Polypharmacy in older adults with HIV infection: Effects on the brain

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Over the past decade, antiretroviral therapy (ART) has substantially evolved so that the medications are safer, much more potent, and require less frequent dosing than early in the pandemic. Widespread use of ART has led to a dramatic decline in opportunistic complications and mortality associated with acquired immunodeficiency syndrome (AIDS), and as a result, the survival of people with HIV (PWH) is approaching that of the general population. As PWH age, however, they are spending more years of life contending with the long-term health issues associated with aging and with age-related comorbidities that typically occur in the geriatric population. In other words, their healthspan has not improved to the same extent as their lifespan. This has led to a higher burden of non-antiretroviral medications used to treat these comorbidities in PWH than persons without human immunodeficiency virus (HIV).

HIV INFECTION IS ASSOCIATED WITH FREQUENT AGE-RELATED COMORBIDITIES AND HIGHER RATES OF POLYPHARMACY

PWH are developing age-related comorbidities more frequently and at earlier ages than the general population.1,2 Among the age-related comorbidities that are most pronounced in PWH are cardiovascular disease, impaired renal function, impaired neurocognitive function, and neuropathy/distal neuropathic pain.1,3,4 The reasons for this are likely multifactorial and may be due in part to the acceleration of immunological and biological age by HIV. The phenomenon of premature epigenetic aging in PWH appears to be pronounced in the brain: Horvath and Levine demonstrated that HIV infection accelerates biological age by 7 years in brain tissue from autopsy and by 5 years in blood.5

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Alongside this rise in age-related multimorbidity is an increase in polypharmacy, typically defined as use of at least five medications. PWH take more medications than those without HIV, even when excluding ART.6–9 A recent study on PWH older than 60 years found that polypharmacy occurred in 65% of adults in this population.10 Likewise, emerging data from the Pharmacokinetic and Clinical Observations in People Over Fifty (POPPY) Study, Medicare claims, and from the Multicenter AIDS Cohort Study all demonstrate consistently more frequent polypharmacy among PWH compared with uninfected controls, even when excluding ART from the medication counts.6–8 Polypharmacy is thus a special challenge for older PWH, placing them at high risk for drug–drug interactions (DDIs) and potentially inappropriate medication use, and for poor clinical outcomes including falls, hospitalizations, and increased mortality.

**POLYPHARMACY MAY EXACERBATE HIV-ASSOCIATED NEUROLOGICAL DYSFUNCTION**

In older adults without HIV infection, polypharmacy is strongly linked with adverse clinical outcomes, including increased hospitalization and falls.11 “Hyperpolypharmacy,” or the use of at least 10 medications, is further associated with cognitive decline.12 Among virally suppressed PWH aged 45–65 years in Colorado, Erlandson et al. likewise found that polypharmacy was associated with frailty, slower 400 meter walk time, and poorer performance on the Short Physical Performance Battery.13 In PWH, each additional prescribed medication is associated with a 40% higher risk for falls.14 The association between polypharmacy in PWH and poor outcomes, including frailty and hospitalizations, is also present in resource-limited settings.15

Among the potential poor outcomes associated with polypharmacy, neurological impairment is of particular concern in PWH. Multiple studies have demonstrated an excess of cognitive impairment in PWH despite adequate virologic suppression, with impairment affecting multiple domains including episodic memory, motor function, information processing, and executive functioning. While this higher baseline risk is likely multifactorial, HIV and aging seem to synergistically contribute to neurological dysfunction, with HIV accelerating deleterious effects on specific neurocognitive domains commonly associated with aging.3 HIV-associated neurologic dysfunction may be especially exacerbated by the frequent use of psychoactive medications in PWH. Women with HIV are more likely to be prescribed medications with neuropsychiatric effects than those without HIV. Among medications with known neuropsychiatric effects, anticholinergic effects are particularly concerning. A study that examined the effect of anticholinergic burden on the brain in people with and without HIV found significantly worse performance in neuropsychological testing in PWH (specifically, learning and executive function domains), with associated reduced brain volumes and white matter microstructural integrity.16 Other studies suggest that anticholinergic medications may interact with HIV proteins to worsen cognitive functioning; for example, neurotoxic viral proteins could have synergistic adverse effects with anticholinergic drugs.17

**DDIs MUST BE CAREFULLY CONSIDERED IN PWH**

DDIs are of special concern in older PWH. In people with and without HIV, aging influences pharmacokinetics, which can elicit changes in drug distribution, binding proteins, drug metabolism, and drug elimination, ultimately leading to greater drug exposure in older adults, including higher exposure to both ART and non-ART drugs and greater associated toxicity.18–20 Altered pharmacokinetics within protected compartments, like the brain, may lead to ART concentrations that fall below HIV inhibitory concentrations or above those that can cause toxicity.21 Of note, drug concentrations in tissues, including the brain, may not be accurately reflected by measured drug concentrations in body fluids, such as blood or cerebrospinal fluid. Thus, PWH may have therapeutic ART concentrations in blood, but have higher concentrations in tissue compartments such as the brain, which may be toxic. Aging can also elicit structural changes to the blood–brain barrier (BBB), including decreasing endothelial cell number, choroid plexus epithelium flattening and calcification, and thickening of basement and arachnoid membranes, resulting in increased BBB permeability.22 HIV infection itself is also associated with an impaired BBB, in the form of structural changes triggered by HIV proteins, macrophage activation products, and vascular disease.23–25 Although the clinical relevance of these structural changes remains unclear, it suggests that aging PWH may be uniquely susceptible to adverse DDIs, and particularly those that impact the CNS.

**ADDRESSING POLYPHARMACY IN OUR PATIENTS WITH HIV**

Guidelines exist in the United States, UK, and Canada to help clinicians reduce the burden of polypharmacy in older adults following evidence-based practice. However, directly applying these guidelines to older PWH is challenging as
they face unique dilemmas with regard to polypharmacy, including the need for ART to maintain virologic suppression, development of some comorbidities at an earlier age, and dramatically higher rates of some comorbidities (e.g., cardiovascular disease) that are often managed by several medications. It is especially urgent to address polypharmacy in PWH, as polypharmacy may contribute to pill burden and regimen complexity, and therefore to the likelihood that a patient will miss crucial doses of life-saving ART. This is important because incomplete ART adherence may lead to low-level HIV replication and worsening of chronic inflammation, even in those who achieve clinical viral suppression.26

Should ART itself be reduced to the fewest number of drugs? While most ART-treated PWH are prescribed a three- or four-drug regimen (often combined in one pill), newer two-drug regimens hold promise for simplifying the ART regimen, thus reducing the risk for DDIs and toxicity. Newly developed long-acting medications, administered monthly, will further reduce the dosing burden among PWH. However, these approaches have not yet been assessed in older PWH, and how two-drug or long-acting regimens perform in this population of PWH is unknown. Guaraldi et al. have proposed an experimental algorithm to guide “deprescribing” of ART, using a set of inclusion criteria based on “medication-related burden” and frailty rather than age or number of medications.27 They recommend deprescribing ART drugs in the setting of viral suppression and favorable ART history and resistance testing using one of the three strategies: reduction of ART pill burden, simplification to a two-drug regimen, or use of long-acting therapy.

For non-ART, Blanco et al. describe an approach to medication deprescribing in PWH. Options include “pruning” versus “cutting,” where “cutting” entails discontinuing any medications that are considered inappropriate for a given population based on scientific evidence (e.g., Beer’s and STOPP/START criteria), while “pruning” is a patient-specific approach requiring careful analysis of a patient’s medication regimen, risk–benefit considerations, and subsequent discontinuation and addition of medications as necessary.28 Along with guidelines for deprescribing of specific medications such as benzodiazepines and antipsychotics, they list a number of general principles including the importance of regular medication review, dose adjustment based on kidney and liver function, limiting the number of prescribers, and emphasizing the need to carefully consider before prescribing a potentially dangerous medication. The impact of a deprescribing approach on HIV-associated neurocognitive impairment, however, remains unclear and additional evidence will be needed to guide the clinical approach.

**CONCLUSION**

While celebrating the longer lifespan and improved health of PWH, we must contend with the greater risks for multimorbidity, geriatric syndromes, and polypharmacy that come alongside these gained years of life. Advances in geriatric sciences have led to an increased focus on the risks and management of polypharmacy in older adults. We must now tailor these approaches, including consideration of DDIs and deprescribing, to promote healthy aging in adults with HIV infection.

**CONFLICT OF INTEREST**

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**AUTHOR CONTRIBUTIONS**

All authors wrote and revised the manuscript.

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None.

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