TITLE: **Delirium Among People Aging with and without HIV: Role of Alcohol and Neurocognitively Active Medications**

Running title: Delirium, alcohol and medications by HIV status

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Impact Statement: We certify that this work is novel and builds on other recent clinical research by quantifying the combined effects of neurocognitively active medications and unhealthy alcohol use, defined as moderate and high-risk self-reported use on the AUDIT-C, and their association with delirium.

Prior work from our group already demonstrated the associated harms of polypharmacy on hospitalization (Justice AC et al. Polypharmacy-associated risk of hospitalization among people ageing with and without HIV: an observational study. Lancet Health Longev 2021; 2(10):e639-e650) and frailty outcomes (Sung M, Gordon K, Edelman EJ, Akgun KM, Oursler KK, Justice AC. Polypharmacy and frailty among persons with HIV. AIDS Care 2021; 33(11):1492-1499). These results extend existing evidence to identify additional harms of polypharmacy (delirium), while also quantifying the additive effects of unhealthy alcohol use to polypharmacy and delirium incidence.

Key Points – Up to three bullet points, each limited to one sentence.

- Delirium incidence is higher among people aging with HIV than in uninfected comparators, with the greatest difference observed in the 55-59 year-old age group.
- Increasing number of neurocognitively active medications (NCAMs), generally, and anticholinergic medications, specifically, and unhealthy alcohol use are each independently associated with delirium risk in persons aging with HIV and uninfected comparators.
- The effects of NCAMs and delirium risk is stronger in the presence of concurrent unhealthy alcohol use in both groups.

Why does this matter?

Limiting use of neurocognitively active medications and alcohol use in older persons may reduce delirium risk, especially in persons aging with HIV.

ABSTRACT

Background: People aging with and without HIV (PWH and PWoH) want to avoid neurocognitive dysfunction, especially delirium. Continued use of alcohol in conjunction with neurocognitively active medications (NCAMs) may be a largely underappreciated cause, especially for PWH who experience polypharmacy a decade earlier than PWoH. We compare absolute and relative risk of delirium among PWH and PWoH by age, level of alcohol use, and exposure to NCAMs.

Methods: Using the VACS cohort, we compare absolute and relative risk of inpatient delirium among PWH and PWoH by age, level of alcohol use, and exposure to NCAMs between 2007-2019. We matched each case based on age, race/ethnicity, sex, HIV, baseline year, and observation time with up to 5 controls. The case/control date was defined as date of admission for cases and the date corresponding to the same length of time on study for controls. Level of alcohol use was defined using Alcohol Use Disorder Identification Test–Consumption (AUDIT-C). Medication exposure was measured from 45 to 3 days prior to index date; medications were classified as anticholinergic NCAM, non-anticholinergic NCAM, or non NCAM and counts generated. We used logistic regression to determine odds ratios (ORs) for delirium associated with medication counts stratified by HIV status and adjusted for demographics, severity of illness and related diagnoses.

Results: PWH experienced a higher incidence of delirium (5.6, [95% CI 5.3-5.9/1000 PY]) than PWoH (5.0, [95% CI 4.8-5.1/1000 PY]). In multivariable analysis, anticholinergic and non-anticholinergic NCAM counts and level of alcohol use demonstrated strong independent dose-response associations with delirium.

Conclusions: Decreasing alcohol use and limiting use of neurocognitively active medications may help decrease excess rates of delirium, especially among PWH.

INTRODUCTION

Delirium, a transient neurocognitive disorder complicating one in five hospitalizations (1), may be the first harbinger of dementia, a fear shared by people aging with and without HIV (PWH and PWoH). Delirium is also independently associated with poor health and frailty (2, 3). PWH may be at particular risk for delirium as they age for several reasons. First, HIV itself is known to cause neurocognitive dysfunction (4, 5). Second, some antiretrovirals have neurocognitive side effects (6). Third, PWH initiate polypharmacy (five or more medications), including neurocognitively active medications (NCAMs), a decade earlier than PWoH (7, 8). Finally, PWH continue to drink alcohol despite taking these medications and may be more susceptible to alcohol's harmful effects (9, 10).

With aging of PWH and increasing access to combination antiretroviral therapy, underlying etiologies for neurocognitive impairment among PWH have shifted(11). Earlier in the epidemic, HIV-associated Neurocognitive Disorder and HIV-associated Dementia were disturbingly commonplace, but since the advent of combination antiretrovirals, these conditions are rare (12). However, Mild Neurocognitive Disorder and Asymptomatic Neurocognitive Impairment still occur and may make PWH more susceptible to the effects of medications and alcohol.

Among PWoH, NCAMs including both anticholinergic medications, such as diphenhydramine, paroxetine and quetiapine, and non-anticholinergic medications including opioids, sedatives and anticonvulsants have potentially serious drug interactions contributing to delirium in addition to their independent risk for delirium, especially in the setting of polypharmacy (13-17). As a result, medications, especially benzodiazepines, anticholinergics and antipsychotics, are often considered "potentially inappropriate" especially in the context of aging (18). Similarly, among PWoH, unhealthy alcohol use is an independent risk factor for delirium (15) and the neurocognitive effects of NCAMs are known to interact with unhealthy alcohol use.

We have limited information about the effects of NCAMs and their interactions with alcohol among PWH. Research from the Women's Interagency HIV Study found that anticholinergic medications were associated with greater decrements in cognitive function among women with HIV compared with uninfected women (19). Womack et al. demonstrated that neurocognitive medications and unhealthy alcohol use are strongly associated with the frailty-related outcomes of falls and fractures (20). Further, PWH have demonstrated a greater susceptibility to harm from alcohol at lower levels of consumption (9, 10) but the association of NCAMS and alcohol with delirium has not been described.

We hypothesized that PWH are at increased risk for delirium, particularly in the setting of NCAMS, both anticholinergics and non-anticholinergics, and unhealthy alcohol use (21). To address this hypothesis, we determined independent and potential interactions between outpatient NCAMS and unhealthy alcohol use, defined as self-reported moderate and high-risk alcohol use, and delirium and assessed whether associations varied by HIV status.

METHODS

Data source and study population: Eligible patients were selected from the Veterans Aging Cohort Study (VACS), a national cohort of 50,000 PWH from the United States (U.S.) matched 1:2 on age, race, sex, and site of clinical care to PWoH. Data include hospital and outpatient diagnoses (recorded using International Classification of Diseases, Ninth Revision [ICD-9] or Tenth Revision [ICD-10] codes), procedures (recorded using Current Procedural Terminology [CPT] codes), laboratory results, smoking status and pharmacy data. Deaths are identified from the VA Vital Status file. Additionally, U.S. Medicare claims data are available and have been merged with VACS data.

Base cohort: Patients were eligible if they were entered VACS by 12/31/2016 and were alive as of 10/1/2007. Included patients had an Alcohol Use Disorder Identification Test – Consumption (AUDIT-C) between 10/1/2007 and 12/31/2017, that was at least one year after cohort entry, and filled any non-

antiretroviral prescription within +/- 30 days of the AUDIT-C date. We used the first AUDIT-C that met criteria and defined the baseline period as two years before to 14 days after the AUDIT-C date (schematic in Appendix Figure 1). We excluded patients who during baseline received chemotherapy or immunosuppressive medications had VACS Index 2.0 score greater than 100, had diagnosis of delirium, and all those with no follow-up after baseline. We followed patients through 12/31/2019 (latest available Medicare data) for incident delirium inpatient ICD-9 or ICD-10 diagnoses from VA or Medicare data (Appendix Table 1) (23, 24). Follow-up ended at the earliest of delirium diagnosis, 2 years after last VA visit, 12/31/2019 or death. We used this base cohort to calculate incidence rates stratified by HIV status and age.

To characterize severity of illness and burden of disease at baseline we used VACS Index 2.0 and the Charlson Comorbidity Index (score and individual conditions, including dementia). VACS Index 2.0 predicts mortality and hospitalization and includes HIV-specific and general biomarkers (22). We used laboratory values closest to the baseline date that were within 2 years before to 14 days after. We also used ICD codes to capture other conditions that could be associated with delirium - alcohol use disorder, substance use disorder, anxiety and serious mental illness (bipolar disorder, major depression, post-traumatic stress disorder and schizophrenia). All ICD diagnostic codes used are in Appendix Table 1. HIV was not included in the Charlson score.

Nested case-control design: From the base cohort we created a nested case-control design using risk set sampling (also called incidence density sampling). Cases were identified as described above. At the time each case was diagnosed we randomly selected 5 controls without delirium matched by age (+/- 1 year), sex, race/ethnicity, HIV status, baseline year (+/- 1 year) and duration of observation, thus creating a risk set. Within each risk set the case/control date was defined as date of admission for cases and the date corresponding to the same length of time on study for controls. Controls could go on to be

diagnosed with delirium at a later date and could be used more than once. Cases and controls with missing VACS Index 2.0 at baseline were excluded from the analytic sample. In sensitivity analysis, we excluded the matched controls for excluded cases. Characteristics of the full sample, the analytic sample and the sensitivity sample were similar (Appendix Table 2).

Proximal exposure to medications and alcohol: We considered medication use for any duration between 45 days to 3 days prior to the case/control date, operationalized as a fill that would be active during that time period. Anticholinergics were those classified as high risk according to Salahudeen 2015 (25)**.** Non-anticholinergic NCAMS included antidepressants, opioids, sedatives (including benzodiazepines), antipsychotics and anticonvulsants (26). We did not count multiple medications within class of NCAM as this was uncommon and may reflect prescription changes during the fill interval. We also captured other medications that may be associated with delirium including corticosteroids and select antiretrovirals (ritonavir, cobicistat, efavirenz, dolutegravir). Inhaled or topical formulations of any medication were not included.

For alcohol exposure, we used AUDIT-C score closest to, and within one year prior to, the case/control index date. The median time between AUDIT-C and the case/control date was less than 160 days. We categorized AUDIT-C scores into alcohol use as: 0=Abstinent/sick quitter; lower risk = 1-3 for men, 1-2 for women; moderate risk = 4-5 for men, 3-5 for women; high risk= ≥6 for men and women; and missing (no AUDIT-C in the year prior to the case/control date). We categorized moderate and heavy risk alcohol use as unhealthy alcohol use. Consistent with previous work, preliminary analysis showed that associations with AUDIT-C and delirium differed depending on presence or absence of a history of alcohol use disorder, identified by ICD codes, in the two years prior to baseline. Therefore, we created a 10-level composite variable to characterize patterns of alcohol use (alcohol use disorder present/absent x AUDIT-C=zero/lower/moderate/high/missing).

Statistical analysis: Unadjusted delirium rates and 95% confidence intervals were calculated using the Poisson method. We compared characteristics of cases and controls using chi-square test for proportions and Wilcoxon test for medians. In the nested case-control sample we estimated relative risk of delirium associated with anticholinergics, NCAMs, and alcohol use with multivariable logistic regression, stratified by HIV status. We evaluated independent associations of anticholinergics, NCAMS and alcohol categories with delirium. We explored adding interaction terms to the model to allow for differences in association of one exposure with the outcome, depending on the levels of another exposure**.** Because matching is done to increase precision by ensuring similar numbers of cases and controls in important strata, such as age, not to control confounding, we adjusted for matching variables and other potential confounders. Models included age, race, smoking status (27), corticosteroid and anticholinergic prescription, VACS Index, CCI and specific, common comorbidities (specified above) that may confound the associations, all ascertained at baseline. Those with missing smoking status (<0.5%) were considered current smokers. We also adjusted for proximal exposure to corticosteroids and select antiretrovirals. We found that anxiety and PTSD were no longer associated with delirium after adjustment for other covariates. We retained specific Charlson conditions associated with delirium and removed assigned points to create a modified summary score. In four sensitivity analysis we repeated models in samples that 1. excluded matched controls of cases with missing VACS Index, 2. excluded cases and controls with missing AUDIT-C at the case-control date and 3. restricted to age 65 and older, 4. restricted to cases with principal diagnosis of delirium. We report odds ratios (ORs) with 95% confidence intervals (95% CI). We used SAS 9.4 for all analyses and generated additive effects with "estimate" statements.

RESULTS

There were 140,783 eligible patients (29% were PWH), of whom 122,453 met inclusion criteria. After exclusions, the base cohort comprised 117,912 patients (28% PWH). During a median of 4.6 (IQR 2.2-7.1) years follow-up, delirium was diagnosed in 1,456 PHW and 3,419 PWoH. Overall, unadjusted incidence rates of delirium per 1000 person years were higher in PWH [5.6 (95% confidence interval 5.3-5.9)] than PWoH [5.0 (4.8-5.1)] and increased with age (Figure 1). After 60 years of age, delirium rates were not significantly different by HIV status.

In the nested case-control study, most delirium cases matched to 5 controls, 97% among PWH and 99% among PWoH. After excluding cases and controls with missing VACS Index at baseline, the analytic sample included 4,149 cases and 20,716 controls (27% cases, 29% controls were PWH). Median age of cases was 56 years for PWH and 58 years for PWoH (Table 1). The proportion of cases 65 years of age and older was 14.1% among PWH compared with 20.3% among PWoH. Because of matching, the age race and sex distribution of controls was very similar to that of cases. Nearly all patients were men; 38% of PWH and 44% of PWoH were white; 50% and 46% were black, respectively. Median time to the case/control date was slightly less among PWH.

Baseline covariates were significantly different between cases and controls, in both PWH and PWoH (Table 1). VACS Index 2.0 scores were higher, current cigarette smoking was more common, and Charlson Comorbidity Index was higher, in cases compared with controls (Table 1). Both alcohol use disorder and substance use disorder were more than twice as likely in cases than controls. Anxiety and serious mental illness were also more common in cases. Among PWH, cases were less likely to be virally suppressed than controls.

Proximal exposures also differed by case-control status (Table 2). Over 35% of cases were exposed to anticholinergics and 60% to non-anticholinergic NCAMs, particularly antidepressants and opioids. Each class of NCAMS was more commonly prescribed in cases compared with controls, for

example, in PWH anticholinergics: cases 36.4% vs controls 19.4%; antidepressants: 34.7% vs 21.9%; opioids: 33.4% vs 17.8%) and PWoH anticholinergics: cases 37.7% vs controls 24.9%; antidepressants: 34.2% vs 22.7%; opioids: 29.2% vs 20.4%. Cases were more likely than controls to be on 2 or more anticholinergics or non-anticholinergic NCAM. Corticosteroids were more commonly prescribed in cases compared with controls in both groups. Among PWH, cases were less likely than controls to be exposed to cobicistat or efavirenz. AUDIT-C scores were higher in cases. Notably, high-risk drinking, identified by high-risk AUDIT-C score, was reported in 7.6% of cases and 3.3% of controls among PWH, and 10.7% of cases and 3.9% of controls in PWoH.

In multivariable analyses, adjusted for demographics, comorbidities, smoking status and VACS Index 2.0, both medication exposure and alcohol use patterns and were strongly associated with risk of delirium (Figure 2, full model in Appendix Table 4). Dose response gradients were observed with anticholinergics, other NCAMs and AUDIT-C. Specifically, adjusted odds ratios and (95% CI), for 1 and 2 or more anticholinergics were respectively 1.52 (1.25, 1.84) and 2.14 (1.63, 2.82) among PWH and 1.15 (1.03, 1.30) and 1.78 (1.52,2.08) among PWoH, compared to no anticholinergics. For 1, 2 and 3 or more non-anticholinergic NCAMs respectively, odds ratios were 1.67 (1.37, 2.05); 2.19 (1.72, 2.78) and 2.95 (2.21, 3.96) among PWH and 1.35 (1.18, 1.53); 1.87 (1.62, 2.17) and 2.76 (2.33, 3.28) among PWoH. Associations were consistently stronger among PWH than PWoH for both anticholinergic and other NCAMs.

For all levels of alcohol use associations were stronger for PWoH than PWH (Figure 2). Compared to lower alcohol use, risk of delirium increased among PWoH who did not have alcohol use disorder with moderate [OR 1.65 (1.28, 2.11)] and high-risk consumption [3.21 (2.35, 4.38)] by AUDIT-C scores. Similar patterns were observed for PWH but were not statistically significant. Among those with history of alcohol use disorder, delirium risk increased in both groups [PWH OR 2.56 (1.61, 4.08) moderate and 2.78 (1.86, 4.16) high; PWoH 3.21 (2.35, 4.38) and 5.22 (4.13, 6.59)]. Note that odds ratios

were higher in those with alcohol use disorder at all levels of alcohol use, even lower risk [OR (1.46 (1.03, 2.07) in PWH and 2.35, (1.86, 2.98)]. We also note that delirium risk was consistently elevated in those reporting zero alcohol use, suggesting underreporting or "sick quitters" (37).

The associations of NCAMs and alcohol use patterns with delirium were additive, meaning that we found no clinically meaningful or statistically significant interactions. We illustrate these additive effects in Figure 3. For example, in the absence of alcohol use disorder, among PWH, the odds ratio for 2 or more anticholinergic medications is 2.24 (1.72, 2.91) in those with lower risk alcohol use, 2.67 (1.65,4.32) with moderate risk and 2.85 (1.56, 5.20) in high risk and among PWoH, 1.77 (1.52, 2.06), 2.90 (2.17, 3.88) and 5.45 (4.00, 7.42) for lower, moderate and high risk respectively. Similar patterns were seen for non-anticholinergic NCAMs. In other words, at each level of medication use the association with delirium was stronger in those with unhealthy alcohol use and stronger in those with alcohol use disorder, even at lower-risk alcohol use. Similar patterns were seen in all sensitivity analyses (described above), but with wider confidence intervals. These model results are also shown in Appendix Table 4.

DISCUSSION

PWH experienced a greater absolute risk of delirium compared to PWoH. PWH and PWoH demonstrated similar relative risk of delirium associated with NCAMS and alcohol. Both anticholinergic and nonanticholinergic NCAMs are associated with higher likelihood of delirium during hospitalization, especially in the setting of concurrent unhealthy alcohol use, defined as moderate and high-risk AUDIT-C scores. The individual associations of NCAMS and unhealthy alcohol use followed a dose-response relationship, with increasing number NCAM and increasing self-reported unhealthy alcohol use based on AUDIT-C scores, each contributing to an increasing relative risk of delirium. Combined, NCAMs and unhealthy alcohol use further augmented relative risk of delirium. Taken together, these results

highlight the urgent need for medication de-prescribing strategies and efforts to reduce unhealthy alcohol use to reduce the potential for delirium, particularly among PWH.

This is the first study to determine relative delirium risk compared with demographically and HIV-matched controls in the current antiretroviral era while also addressing an important and common exposure, unhealthy alcohol use, that contributes to delirium risk. While dementia is recognized as a risk factor for delirium, delirium is increasingly recognized as a causative factor contributing to dementia risk (28-30). Delirium is likely on the causal pathway for dementia, and efforts to reduce delirium are likely to reduce longer term dementia risk (2, 29). Delirium rates increased with age and were highest in the 65 years and older age group among PWoH. On the other hand, PWH age 50 years and older experienced comparable delirium rates to the oldest group among PWoH (age 65 years and older), although general trends were similar in the youngest compared with older age groups. This raises questions regarding aging in PWH on ARVs having an earlier risk of delirium. In addition, our findings suggest that reducing polypharmacy and alcohol use in PWH and PWoH may be an effective means of decreasing delirium risk.

Unhealthy alcohol use is associated with cognitive impairments in PWH and remains an important target for improving patient-centered outcomes in PWH (31, 32). Beyond acute intoxication, alcohol use disorders have been associated with neurocognitive impairment in PWH, with specific areas of executive functioning and episodic memory (32-36). As importantly, increasing alcohol use is associated with poorer control of HIV infection (37-39). These findings of alcohol misuse and neurocognitive impairment are clinically important and are consistent compared with studies in older populations (40, 41). Interventions aiming to decrease alcohol use could be important targets to improve neurocognitive outcomes for PWH as well as uninfected persons.

Combined with prior studies, our findings suggest that PWH are uniquely vulnerable to negative neurocognitive outcomes compared with the general aging population. Dementia and HIV-associated

neurocognitive disorders have been well described, with traditional cerebrovascular risk factors contributing, but the risk may be higher for PWH compared with PWoH (42). PWH are at 17% increased risk for ischemic stroke compared with PWoH, even after adjusting for age, race/ethnicity, diabetes, hypertension (including both treated and untreated), hyperlipidemia and smoking status (43). Certain antiretrovirals such as efavirenz have been associated with adverse neuropsychological symptoms and impairments, although delirium has not been specifically reported (44, 45).

Our results extend prior work in polypharmacy among PWH (7, 8). Polypharmacy is associated with substantial adverse events including falls in PWH and PWoH patients (20). There is also previous research suggesting that risks of adverse events may be differential by HIV status. For example, benzodiazepines and muscle relaxants were only associated with harm in PWH (20). PWH are taking more medications (antiretroviral to control HIV infection) and at younger ages compared with general populations of older adults. Indeed, our results demonstrate PWH are younger yet have greater burden of comorbidity burden, reflected in higher VACS Index scores and similar Charlson comorbidity Index. Our results suggest that reducing unnecessary NCAMS and alcohol use could be especially important to reduce delirium risk for PWH.

Our study has several limitations. First, we relied on ICD codes to identify delirium that have not been validated in hospitalized PWH (24); future studies would benefit from prospective evaluation of delirium incidence, severity and duration using validated, condition-specific measures. In addition, we only used self-reported alcohol; investigations using biomarkers of alcohol use such as phosphatidylethanol may further ascertain associations between unhealthy alcohol exposure risk and poor neurocognitive outcomes (46). Similarly, we used medication prescription fill-refill pharmacy data and did not evaluate presence of NCAMS with serum or urine measures for the medications. Further, we only relied on VA-based medication count. This may have led to underreporting of total medication count as well as NCAMS obtained from non-VA prescribers or recreational use of these medications.

However, that would likely bias our findings towards the null, suggesting the impact of polypharmacy and NCAMS and delirium is at least as strong as demonstrated in our study. We were also unable to assess cumulative drug dose exposures to more granularly determine how delirium risk varies with greater exposure. Future studies are warranted to examine this with validated pharmacy data. Finally, nearly all participants in this study were men, limiting generalizability to populations with more proportional representation in women.

Use of both anticholinergic and nonanticholinergic neurocognitively active medications and consumption of alcohol are common among PWH and PWoH. Each adds to the risk of delirium in a dose-response fashion. PWH are likely more susceptible to these effects. If PWH are to avoid delirium events as they age, greater attention should be paid to reducing the use of NCAMs and alcohol.

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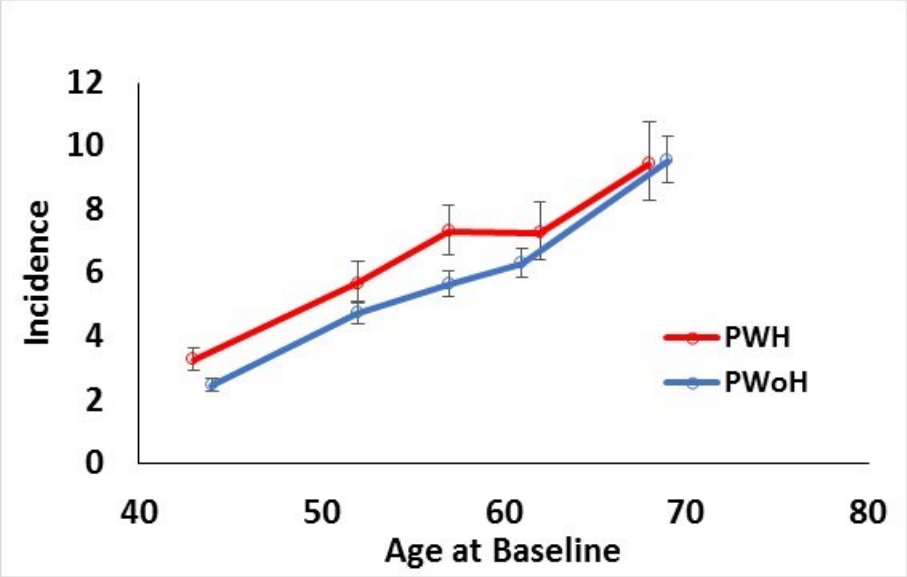

Figure 1. Delirium Incidence per /1000 person years, by HIV status. PWH = People with HIV; PWoH = People without HIV.

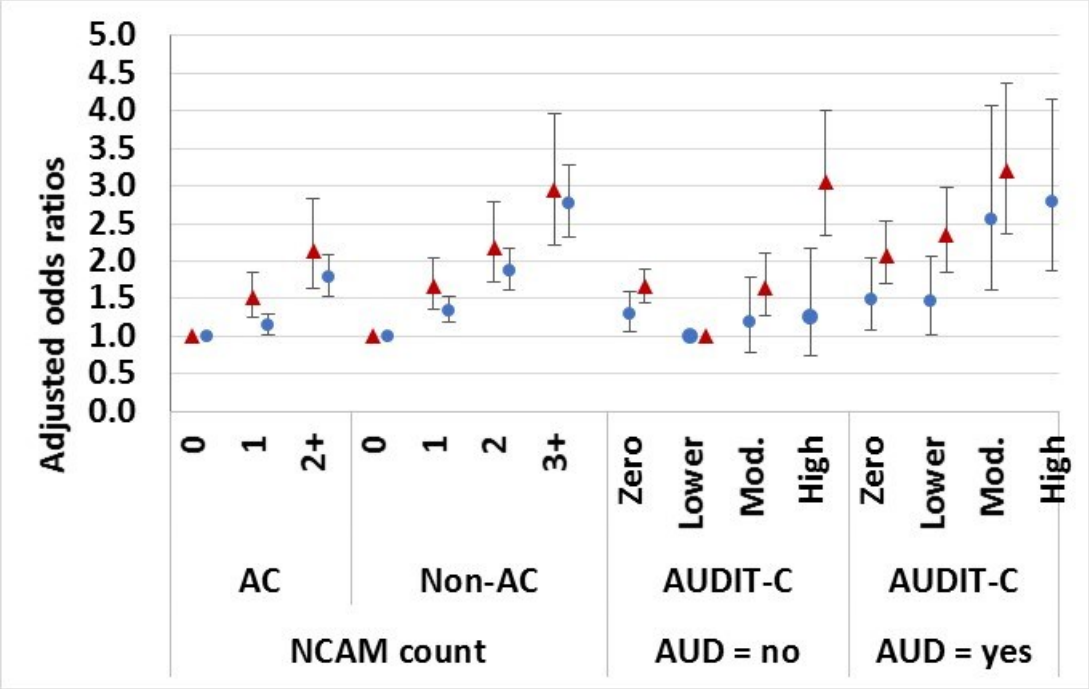

Figure 2. Multivariable association of medications and alcohol use patterns with incident, inpatient delirium; stratified by HIV status, adjusted for age, sex, race, severity of illness. Red triangle = People with HIV; Blue circle = People without HIV; NCAM = neurocognitively active medication; AC = anticholinergic; Non-AC = non-anticholinergic; AUDIT-C = Alcohol Use Disorder Test, Consumption; lower 1-3 men, 1-2 women; moderate 4-5 men, 3-5 women; high 6+; AUD = alcohol use disorder.

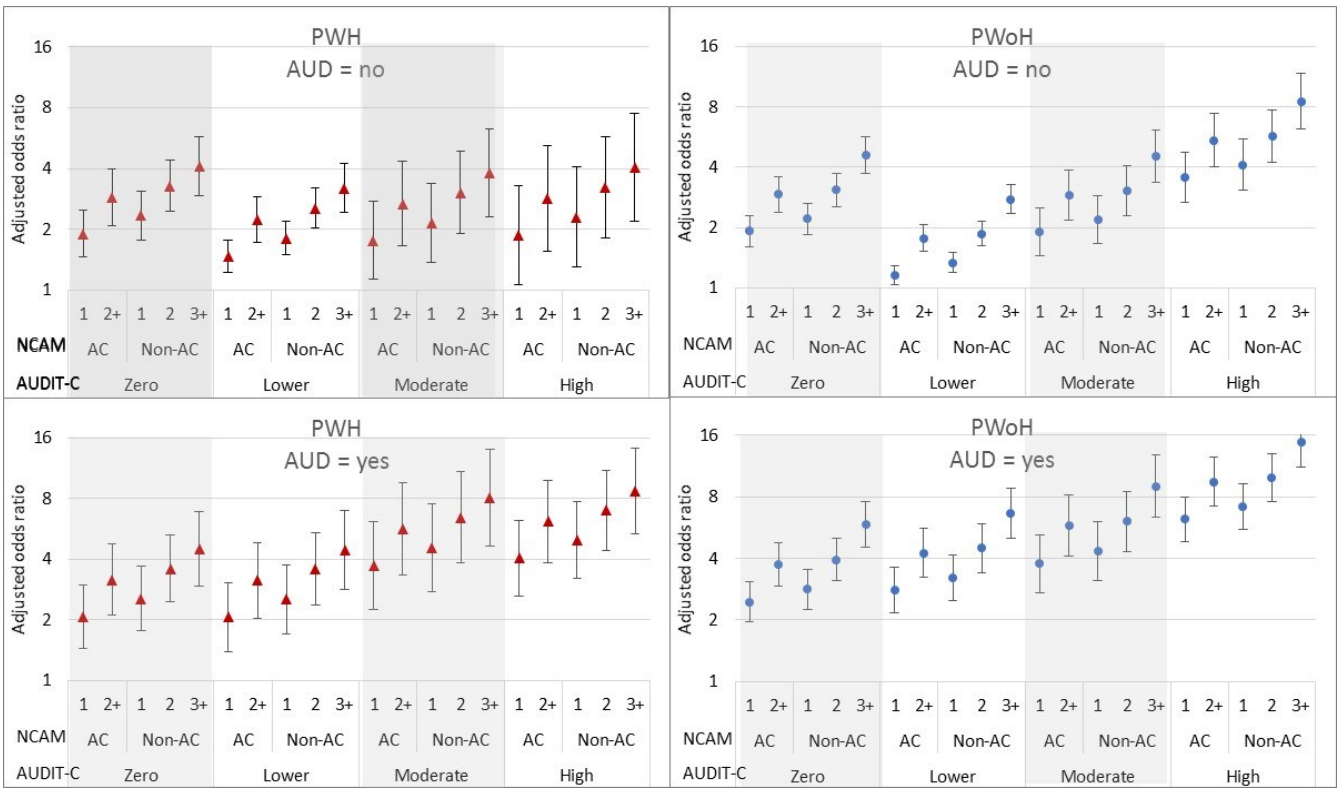

Figure 3. Multivariable association showing additive effects of medications and alcohol use patterns with incident, inpatient delirium; stratified by HIV status and history of alcohol use disorder (AUD), adjusted for age, sex, race, severity of illness. Red triangle = People with HIV; Blue circle = People without HIV; NCAM = neurocognitively active medication; AC = anticholinergic; Non-AC = non-anticholinergic; AUDIT-C = Alcohol Use Disorder Test, Consumption; lower 1-3 men, 1-2 women; moderate 4-5 men, 3-5 women; high 6+

Table 1. Characteristics of cases and controls, stratified by HIV status. Values are n (%) except as noted.						
	People with HIV			People without HIV		
	Cases	Controls	P value	Cases	Controls	P value
	N=1118	N=5972		N=3031	N=14744	
Matched characteristics						
Age at baseline, years, median (IQR)	56 (50, 61)	56 (50, 61)		58 (52, 63)	58 (52, 63)	
<50	273 (24.4)	1397 (23.4)		463 (15.3)	2274 (15.4)	
50-64	687 (61.4)	3769 (63.1)		1954 (64.5)	9489 (64.4)	
≥ 65	158 (14.1)	806 (13.5)		614 (20.3)	2981 (20.2)	
Male sex	1095 (97.9)	5867 (98.2)		2987 (98.5)	14549 (98.7)	
Race						
White, non-Hispanic	429 (38.4)	2372 (39.7)		1334 (44.0)	6488 (44.0)	
Black, non-Hispanic	570 (51.0)	2975 (49.8)		1412 (46.6)	6855 (46.5)	
Hispanic	102 (9.1)	558 (9.3)		245 (8.1)	1209 (8.2)	
Other	17 (1.5)	67 (1.1)		40 (1.3)	192 (1.3)	
Baseline year						
2007-2008	648 (58.0)	3394 (56.8)		1838 (60.6)	8937 (60.6)	
2009-2010	295 (26.4)	1656 (27.7)		737 (24.3)	3661 (24.8)	
2011-2017	175 (15.7)	922 (15.4)		456 (15.0)	2146 (14.6)	
Years to case/control date, median (IQR)	4.3 (2.1, 7.2)	4.2 (2.0, 7.0)		4.8 (2.3, 7.7)	4.8 (2.3, 7.7)	
Baseline covariates						
VACS Index 2.0, median (IQR)	57 (48, 69)	50 (41, 60)	<0.0001	38 (31, 46)	33 (27, 40)	<0.0001
Virally suppressed	817 (73.1)	4762 (79.7)	<0.0001	N/A	N/A	
Smoking						
Never	204 (18.2)	1693 (28.3)	<0.0001	533 (17.6)	4327 (29.3)	<0.0001
Current	747 (66.8)	2854 (47.8)		1936 (63.9)	6426 (43.6)	
Former	162 (14.5)	1402 (23.5)		550 (18.1)	3965 (26.9)	
Missing	5 (0.4)	23 (0.4)		12 (0.4)	26 (0.2)	
Charlson Comorbidity Index						
0	463 (41.4)	3254 (54.5)	<0.0001	1117 (36.9)	7324 (49.7)	<0.0001
1	311 (27.8)	1487 (24.9)		882 (29.1)	4142 (28.1)	
2	165 (14.8)	698 (11.7)		474 (15.6)	1870 (12.7)	
≥3	179 (16.0)	533 (8.9)		558 (18.4)	1408 (9.5)	
Myocardial infarction	22 (2.0)	87 (1.5)	0.2	63 (2.1)	239 (1.6)	0.08
Congestive heart failure	61 (5.5)	153 (2.6)	<0.0001	210 (6.9)	519 (3.5)	<0.0001
Peripheral vascular disease	47 (4.2)	144 (2.4)	0.001	189 (6.2)	506 (3.4)	<0.0001
Cerebrovascular disease	47 (4.2)	173 (2.9)	0.02	226 (7.5)	625 (4.2)	<0.0001
Dementia	9 (0.8)	30 (0.5)	0.2	36 (1.2)	67 (0.5)	<0.0001
Chronic pulmonary disease	157 (14.0)	545 (9.1)	<0.0001	506 (16.7)	1742 (11.8)	<0.0001
Rheumatic disease	6 (0.5)	15 (0.3)	0.1	20 (0.7)	54 (0.4)	0.02
Peptic ulcer disease	15 (1.3)	45 (0.8)	0.05	45 (1.5)	160 (1.1)	0.06
Diabetes without chronic complications	167 (14.9)	767 (12.8)	0.06	742 (24.5)	3336 (22.6)	0.03
Diabetes with chronic complications	53 (4.7)	129 (2.2)	<0.0001	273 (9.0)	822 (5.6)	<0.0001
Hemiplegia or paraplegia	12 (1.1)	50 (0.8)	0.4	69 (2.3)	170 (1.2)	<0.0001
Renal disease, mild to moderate	56 (5.0)	263 (4.4)	0.4	161 (5.3)	478 (3.2)	<0.0001
Renal disease, severe	47 (4.2)	106 (1.8)	<0.0001	104 (3.4)	170 (1.2)	<0.0001
Liver disease, mild	282 (25.2)	872 (14.6)	<0.0001	358 (11.8)	798 (5.4)	<0.0001

Liver disease, moderate to severe	7 (0.6)	25 (0.4)	0.3	26 (0.9)	34 (0.2)	<0.0001
Any malignancy	78 (7.0)	491 (8.2)	0.2	217 (7.2)	935 (6.3)	0.1
Metastatic solid tumor	4 (0.4)	9 (0.2)	0.1	13 (0.4)	25 (0.2)	0.005
Alcohol use disorder	348 (31.1)	777 (13.0)	<0.0001	950 (31.3)	1893 (12.8)	<0.0001
Substance use disorder	474 (42.4)	1059 (17.7)	<0.0001	901 (29.7)	1789 (12.1)	<0.0001
Anxiety	119 (10.6)	380 (6.4)	<0.0001	292 (9.6)	895 (6.1)	<0.0001
Serious mental illness	408 (36.5)	1245 (20.8)	<0.0001	1332 (43.9)	4225 (28.7)	<0.0001
Bipolar disorder	105 (9.4)	232 (3.9)	<0.0001	315 (10.4)	630 (4.3)	<0.0001
Major depression	189 (16.9)	587 (9.8)	<0.0001	408 (13.5)	1176 (8.0)	<0.0001
Post traumatic stress disorder	162 (14.5)	528 (8.8)	<0.0001	663 (21.9)	2366 (16.0)	<0.0001
Schizophrenia	97 (8.7)	196 (3.3)	<0.0001	411 (13.6)	1038 (7.0)	<0.0001
IQR=interquartile range VACS=Veterans Aging Cohort Study N/A=not applicable						

Table 2. Proximal exposures to medications and alcohol use relative to AUDIT-C.						
	People with HIV			People without HIV		
	Cases	Controls	P value	Cases	Controls	P value
	N=1118	N=5972		N=3031	N=14744	
Non-Antiretroviral medications, n (%) unless otherwise noted						
Total medications, median (IQR)	8 (3, 15)	6 (2, 12)	<0.0001	9 (3, 17)	8 (3, 14)	<0.0001
Anticholinergics, any	407 (36.4)	1161 (19.4)	<0.0001	1143 (37.7)	3666 (24.9)	<0.0001
1	264 (23.6)	911 (15.3)		728 (24.0)	2802 (19.0)	
2 or more	143 (12.8)	250 (4.2)		415 (13.7)	864 (5.9)	
Neurocognitively active medications (NCAM), any	710 (63.5)	2499 (41.8)	<0.0001	1824 (60.2)	6722 (45.6)	<0.0001
1	320 (28.6)	1486 (24.9)		750 (24.7)	3743 (25.4)	
2	240 (21.5)	687 (11.5)		600 (19.8)	1961 (13.3)	
3 or more	150 (13.4)	326 (5.5)		474 (15.6)	1018 (6.9)	
Anti-depressants	388 (34.7)	1305 (21.9)	<0.0001	1037 (34.2)	3348 (22.7)	<0.0001
Opioids	373 (33.4)	1062 (17.8)	<0.0001	885 (29.2)	3009 (20.4)	<0.0001
Sedatives/hypnotics	197 (17.6)	653 (10.9)	<0.0001	560 (18.5)	1670 (11.3)	<0.0001
Anti-psychotics	93 (8.3)	192 (3.2)	<0.0001	308 (10.2)	799 (5.4)	<0.0001
Anticonvulsants	247 (22.1)	703 (11.8)	<0.0001	735 (24.2)	2134 (14.5)	<0.0001
Corticosteroid use	61 (5.5)	98 (1.6)	<0.0001	157 (5.2)	375 (2.5)	<0.0001
Antiretroviral medications						
Ritonavir	278 (24.9)	1488 (24.9)	0.97	N/A	N/A	
Cobicistat	44 (3.9)	330 (5.5)	0.029	N/A	N/A	
Efavirenz	161 (14.4)	1261 (21.1)	<0.0001	N/A	N/A	
Dolutegravir	86 (7.7**)**	467 (7.8)	0.88	N/A	N/A	
AUDIT-C						
Abstinent/sick quitter (0)	535 (47.9)	2535 (42.4)	<0.0001	1531 (50.5)	6970 (47.3)	<0.0001
Lower risk (1-3 men, 1-2 women)	254 (22.7)	1766 (29.6)		497 (16.4)	3808 (25.8)	
Moderate risk (4-5 men, 3-5 women)	74 (6.6)	299 (5.0)		184 (6.1)	817 (5.5)	
High risk (>=6)	85 (7.6)	199 (3.3)		323 (10.7)	572 (3.9)	
Missing	170 (15.2)	1173 (19.6)		496 (16.4)	2577 (17.5)	
Days between AUDIT-C and case/control date (IQR)	131 (48,243)	159 (76,250)	<0.0001	140 (58,236)	158 (76,250)	<0.0001

IQR=interquartile range
AUDIT-C=alcohol use disorder identification test-consumption
N/A=not applicable