Prescribing issues in older adults living with HIV: thinking beyond drug–drug interactions with antiretroviral drugs

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Introduction

Thanks to potent antiretroviral therapy, the life expectancy of people living with HIV (PLWH) has increased significantly and has become comparable to the general population.[1–3] Consequently, this population is aging, living long enough to face age-related chronic comorbidities, including cardiovascular diseases, kidney disease, diabetes mellitus, chronic obstructive pulmonary disease, cancer, osteoarthritis or neurocognitive impairment.[4–6] The age-related comorbidities burden leads inevitably to polypharmacy, which is commonly defined in HIV medicine as being on at least five concomitant non-HIV medications. The prevalence of polypharmacy has been shown to be high in different European and American HIV cohorts, ranging from 37% up to 94% in PLWH aged ⩾50 years up to ⩾75 years.[7–12]

Simulations based on the data of the Dutch HIV cohort ATHENA predicted that the median age would increase from 43 years in 2010 to 56 in 2030, resulting in 40% of HIV-infected individuals being 60 years old or older and 28% having at least three comorbidities. In 2030, about one-half of PLWH are anticipated to take comedications, compared with 13% in 2010, with 20% taking three or more comedications.[13] Similar forecasts were obtained for Italian and US PLWH.[14] Additional prescribing issues are emerging with the aging of the HIV population.

Inappropriate prescribing in older PLWH

The definition of inappropriate prescribing includes the use of medications associated with more potential risks than potential benefits, or prescribing that does not comply with accepted medical standards.[15–19] Inappropriate prescribing has been shown to be frequent in older individuals (⩾65 years) and to be related to negative health outcomes.[6,20–24] Studies in older PLWH have focused mainly on drug–drug interactions (DDIs) with antiretroviral drugs (ARVs), whereas other prescribing issues have been poorly addressed. In a retrospective analysis of the over 60 HIV Cohort from the University of San Francisco, older PLWH had a median of 13 medications including ARVs, and all had one clinically significant DDI. Overall, half of the patients had one, or more than one, inappropriate prescription looking at the Beers criteria,[25] with 17% taking anticholinergic drugs. Hyperlipidemia, hypertension and depression were the most frequently reported comorbidities. The number of comorbidities and medication problems were more prevalent in PLWH compared with an uninfected control group matched for age and gender.[10]

In a prospective study performed at the San Francisco General Hospital, PLWH aged >50 had a mean of 11 comedications besides ARVs. Contraindicated DDIs were detected in 8% of patients. Inappropriate prescriptions were identified in 54% and 63% of patients using the STOPP and Beers criteria, respectively.[11,26] The number of medications was significantly associated with prescribing errors. The latter were resolved; however, the study did not evaluate the impact of the intervention. Hypertension, depression, asthma, chronic obstructive pulmonary disease, dyslipidemia, coronary heart disease and diabetes mellitus were the main comorbidities.[11]

Finally, in a retrospective analysis of the Swiss HIV Cohort data, PLWH aged ⩾75 had a median of five comedications in addition to ARVs. The median number of comorbidities was seven, including mostly hypertension, chronic kidney disease (stage III or below, KDIGO),[27] neurocognitive

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impairment, dyslipidemia and polyneuropathy. Prescription analysis was done using the following resources: Beers and STOPP/START criteria,[28,29] Anticholinergic Risk Scale,[30] DDIs checker from the University of Liverpool (www.hiv-druginteractions.org), DDIs data from published studies or package inserts. In total, 169 prescribing problems were identified including unadjusted dosage (25%), no indication (21%), medication omission (19%), medication not appropriate in older individuals (19%), deleterious DDIs (14%) and treatment going beyond the recommended duration (2%). The patients with the highest disease burden and polypharmacy presented a higher risk of having more than one prescribing error.[9]

Taken together, these studies highlight that prescribing issues in older PLWH more often include non-HIV drugs and go beyond the problem of DDIs with ARVs. Furthermore, these data suggest that older PLWH encounter at least as many prescribing issues as observed in older uninfected individuals. As expected, polymedicated patients with high comorbidity burden are most at risk.

Appropriate prescribing: a focus on older patients including PLWH

Tailored appropriate prescribing is recommended for any patient but is hard to achieve, particularly in older patients with comorbidities. Older PLWH are not much different than older uninfected individuals, except for HIV infection, ARVs, and comorbidities generally occurring at an earlier age. These are likely explained by factors such as chronic immune activation and immune senescence,[31] lifestyle (e.g. smoking, alcohol use, illicit drug consumption), viral co-infections (e.g. hepatitis, sexually transmitted diseases) and ARV toxicity, particularly first generation.[32–35]

Key points to consider when prescribing, regardless of age or virological status, are indication, efficacy and effectiveness, dosage, DDIs and monitoring.

Indication, efficacy and effectiveness

Before prescribing, the very first questions to be asked are as follows:

(1) Is the medication indicated for the problem and is it indicated in this specific patient?;
(2) Is the medication efficacious for a given condition? What is the number needed to treat (NNT), that is, what is the number of individuals that need to be treated to prevent one additional bad outcome (see appendix)? Is it expected to be effective in this specific patient?;
(3) What about the medication's risks? What is the number needed to harm (NNH), that is, what is the number of individuals that need to be exposed to observe one adverse drug reaction (see Appendix)? Is this specific patient particularly at risk for an adverse drug reaction of this medication?[36]

Assessing the benefit *versus* harm of a medication prospectively in a specific individual is often difficult and based on many assumptions. One of the reasons is that the benefit *versus* harm assessment from clinical trials cannot be extrapolated to an individual patient without further consideration. This is even more true when it comes to older multimorbid patients who are almost never included in clinical trials.

Guidelines should also be appraised critically, as they are not individualized and not always based on strong evidence. Furthermore, they generally focus on single diseases and do not provide guidance on how to prioritize medications in multimorbid older patients for whom a global approach is warranted.[6] The risk/benefit of each medication, the care goals, the remaining life expectancy and the current level of functioning as well as patient preference (patient-centered approach) should be carefully considered when prescribing.[6,37]

Dosage individualization

Advanced age is associated with physiological changes that can alter pharmacokinetics, with drug clearance being the most affected parameter. Older age has been linked to a decreased metabolic clearance (30–40%), explained mainly by the decline in liver weight and liver blood flow.[38] A reduction in the glomerular filtration rate (GFR) is also observed with aging, resulting in a lower clearance of drugs eliminated unchanged by the kidney. The GFR progressively declines, reaching 50% of the young adult value by the age of 90 when accounting for age-related physiological changes only.[39] Not uncommonly, diseases (e.g.

diabetes mellitus, hypertension, atherosclerosis, liver cirrhosis) superimpose on the aging process and further decrease drug clearance. Since older individuals are often excluded from clinical trials, the effect of older age on the pharmacokinetics of antiretroviral drugs is poorly documented. Available studies have shown that the levels of the ARVs efavirenz and raltegravir are not significantly modified in older PLWH, whereas the protease inhibitors darunavir/ritonavir or lopinavir/ritonavir are mostly increased.[40–42] The maximal concentrations of dolutegravir were shown to be raised by 25%.[43] Finally, the exposure of the nucleoside reverse transcriptase inhibitors was shown to be either decreased or increased.[44]

Aging can also alter pharmacodynamics, leading mostly to a stronger effect of drugs, or sometimes a decreased effect. Differences in the affinity to receptor sites or in the number of receptors with aging or the alteration of homeostatic processes can explain changes in the pharmacodynamic response.[6,45] These changes have been best documented for cardiovascular and central nervous system (CNS) drugs. For instance, older patients have more pronounced effects of benzodiazepines. For instance, sedation was achieved in individuals aged ⩾65 with half the dose of midazolam compared with young adults.[46] Due to a reduction in cholinergic receptors in the brain, older patients are more prone to present CNS side effects (e.g. delirium, cognitive impairment) when treated with anticholinergic drugs (e.g. first generation antihistamines, tricyclic antidepressants), which should therefore be avoided.[47] Conversely, beta-blockers have a reduced effect in older patients partly because of the diminished sensitivity of beta-adrenergic receptors.[48]

Dosage adjustment recommendations provided by manufacturers are mostly available for moderate renal function impairment (stage III KDIGO), but are scarce in more advanced stages, due to lack of specific studies. Of note, equations such as Cockcroft-Gault clearance or eGFR CKD-EPI perform better than plasma creatinine, but remains rough estimates.

The management of patients becomes more challenging in the presence of a combination of different organ impairments (e.g. liver, kidney, heart), as there are no validated dosage recommendations. With a few exceptions (e.g. anti-infectives, glucocorticoids, carbimazole), one key principle is to start with a low dose and increase gradually while monitoring the effect to guide changes in dose.[36]

DDIs

One major prescribing problem in older PLWH includes DDIs notably with ARVs. An analysis of the Swiss HIV Cohort Study showed a higher frequency of DDIs in patients aged ⩾50 compared with patients <50 with fewer medications.[49] Similar observations were reported in other studies.[50,51] ARVs have a well-known high potential of pharmacokinetic DDIs, as most of them can be either victim or perpetrator of DDIs, or both. However, the last generation of ARVs, such as raltegravir, dolutegravir and bictegravir (integrase inhibitors), or rilpivirine and doravirine (nonnucleoside reverse transcriptase inhibitors), have a lower potential for DDIs; they are impacted mainly by inhibitors or inducers of drug metabolizing enzymes or transporters, and therefore are potential victims of DDIs.

The first step to detect DDIs is to look for a perpetrator, either an enzyme/transporter inhibitor or inducer. If there is a perpetrator, the second step is to look for potential victims. Freely available resources to detect and manage DDIs with ARVs include: HIV drug interactions database from the University of Liverpool (http://www.hiv-druginteractions.org); Toronto General Hospital Immunodeficiency Clinic's drug therapy guide (http://app.hivclinic.ca) and the University of California HIVInSite website (http://hivinsite.ucsf.edu).[6]

The number of drug combinations assessed in clinical studies is limited, thus the likelihood of having a DDI is evaluated based mostly on the knowledge of the metabolic pathway of the drugs. Furthermore, DDIs studies are restricted to pairs of medications and performed mostly in healthy volunteers; thus, available data may not fully apply to older multimorbid and polymedicated patients. The safest attitude is to avoid DDIs by switching perpetrator or victim whenever possible.

The presence of age-related comorbidities increases the risk not only of DDIs but also of drug–disease interaction,[6] also termed therapeutic competition. This is when the prescription of an additional medication to treat one medical problem may worsen a coexisting condition.[52]

For instance, medications for heart failure may worsen a pre-existing urinary incontinence, or the use of tenofovir disoproxil may further reduce bone mineral density in PLWH with pre-existing osteoporosis.[52,53] Thus, the greater the comorbidities, the narrower the scope of therapeutic options.

Monitoring

Monitoring may apply to therapeutic effect or adverse reactions. Methods involve symptoms and biomarkers of therapeutic or adverse outcomes (e.g. glycosylated hemoglobin for antidiabetic agents, blood pressure for antihypertensive agents, electrolytes for diuretics).[36] Therapeutic drug monitoring of plasma drug concentrations can be helpful, particularly in multimorbid patients for whom an *a priori* dosage may be inappropriate, provided the concentration target is well established.

A therapeutic goal, as well as an appropriate monitoring strategy, should ideally be set and shared with the patient whenever a medication is prescribed. The patient should also be informed about the importance of being compliant to the treatment, and about the potential occurrence of common or serious adverse drug reactions in order to be able to promptly recognize them. The effect (beneficial and harmful) of the medication should be regularly assessed in relation to the therapeutic goal, and any potential adjustments made accordingly. In case of doubtful effectiveness, withdrawal should be considered, even if the medication is well tolerated.

Conclusion

Prescribing remains a challenging and risky task, particularly in older patients, including PLWH, who are under-represented in observational studies and randomized clinical studies, thus resulting in low evidence-based prescribing.

A multidisciplinary team including HIV physicians, general practitioners/geriatricians and clinical pharmacologists/pharmacists is advised to optimize treatments of multimorbid older PLWH and thereby achieve the goals of appropriate prescribing. In order to ensure a good communication and coordination between healthcare providers, a coordinator of care has to be designated.[6]

Education and training in clinical pharmacology are critical to ensure appropriate prescribing, particularly in the complex field of geriatrics and in an era of sustained launching of new drugs. Thus, pre- and postgraduate education in clinical pharmacology, including geriatric principles, should be reinforced.

The STOPP/START and Beers criteria may help prescribe in older PLWH. However, these explicit criteria should neither be a substitute for careful clinical judgement based on knowledge and experience, nor hinder a holistic individualized management, as these tools are mostly disease/drug-oriented and do not address patients' complexity and specificities.[6]

Finally, time devoted to prescribing is usually very limited,[54,55] essentially due to multiple medical issues beyond medication and time limit per visit. Prescribers should be allocated more time to deal with prescribing issues, especially in complex and vulnerable patients.

Computerized prescription systems including the patient's clinical information, medication history, as well as information on medications, tools to screen for inappropriate drug use, drug omission and DDIs should be developed to assist clinicians in prescribing.[6]

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Appendix: Determination of the number needed to treat (NNT) and number needed to harm (NNH)[56]

	Event	No event
Treatment	a	b
Placebo	c	d

NNT is calculated using the inverse of the absolute risk reduction (ARR) (efficacy data):

$$ARR = \left[c / (c + d)\right] - \left[a / (a + b)\right]$$

$$NNT = 1 / ARR$$

NNH is calculated using the inverse of the absolute risk increase (ARI) (adverse event data):

$$ARI = \left[a / (a + b)\right] - \left[c / (c + d)\right]$$

$$NNH = 1 / ARI$$

Example:

	Blood clot	No blood clot	Risk
Treatment	70	430	70/500 = 14%
Placebo	150	350	150/500 = 30%

ARR = 30–14% = 16% (16% lower incidence of developing one blood clot in the treatment compared with the placebo group).
NNT = 1/0.16 = 6.25 (about six patients will need to be treated to prevent one blood clot).

On the other hand, the treatment caused a minor hemorrhagic event in 4% of patients in the treatment group compared with 3% in the placebo group:

$$ARI = 4 - 3 = 1\%$$

NNH = 1/0.01 = 100 (100 patients will have to be treated to observe one minor hemorrhagic event). Thus, this treatment would be considered to have a favourable benefit-risk ratio.

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