat; CYP = cytochromes; DDI = drug-drug interaction; DTG = dolutegravir; EVG/c = elvitegravir/cobicitat; LPV = lopinavir; OCT2 = organic cation transporter; PI = protease inhibitor; PI/c = protease inhibitor boosted with cobicistat, PI/r = protease inhibitor boosted with ritonavir, RAL = raltegravir; RPV = rilpivirine; SQV = saquinavir; TDF = tenofovir disoproxil fumarate.
[a]Non-nucleoside reverse transcriptase inhibitors such as efavirenz, etravirine and nevirapine can lower the exposure. For more information on DDIs, refer to the University of Liverpool HIV drug interactions website: www.hiv-druginteractions.org [129]

should be encouraged to prevent deleterious drug associations.

6. Conclusion

The graying of the HIV epidemic brings new challenges in the treatment of patients. Available data indicate that inappropriate prescribing is common in older PLWH thus highlighting the need for education on prescribing principles in elderly as well as interventions to prevent unnecessary polypharmacy and harmful medications. In addition, the under-representation of elderly PLWH in clinical trials leads to a poor understanding on drug pharmacokinetics, DDIs or drug responses in this vulnerable, growing population thus future research is warranted to address this gap.

7. Expert opinion

The high prevalence of inappropriate prescribing in elderly PLWH is likely due to multiple factors comprising: prescriber-limited training in geriatric pharmacotherapy, multiple prescribers, and busy work environments limiting the time allocated for prescribing.

Although the age demographic is shifting, pre-graduate and post-graduate training on geriatric medicine principles remains limited thus efforts should be made to address this educational gap. The Beers and STOPP/START criteria can

provide an aid in detecting potential inappropriate prescribing in elderly PLWH; however, these tools are not meant to replace clinical judgment. Furthermore, their use can be time-consuming and limit their application in busy clinical environments. The development of computerized decision support systems, integrating the patient's drug history and specific clinical information as well as drug information references and guidelines, is warranted to efficiently assist clinicians with appropriate prescribing.

A multidisciplinary team comprising HIV specialists, geriatricians, and clinical pharmacologists/pharmacists is recommended to optimize treatments of multimorbid elderly PLWH. In this regard, several interventions can be applied to prevent/limit inappropriate prescribing including (Table 6) [68,170]:

- *Medication reconciliation*: this process aims at providing the most up-to-date list of medications that the patient is taking. The 'brown bag' review, where the patient is asked to bring all his medications to the visit, has proved useful in this process.
- *Medication review*: this process implies to check whether the indication of each medication is still relevant and adapted to the care goals, whether the dosing is adequate (e.g. drugs adapted to the renal function of the patient) and whether the treatment duration is correct. In addition, DDIs with antiretroviral drugs or between non-HIV drugs should be screened systematically using available online tools (i.e. Liverpool HIV DDIs database, Toronto General Hospital HIV drug therapy guide; University of California HIVInsite website, Micromedex, Lexicomp). Drug–disease interactions and drug omission should be checked considering the patient's comorbidities. Adverse drug reactions should be actively looked for and, in case of adverse drug reactions, the suspected agent should be discontinued or reduced. The principle 'start low and go slow' should be applied whenever possible. Particular attention should be paid to choose drugs with the highest therapeutic index; drugs covering multiple indications to simplify treatment as much as possible (e.g. angiotensin-converting enzyme inhibitors treat both hypertension and systolic heart failure). Finally, due to the occurrence of visual and motor disabilities with aging, drug formulations such as drops as well as pills requiring splitting or large size pills should be avoided.
- *Medication prioritization*: a balance is required between over- and under-prescribing. Several medications are often required to manage elderly individuals with multiple conditions. Decision to prescribe is often based on disease-specific clinical practice guidelines, which may result in care that is impractical or harmful particularly if the guidelines are not interpreted critically considering the clinical context of a specific patient [171,172]. For a hypothetical elderly patient with chronic obstructive pulmonary disease, diabetes mellitus, osteoporosis, hypertension and arthrosis, clinical practice guidelines would require prescribing 12 different medications [171]. Thus, the appropriateness of pharmacological treatments should be assessed critically and tailored to the needs of individuals (patient-centered care) [173]. The decision to prescribe should consider the risk/benefit of each medication, the care goals, the remaining life expectancy and current level of functioning as well as the patient preference, particularly in frail individuals.

In this context, the concept of deprescribing has gained increasing attention as a means to reduce unnecessary/inappropriate polypharmacy in elderly individuals [174,175]. Deprescribing is the act of tapering and/or stopping drugs whose potential harms outweigh benefits under the close supervision of healthcare providers. The decision to discontinue a treatment should take into account the indication and the tolerance of the medication, the potential for DDIs and the treatment goals for a given patient. Despite proven benefits, clinicians are often reluctant to stop medications, especially if they did not initiate the treatment, and the patient seems to be tolerating the medication, maybe due to some subjective irrational fear for potential deleterious consequences. On the other hand, deprescribing can also be interpreted by the patient and the family as 'giving up care', especially if adequate explanation is not provided.

Freely accessible resources to help deprescribe are available [176,177].

Finally, adapted consultation length to allow sufficient time for medication reconciliation, review and counseling should be encouraged to reduce the risk of inappropriate prescribing. However, this approach might be difficult to implement

Table 6. Interventions to limit the risk of polypharmacy and inappropriate prescribing.

1) Medication reconciliation
- Establish list of current prescription and over-the-counter drugs to be updated at each medical visit

2) Periodic medication review
- Check indication => discontinuation of unnecessary drugs
- Check dosing of medications => simplification of dosing regimen when possible
- Check duration of treatment => compliance with recommendations
- Check for DDIs: HIV/non-HIV comedications + non-HIV/non-HIV comedications
- Check for drug–disease interactions
- Check for drug duplication
- Check for missing medicine
- Check for inappropriate drugs for use in elderly
- Check for medications treating adverse effects of other medications

3) Medication prioritization
- Consider risk/benefit of each medication within the context of a given patient's care goals, current level of functioning, life expectancy, and preference

DDIs = drug–drug interactions.

considering the pressure from hospitals and health-care systems to reduce consultation times.

Future research should aim at specifically including PLWH aged ≥65 years to better document drug pharmacokinetics, pharmacodynamics, and DDIs and thereby prevent unwanted drug effects in this vulnerable, growing population. In addition, efforts should be made to understand how comorbidities cluster together. This would enable to develop targeted interventions and guidelines addressing more specifically the needs of PLWH with multiple comorbidities. Randomized clinical studies evaluating strategies to reduce unnecessary polypharmacy and their impact on the quality of life of aging PLWH are warranted.

From a clinical standpoint, the development and validation of computerized prescription systems combining several tools to screen for inappropriate drug use, drug omission, incorrect dosing, and DDIs are needed to be able to efficiently perform medication reviews and assist clinicians with the identification and prevention of prescribing errors. Of interest, the European Union funded the SENATOR and OPERAM clinical trials to examine the impact of software engines integrating several prescribing tools in reducing medication-related morbidity, avoidable costs and re-hospitalization in older individuals with multiple comorbidities [178,179]. The trials are ongoing, more information can be found in Clinical.Trials.gov under the following registration numbers: NCT02097654 (SENATOR) and NCT02986425 (OPERAM). These prescriptions systems may serve as a starting point for the development of a prescription tool adapted to elderly PLWH.

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Declaration of interest

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