Polypharmacy and risk of admission to hospital in people ageing with HIV: what is the contribution of drug–drug interactions?

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Few studies in HIV medicine have assessed adverse health outcomes related to polypharmacy. Amy Justice and colleagues[1] previously showed in the Veterans Aging Cohort Study (VACS) that the risk of hospitalisation and mortality increases with the number of medications an individual is taking concurrently after accounting for severity of illness.[1] However, the observation that the severity of illness alone does not explain the association between polypharmacy and risk of hospitalisation prompted the same authors to further investigate, in this issue of *The Lancet Healthy Longevity*, how much of this association is explained by drug interactions and whether this association differs by HIV status.[2]

To address this question, Justice and colleagues used an innovative approach combining machine learning with known pairwise drug interactions (KPDI) identified by linking drug–drug interaction data in the DrugBank database to active medications retrieved from VACS for the period Oct 1, 2008, to Sept 30, 2009. The analysis included 9186 people ageing with HIV and 37 930 demographically similar uninfected individuals. The authors found that both KPDIs and the risk of hospitalisation increased for each additional medication. Compared with people ageing without HIV, people ageing with HIV had more KPDIs and had a slightly higher related risk of hospitalisation, suggesting that they might be more susceptible to harm from polypharmacy. A substantial proportion of the risk of hospitalisation was not explained after adjusting for demographics, severity of illness, and the KPDI index, supporting the presence of additional contributing factors.

This study adds novel insights into the complex problem of polypharmacy. One strength of this analysis is that the investigators were able to control for the severity of illness (ie, physiological frailty) to account for confounding by indication. Another strength is the careful matching of the two cohorts, notably for traditional risk factors for chronic comorbidities, thereby reducing the probability that observed differences between groups are due to these factors.

The finding that people ageing with HIV have more KPDIs and have a higher risk of hospitalisation than the comparator group should nevertheless be interpreted with caution considering that the analysis was based on pharmacy data from 2008–09, when protease inhibitors were commonly used as ART medication. Protease inhibitors are no longer recommended as first-line agents and are known to have many drug–drug interactions,[3] which might account for the differences between people ageing with and without HIV in this cohort. Nevertheless, a difference in susceptibility to polypharmacy remains plausible because people ageing with HIV typically have multimorbidities a decade earlier than uninfected individuals, possibly due to chronic immune activation or immune senescence.[4] Thus, the extended exposure and accumulated toxicity of medications could make people with HIV more susceptible to the adverse effects of polypharmacy. The duration of HIV infection, HIV-induced immune deficits, and a low socioeconomic level are also risk factors for multimorbidities and the related longer exposure to medications.

For the **DrugBank website** see https://go.drugbank.com/drug-interaction-checker

The finding that KPDIs explain only part of the association between polypharmacy and risk of hospitalisation should prompt future studies to investigate the role of prescribing issues other than drug–drug interactions (eg, inappropriate medication, unadjusted dosing), which were found to be common in people ageing with HIV[5] and which might also lead to adverse health outcomes. Previous analyses have shown that women have more polypharmacy and medication errors.[5,6] The current study did not observe a sex difference in harm from polypharmacy; however, women comprised less than 3% of the study population, thus preventing any definitive conclusion relating to sex differences. Future studies are needed to address this uncertainty and to assess the role of frailty as a potential contributor to the risk of hospitalisation related to polypharmacy. Frailty is common in people ageing with HIV and has been linked to polypharmacy in a bi-directional way (ie, frailty can lead to polypharmacy

or the other way around). Frailty and polypharmacy are independent risk factors for mortality but the combination of the two was shown to significantly increase the risk of death.[7] Importantly, frail and pre-frail uninfected individuals have been shown to be susceptible to harm from polypharmacy whereas non-frail individuals were not;[8] thus, assessment of frailty and polypharmacy should be integrated in the care of people ageing with HIV aged 50 years and older.

Justice and colleagues[2] discuss also the observation that a health benefit might be seen when using few medications whereas the benefit is lost as the number of medications increases, particularly if associated with a high KPDI index. Although polypharmacy is often unavoidable in people ageing with HIV with multimorbidities, efforts should be made to minimise unnecessary or inappropriate polypharmacy to reduce the risk of drug–drug interactions and related harm. Interventions to limit polypharmacy include periodic medication reconciliation, review, and prioritisation.[3] A patient-centred approach, taking into account the risk and benefit of each medication for a given patient, should be considered, particularly in those who are frail. This approach, together with the training of HIV-care providers to include prescribing principles for geriatric care, have been identified as valuable measures to improve the care of people ageing with HIV.[9] A multidisciplinary team including, but not restricted to, HIV practitioners, geriatricians, and pharmacologists or pharmacists is recommended to optimise treatments of multimorbid people ageing with HIV. Finally, a comprehensive collection of medications and computerised prescription systems combining several tools to screen for inappropriate prescribing (including drug–drug interactions) are warranted to efficiently perform medication reviews.

CA has received personal payment from Gilead, Janssen, MSD, and ViiV Healthcare. CM has received research funding from Gilead and speaker honoraria from ViiV Healthcare and MSD paid to her institution.

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