Anticholinergic medications associated with falls and frailty in people with HIV

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Abstract

Background: Anticholinergic medications (ACMs) are associated with poorer age-related outcomes including falls and frailty. We investigate associations of ACM use with recurrent falls and frailty among older (≥50 years) people with HIV in the POPPY study.

Methods: Anticholinergic potential of co-medications at study entry was coded using the anticholinergic burden score, anticholinergic risk score and Scottish Intercollegiate Guidelines Network score; drugs scoring ≥1 on any scale were defined as ACM. Associations with recurrent falls (≥2 falls in the previous 28 days) and frailty (modified Fried's) were assessed using logistic regression adjusting for 1) possible demographic/lifestyle confounders, and additionally 2) clinical factors and depressive symptoms (PHQ-9).

Results: ACM use was reported by 193 (28%) of 699 participants, with 64 (9%) receiving ≥2 ACM; commonly prescribed ACMs were codeine (12%), citalopram (12%), loperamide (9%) and amitriptyline (7%). Falls were reported in 63/673 (9%) and 126/609 (21%) met the frailty criteria. Both recurrent falls and frailty were more common in ACM users than non-users (recurrent falls: 17% in users vs. 6% in non-users, p<0.001; frailty: 32% vs. 17%, respectively, p<0.001). Use of ≥2 ACMs was associated with increased odds of falls after adjustment for demographic/lifestyle factors (odds ratio 4.53 [95% confidence interval 2.06-9.98]) and additionally for clinical factors (3.58 [1.37-9.38]). Similar, although weaker, associations were seen with frailty (2.26 [1.09-4.70] and 2.12 [0.89-5.0] respectively).

Conclusions: ACM are commonly prescribed for PLWH, with evidence for an association with recurrent falls and frailty. Clinicians should be alert to this and reduce ACM exposure where possible.

Background

Anticholinergic medication (ACM) use has increased significantly over the last 20 years, particularly in the older population, with prevalence of their use estimated to be between 37%-65% (1,2). ACMs act against both muscarinic and nicotinic acetylcholine receptor signalling in the central and peripheral nervous system. They are used in the management of a broad range of medical conditions including psychiatric disorders, nausea, pain, allergy and bladder dysfunction. The anticholinergic activity of many drugs is well known, but a number of drugs with milder activity are not commonly considered as ACMs. Typical side effects of anticholinergic activity include drowsiness, urinary retention, constipation, dry mouth, blurred vision and confusion. Elderly people are particularly susceptible to ACM side effects due to reduced drug clearance and a decrease in cholinergic transmission (3). Amongst older populations, it is also widely documented that ACM use is associated with age-related health outcomes such as incident dementia, cognitive impairment, falls and frailty (4–10). These effects are little studied amongst people living with HIV and clinicians and guidelines are not generally alert to this effect.

Globally, successful efforts to diagnose and effectively treat people with HIV have resulted in the median age of this group rising over time as they live longer (11). Population surveillance data show that in 2019, 42.4% (41,855) of people accessing HIV specialist care in the UK were over 50 years of age, a more than doubling from the rate of 20.6% reported in 2010 (12). The focus of clinical care is thus shifting to the management of complex comorbidities, poly-pharmacy and consequences of ageing which occur with a higher frequency in people with HIV compared to the general population (13,14). This may be due to chronic inflammation of the virus itself, exposure to antiretroviral medications and higher prevalence of certain lifestyle factors and mental health concerns (15).

The prevalence of ACM use in older people with HIV is estimated to be between 15 and 30% (16–18). In this population there is some evidence of an association of ACM use with self-reported cognitive impairment (19), worse neuro-psychometric performance (20–22) and reduced structural brain volume and fractional anisotropy on magnetic resonance imaging, although the latter may demonstrate reversibility following reduction of ACM use (23). Whilst poly-pharmacy and use of “cognitive

adverse effects medications" (including ACMs) increased the odds of recurrent falls in one large US cohort of people with HIV (24), other studies that have considered associations of ACM use with falls and frailty in this population are rare.

Several anticholinergic burden scales have been developed to identify and quantify the cumulative anticholinergic activity of an individual's medications and hence their risk of developing adverse effects. These scales are generally based on expert opinion and *in vitro* evidence, and include the AntiCholinergic Burden (ACB) scale (25,26), Anticholinergic Risk Scale (ARS) (27) (both US-based scores that grade a medication as having either low, moderate or high anticholinergic activity) and the UK Scottish Intercollegiate Guideline Network (SIGN) scale (which classifies medications that are to be used with caution or avoided if possible) (28). Low to moderate concordance of the scales available has been seen (29); a review of 16 ACM burden scores showed that ARS and ACB were correlated with a Spearman correlation coefficient of 0.6 (30). Currently, however, the concordance between these scales for identifying common medications used by people with HIV on ACMs is unclear.

The Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) study is a multicentre prospective cohort study designed to evaluate the consequences of aging with HIV. This cohort therefore provides an ideal setting within which to study the potential effects of ACM use on adverse consequences of ageing. Here, we describe the prevalence of ACM use, the concordance between three widely used scales from assessing the anti-cholinergic properties of commonly used medications in people with HIV and the association of ACM use with the prevalence of falls and frailty in older people with HIV in this cohort.

Our hypothesis is that ACM use may be associated with falls and frailty in older people with HIV as suggested by the studies in the general population.

Methods

The POPPY Study

POPPY is a prospective cohort study at seven clinical sites in the UK and one in Ireland that aims to investigate the impact of HIV on the development and outcomes of comorbidities and pharmacotherapy among older people with HIV (31). Three sub-groups are studied: older people with HIV (age ≥50 years at study entry, n=699), younger people with HIV (age <50 years, n=374) and older people without HIV (age ≥50 years, n=304). Eligible people with HIV acquired HIV through sexual transmission (sex between men or sex between men and women; those acquiring HIV through other routes, including injection drug use, were excluded), were cisgender, and were either of white or black African ethnicity. The study was approved by the UK National Research Ethics Service (NRES; Fulham, London, UK; reference number 12/LO/1409) and written informed consent was obtained from all participants. The present analyses included only the older group of people with HIV, and used cross-sectional data from the baseline POPPY visit conducted between April 2013 and February 2016.

The POPPY dataset includes information on socio-demographics, pharmacotherapy, personal and family medical history, healthcare utilisation and quality-of-life. Information collected includes self-reported use of any medications in the year prior to study enrolment. The POPPY dataset is linked to the UK Collaborative HIV Cohort (UK sites (32)) and to the UCD ID Cohort (Dublin (33)) for historic data on antiretroviral therapy, CD4+ T-cell counts and HIV RNA values.

ACM definition

In order to create an inclusive list of ACMs, each medication used was allocated a score from the ACB (which covers a total of 99 medications within the scale), the ARS (50 medications) and SIGN (which scores 47 medications and additionally assigns a class score to drugs in three broad groups: opiates, serotonin re-uptake inhibitors and tricyclic antidepressants). Medications scoring 1 or higher on any of the three scales were defined as an ACM.

Outcomes

Two outcome measures were investigated. **Recurrent falls:** recent fall history was captured using the Cambridge Falls questionnaire (34) through a question which asked whether the participant had experienced any falls over the past 28 days. Those reporting more than one fall over this period were considered to have experienced a recurrent fall. **Frailty** was measured using a modified version of Fried's criteria for frailty (14,35), however only 4 out of the 5 components of the original score were used (grip strength, time taken to walk 15 feet, self-reported exhaustion and self-reported low physical activity) as weight loss was not assessed; those meeting 3 or 4 of these criteria were deemed to be frail.

Based on the published literature, the following covariates were considered as potential confounders: *demographic factors* (gender, ethnicity [black African, white], age at baseline, marital status [single, not single]); *socioeconomic factors* (current work status [employed, unemployed, sick/disabled, retired], housing [owner occupier, renting, temporary accommodation, homeless], educational attainment [low - GCSE/O levels and below, high - A levels and above]); *lifestyle characteristics* (smoking [current, ex-, never], alcohol use [yes, no], recreational drug use in the last 6 months [yes, no]); *HIV-related laboratory data* (current and nadir CD4+ T-cell count, HIV RNA level, CD8+ T-cell count); and *medical history* (diagnosis of major system illness, including any neurological diagnosis, mental health disorder, cardiovascular, endocrine, chest disease and cancer, total number of co-morbidities present, use of any concomitant medication, and total number of concomitant medications used (both excluding ACM and antiretroviral medications).

Depressive symptoms were captured using the Patient Health Questionnaire-9 (PHQ-9) (36) with scores of 0-4 representing none/minimal symptoms, 5-14 mild/moderate symptoms, and 15-27 moderate-severe/severe symptoms.

Statistical analysis

Associations of each covariate with receipt of any ACM were investigated using Chi-squared tests for categorical variables (or Fisher's exact tests when the expected number in any cell of the table was <5), Chi-squared test for trend for ordinal variables, unpaired t-tests for normally distributed continuous variables and Mann-Whitney/Kruskal-Wallis tests for non-normally distributed continuous variables.

Logistic regression models investigated the relationship of ACM use with the two binary outcomes of interest: (1) recurrent falls and (2) frailty. At the first stage, socio-demographic and lifestyle factors demonstrating a significant association with the use of ACM in univariate analyses were included in the multivariable models and were generally retained in these models, regardless of significance, with the exception of ethnicity which was subsequently excluded due to multicollinearity concerns (level 1). Next, we added the measure of depressive symptoms (PHQ-9 score), clinical indicators (number of comorbidities and number of non ACM co-medications) and HIV-related variables that were significantly associated with each outcome in descriptive analyses ($p<0.05$, level 2). Analyses (level 1 and 2) were repeated after considering the exposure as an ordinal (receipt of 0, 1 or ≥2 ACMs) rather than binary variable, allowing us to investigate a possible dose-response relationship with the exposure.

All statistical analysis used Stata version 16 or 17, with p-values <0.05 considered indicative of statistical significance.

Results

Participants had a median age of 57 years (interquartile range 53-62), 88% were male, 86% White, 60% single and 34% unemployed or sick/disabled (Table 1). Overall, the study population had successfully treated HIV: 99% (692/699) were on antiretroviral therapy, 92% (642/699) had an HIV RNA <50 copies/ml and 89% (607/699) a CD4+ T-cell count >350 cells/mm^3.

A total of 50 different medications used by participants were identified as ACMs based on at least one of the three scales; 31 were identified by the ACB, 21 by the ARS and 33 by SIGN guidelines. Of these 50 medications, 17 of the 31 identified by ACB (55%) had a low ACB score (score=1) and 7 of the 21 identified by ARS (33%) had an ARS score of 1. Twenty-four of the 33 identified by the SIGN guidelines (73%) were graded as low or “caution”. Only a quarter of the 50 medications (n=12, 24 %) were identified as ACMs on all three scales. The most commonly prescribed ACMs and their scores on each scale are shown in Table 2 (full list appendix 1); amitriptyline had the highest score with scores of 3 on both the ARS and ACB scale. In total, 28% (193/699) reported use of any ACM with 9% (64/699) reporting use of ≥2 such medications. There was no significant difference in use of ACM between female and male participants (23% vs 25% respectively, p=0.61). Those reporting use of any ACM were more likely to be White (92% vs 84%, p=0.005), single (69% vs 60%, p=0.02), sick/disabled (30% vs 15%, p<0.001) and report recent recreational drug use in the previous 6 months (31% vs 23%, p=0.05) than non-ACM users. They were also more likely to have a higher PHQ-9 score indicating more severe depressive symptoms, to have a higher number of comorbidities and to use a higher number of co-medications [Table 1]. There were no significant differences in HIV-specific parameters between those with and without use of ACMs; viral load <50 copies/ml (93% vs 92%, p=0.72), CD4<350 cells/mm^3 (14% vs 10%, p=0.12) and CD4 nadir <200 cells/mm^3 (52% vs 47%, p=0.15).

For those with data available, 9% (63/673) reported recurrent falls with falls being more commonly reported among ACM users 17% (32/190) than non-users 6% (31/483), p<0.001. The unadjusted odds ratio (OR) for recurrent falls in people exposed to any ACM vs none was 3.33 (95% confidence interval [95% CI] 1.88-5.90, p<0.001) [Figure 1]. After adjustment for socio-demographic and clinical factors, the odds remained

raised if there was exposure to any ACM (aOR 1.93 [0.93-3.97], p=0.08). In subsequent analyses that considered the use of ACMs as an ordinal variable, the use of 1 ACM alone was associated with an increased odds of 2.09 and the use of ≥2 ACMs an increased odds of 6.83, indicating a dose-response relationship [Figure 1]. After adjustment for demographic, lifestyle and clinical factors, the use of ≥2 ACMs was associated with an increased odds of recurrent falls (aOR after adjustment for demographic and lifestyle factors only: 4.53 [2.06-9.98]; aOR after additional adjustment for clinical factors: 3.58 [1.37-9.38]).

Overall, 126 of 609 participants (21%) met frailty criteria. Of those meeting frailty criteria 14% (17/126) also reported recurrent falls in the previous 28 days. Those reporting any ACM use were more likely to meet the criteria 32% (52/163) than non-users 17% (74/446) p<0.001. The odds of frailty were higher among participants exposed to any ACM vs none in univariate analysis (OR 2.29 [1.48-3.55]). After adjustment for demographic, lifestyle and clinical factors, the odds ratio for frailty if exposed to any ACM was 1.66 [95% CI 0.94-2.95, p=0.08] [Figure 1]. In subsequent analysis with the ordinal exposure, a similar although weaker dose-response relationship was seen with frailty; unadjusted odds ratio for frailty if exposed to a single ACM was 1.93 [1.16-3.20] and to two or more was 3.33 [1.71-6.47]. After full adjustment these ORs were attenuated to 1.52 [0.82-2.84] and 2.12 [0.89-5.02], respectively [Figure 1].

Discussion

Our analysis of ACM use and age-related outcomes in the POPPY cohort suggests that over a quarter of people with HIV over the age of 50 years may be prescribed ACMs, with roughly one in ten of this group receiving multiple ACMs. Use of two or more ACMs was associated with a doubling in the odds of recurrent falls in this population as well as a similar, although slightly weaker, association with frailty. These associations persisted even after controlling for a range of socio-demographic, lifestyle and clinical confounders. Early diagnosis and modern antiretroviral therapy has transformed care for people with HIV, who now are an ageing population. As age-associated falls and frailty become more prevalent, greater emphasis on reducing the modifiable risk factors for these events is needed (14,37–39).

There is sparse existing literature on the association between ACM use and age-related co-morbidities among people living with HIV. There are some data showing associations of their use with self-reported (19,22) and objective cognitive impairment (17,20,23). Consistent with our findings, Jakeman et al. identified most ACMs used by over 65 year olds within the Swiss HIV Cohort Study (SHCS) (19) and subsequently a subset of over 45 year olds of the SHCS who underwent formal cognitive testing (20), as those of low anti-cholinergic potential. Looking at the use of ACMs and other “neurocognitive adverse effect medications”, Psomas et al. recently reported a relationship between ACM use and falls in a cohort of women with HIV in the USA. As with our study, they also found a cumulative dose-response relationship with the number of ACMs used (24).

Our findings concord with studies of the general geriatric population showing association of ACM use with falls and frailty, however geriatric study cohorts participants are generally over 65 year olds (5,7,9). Notably, falls and frailty are seen at a younger age in people with HIV (40), possibly due to lifestyle factors and a higher burden of comorbidities. People living with HIV may also be more sensitive to the effects of ACM use due to interaction with antiretroviral medications (41,42).

ACM drugs identified here are mostly not well known to have anti-cholinergic potential and are widely prescribed by a variety of clinicians providing healthcare. Our findings thus indicate the need for greater awareness amongst prescribers of drugs with

anti-cholinergic potential and their adverse effects amongst people with HIV. De-prescribing requires a focussed and careful medical review to determine if medications can be dose-reduced or stopped if they are no longer needed or may be causing harm. Broad barriers to de-prescribing in general have been highlighted as lack of time, low clinician confidence, resistance to interdisciplinary working and a lack of clarity around responsibility for management of medications (43). However an improvement in falls and frailty in elderly patients after de-prescribing ACMs has been demonstrated in the general geriatric population (44). Strong communication with patients and collaboration between specialty and primary care has been shown to facilitate de-prescribing (43,45) as well as strong specialist pharmacy support (46).

There are currently many scales in widespread use to classify the anti-cholinergic potential of medications. We chose the ACB and ARS scales since these have previously been used in the HIV population and SIGN guidelines scale since this is specific for the UK formulary. There is currently a lack of consensus of which scale best defines ACM potential; NICE guidelines for the management of dementia advise caution in prescribing of ACMs but do not recommend which scale to use (47). Our study demonstrates that only 24% of the ACMs used in our study population were defined as an ACM on all three scales and therefore a consensus is needed for clinical guidance.

There are limitations to this study. Our cross-sectional data arise from an observational study and we cannot establish causality or temporality. Whilst every effort was made to control for confounders, unmeasured confounders may exist. For example, significant efforts were made to control for the underlying reason why people were on these medications by including the number of main comorbidities and poly-pharmacy measures, but it is still difficult to disentangle whether it is the underlying health condition or the medication which predisposes an individual to falls and frailty. Further analyses are planned of longitudinal data from the study which will allow us to describe changes in ACM use over time, and to investigate the direction of any associations seen. We note that neither duration nor dose of use were available for this analysis and these factors may conceivably impact estimation of anti-cholinergic burden; some medications may be used for very short periods of time and therefore not have a sizeable effect on overall ACM burden. Thirdly the exposure and part of the outcome

measures were self-reported which may introduce inaccuracies. Our definition of falls experienced is limited to events occurring within the last four weeks, which may underestimate the prevalence. Similarly, frailty is a complex, difficult to define condition that indicates vulnerability to poor health outcomes due to physiological decline. Single or combinations of other underlying physical and mental health conditions can result in a frailty-like phenotype, thus this is a heterogeneous category. Finally, as noted, this is a population of mainly well-treated people with HIV with high levels of viral suppression and is not generalizable to all populations of people living with HIV.

Overall, this work has potentially significant implications for clinical practice. It strongly supports an association of ACM use with falls and frailty amongst aging people living with HIV in the UK. Current practice should be updated to review medications regularly, with the intention to de-prescribe or avoid medications with anticholinergic activity if not essential, particularly in people aged 50 years and above. A comprehensive list of medications with anticholinergic potential in this population should be recommended nationally and further work to guide implementation in this population is needed.

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Conflicts of interest

AW has been an investigator on studies sponsored by, received research grants, speaker honoraria or advisory board fees from ViiV Healthcare, Gilead Sciences, MSD and Janssen.

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Author contribution statement

CAS, KMK, PWGM and AW designed and obtained funding for the study. JD performed all data analyses, undertook a literature search and prepared the first draft of the manuscript. DB provided study co-ordination and, together with EB, supported essential data collection and preparation of the data sets. KMK provided expert input to the interpretation of respiratory symptom data. FAP and MB provided clinical interpretation of study findings and are members of the POPPY study management team (with CAS, PWGM, MS and AW). JA, IW, JHV and MJ provided intellectual input to the POPPY study design, and supported study recruitment, data collection and clinical management. MS provided liaison with the HIV-infected patient community for all aspects of the study design and management. All authors provided critical review of the draft manuscript and have seen an approved the final version.

Bibliography

1. Grossi CM, Richardson K, Savva GM, Fox C, Arthur A, Loke YK, et al. Increasing prevalence of anticholinergic medication use in older people in England over 20 years: Cognitive function and ageing study i and II. BMC Geriatr. 2020;20(1):1–8.
2. Richardson K, Bennett K, Maidment ID, Fox DC, Smithard D, Kenny RA. Use of Medications with Anticholinergic Activity and Self- Reported Injurious Falls in Older Community-Dwelling Adults. 2015;1561–9.
3. Gasiorowska A, Wydrych M, Drapich P, Zadrozny M, Steczkowska M, Niewiadomski W, et al. The Biology and Pathobiology of Glutamatergic, Cholinergic, and Dopaminergic Signaling in the Aging Brain. Front Aging Neurosci. 2021;13(July).
4. Ziad A, Olekhnovitch R, Ruiz F, Berr C, Bégaud B, Goldberg M, et al. Anticholinergic drug use and cognitive performances in middle age : findings from the CONSTANCES cohort. 2019;1107–15.
5. Machado-Duque ME, Castaño-Montoya JP, Medina-Morales DA, Castro-Rodríguez A, González-Montoya A, Machado-Alba JE. Drugs With Anticholinergic Potential and Risk of Falls With Hip Fracture in the Elderly Patients: A Case–Control Study. J Geriatr Psychiatry Neurol. 2018;31(2):63–9.
6. Suehs BT, Caplan EO, Hayden J, Ng DB, Gaddy RR. The Relationship Between Anticholinergic Exposure and Falls, Fractures, and Mortality in Patients with Overactive Bladder. Drugs and Aging [Internet]. 2019;36(10):957–67. Available from: https://doi.org/10.1007/s40266-019-00694-5
7. Zia A, Kamaruzzaman S, Myint PK, Tan MP. Anticholinergic burden is

associated with recurrent and injurious falls in older individuals. Maturitas [Internet]. 2016;84:32–7. Available from: http://dx.doi.org/10.1016/j.maturitas.2015.10.009

8. Ruiz SJ, Cevallos V, Baskaran D, Mintzer MJ, Ruiz JG. The cross-sectional association of frailty with past and current exposure to strong anticholinergic drugs. Aging Clin Exp Res [Internet]. 2021;33(8):2283–9. Available from: https://doi.org/10.1007/s40520-020-01742-6

9. Marcum ZA, Wirtz HS, Pettinger M, Lacroix AZ, Carnahan R, Cauley JA, et al. Anticholinergic medication use and falls in postmenopausal women: Findings from the women's health initiative cohort study. BMC Geriatr [Internet]. 2016;16(1):1–9. Available from: http://dx.doi.org/10.1186/s12877-016-0251-0

10. Reallon E, Chavent B, Gervais F, Dauphinot V, Vernaudon J, Krolak-Salmon P, et al. Medication exposure and frailty in older community-dwelling patients: a cross-sectional study. Int J Clin Pharm [Internet]. 2020;42(2):508–14. Available from: https://doi.org/10.1007/s11096-020-01007-2

11. Autenrieth CS, Beck EJ, Stelzle D, Mallouris C, Mahy M, Ghys P. Global and regional trends of people living with HIV aged 50 and over: Estimates and projections for 2000–2020. PLoS One. 2018;13(11):1–11.

12. Public Health England. Trends in HIV testing , new diagnoses and people receiving HIV-related care in the United Kingdom : data to the end of December 2019. 2020;14(20):1–15.

13. Schouten J, Wit FW, Stolte IG, Kootstra NA, Van Der Valk M, Geerlings SE, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between hiv-infected and uninfected individuals: The age H IV cohort study. Clin Infect Dis. 2014;59(12):1787–97.

14. Kooij KW, Wit FWNM, Schouten J, van der Valk M, Godfried MH, Stolte IG, et al. HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls. AIDS. 2016;30(2):241–50.

15. De Francesco D, Underwood J, Bagkeris E, Boffito M, Post FA, Mallon PWG, et al. Depression, lifestyle factors and cognitive function in people living with HIV and comparable HIV-negative controls. HIV Med. 2019;20(4):274–85.

16. Casajús-Navasal A, Marín-Gorricho R, Gallardo-Anciano J, Nebot-Villacampa MJ, Zafra-Morales R, González-Pérez Y. Prevalence of the consumption of anticholinergic drugs in HIV patients. Farm Hosp. 2018;42(1):1–4.

17. Rubin LH, Radtke KK, Eum S, Tamraz B, Kumanan KN, Springer G, et al. Cognitive burden of common non-antiretroviral medications in HIV-infected women. J Acquir Immune Defic Syndr. 2018;79(1):83–91.

18. Mazzitelli M, Milinkovic A, Pereira B, Palmer J, Tong T, Asboe D, et al. Polypharmacy and evaluation of anticholinergic risk in a cohort of elderly people living with HIV. Aids. 2019;33(15):2439–41.

19. Jakeman B, Scherrer A, Battegay M, Gunthard HF, Hachfeld A, Calmy A, et al. Anticholinergic medication use in elderly people living with HIV and self-

reported neurocognitive impairment: a prospective cohort study. 2022;(November 2021):492–9.

20. Jakeman B, Scherrer AU, Darling KEA, Damas J, Bieler-aeschlimann M, Hasse B, et al. Anticholinergic and Sedative Medications Are Associated With Neurocognitive Performance of Well Treated People With Human Immunodeficiency Virus. Open Forum Infect Dis [Internet]. 9(9):1–8. Available from: https://doi.org/10.1093/ofid/ofac457

21. Rubin LH, Neijna AG, Shi Q, Hoover DR, Tamraz B, Anastos K, et al. Degree of Polypharmacy and Cognitive Function in Older Women with HIV. AIDS Res Hum Retroviruses. 2022;38(7):571–9.

22. Dastgheyb RM, Buchholz AS, Fitzgerald KC, Xu Y, Williams DW, Springer G, et al. Patterns and Predictors of Cognitive Function Among Virally Suppressed Women With HIV. Front Neurol. 2021;12(February):1–14.

23. 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. 2020;Publish Ah(November 2020):381–91.

24. Psomas CK, Hoover DR, Shi Q, Brown TT, Vance DE, Holman S, et al. Polypharmacy Is Associated With Falls in Women With and Without HIV. 2022;90(3):351–9.

25. Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: A review and practical application. Aging health. 2008;4(3):311–20.

26. Campbell N, Maidment I, … CF-J of the, 2013 undefined. The 2012 update to the anticholinergic cognitive burden scale. research.aston.ac.uk [Internet]. [cited 2021 Oct 5]; Available from: https://research.aston.ac.uk/en/publications/the-2012-update-to-the-anticholinergic-cognitive-burden-scale

27. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008;168(5):508–13.

28. NHS Scotland. Polypharmacy Guidance Realistic Prescribing. state 3D Print [Internet]. 2018;1–29. Available from: https://learn-eu-central-1-prod-fleet01-xythos.learn.cloudflare.blackboardcdn.com/5efb3ace8ea0a/7003322?X-Blackboard-Expiration=1620324000000&X-Blackboard-Signature=gL27EeAufh%2BcsQAmn8v8SmP7lZcfz4ml4kdfbJUYrfs%3D&X-Blackboard-Client-Id=147883&response-ca

29. Naples JG, Marcum ZA, Perera S, Gray SL, Newman AB, Simonsick EM, et al. Concordance Between Anticholinergic Burden Scales. J Am Geriatr Soc. J Am Geriatr Soc ... 2015;63(10):2120–4.

30. Lozano-Ortega G, Johnston KM, Cheung A, Wagg A, Campbell NL, Dmochowski RR, et al. A review of published anticholinergic scales and measures and their applicability in database analyses. Arch Gerontol Geriatr. 2020;87(November 2018).

31. Bagkeris E, Burgess L, Mallon PW, Post FA, Boffito M, Sachikonye M, et al. Cohort profile: The Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) study. [cited 2021 Oct 6]; Available from: https://academic.oup.com/ije/article/47/5/1391/4994261

32. The creation of a large UK-based multicentre cohort of HIV-infected individuals: The UK Collaborative HIV Cohort (UK CHIC) Study. HIV Med. 2004;5(2):115–24.

33. McGettrick P, Ghavami-Kia B, Tinago W, Macken A, O'Halloran J, Lambert JS, et al. The HIV Care Cascade and sub-analysis of those linked to but not retained in care: the experience from a tertiary HIV referral service in Dublin Ireland. HIV Clin Trials. 2017;18(3):93–9.

34. Lord SR. Falls in older people : risk factors and strategies for prevention. 2nd ed. Lord SR (Stephen R, editor. Cambridge: Cambridge University Press; 2007.

35. Fried L, Tangen C, … JW-TJ of, 2001 undefined. Frailty in older adults: evidence for a phenotype. academic.oup.com [Internet]. [cited 2021 Oct 5]; Available from: https://academic.oup.com/biomedgerontology/article-abstract/56/3/M146/545770

36. Kroenke K, Spitzer RL. The PHQ-9: A New Depression Diagnostic and Severity Measure. Psychiatr Ann. 2002;32(9):509–15.

37. Guaraldi G, De Francesco D, Milic J, Franconi I, Mussini C, Falutz J, et al. The Interplay Between Age and Frailty in People Living With HIV: Results From an 11-Year Follow-up Observational Study. [cited 2021 Oct 6]; Available from: http://www.who.int/ageing/events/world-report-

38. Rees HC, Ianas V, Mccracken P, Smith S, Georgescu A, Zangeneh T, et al. Measuring Frailty in HIV-infected Individuals . Identification of Frail Patients is the First Step to Amelioration and Reversal of Frailty. 2013;(July):1–5.

39. Id GG, Zona S, Rita A, Id S, Menozzi M, Dolci G, et al. The dynamic association between Frailty , CD4 and CD4 / CD8 ratio in people aging with HIV. 2019;1–11.

40. Önen NF, Agbebi A, Shacham E, Stamm KE, Önen AR, Overton ET. Frailty among HIV-infected persons in an urban outpatient care setting. J Infect. 2009;59(5):346–52.

41. Hader RIIS. Inhibition of Desipramine Hydroxylation (Cytochrome P450-2D6) in Vitro by Quinidine and by Viral Protease Inhibitors : Relation to Drug Interactions in Vivo. 1998;87(10).

42. Disposition D. Ritonavir increases loperamide plasma concentrations without evidence for. 2001;70(5).

43. Stewart C, Gallacher K, Nakham A, Cruickshank M, Newlands R, Bond C, et al. Barriers and facilitators to reducing anticholinergic burden: a qualitative systematic review. Int J Clin Pharm [Internet]. 2021;43(6):1451–60. Available from: https://doi.org/10.1007/s11096-021-01293-4

44. Ailabouni N, Mangin D, Nishtala PS. DEFEAT-polypharmacy: deprescribing

anticholinergic and sedative medicines feasibility trial in residential aged care facilities. Int J Clin Pharm [Internet]. 2019;41(1):167–78. Available from: https://doi.org/10.1007/s11096-019-00784-9

45. Kiplagat J, Tran DN, Barber T, Njuguna B, Vedanthan R, Triant VA, et al. How health systems can adapt to a population ageing with HIV and comorbid disease. Lancet HIV [Internet]. 2022;9(4):e281–92. Available from: http://dx.doi.org/10.1016/S2352-3018(22)00009-1

46. Gannon JM, Lupu A, Brar J, Brandt M, Zawacki S, John S, et al. Deprescribing anticholinergic medication in the community mental health setting: A quality improvement initiative. Res Soc Adm Pharm [Internet]. 2021;17(10):1841–6. Available from: https://doi.org/10.1016/j.sapharm.2020.12.010

47. wwwniceorguk N. Dementia: assessment, management and support for people living with dementia and their carers [Internet]. NICE guideline [NG97]. Available from: https://www.nice.org.uk/guidance/ng97/chapter/Recommendations#interventions-to-promote-cognition-independence-and-wellbeing

Table 1: Socio-demographic, lifestyle and clinical factors and their association with ACM use in the cohort					
Variable	Category	Number of people n= 699	On an ACM		p-value
			No (n=506) n (%)	Yes (n=193) n (%)	
Age (years), median (IQR)		57 (53-62)	57 (53-62)	56 (52-61)	*0.56
Gender	Male	612 (87.6)	441 (87.2)	171 (88.6)	0.61
Ethnicity	White	603 (86.2)	425 (84.0)	178 (92.2)	0.005
Marital status	Single	435 (62.2)	301 (59.5)	134 (69.4)	0.02
Work	Employed	283 (40.5)	220 (43.5)	63 (32.6)	<0.001
	Unemployed	99 (14.2)	67(13.2)	32 (16.6)	
	Sick/disabled/unknown	136 (19.5)	78 (15.4)	58 (30.1)	
	Retired	181 (25.9)	141 (27.9)	40 (20.7)	
Educational attainment	High	479 (68.5)	348 (68.8)	131 (67.9)	0.82
Smoking	Current Smoking	158 (22.6)	114 (22.5)	44 (22.8)	0.21
	Ex-smoker	263 (37.6)	186 (36.8)	77 (39.9)	
	Never smoked/unknown	278 (39.8)	206 (40.7)	72 (37.3)	
Current Alcohol use		555 (79.4)	405 (80.0)	150 (77.7)	0.79
Recreational drug use in the last 6 months		177 (25.3)	118 (23.3)	59 (30.6)	0.05
Depressive symptoms (PHQ-9)	None/minimal/unknown	396 (56.7)	312 (61.7)	82 (42.5)	**<0.001
	Mild/moderate	223 (31.9)	143 (28.3)	80 (41.5)	
	Moderate-severe/severe	80 (11.4)	49 (9.7)	31 (16.1)	
Number of comorbidities, mean (SD)		3.2 (1.7)	2.8 (1.6)	4.2 (1.5)	***<0.001
Number of co-medications	0	228 (32.6)	209 (41.3)	19 (9.8)	<0.001
	1-4	357 (51)	253 (50.0)	104 (53.9)	
	≥5	114(16)	44 (8.7)	70 (36.3)	

All p-values were generated through Chi-squared tests with the following exceptions: *Mann-Whitney ** Chi squared test for trend ***unpaired t-test

Table 2: Most frequently prescribed ACM and their assigned ACM score				
		Score assigned to each medications by anticholinergic medication scale		
Medication	Freq. n (%) n=410*	ACB[1]	ARS[2]	SIGN[3]
Codeine	36 (12.2)	1	0	1
Citalopram	34 (11.5)	0	0	1
Loperamide	25 (8.5)	1	2	1
Amitriptyline	21 (7.1)	3	3	0
Diazepam	17 (5.8)	1	0	1
Cetirizine	16 (5.4)	1	2	1
Mirtazapine	14 (4.8)	0	1	1
Dihydrocodeine	13 (4.4)	0	0	1
Tramadol	13 (4.4)	0	0	1
Sertraline	11 (3.7)	0	0	1
Ranitidine	10 (3.4)	1	1	1

*295 ACM prescriptions for all study participants included
[1] Anticholinergic Burden Scale, [2] Anticholinergic Risk Scale, [3] SIGN Guidelines

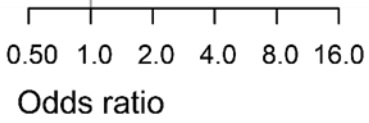
Appendix 1: Comprehensive list of all 50 medications scored ≥1 on any of the anticholinergic list scales used in the study population					
			Score assigned to each medications by ACM scale		
	Freq. (n=295)	Percent	ACB	ARS	SIGN
Codeine	36	12.2	1	0	1
Citalopram	34	11.5	0	0	1
Loperamide	25	8.5	1	2	1
Amitriptyline	21	7.1	3	3	0
Diazepam	17	5.8	1	0	1
Cetirizine	16	5.4	1	2	1
Mirtazapine	14	4.8	0	1	1
Dihydrocodeine	13	4.4	0	0	1
Tramadol	13	4.4	0	0	1
Sertraline	11	3.7	0	0	1
Ranitidine	10	3.4	1	1	1
Warfarin	7	2.4	1	0	0
Loratadine	6	2.0	1	2	1
Morphine	6	2.0	1	0	1
Metoclopramide	5	1.7	0	1	0
Prednisolone	5	1.7	1	0	0
Fluoxetine	4	1.4	0	0	1
Solifenacin	4	1.4	3	0	2
Chlorpheniramine	3	1.0	3	3	2
Levomepromazine	3	1.0	2	0	2
Olanzapine	3	1.0	3	2	1
Paroxetine	3	1.0	3	1	1
Buprenorphine	2	0.7	0	0	1
Dipyridamole	2	0.7	1	0	0

Hydrocortisone	2	0.7	1	0	0
Hydroxyzine	2	0.7	3	3	2
Hyoscine butylbromide	2	0.7	0	0	1
Oxybutynin	2	0.7	3	3	2
Promethazine	2	0.7	3	3	2
Quetiapine	2	0.7	3	1	1
Alprazolam	1	0.3	1	0	0
Bupropion	1	0.3	1	0	0
Carbidopa-levodopa	1	0.3	0	1	0
Colchicine	1	0.3	1	0	0
Cyproheptadine	1	0.3	2	3	2
Desloratadine	1	0.3	1	0	0
Diphenhydramine	1	0.3	3	3	0
Dosulepin	1	0.3	0	0	1
Doxylamine	1	0.3	3	0	0
Escitalopram	1	0.3	0	0	1
Fexofenadine	1	0.3	0	0	1
Frusemide	1	0.3	1	0	0
Ipratropium	1	0.3	0	0	1
Lithium	1	0.3	0	0	1
Nortriptyline	1	0.3	3	2	0
Pramipexole	1	0.3	0	1	0
Prochlorperazine	1	0.3	0	2	1
Propantheline	1	0.3	0	0	2
Tizanidine	1	0.3	0	3	2
Venlafaxine	1	0.3	1	0	0

*295 ACM prescriptions for all study participants included
[1] Anticholinergic Burden Scale, [2] Anticholinergic Risk Scale, [3] SIGN Guidelines

Figure 1: Results from logistic regression analysis of the association between the use of ACM and recurrent falls and frailty

Outcome	Number of ACMs	Adjustment	OR (95% CI)	p-value
Falls	Any	Unadjusted	3.33 (1.88 - 5.9)	<0.001
		Level 1	2.47 (1.34 - 4.56)	0.004
		Level 2	1.93 (0.93 - 3.97)	0.076
	1	Unadjusted	2.09 (1.03 - 4.23)	0.04
		Level 1	1.66 (0.79 - 3.49)	0.177
		Level 2	1.43 (0.63 - 3.25)	0.389
	2 or more	Unadjusted	6.83 (3.31 - 14.11)	<0.001
		Level 1	4.53 (2.06 - 9.98)	<0.001
		Level 2	3.58 (1.37 - 9.38)	0.009
Frailty	Any	Unadjusted	2.29 (1.48 - 3.55)	<0.001
		Level 1	1.8 (1.12 - 2.92)	0.016
		Level 2	1.66 (0.94 - 2.95)	0.081
	1	Unadjusted	1.93 (1.16 - 3.2)	0.011
		Level 1	1.62 (0.93 - 2.82)	0.087
		Level 2	1.52 (0.82 - 2.84)	0.186
	2 or more	Unadjusted	3.33 (1.71 - 6.47)	<0.001
		Level 1	2.26 (1.09 - 4.70)	0.028
		Level 2	2.12 (0.89 - 5.02)	0.089



Level 1 adjustment was for age, work, marital status and recent recreational drug use.
Level 2 adjustment was for Level 1 factors plus number of non ACM co-medications, number of comorbidities and PHQ-9 score.