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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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REFERENCES

1. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis*. 2014;59(12):1787-1797.
2. Rasmussen LD, May MT, Kronborg G, et al. Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study. *Lancet HIV*. 2015;2(7):e288-e298.
3. Goodkin K, Miller EN, Cox C, et al. Effect of ageing on neurocognitive function by stage of HIV infection: evidence from the Multicenter AIDS Cohort Study. *Lancet HIV*. 2017;4(9):e411-e422.
4. So-Armah K, Freiberg MS. Cardiovascular disease risk in an aging HIV population: not just a question of biology. *Curr Opin HIV AIDS*. 2014;9(4):346-354.
5. Horvath S, Levine AJ. HIV-1 infection accelerates age according to the epigenetic clock. *J Infect Dis*. 2015;212(10):1563-1573.
6. Halloran MO, Boyle C, Kehoe B, et al. Polypharmacy and drug-drug interactions in older and younger people living with HIV: the POPPY study. *Antivir Ther*. 2019;24(3):193-201.
7. Kong AM, Pozen A, Anastos K, Kelvin EA, Nash D. Non-HIV comorbid conditions and polypharmacy among people living with HIV age 65 or older compared with HIV-negative individuals age 65 or older in the United States: a retrospective claims-based analysis. *AIDS Patient Care STDS*. 2019;33(3):93-103.

8. Ware D, Palella FJ Jr, Chew KW, et al. Prevalence and trends of polypharmacy among HIV-positive and -negative men in the Multicenter AIDS Cohort Study from 2004 to 2016. *PLoS One*. 2018;13(9):e0203890.
9. Edelman EJ, Rentsch CT, Justice AC. Polypharmacy in HIV: recent insights and future directions. *Curr Opin HIV AIDS*. 2020;15(2):126-133.
10. Greene M, Steinman MA, McNicholl IR, Valcour V. Polypharmacy, drug-drug interactions, and potentially inappropriate medications in older adults with human immunodeficiency virus infection. *J Am Geriatr Soc*. 2014;62(3):447-453.
11. Tinetti ME. Clinical practice. Preventing falls in elderly persons. *N Engl J Med*. 2003;348(1):42-49.
12. Jyrkka J, Enlund H, Lavikainen P, Sulkava R, Hartikainen S. Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. *Pharmacoepidemiol Drug Saf*. 2011;20(5):514-522.
13. Erlandson KM, Allshouse AA, Jankowski CM, et al. Comparison of functional status instruments in HIV-infected adults on effective antiretroviral therapy. *HIV Clin Trials*. 2012;13(6):324-334.
14. Erlandson KM, Allshouse AA, Jankowski CM, et al. Risk factors for falls in HIV-infected persons. *J Acquir Immune Defic Syndr*. 2012;61(4):484-489.
15. Ssonko M, Stanaway F, Mayanja HK, et al. Polypharmacy among HIV positive older adults on anti-retroviral therapy attending an urban clinic in Uganda. *BMC Geriatr*. 2018;18(1):125.
16. Cooley SA, Paul RH, Strain JF, Boerwinkle A, Kilgore C, Ances BM. Effects of anticholinergic medication use on brain integrity in persons living with HIV and persons without HIV. *AIDS*. 2021;35(3):381-391.
17. Rubin LH, Radtke KK, Eum S, et al. Cognitive burden of common non-antiretroviral medications in HIV-infected women. *J Acquir Immune Defic Syndr*. 2018;79(1):83-91.
18. Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev*. 2009;41(2):67-76.
19. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2004;57(1):6-14.
20. Winston A, Jose S, Gibbons S, et al. Effects of age on antiretroviral plasma drug concentration in HIV-infected subjects undergoing routine therapeutic drug monitoring. *J Antimicrob Chemother*. 2013;68(6):1354-1359.
21. Cory TJ, Schacker TW, Stevenson M, Fletcher CV. Overcoming pharmacologic sanctuaries. *Curr Opin HIV AIDS*. 2013;8(3):190-195.
22. Erdo F, Denes L, de Lange E. Age-associated physiological and pathological changes at the blood-brain barrier: a review. *J Cereb Blood Flow Metab*. 2017;37(1):4-24.
23. Berger JR, Avison M. The blood brain barrier in HIV infection. *Front Biosci*. 2004;9:2680-2685.
24. Gras G, Kaul M. Molecular mechanisms of neuroinvasion by monocytes-macrophages in HIV-1 infection. *Retrovirology*. 2010;7:30.
25. Ivey NS, MacLean AG, Lackner AA. Acquired immunodeficiency syndrome and the blood-brain barrier. *J Neurovirol*. 2009;15(2):111-122.
26. Castillo-Mancilla JR, Phillips AN, Neaton JD, et al. Incomplete ART adherence is associated with higher inflammation in individuals who achieved virologic suppression in the START study. *J Int AIDS Soc*. 2019;22(6):e25297.
27. Guaraldi G, Milic J, Marcotullio S, Mussini C. A patient-centred approach to deprescribing antiretroviral therapy in people living with HIV. *J Antimicrob Chemother*. 2020;75(12):3425-3432.
28. Blanco JR, Morillo R, Abril V, et al. Deprescribing of non-antiretroviral therapy in HIV-infected patients. *Eur J Clin Pharmacol*. 2020;76(3):305-318.

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