Polypharmacy, hazardous alcohol and illicit substance use and serious falls among PLWH and uninfected comparators

Running head: Polypharmacy, substance use, and falls among PLWH and uninfected comparators

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Abstract

Background. Medication classes, polypharmacy, hazardous alcohol and illicit substance abuse may exhibit stronger associations with serious falls among persons living with HIV (PLWH) than with uninfected comparators. We investigated whether these associations differed by HIV status.

Setting. Veterans Aging Cohort Study

Methods. We employed a nested case-control design. Cases (N=13,530) were those who fell. Falls were identified by external cause of injury codes and a machine learning algorithm applied to radiology reports. These were matched to controls (N=67,060) by age, race, sex, HIV status, duration of observation, and baseline date. Risk factors included medication classes, count of unique non-antiretroviral (non-ART) medications, and hazardous alcohol and illicit substance use. We used unconditional logistic regression to evaluate associations.

Results. Among PLWH, benzodiazepines (odds ratio (OR) 1.24; 95% confidence interval (CI) 1.08, 1.40) and muscle relaxants (OR 1.29; 95% CI 1.08, 1.46) were associated with serious falls but not among uninfected ($p>0.05$). In both groups, key risk factors included non-ART medications (per five medications) (OR 1.20, 95% CI 1.17, 1.23), illicit substance use/abuse (OR 1.44; 95% CI 1.34, 1.55), hazardous alcohol use (OR 1.30; 95% CI 1.23, 1.37), and an opioid prescription (OR 1.35; 95% CI 1.29, 1.41).

Conclusion. Benzodiazepines and muscle relaxants were associated with serious falls among PLWH. Non-ART medication count, hazardous alcohol and illicit substance use, and opioid prescriptions were associated with serious falls in both groups. Prevention of serious falls should focus on reducing specific classes and absolute number of medications and both alcohol and illicit substance use.

Key words. HIV, falls, risk factors, benzodiazepines, muscle relaxants

INTRODUCTION

Falls are associated with fractures,[1] traumatic brain injury,[1] disability,[2] and death[3] and are a growing concern for people aging with HIV.[4-8] Of particular importance are falls that cause a patient to seek health care (serious falls). Previous research has provided conflicting evidence about fall risk factors among persons living with HIV (PLWH) and whether or not these risk factors differ for PLWH and uninfected comparators.

Established risk factors for falls among older adults include medication classes (cardiovascular medications,[9] psychotropics,[10] opioids, anticonvulsants, and proton pump inhibitors[11]) and polypharmacy. Among PLWH, Erlandson and colleagues found that cardiovascular medications, psychotropics, and multiple comorbidities were associated with increased risk of falls, but this study did not include an uninfected comparison group.[4] Another study that included uninfected individuals found that hepatitis C virus infection (HCV), female sex, obesity, smoking and clinical imbalance symptoms were associated with falls, but that age, HIV serostatus, and other comorbidities were not.[5] Others suggest that comorbidity count[7] and the number of medications prescribed[11,12] are associated with fall risk among PLWH, but neither of these studies provided comparisons with uninfected individuals.

Of particular importance to our work, hazardous alcohol and illicit substance use have been inconsistently associated with falls among PLWH. Sharma and colleagues found that heavy alcohol use was associated with recurrent but not with single falls.[6] Erlandson and colleagues found no association between alcohol use and falls[4,5] but reported that current illicit substance use was associated with a lower risk of falling.[4] This association may have been confounded by individuals who stopped using substances due to chronic illness.[13] Sharma and colleagues found that marijuana use – but not use of heroin, cocaine, or crack -- was independently associated with falls.[6]

Also of note, PLWH experience polypharmacy a decade earlier than uninfected individuals.[14] They are more susceptible to harm from polypharmacy due to increased physiologic frailty [15] and persistent use of alcohol[14] and other substances into older age.[16,17] Therefore, alcohol, illicit substance use and polypharmacy may play a more important role in serious falls among PLWH than among uninfected comparators.

Most prior studies have been limited in size and regional variation, and few have compared risks among PLWH and uninfected individuals. In this large national study, we explore the association between falls and specific medications, polypharmacy, harmful alcohol use, and substance use disorder using data from the Veterans Aging Cohort Study (VACS). We investigate whether these associations differ by HIV status and identify the relative importance of fall risk factors in this population.

METHODS

We used a nested case-control study design to explore these questions.

Sample

VACS is a national, prospective, observational cohort that includes all Veterans diagnosed with HIV within the Veterans Health Administration (VA) and demographically matched uninfected comparators.[18] We included data from 10/01/2007 through 09/20/2015. We used 10/01/2007 as the lower cutoff because we wanted to include Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) as our measure of hazardous alcohol use. AUDIT-C was not consistently available in the VA electronic health record before 10/01/2007. We used 09/30/2015 as the upper cut off because this was the last date through which we had access to radiology reports and could thus use our machine learning algorithm to identify serious falls from that source. From 133,658 individuals who received care between 10/01/2007 and 09/30/2015, we established a base cohort of 115,426 individuals who had at least one AUDIT-C measure

available. We defined baseline as the date of the first AUDIT-C that occurred after 10/01/2007, with a concurrent outpatient prescription within 30 days of the AUDIT-C, at least 12 months after VACS enrollment. We excluded individuals (Figure 1): a) with VACS Index score >100 at baseline (N=244); b) who seroconverted (N=327); or c) who had a serious fall on or before baseline (N=16,395). We identified cases (those with a serious fall: N= 13,530) and matched them to at-risk individuals by age within one year, race, sex, HIV status, duration of observation since baseline, and baseline date within one year. We matched 98.6% of individuals who fell to 5 controls each.

Serious falls

Cases were the first serious fall experienced by participants. We identified serious falls using International Classification of Disease (ICD) codes and radiology reports. We used ICD-9 external cause of injury codes (Ecodes): E880.X, E881.X, E884.X, E885.9, E886.9, E888.X.[19] As Ecodes are specific but not sensitive for serious falls, we also used a machine learning algorithm that identified serious falls in radiology reports.[20] This algorithm has been validated (positive predictive value: 93%; sensitivity: 95%; F measure (the harmonic mean of positive predictive value and sensitivity): 94%; and accuracy: 99%).[20]

Primary predictors

Primary predictors were specific medication classes, count of unique non-antiretroviral (ART) outpatient medications, hazardous alcohol use, and illicit substance use. Active medications were identified in the window 3 to 45 days before the serious fall or match date. Medication classes (Appendix) were identified using VHA fill-refill data and included: mental health medications (antipsychotics, atypical antidepressants, monoamine oxidase inhibitors [MAOIs], selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs]), central nervous system (CNS)-active medications

(opioids, benzodiazepines, muscle relaxants, anticonvulsants, and antihistamines), cardiovascular medications (antiarrhythmics, antihypertensives, antithrombotics, nitrates), hypoglycemics, and proton pump inhibitors. We included a count of active non-ART medications in the 3-45 day window prior to the fall or match date. Hazardous alcohol use was defined as AUDIT-C summated score $\geq$3 for women and $\geq$4 for men.[21] We used the AUDIT-C score closest to serious fall date (or match date for controls) up to one year prior to that date. We identified illicit substance use from ICD9 codes prior to baseline (ICD9 codes 292.0, 292.11, 292.12, 304.XX, 305.XX).

Comorbidities, identified using ICD9 codes (one inpatient or two outpatient), included: osteoarthritis, hypertension, heart failure, coronary artery disease, stroke, transient ischemic attack, dementia (inpatient only), chronic obstructive pulmonary disease (COPD), asthma, anxiety, bipolar disorder, major depression, mild depression, psychosis, and schizophrenia. Hepatitis C virus (HCV) infection status was identified by detectable plasma HCV-RNA, positive antibody test, or documented diagnosis. To adjust for comorbid disease severity, we used the VACS Index 2.0 score closest to serious fall or match date. The Index uses demographic information and routinely assessed laboratory measures associated with all-cause mortality: age, CD4 count, HIV-1RNA, hemoglobin, FIB-4 ((age[years]xAST[IU/L]/platelet count[expressed as platelets x 10^9/L] x ($ALT^{1/2}$[IU/L])), eGFR ((186.3 x serum $creatinine^{-1.154}$) x ($age^{-0.203}$) x (1.21 if black)), hepatitis C status, body mass index (BMI), albumin, and white blood cell (WBC) count.[22] The VACS Index has been validated in PLWH and in uninfected populations.[22,23] We did not include smoking as the VACS Index accounts for most of the upstream effects of smoking.

Ethics

VACS was approved by the Institutional Review Boards of VA Connecticut Healthcare System and Yale University. It has been granted a waiver of informed consent and is HIPAA compliant.[18]

Statistical methods

Analyses began with a comparison of the distributions of primary predictors between cases and controls within strata defined by HIV status. Continuous variables were compared with a t-test and categorical with a chi-square statistic.

Multivariable unconditional logistic regression[24] was used to evaluate the associations between primary predictors of interest and occurrence of a serious fall with adjustment for covariates. The four matching variables with potential for confounding were age, race, sex, and HIV status. Each of these four were removed one at a time to detect substantive change (>10% on the log-odds scale) in the associations of primary interest. Because only the removal of HIV resulted in such a change, HIV was the only matching variable retained in the final multivariable model. We subsequently explored multivariable models stratified by HIV status to identify potential differential associations between predictors and serious falls. We fit the same multivariable model, adding HIV and interaction terms, to the entire cohort to identify significant interactions using estimate statements.

Among PLWH, we explored the association between ART and serious falls. Among those on ART, we explored associations among ART classes (protease inhibitors (PIs), nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and integrase inhibitors (INSTIs) and serious falls. Finally, we included all individual ART medications in one analysis and then limited our model to include those with the most signal (ritonavir, tenofovir, raltegravir, and efavirenz).

The percent of missing data ranged from 0% to 13%. BMI and laboratory data had the highest rates of missingness (13% for PLWH and 9% for uninfected). We assumed that the missing values were missing at random and employed multiple imputation using a fully conditional specification as implemented in the SAS procedure MI.[25] The imputation model included serious

falls and all aforementioned covariates. Models were fit to each of the five imputed datasets and the resulting coefficients were used to derive the reported results. This was implemented using the SAS procedure MIANALYZE which combines the imputation-specific coefficients based on Rubin's Rules.[25] To compare the relative importance of the variables that we included in our models, We used the t- value obtained from logistic regression to compare the relative importance of the variables that we included in our models. All analyses were performed using SAS Version 9.4 with statistical significance defined as a two-tailed p-value<0.05.

Role of the funding source

The funding sources had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

RESULTS

Our analysis included 80,590 Veterans; 23,252 (29%) were PLWH. Median follow-up time was 2.3 years (IQR 1.0-4.0 years). We observed 13,530 serious falls (3919 among PLWH and 9611 among uninfected). The mean age at time of serious fall was 57 years for PLWH and 58 for uninfected (p<0.001).

The sample was primarily black (49%) and male (96%). Baseline characteristics of cases and controls within strata defined by HIV status are included in Table 1. Among PLWH, there were no differences in BMI between cases or controls. Among PLWH and uninfected comparators, cases were more likely to take medications from the medication classes of interest with three exceptions. First, among uninfected individuals, controls were far more likely to have a prescription for an antithrombotic (66% vs 8%, p<0.001). Second, among PLWH, controls were somewhat more likely to have a prescription for a benzodiazepine (14% vs 13%, p<0.001). Third, there was no difference between cases and controls for prescriptions for MAO inhibitors (0.03% and 0.01%, p=0.45). Among PLWH and uninfected, cases had a higher mean

medication count than controls. Prevalence of substance use and comorbidities was higher among cases regardless of HIV status. Among PLWH, cases were less likely to take NRTI (69% vs 73%, p=0.01), or NNRTI (33% vs 37%, p<0.001), but were more likely to take an integrase inhibitor (14% vs 12%, p=0.01). Controls were more likely to take epivir (3TC) (24% vs 22% p=0.02).

In models stratified by HIV status, receipt of benzodiazepines (PLWH odds ratio (OR) 1.25; 95% confidence interval (CI) 1.11, 1.39; uninfected OR 1.02; 95% CI 0.95, 1.10; p=0.002) or muscle relaxants (PLWH OR 1.32; 95% CI 1.15, 1.41; uninfected OR 1.04; 95% CI 0.96, 1.12; p=0.001) was associated with serious falls among PLWH but not among uninfected (Figure 2) (Table 2). Other covariates strongly associated with serious falls did not differ by HIV status.

In the combined model (Table 2), the most important covariates (listed from highest to lowest t-value) associated with increased risk of serious fall were count of non-ART medications (per five medications) (OR 1.19, 95% CI 1.16, 1.22), diagnosis of drug use/abuse (OR 1.36; 95% CI 1.30, 1.42), VACS Index 2.0 (increments of five) (OR 1.06; 95% CI 1.05, 1.06), and hazardous alcohol use (OR 1.32; 95% CI 1.24, 1.39). Individual medication classes were also associated with serious falls: opioids (OR 1.34; 95% CI 1.28, 1.41), anticonvulsants (OR 1.32; 95% CI 1.25, 1.39), SSRIs (OR 1.22; 95% CI 1.16, 1.28), antithrombotics (OR 1.20; 95% CI 1.11, 1.30), antiarrhythmics (OR 1.32; 95% CI 1.16, 1.50), SNRIs (OR 1.16; 95% CI 1.05, 1.29), and MAOIs (OR 2.37; 95% CI 1.05, 5.33).

Antihypertensives (OR 0.85; 95% CI 0.81, 0.89) and antipsychotics (OR 0.90; 95% CI 0.85, 0.96) were associated with a lower risk of serious falls, as was ART use (OR 0.85; 95% CI 0.78, 0.92) among PLWH. Neither ART classes; nor individual ART -- specifically ritonavir, tenofovir, raltegravir or efavirenz -- were associated with serious falls (Figure 2).

DISCUSSION

In the largest and most in-depth study of serious falls among PLWH and uninfected comparators to date, we found that benzodiazepines and muscle relaxants were associated with serious falls among PLWH but not among uninfected. Other medication classes including opioids, anticonvulsants, antiarrhythmics, antithrombotics, MAOIs, SSRIs, and SNRIs were strongly associated with serious falls, but the association did not differ by HIV status. The risk factors most strongly associated with falls in both groups were the number of medications prescribed, higher VACS Index 2.0 score, illicit substance use, prescription opioids, anticonvulsants, and hazardous alcohol use. Among PLWH, ART use was associated with lower risk of serious falls. Among those on ART, serious falls were associated with neither ART class nor individual ART.

Our results highlight the importance of both classes and counts of medications in risk of serious falls among PLWH. This association is established among older adults[26,27] and has been suggested by other investigators among PLWH.[4,12] The stronger association between benzodiazepines, muscle relaxants and serious falls among PLWH relative to uninfected comparators is particularly striking. These medications may interact with ART or direct effects of the virus may increase their impact. For example, midazolam, triazolam, alprazolam and many of the muscle relaxants are metabolized by CYP3A4.[28] Protease inhibitors, particularly ritonavir, are known inhibitors of this liver enzyme system. Co-administration may increase the bioavailability of benzodiazepines and muscle relaxants, accentuating the association of these medications with serious falls.[29] HIV is also known to compromise the integrity of the blood brain barrier.[30] This may result in higher concentrations of benzodiazepines and muscle relaxants in the brain, again increasing risk of serious falls.

Even after adjusting for specific medication classes, illicit substance use/abuse, hazardous alcohol use, and severity of illness, medication count was the factor most strongly associated with serious falls in our study. Medication reconciliation, discontinuing medications, changing to

safer alternative medications, and reducing medications to the lowest effective dose[31] are important interventions to reduce polypharmacy (deprescribing). How to implement this policy in a largely middle-aged population in care for HIV remains to be explored.[32]

Most of our findings correlate well with the geriatric literature. The lack of association seen between benzodiazepines and muscle relaxants and serious falls among uninfected comparators may be due to the fact that the mean age for uninfected comparators at the time of fall or match was 58±9 years. This is much younger than the geriatric population which typically includes individuals 65 years of age or older. It is possible that in younger members of the general population, these medications may not have the same fall-related impact as in older adults. Importantly, neither hazardous alcohol nor illicit substance use are targeted in existing fall prevention efforts such as the CDC's STEADI program.[31] Prior research on falls in the general population was carried out at a time when continued use of alcohol and illicit substances was less common in an aging population.[33] Our data suggests its importance has increased in both those aging with and without HIV infection. Efforts to reduce hazardous alcohol and illicit substance use need to be integrated with the more established interventions of exercise and balance/strength training to reduce serious falls among PLWH.

This study has strengths and limitations. VACS is the largest cohort of individuals aging with HIV in North America. We were well-powered to explore serious falls in this population. Because VACS is an electronic health record (EHR)-based cohort, we had access to a greater range of clinical variables than other cohorts. We also had access to detailed information on medication exposure and alcohol use. Our analytic approach ensured that we identified exposures of interest prior to the outcome, thus reducing the risk of reverse causality. It is important to remember that we used a nested case-control study for this study. We identified cases (those who fell) and then matched them to other at-risk individuals as described earlier. Because of this matching, our sample should reflect those who fell and not PLWH or uninfected individuals more

generally. Characteristics may therefore differ from what would be expected from VACS as a whole.

An important limitation is our operationalization of serious falls. Our definition included those falls that cause a patient to present for health care. We therefore did not identify all falls. However, we likely identified those falls that were most concerning to the patient and provider. We were also unable to adjust for all potentially significant fall risk factors. Most importantly, we could not accurately identify those with peripheral neuropathy. Peripheral neuropathy is notoriously under assessed and thus administrative codes or even machine learning algorithms will not capture all those with the condition. Other conditions that we did not include (e.g Parkinson disease) are extremely rare among PLWH. Parkinson disease increases with age, reaching a prevalence of 2.6% in people aged 85-89 years in the generally population. No one in our sample was over 85 years of age. Furthermore, only 3% of the sample were women. Additional research is needed to explore models for serious fall risk factors that stratify by sex.

In conclusion, our analysis suggests that use of specific medication classes, higher numbers of chronic medications, hazardous alcohol and ongoing substance use are potent risk factors for serious falls. Benzodiazepines and muscle relaxants are associated with increased risk of a serious fall among PLWH but not in uninfected comparators. Fall prevention programs that target the needs of PLWH will need to address the risk factors identified in this study. In addition to emphasizing exercise, balance, gait, strength training and polypharmacy, these programs will need to confront ongoing hazardous alcohol and illicit substance use and identify approaches to deprescribing that will balance the needs of this middle-aged population against their elevated risk of serious falls.

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Table 1. Sample description by HIV status

Variables	PLWH			Uninfected		
	Cases N=3919	Controls N=19,333	p	Cases N=9611	Controls N=47,727	p
Demographics (matched)						
Mean age at baseline (years)†	54±9			55±9		
Mean age at time of fall or match (years)†	57±10			58±9		
Race/ethnicity						
White	41%			39%		
Black	48%			50%		
Hispanic	9%			9%		
Other	2%			2%		
Women	3%			4%		
Health Factors						
Smoking			<0.001			<0.001
Never	25%	29%		27%	30%	
Current	57%	52%		53%	49%	
Former	18%	19%		20%	21%	
BMI†	26±5	26±5	0.45	30±6	30±6	0.13
Underweight (<18.5)	2%	2%	0.07	1.0%	0.74%	0.001
Normal weight (18.5 – 25)	35%	36%	0.46	18%	16%	<0.001
Overweight (25-30)	30%	32%	0.09	31%	32%	0.03
Obese (>30)	17%	17%	0.68	42%	42%	0.15
Specific Medications						
Opioid	30%	18%	<0.001	33%	22%	<0.001
Benzodiazepine	13%	14%	<0.001	14%	10%	<0.001
Muscle relaxant	9%	5%	<0.001	12%	9%	<0.001
Anticonvulsant	19%	11%	<0.001	22%	14%	<0.001
Antihistamine	19%	13%	<0.001	17%	14%	<0.001
Antiarrhythmics	3%	1%	<0.001	3%	1%	<0.001
Antihypertensives	47%	44%	0.003	59%	56%	<0.001
Antithrombotics	6%	5%	<0.001	8%	6%	<0.001
Nitrates	4%	2%	<0.001	5%	3%	<0.001
Antipsychotics	11%	8%	<0.001	14%	12%	<0.001
Atypical antidepressants	18%	13%	<0.001	19%	14%	<0.001
MAO Inhibitors	0.03%	0.01%	0.45	0.08%	0.03%	0.03
SNRI	4%	2%	<0.001	4%	3%	<0.001
SSRI	20%	14%	<0.001	22%	16%	<0.001
Tricyclic antidepressants	5%	3%	<0.001	4%	3%	0.001
Hypoglycemics	11%	9%	<0.001	19%	16%	<0.001
Proton pump inhibitors	21%	15%	<0.001	31%	24%	<0.001
Polypharmacy						
Medication count (with ART)†	10±7	8±6	<0.001	9±7	7±6	<0.001
Medication count (without ART)†	8±6	6±5	<0.001	9±7	7±6	<0.001
Substance Use						
Hazardous alcohol use (>=3 for women and >=4 for men)	13%	9%	<0.001	14%	11%	<0.001

Illicit substance use	36%	27%	<0.001	28%	20%	<0.001
Comorbidities						
VACS Index Score V2.0†	54±16	51±15	<0.001	34±11	32±10	<0.001
Osteoarthritis	21%	15%	<0.001	40%	35%	<0.001
HCV	30%	24%	<0.001	16%	11%	<0.001
CNS diagnoses						
Stroke	0	0	NA	0	0	NA
TIA	1%	1%	0.002	2%	1%	0.001
Dementia	1%	0.72%	<0.001	0.28%	0.12%	<0.001
Respiratory diagnoses						
COPD	19%	14%	<0.001	19%	15%	<0.001
Asthma	8%	5%	<0.001	8%	7%	0.006
Cardiovascular diagnoses						
Hypertension	52%	49%	0.001	66%	63%	<0.001
Coronary artery disease	13%	11%	0.001	18%	16%	<0.001
Heart failure	5%	3%	<0.001	5%	4%	<0.001
Mental health diagnoses						
Anxiety	19%	14%	<0.001	19%	15%	<0.001
Bipolar disorder	14%	9%	<0.001	14%	10%	<0.001
Major depression	26%	20%	<0.001	24%	17%	<0.001
Mild depression	48%	39%	<0.001	41%	33%	<0.001
Psychosis	17%	12%	<0.001	13%	10%	<0.001
Schizophrenia	7%	5%	<0.001	11%	10%	0.003
Antiretroviral therapy						
On ART	79%	82%	0.10			
ART Classes (among those on ART						
Protease inhibitors (excluding RTV)	37%	37%	0.71			
Nucleoside/nucleotide reverse transcriptase inhibitors	69%	73%	0.01			
Non-nucleoside reverse transcriptase inhibitors	33%	37%	<0.001			
Integrase inhibitors	14%	12%	0.01			
Fusion inhibitors	2%	1%	0.10			
Boosters (RTV or cobicistat)	33%	33%	0.75			
Individual ART (among those on ART)‡						
3TC	22%	24%	0.02			
Abacavir	13%	13%	0.94			
Tenofovir	49%	51%	0.09			
FTC	44%	46%	0.24			
Zidovudine	11%	13%	0.001			
Efavirenz	25%	29%	<0.001			
Ritonavir	33%	33%	0.82			
Atazanavir	15%	16%	0.27			
Darunavir	9%	8%	0.07			
Lopinavir/ritonavir	9%	9%	0.69			
Raltegravir	13%	11%	0.03			

† Mean±SD

‡ ART used by ≤5% of the sample were excluded from the table. These include: didanosine, Maraviroc, enfuvirtide, nevirapine, rilpivirine, etravirine, zalcitabine, nelfinavir, fosamprenavir, indinavir tipranavir, saquinavir, cobicistat, dolutegravir, elvitegravir

Table 2. Multivariable associations with serious falls among PLWH and uninfected comparators

Variables	Odds ratios (95% confidence intervals)	T statistic
Specific medications		
CNS active medications		
Benzodiazepines among PLWH	1.25 (1.12, 1.39)	3
Benzodiazepines among uninfected	1.02 (0.95, 1.10)	0.6
Muscle relaxants among PLWH	1.32 (1.14, 1.41)	3
Muscle relaxants among uninfected	1.04 (0.96, 1.12)	0.9
Opioids	1.33 (1.27, 1.39)	13
Anticonvulsants	1.32 (1.25, 1.39)	11
Antihistamines	0.98 (0.93, 1.04)	-0.6
Cardiovascular medications		
Antithrombotics	1.20 (1.11, 1.30)	5
Antiarrhythmics	1.32 (1.16, 1.50)	4
Antihypertensives	0.85 (0.81, 0.89)	-7
Nitrates	0.99 (0.90, 1.10)	-0.10
Mental health medications		
SSRI	1.22 (1.16, 1.28)	8
SNRI	1.16 (1.05, 1.29)	3
Atypical antidepressants	1.04 (0.99, 1.10)	2
MAOI	2.37 (1.05, 5.33)	2
TCA	0.95 (0.86, 1.05)	-1
Antipsychotics	0.90 (0.85, 0.96)	-3
Hypoglycemics	0.97 (0.91, 1.03)	-1
Proton pump inhibitors	1.06 (1.01, 1.11)	2
Polypharmacy		
Medication count (excluding ART) (increments of 5)	1.19 (1.16, 1.22)	14
Substance use		
Hazardous alcohol use (AUDIT-C score $\geq$3 for women and $\geq$4 for men)	1.32 (1.24, 1.39)	10
Illicit substance use	1.36 (1.30, 1.42)	14
Additional covariates		
VACS Index 2.0 (increments of 5)	1.06 (1.05, 1.06)	13
Body Mass Index		
<18.5	0.99 (0.84, 1.17)	-0.1
18.5 – 25	REF	REF
25 – 30	1.00 (0.95, 1.06)	0.01
> 30	1.00 (0.95, 1.06)	0.1

Smoking was not included in the model as it is collinear with VACS Index Score 2.0

The matching variable, HIV, was included in the model but is not shown here

Abbreviations: CNS: central nervous system; SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin/norepinephrine reuptake inhibitors; MAOI: monoamine oxidase inhibitors; TCA: tricyclic antidepressants; ART: antiretroviral therapy; AUDIT-C: Alcohol Use Disorders Identification Test – Consumption.

Figure 1. Derivation of study sample

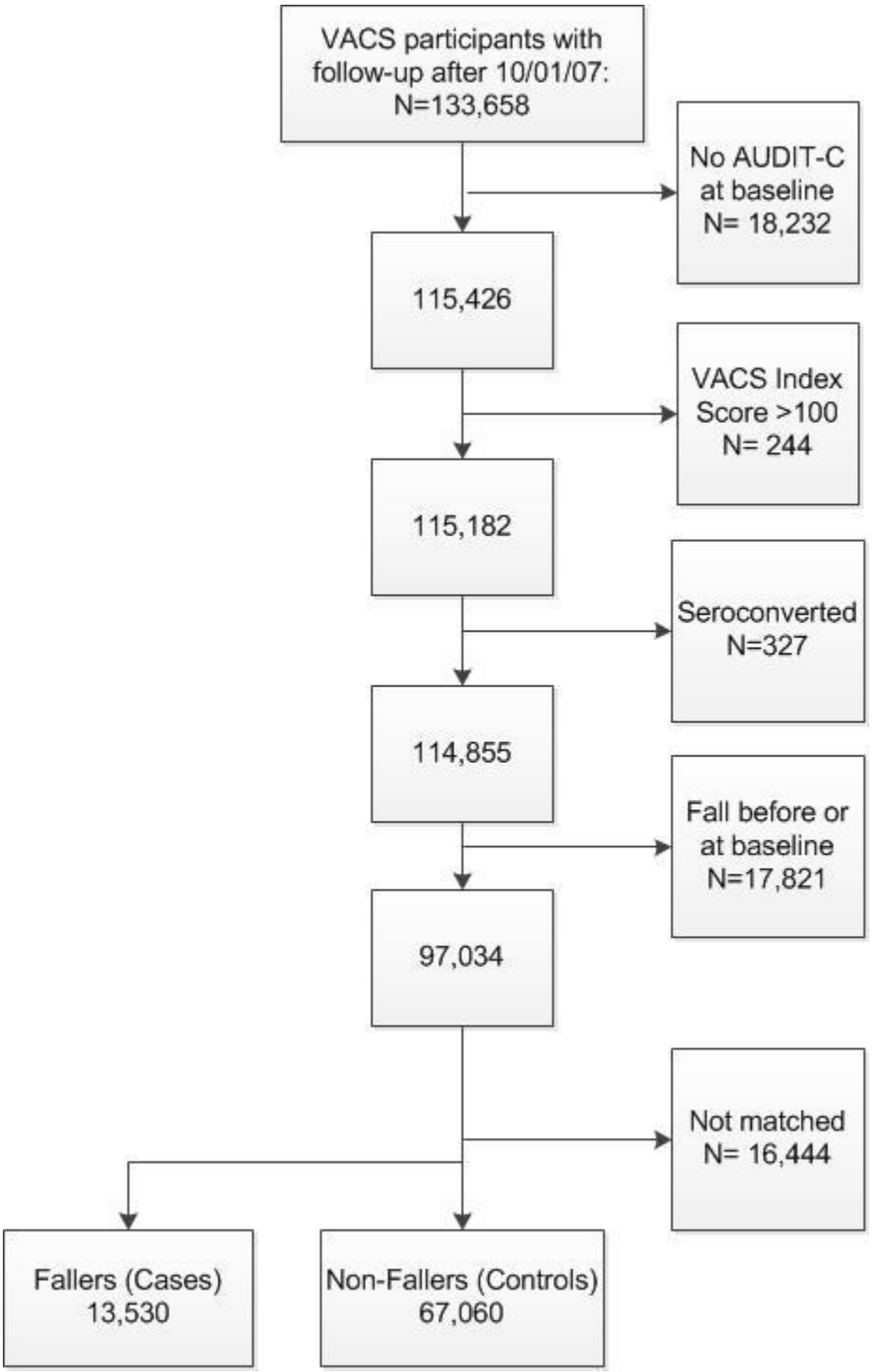
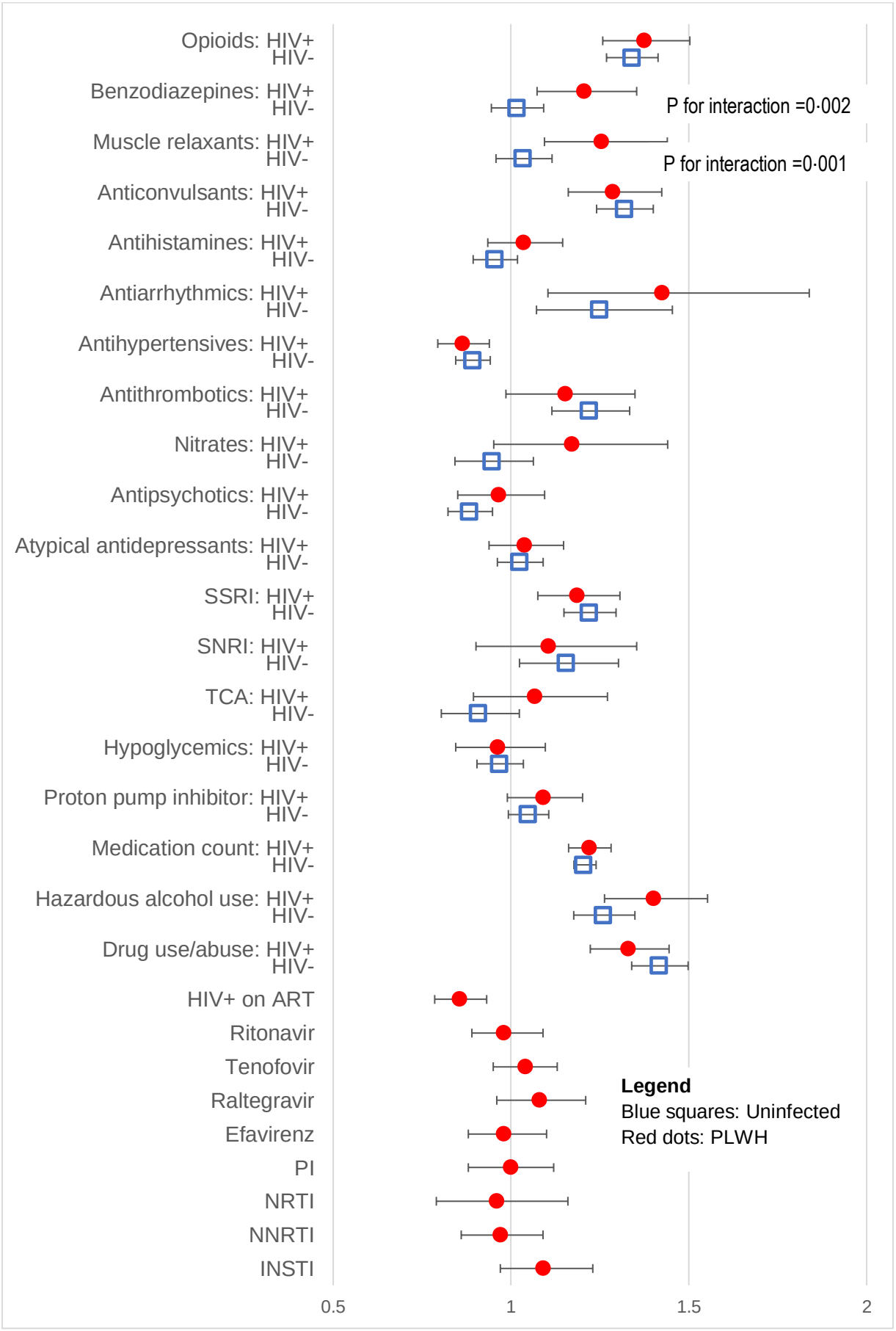


Figure 2. Associations stratified by HIV status



Appendix

Table. Medications included in the different drug classes

Medication class	Medications included
Opioids	ACETAMINOPHEN/BUTALBITAL/CAFFEINE/CODEINE ACETAMINOPHEN/CODEINE ACETAMINOPHEN/HYDROCODONE ACETAMINOPHEN/OXYCODONE ACETAMINOPHEN/PENTAZOCINE ACETAMINOPHEN/PROPOXYPHENE ASPIRIN/BUTALBITAL/CAFFEINE/CODEINE ASPIRIN/CAFFEINE/PROPOXYPHENE ASPIRIN/CODEINE ASPIRIN/OXYCODONE BUPRENORPHINE CHLORPHENIRAMINE/CODEINE/PSEUDOEPHEDRINE CHLORPHENIRAMINE/HYDROCODONE CODEINE CODEINE COMBINATION CODEINE/ASPIRIN CODEINE/GUAIFENESIN CODEINE/GUAIFENESIN/PSEUDOEPHEDRINE CODEINE/PHENYLEPHRINE/PROMETHAZINE CODEINE/PROMETHAZINE FENTANYL GUAIFENESIN/HYDROCODONE GUAIFENESIN/HYDROCODONE/PSEUDOEPHEDRINE HOMATROPINE/HYDROCODONE HYDROCODONE/IBUPROFEN HYDROMORPHONE LEVORPHANOL MEPERIDINE METHADONE MORPHINE NALOXONE/PENTAZOCINE OXYCODONE OXYCODONE (OPT) - (SUSTAINED RELEASE) OXYMORPHONE PROPOXYPHENE TAPENTADOL TRAMADOL TRAMADOL/ACETAMINOPHEN
Benzodiazepines	ALPRAZOLAM CHLORDIAZEPOXIDE CLONAZEPAM CLORAZEPAM DIAZEPAM

	ESTAZOLAM FLURAZEPAM HALAZEPAM LORAZEPAM MIDAZOLAM OXAZEPAM PRAZEPAM QUAZEPAM TEMAZEPAM TRIAZOLAM
Muscle relaxant	ACETAMINOPHEN/CHLORZOXAZONE ASPIRIN/CAFFEINE/ORPHENADRINE ASPIRIN/CARISOPRODOL ASPIRIN/METHOCARBAMOL BACLOFEN CARISOPRODOL CHLORPHENESIN CARBAMATE CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METAXALONE METHOCARBAMOL ORPHENADRINE CITRATE ORPHENADRINE HYDROCHLORIDE TIZANIDINE
Anticonvulsant	CARBAMAZEPINE DIVALPROEX ETHOSUXIMIDE ETHOTOIN FELBAMATE FOSPHENYTOIN GABAPENTIN LAMOTRIGINE LEVETIRACETAM MEPHENYTOIN MEPHOBARBITAL METHARBITAL METHSUXIMIDE OXCARBAZEPINE PARALDEHYDE PARAMETHADIONE PHENACEMIDE PHENOBARBITAL/PHENYTOIN PHENSUXIMIDE PHENYTOIN PRIMIDONE TIAGABINE

	TOPIRAMATE TRIMETHADIONE VALPROATE SODIUM VALPROIC ACID ZONISAMIDE
Antihistamine	BROMPHENIRAMINE BROMPHENIRAMINE MALEATE CARBINOXAMINE CETIRIZINE CHLORPHENIRAMINE CLEMASTINE CYPROHEPTADINE DESLORATADINE DEXBROMPHENIRAMINE DEXCHLORPHENIRAMINE DIMENHYDRINATE DIPHENHYDRAMINE DIPHENYLPYRALINE DOXYLAMINE FEXOFENADINE HYDROXYZINE LORATADINE METHDILAZINE PHENIRAMINE/PHENYLTOLOXAMINE/PYRILAMINE PROMETHAZINE PYRILAMINE TRIPELENNAMINE TRIPROLIDINE
Antiarrhythmics	ADENOSINE AMIODARONE BRETYLIUM DISOPYRAMIDE DOFETILIDE ENCAINIDE FLECAINIDE IBUTILIDE LIDOCAINE MEXILETINE MORICIZINE PROCAINAMIDE PROPAFENONE QUINIDINE TOCAINIDE
Antihypertensives	ALISKIREN AMILORIDE AMILORIDE/HYDROCHLOROTHIAZIDE AMLODIPINE

	AMLODIPINE/ATORVASTATIN AMLODIPINE/BENAZEPRIL ATENOLOL ATENOLOL/CHLORTHALIDONE BENAZEPRIL BENAZEPRIL/HYDROCHLOROTHIAZIDE BENDROFLUMETHIAZIDE BENDROFLUMETHIAZIDE/NADOLOL BENDROFLUMETHIAZIDE/POTASSIUM CHLORIDE BENDROFLUMETHIAZIDE/POTASSIUM CHLORIDE/RAUWOLFIA SERPENTINA BEPRIDIL BETAXOLOL BISOPROLOL BISOPROLOL/HYDROCHLOROTHIAZIDE BUMETANIDE CANDESARTAN CANDESARTAN/HYDROCHLOROTHIAZIDE CAPTOPRIL CAPTOPRIL/HYDROCHLOROTHIAZIDE CARVEDILOL CHLOROTHIAZIDE CHLOROTHIAZIDE/METHYLDOPA CHLORTHALIDONE CHLORTHALIDONE/CLONIDINE CLONIDINE CYCLOTHIAZIDE DILTIAZEM DILTIAZEM/ENALAPRIL ENALAPRIL ENALAPRIL/FELODIPINE ENALAPRIL/HYDROCHLOROTHIAZIDE ENALAPRILAT EPROSARTAN EPROSARTAN/HYDROCHLOROTHIAZIDE ETHACRYNIC ACID FELODIPINE FOSINOPRIL FOSINOPRIL/HYDROCHLOROTHIAZIDE FUROSEMIDE GUANETHIDINE/HYDROCHLOROTHIAZIDE HYDRALAZINE HYDRALAZINE/HYDROCHLOROTHIAZIDE HYDRALAZINE/ISOSORBIDE HYDROCHLOROTHIAZIDE HYDROCHLOROTHIAZIDE/IRBESARTAN HYDROCHLOROTHIAZIDE/LABETALOL

	HYDROCHLOROTHIAZIDE/LISINOPRIL HYDROCHLOROTHIAZIDE/LOSARTAN HYDROCHLOROTHIAZIDE/METHYLDOPA HYDROCHLOROTHIAZIDE/METOPROLOL HYDROCHLOROTHIAZIDE/MOEXIPRIL HYDROCHLOROTHIAZIDE/OLMESARTAN HYDROCHLOROTHIAZIDE/PROPRANOLOL HYDROCHLOROTHIAZIDE/QUINAPRIL HYDROCHLOROTHIAZIDE/SPIRONOLACTONE HYDROCHLOROTHIAZIDE/TELMISARTAN HYDROCHLOROTHIAZIDE/TRIAMTERENE HYDROCHLOROTHIAZIDE/VALSARTAN HYDROFLUMETHIAZIDE INDAPAMIDE IRBESARTAN ISRADIPINE LABETALOL LISINOPRIL LOSARTAN METHYCLOTHIAZIDE METHYLDOPA METHYLDOPATE METOLAZONE METOPROLOL MIBEFRADIL MOEXIPRIL NICARDIPINE NIFEDIPINE NIMODIPINE NISOLDIPINE OLMESARTAN PENBUTOLOL PERINDOPRIL PINDOLOL POLYTHIAZIDE PROPRANOLOL QUINAPRIL QUINETHAZONE RAMIPRIL SPIRONOLACTONE TELMISARTAN TORSEMIDE TRANDOLAPRIL TRIAMTERENE TRICHLORMETHIAZIDE VALSARTAN VERAPAMIL

Antithrombotics	ANISINDIONE BIVALIRUDIN DANAPAROID DICUMAROL FACTOR VIIA,RECOMBINANT LEPIRUDIN PHENPROCOUMON TINZAPARIN WARFARIN CLOPIDOGREL ENOXAPARIN ASPIRIN/DIPYRIDAMOLE DIPYRIDAMOLE HEPARIN FONDAPARINUX DALTEPARIN TICLOPIDINE ARGATROBAN EPTIFIBATIDE ABCIXIMAB TIROFIBAN
Nitrates	AMYL NITRITE ISOSORBIDE DINITRATE ISOSORBIDE MONONITRATE NITROGLYCERIN PHENOBARBITAL/SODIUM NITRITE
Antipsychotics	ACETOPHENAZINE MALEATE ARIPIPRAZOLE CHLORPROMAZINE CHLORPROTHIXENE CLOZAPINE CLOZAPINE (CARACO) CLOZAPINE (CLOZARIL) CLOZAPINE (FAZACLO) CLOZAPINE (IVAX) CLOZAPINE (MYLAN) CLOZAPINE (TEVA) CLOZAPINE (UDL) FLUPHENAZINE HALOPERIDOL LOXAPINE MESORIDAZINE BESYLATE METHOTRIMEPRAZINE MOLINDONE OLANZAPINE PALIPERIDONE PERPHENAZINE PIPERACETAZINE

	PROMAZINE QUETIAPINE RISPERIDONE THIORIDAZINE THIOTHIXENE TRIFLUOPERAZINE TRIFLUPROMAZINE ZIPRASIDONE
Atypical antidepressants	BUPROPION MAPROTILINE MIRTAZAPINE NEFAZODONE TRAZODONE
MAO Inhibitors	PHENELZINE SULFATE SELEGILINE TRANYLCYPROMINE
SNRI	DULOXETINE VENLAFAXINE
SSRI	CITALOPRAM ESCITALOPRAM FLUOXETINE FLUVOXAMINE PAROXETINE SERTRALINE
Tricyclic antidepressants	AMITRIPTYLINE AMOXAPINE CLOMIPRAMINE DESIPRAMINE DOXEPIN IMIPRAMINE NORTRIPTYLINE PROTRIPTYLINE TRIMIPRAMINE
Hypoglycemics	IINSULIN ACETOHEXAMINE CHLORPROPAMIDE GLIMEPIRIDE GLIMEPIRIDE/PIOGLITAZONE GLIMEPIRIDE/ROSIGLITAZONE GLIPIZIDE GLIPIZIDE/METFORMIN GLYBURIDE GLYBURIDE/METFORMIN NATEGLINIDE REPAGLINIDE TOLAZAMIDE TOLBUTAMIDE TROGLITAZONE PRAMLINTIDE
Proton pump inhibitors	ESOMEPRAZOLE LANSOPRAZOLE LANSOPRAZOLE/NAPROXEN OMEPRAZOLE

	OMEPRAZOLE/SODIUM BICARBONATE PANTOPRAZOLE RABEPRAZOLE