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Association of Syndemic Unhealthy Alcohol Use, Smoking, and Depressive Symptoms on Incident Cardiovascular Disease among Veterans With and Without HIV-Infection

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Abstract

Unhealthy alcohol use, smoking, and depressive symptoms are risk factors for cardiovascular disease (CVD). Little is known about their co-occurrence – termed a syndemic, defined as the synergistic effect of two or more conditions—on CVD risk in people with HIV (PWH). We used data from 5621 CVD-free participants (51% PWH) in the Veteran's Aging Cohort Study-8, a prospective, observational study of veterans followed from 2002 to 2014 to assess the association between this syndemic and incident CVD by HIV status. Diagnostic codes identified cases of CVD (acute myocardial infarction, stroke, heart failure, peripheral artery disease, and coronary revascularization). Validated measures of alcohol use, smoking, and depressive symptoms were used. Baseline number of syndemic conditions was categorized (0, 1, ≥2 conditions). Multivariable Cox Proportional Hazards regressions estimated risk of the syndemic (≥2 conditions) on incident CVD by HIV-status. There were 1149 cases of incident CVD (52% PWH) during the follow-up (median 10.1 years). Of the total sample, 64% met our syndemic definition. The syndemic was associated with greater risk for incident CVD among PWH (*Hazard Ratio* [*HR*] 1.87 [1.47–2.38], *p* < 0.001) and HIV-negative veterans (*HR* 1.70 [1.35–2.13], *p* < 0.001), compared to HIV-negative with zero conditions. Among those with the syndemic, CVD risk was not statistically significantly higher among PWH vs. HIV-negative (*HR 1.10* [*0.89, 1.37*], *p* = .38). Given the high prevalence of this syndemic combined with excess risk of CVD, these findings support linked-screening and treatment efforts.

Keywords

Introduction

While combination antiretroviral therapy has extended the survival of people with HIV (PWH) by decades, this success has been offset by increasing morbidity of non-AIDS diseases [1, 2]. Cardiovascular disease (CVD) is a common comorbidity and cause of death among PWH [3, 4]. After adjustment for possible confounders, PWH experience an increased risk of acute myocardial infarction [5, 6], heart failure [7], ischemic stroke [8, 9], peripheral artery disease [10], and total coronary heart disease [11], compared to HIV-negative people. This risk persists even with sustained HIV viral suppression [5]. While some of this excess risk is likely due to the virus itself [12, 13], behavioral and mental health

factors [14], including unhealthy alcohol use, cigarette use, and depression [15], likely also play an important role.

Smoking prevalence among PWH is two-fold higher than in HIV-negative populations [16–18] and is associated with 40–100% increase risk for CVD [5, 11, 19, 20], compared to non-smokers. Unhealthy alcohol use is reported in 25–45% [21–23] of PWH and is associated with nearly 50% higher prevalence of CVD [24], compared to low risk use. Depression, the most common psychological condition among PWH, affects 20–30% [25–27] and is associated with 68% higher risk of CVD [20], compared to those without depression. Further, a longitudinal analysis from the Veteran's Aging Cohort Study (VACS) showed that unhealthy alcohol use, smoking, and depressive symptoms among PWH were temporally concordant and that removal of any one factor was associated with the cessation of the other two, suggesting that the co-occurrence of these conditions constitutes a unique syndemic [15].

A syndemic refers to two or more adverse conditions—in this case behavioral and mental health factors – that cluster and interact to exacerbate poor health outcomes [28]. While there are unique challenges to assessing the effect of syndemics, more importantly are the unique opportunities to screen and address them in clinical practice. Unhealthy alcohol use, smoking, and depression are behaviorally and biologically linked [29], offering clinicians the opportunity to perform linked-screening and treatment with combined behavioral therapy and pharmacotherapy. Specifically, there is emerging evidence for parsimonious treatment for alcohol and tobacco use with selective nicotinic receptor partial agonists such as varenicline [30], that could mitigate polypharmacy [31]. In a recent study of veterans, 50% of the participants had two and 15% had all three of these conditions [32]. Among those with the syndemic, PWH had a 36% increased risk of death compared to HIV-negative counterparts [32]. Whether this syndemic contributes to the excess risk of CVD among PWH is unknown. Therefore, our objective was to (1) assess the association between this syndemic and incident CVD among PWH and HIV-negative veterans from the VACS and to (2) determine if the association between the syndemic and incident CVD differed by HIV status.

Methods

We analyzed data from the Veteran's Aging Cohort Study (VACS), an observational, longitudinal cohort of veterans living with HIV and HIV-negative veterans matched 1:1 on age, sex, race/ethnicity, and clinical site [33] to conduct a retrospective longitudinal analysis of prospectively collected cohort data. The VACS undergoes continuous enrollment, beginning June of 2002. Clinical and demographic data are extracted from the VA Corporate Data Warehouse and the VA electronic medical record Health Factor data set. Vital status is determined using the VA vital status file, the Social Security Administration death master file, the Beneficiary Identification and Records Locator Subsystem, and the Veterans Health Administration Medical Statistical Analysis Systems inpatient data sets. Approval of the VACS was obtained from the institutional review board of the Yale School of Medicine. The following analyses were approved by the institutional review board of Vanderbilt University Medical Center.

Participants were included in this analysis if they were CVD-free at baseline and followed from baseline date until date of known cardiovascular disease, death, the last follow-up date, or censored on December 31, 2014 (n = 5995). Based on our previous work [5, 9, 10], prevalent CVD at baseline was defined by validated International Classification of Diseases, Ninth Revision (*ICD-9*) codes and Current Procedures Terminology (*CPT*) codes for acute myocardial infarction [34], ischemic stroke [35], heart failure [36], unstable angina [37], peripheral artery disease [38], and coronary revascularization (i.e., stent placement, coronary artery bypass grafting, and percutaneous coronary intervention) [39]. Those with prevalent CVD at baseline were excluded from the analysis.

Exclusion criteria included those with no follow-up after a baseline visit (n = 22), more than one missing component of the Patient Health Questionnaire (PHQ-9, n = 96), and those who self-reported never drinking (n = 256) as the risk profile between never and former drinkers (which may include "sick-quitters"- previous heavy drinkers who stopped drinking due to declining health) is quite disparate [40, 41]. Further, missing data for never-drinkers was 50% or greater at each follow-up visit.

Independent Variable

Unhealthy alcohol use, cigarette smoking, and depressive symptoms were assessed at survey baseline. The Alcohol Use Disorders Identification Test (AUDIT-C) [42] identified unhealthy drinking (> 14 drinks per week for men and > 7 drinks per week for women) and heavy episodic drinking (> 4 drinks for men and > 3 drinks for women on one occasion). The AUDIT-C has been validated across multiple clinical and research settings, with area under the receiver operator curve > 0.80 [43–48]. The AUDIT-C is widely used in HIV research to quantify alcohol use [49, 50]. Cigarette smoking was measured through self-report. The Patient Health Questionnaire-9 items (PHQ-9) identified clinically significant depressive symptoms and has strong reliability and validity for diagnosing major depressive disorders at a cut-off of 10 [51]. Those with a PHQ-9 score 10 were considered positive for depressive symptoms. The PHQ-9 is widely validated across many clinical populations, including among PWH [52]. We created a syndemic variable, categorized as having zero, one, and two conditions (syndemic). We chose to categorize those with 2 and 3 conditions together for the following reasons: (1) to be consistent with the definition of a syndemic (2 or more conditions that increase risk for poor outcomes); (2) the survival curves of those with 2 and 3 conditions are nearly identical overtime, with the 95% confidence intervals overlapping completely; (3) although 15% have all 3 conditions, the number of CVD cases in this group becomes sparse over follow-up creating an issue with stability of the effects. The syndemic score was included as a time-varying predictor of incident CVD.

Dependent Variable

Incident CVD was defined using the same criteria as prevalent CVD, using relevant *ICD-9* and *CPT* codes.

Covariates

Defined in prior work [5, 11], we adjusted for several baseline demographic and CVD-related variables. Briefly, diabetes was defined as having any of the following indicators:

abnormal glucose measurement (> 200 mg/dL), use of medications for diabetes treatment, or at least one inpatient or two outpatient *ICD-9* codes for diabetes [53]. Hypertension was categorized using American Heart Association cut-offs [54] and integrated use of blood pressure (BP) lowering medication [normal BP (< 140/90 mm Hg with no antihypertensive medication use), controlled (BP < 140/90 mm Hg with antihypertensive medication use), and uncontrolled (BP 140/90 mm Hg)], and was calculated with the average BP measurement of three routine outpatient clinical assessments closest to baseline date. Low density lipoprotein and high density lipoprotein cholesterol and triglycerides were measured during routine clinical practice and were considered as continuous variables. Obesity was defined as a body mass index 30 kg/m2 [55]. Anemia and renal disease were ascertained using laboratory values of hemoglobin (< 13 g/dL men; < 12 g/dL women) [56] and estimated glomerular filtration rate levels (mL/min/1.73m2 < 30, 30–59, 60) [57], respectively. Past year illicit drug use was self-reported using standardized and validated measures [33] which included the use of cocaine/crack, stimulants (amphetamines), and opioids (heroin, morphine, codeine, opium). Opiate use disorder was defined by at least one inpatient or two outpatient *ICD-9* codes. Hepatitis C infection was defined as a positive antibody test or at least one inpatient or two outpatient *ICD-9* codes [58]. Prevalent chronic obstructive pulmonary disease [59] and posttraumatic stress disorder were defined using *ICD-9* codes for diagnoses at baseline. We collected data on CD4 + T-cell counts and HIV-1 RNA values from baseline through the last follow-up date.

Statistical Analysis

Descriptive statistics for all variables by syndemic categories and HIV status were assessed using *t* tests for continuous variables and $\times 2$ tests for categorical variables. We calculated age-adjusted incident CVD rates per 1000 person-years and age-adjusted survival curves by syndemic categories for the total sample and stratified by HIV status. Cox Proportional Hazards models estimated the *hazard ratio* (*HR*) and 95% confidence intervals (CI) to assess the association between the time-updated syndemic and incident CVD. Our primary analysis included the interaction of HIV status and the syndemic categories as a 6-level HIV/syndemic variable on incident CVD, with HIV-negative people with zero conditions as the common referent group. Pairwise comparisons of the syndemic effect by HIV status are presented. Lastly, Cox Proportional Hazards models were conducted among the total sample and by HIV status, controlling for the afore-mentioned covariates. In HIV-stratified models, we included baseline and time-updated HIV viral load and CD4 count as additional covariates to test attenuation of effect.

Missing covariate data were included in the analyses through multiple imputations using chained equations with five separate imputed datasets, generated based on predictive mean matching methods using the Hmisc library of R programming language. Cox survival models were fit in each imputed dataset and finally combined to obtain pooled HRs and standard errors. All analyses were performed using R software (version 3.3.3; www.rproject.org).

Power-analysis

With the observed CVD incident of 14.7% among those without any syndemic conditions (n = 524) and 21.8% among those with 2 conditions (n = 3617), we anticipated a minimum detectable hazard ratio of 1.35 at 90% power with a Type I error rate of 5%.

Results

The total sample included 5621 participants (2864 PWH and 2757 HIV-negative; Table 1) with a median age of 49.1 years (*interquartile range* [*IQR*] 43.6, 54.6). Most of the sample were male (94%) and non-White (65% Black). Of the total sample, 9% had no conditions, 26% had one condition, and 65% had the syndemic (2 conditions; 51% in PWH, 49% in HIV-negative, Table 1). Nearly 15% of the total sample had all three conditions. During the median follow-up period of 10.1 years, there were 1149 incident cases of CVD (21% in PWH, 20% in HIV-negative). Of the total sample, age-adjusted CVD rates increased with each increasing syndemic category (Fig. 1, *Log-Rank Tests P* < 0.001). Incidence rates were not statistically significantly higher among PWH compared to HIV-negative people at each syndemic category (Table 2, zero: 18.3 vs. 13.8 (*p* = 0.22); one: 23.2 vs. 19.8 (*p* = 0.19); two or more 27.7 vs. 25.7 (*p* = 0.29), respectively).

In fully adjusted models (Table 3), compared to HIV-negative people with zero conditions, PWH with the syndemic had 87% higher CVD risk (*HR* 1.87, 95% CI 1.47, 2.38, *p* < 0.001), whereas HIV-negative people with the syndemic had 70% greater risk (*HR* 1.70, 95% CI 1.35, 2.13, *p* < 0.001). Among those with the syndemic, there was no statistically significant difference in CVD incidence by HIV status (*HR* 1.10, 95% CI 1.89, 1.37, *p* = 0.38). In HIV-status stratified models (Table 4), the association between the syndemic and incident CVD among PWH remained after adjustment for baseline HIV viral load and CD4 count (HR 1.37, 95% CI 1.09, 1.72, p = 0.007. After further adjustment for time-updated HIV viral load and CD4 counts, the point estimate remained stable (*HR* = 1.34 95% CI 1.07, 1.68, p = 0.012).

Discussion

Having at least two of the syndemic conditions (i.e., unhealthy alcohol use, smoking, depressive symptoms) was common (64%) among PWH and HIV-negative veterans. The observed prevalence of having all three conditions was 15%, which exceeded the expected prevalence of 6.9% (6.4% for HIV-negative and 7.5% for PWH), based on individual prevalence of each condition. Having two or more of these conditions was associated with increased risk for incident CVD, regardless of HIV-status, even after adjusting for traditional CVD risk factors and comorbidities.

Prior studies have reported that unhealthy alcohol use [24], cigarette smoking [5, 11, 19, 20, 60], and depression [20] are individually associated with higher CVD risk. The current study reports that 2/3 of VACS participants have at least two of these conditions. These results have important implications for the linked-screening and management of unhealthy alcohol use, smoking, and depression among PWH. In the current era, over 50% of PWH are estimated to be over age 50, and non-AIDS related comorbidities are now the leading causes

of mortality among PWH [1, 2]. Even among PWH on treatment with suppressed viremia, there is a 50% excess risk of CVD [5]. While some of this excess risk is attributed to direct effects of the virus on vascular and other tissues [61], it is also likely that the behavioral health factors that comprise this syndemic are under-identified [62–64], under-treated [63, 65–67], and are driving excess risk for CVD. Therefore, a 2-pronged approach to the management of this syndemic should include linked-screening and treatment.

Linked-screening

The US Preventive Services Task Force [68] recommends that clinicians assess all adults aged 18 years and older for unhealthy alcohol use, tobacco use, and depression and provide support to reduce alcohol consumption and tobacco use, and ensure effective diagnosis, treatment, and follow-up to those with depression. Regardless of these recommendations, unhealthy alcohol use, cigarette use, and depression remain under-screened and under-treated among PWH compared to HIV-negative populations [64, 67]. Further, guidelines do not address the simultaneous assessment or management of these conditions. If a patient screens positive for one condition, they will likely screen positive for at least one or both other conditions. Therefore, if screening is not commonplace in practice, then providers may not only be missing one, but potentially all three conditions that have clinical impact on cardiovascular health. Leveraging existing, validated brief screening tools for smoking (one question) [69], unhealthy alcohol use (AUDIT-C, three questions) [44], and depression (PHQ-2, two questions) [70] could make detection of these conditions feasible across general primary care, cardiology, and infectious disease care settings. Further, this process can take place as part of Patient-Reported Outcome Measures [71, 72] programs that many medical centers are adopting.

Treatment

While clinical practice guidelines for addressing unhealthy alcohol use, smoking, and depression [73–75] are available, these conditions are perceived as difficult to effectively treat. Therefore, treatment of these individual conditions is generally low: only 1/3 of smokers making a quit-attempt report using cessation treatments [76]; 24% of those with an alcohol use disorder are ever treated [77]; 37% of those with major depression received related-care within 1-year, with an average delay of eight years from the time of diagnosis [78, 79].

Research supports the combination of behavioral therapy and pharmacotherapy as the most effective treatment for smoking cessation, alcohol use disorder, and depression [80]. Shared biological mechanisms [29, 81, 82] of these conditions support the possibility of parsimonious behavioral and pharmacologic treatment, through cognitive behavior therapy and medications such as varenicline, a partial agonist of the α4β2 nicotinic acetylcholine receptor, which has demonstrated effectiveness for smoking cessation and potential efficacy for treatment of alcohol use in humans [30, 83]. The fact that these conditions are syndemic, are associated with increased risk of CVD, and may be treated parsimoniously is particularly important for PWH and their providers because this clinical population is at great risk for polypharmacy [31]. Models of effective integrated (Screening, Brief

Intervention and Referral to Treatment) [84] and/or collaborative care [85–88] exist that have linked cardiology, infectious disease, and general medicine.

The American College of Cardiology has stressed the importance of recognizing tobacco use and implementing evidence-based therapies into cardiovascular medicine [89]. Further, cardiovascular medicine has been recognized as an important setting to screen and treat depression as a modifiable risk factor for CVD [90]. Our findings bolster these recommendations by adding another reason for doing so – smoking, depressive symptoms, and unhealthy alcohol use are often concurrent, and this combination of conditions is associated with increased risk for CVD. Therefore, cardiovascular medicine provides a unique opportunity to implement, at a minimum, linked-screening and ideally treatment in either an integrative or collaborative fashion.

Limitations

The current study has several limitations. First, CVD was based on *ICD-9* or *CDT* codes and was not adjudicated. Therefore, some misclassification may have occurred, likely biasing our results toward the null. Second, as the sample consisted of mostly men, our findings may not be generalizable to women. Related, while the prevalence of smoking and depressive symptoms among PWH is similar to estimates found in other HIV-cohorts, unhealthy alcohol use was markedly higher in this veteran cohort which may not be representative of non-veteran PWH. Third, this study was not powered to model differential magnitude of effect of each specific condition, which was beyond the scope of this analysis. However, this method is similar to scores used in clinical practice that give equal weight to conditions that cluster, including the AHA Life's Simple 7 [91] and the metabolic syndrome score [92, 93]. Fourth, while illicit drug use (particularly opioid use) is epidemic, the literature linking opioid use and CVD is sparse, with inconsistent findings. We, therefore, chose to focus specifically on the syndemic of unhealthy alcohol use, smoking, and depressive symptoms, each of which is associated with future CVD events. Related, while diagnosis of PTSD is understandably prevalent in this veteran population and relevant to syndemic conditions of interest, the time-varying nature and severity of posttraumatic stress symptoms [94] is not captured in this data. Therefore, we do not include PTSD within the framework of the time-varying syndemic of interest. Since PTSD is associated with unhealthy drinking [95] as well as increased risk for CVD [96], we include ever being diagnosed with PTSD as a potential covariate.

Conclusions

The syndemic of unhealthy alcohol use, cigarette use, and depressive symptoms is common and having two or more of these conditions (syndemic) increased incident CVD risk. This association did not differ significantly by HIV status. Given the high prevalence of this syndemic and the excess risk of CVD, these findings support linked-screening and treatment efforts. Because of the high concurrence of unhealthy alcohol use, smoking, and depression, further research focusing on potential genetic correlates among these conditions is warranted and may provide insight on opportunities for precision medicine. Lastly, this

research should be extended to understand disparities in receipt of care among those with syndemic conditions and how disparities may differ by HIV status.

Acknowledgements

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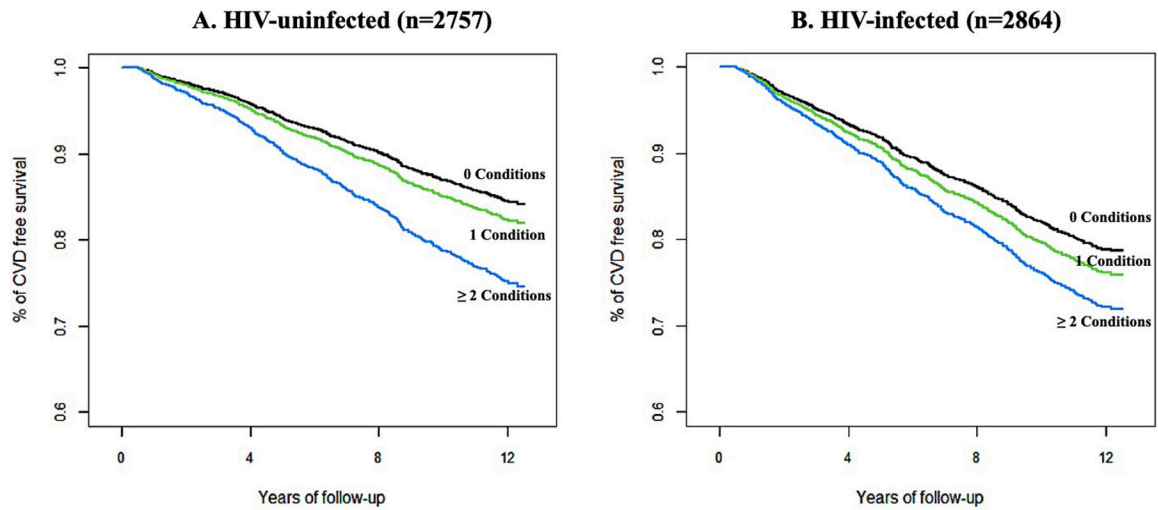
Fig. 1.

Age-adjusted curves of CVD-free survival by baseline number of syndemic conditions by HIV status. p-value of trend test: < 0.001 (HIV−); < 0.012 (HIV +). Age-adjusted (49.1 years) CVD-free survival among HIV-uninfected. (B) Age-adjusted (49.1 years) CVD-free survival among HIV-infected

Table 1

Baseline characteristics of study population by number of syndemic behavioral conditions

Characteristics	Total N = 5621	Number of syndemic conditions		
		0 524 (9.3%)	1 1480 (26.3%)	2 3617 (64.3%)
	Column frequency (%)			
Incident CVD *	1149 (20.4)	77 (14.7)	285 (19.3)	787 (21.8)
Age, years, Median [Interquartile]	49.1 [43.6, 54.6]	45.2 [38.3, 53.6]	48.7 [42.1, 55.2]	49.6 [44.8, 54.4]
Sex				
Women	317 (5.6)	56 (10.7)	115 (7.8)	146 (4.0)
Men	5304 (94.4)	468 (89.3)	1365 (92.2)	3471 (96.0)
Race/Ethnicity				
White, non-Hispanic	1196 (21.3)	127 (24.2)	371 (25.1)	698 (19.3)
Black, non-Hispanic	3651 (65.0)	322 (61.5)	894 (60.4)	2435 (67.3)
Hispanic	567 (10.1)	60 (11.5)	143 (9.7)	364 (10.1)
Other	207 (3.7)	15 (2.9)	72 (4.9)	120 (3.3)
Education				
< High school	352 (6.3)	11 (2.1)	59 (4.0)	282 (7.8)
High school or equivalent	1836 (32.7)	83 (15.8)	408 (27.6)	1345 (37.2)
> High school	3384 (60.2)	426 (81.3)	998 (67.4)	1960 (54.2)
Diabetes (glucose measurement, antidiabetic agent use, and/or at least 1 inpatient/2 outpatient ICD-9 codes for diabetes)	828 (14.7)	79 (15.1)	203 (13.7)	546 (15.1)
Hypertension				
No (BP < 140/90 mm Hg, no antihypertensive medication)	2250 (40.0)	246 (46.9)	596 (40.3)	1408 (38.9)
Controlled (BP < 140/90 mm Hg, on antihypertensive medication)	1946 (34.6)	162 (30.9)	514 (34.7)	1270 (35.1)
Uncontrolled (BP 140/90 mm Hg)	1421 (25.3)	115 (21.9)	369 (24.9)	937 (25.9)
Low-density lipoprotein cholesterol 160 mg/dL, blood	457 (8.1)	46 (8.8)	140 (9.5)	271 (7.5)
High-density lipoprotein cholesterol < 40 mg/dL, blood	2499 (44.5)	260 (49.6)	720 (48.6)	1519 (42.0)
Triglycerides 200 mg/dL, blood	1237 (22.0)	98 (18.7)	351 (23.7)	788 (21.8)
Obesity (body mass index 30)	1496 (26.6)	164 (31.3)	430 (29.1)	902 (24.9)
Chronic obstructive pulmonary disease	515 (9.2)	21 (4.0)	99 (6.7)	395 (10.9)
Hepatitis C infection	1934 (34.4)	53 (10.1)	310 (20.9)	1571 (43.4)
Anemia (hemoglobin < 13 g/dL men; < 12 g/dL women)	1068 (19.0)	84 (16.0)	266 (18.0)	718 (19.9)

Characteristics	Total N = 5621	Number of syndemic conditions		
		0 524 (9.3%)	1 1480 (26.3%)	2 3617 (64.3%)
Renal disease (estimated glomerular filtration rate, mL/min/1·73 m²)				
<30	40 (0.7)	4 (0.8)	7 (0.5)	29 (0.8)
30–59	216 (3.8)	27 (5.2)	62 (4.2)	127 (3.5)
60	5281 (94.0)	481 (91.8)	1389 (93.9)	3411 (94.3)
Posttraumatic stress disorder (ICD-9 code)	792 (14.1)	22 (4.2)	108 (7.3)	662 (18.3)
Illicit drug use	2174 (38.7)	16 (3.1)	259 (17.5)	1899 (52.5)
Opioid use disorder	938 (16.7)	4 (0.8)	88 (5.9)	846 (23.4)
Cigarette Use				
Current	2836 (50.5)	0 (0.0)	417 (28.2)	2419 (66.9)
Former	1369 (24.4)	0 (0.0)	325 (22.0)	1044 (28.9)
Never	1416 (25.2)	524 (100.0)	738 (49.9)	154 (4.3)
Alcohol consumption				
Not current drinker	1791 (31.9)	0 (0.0)	320 (21.6)	1471 (40.7)
Not hazardous	1495 (26.6)	524 (100.0)	825 (55.7)	146 (4.0)
Unhealthy or alcohol use disorder	2335 (41.5)	0 (0.0)	335 (22.6)	2000 (55.3)
Depressive symptoms (PHQ-9 ≥ 10)	1191 (21.2)	0 (0.0)	83 (5.6)	1108 (30.6)
HIV Status				
HIV-negative (HIV-)	2757 (49.0)	276 (52.7)	719 (48.6)	1762 (48.7)
HIV-positive (HIV +)	2864 (51.0)	248 (47.3)	761 (51.4)	1855 (51.3)
HIV-1 RNA viral load ≥ 400 copies/milliliter (among HIV +)	1522 (53.1)	120 (48.4)	406 (53.4)	996 (53.7)
CD4 + T-cell count < 500 cells/microliter[3] (among HIV +)	1954 (68.2)	161 (64.9)	520 (68.3)	1273 (68.6)
On antiretroviral therapy (% of HIV +)	2282 (79.7)	197 (79.4)	628 (82.5)	1457 (78.5)

AUDIT-C Alcohol Use Disorders Identification Test, *BP* blood pressure, *CVD* cardiovascular disease, *ICD-9* International Classification of Diseases, Ninth Revision, *PHQ-9* Patient Health Questionnaire, *%* percentage

*

CVD: acute myocardial infarction, unstable angina, revascularization, ischemic stroke, heart failure, and peripheral artery disease

Diabetes was identified using a previously validated metric that incorporates glucose measurements, antidiabetic agent use, and/or at least 1 inpatient or 2 outpatient ICD-9 codes for diabetes; Hepatitis C virus sero-positivity was defined as a positive hepatitis C virus antibody test result or at least 1 inpatient or 2 outpatient ICD-9 codes for this diagnosis

Table 2

Unadjusted cardiovascular disease incidence rates per 1000 person years (95% CI) by number of syndemic behavioral conditions

	Total N = 5621	Number of conditions		
		0 524	1 1480	2 3617
CVD (column %)	1149 (20.4)	77 (14.7)	285 (19.3)	787 (21.8)
Incidence rates (95% CI)	24.1 (22.8–25.5)	15.9 (12.6–19.7)	21.5 (19.1–24.1)	26.6 (24.8–28.6)
HIV-negative	22.8 (20.9–24.7)	13.8 (9.8–18.8)	19.8 (16.6–23.4)	25.7 (23.2–28.3)
HIV-positive	25.5 (23.5–27.6)	18.3 (13.3–24.5)	23.2 (19.7–27)	27.7 (25.1–30.4)
p-value of test of incidence rate difference	0.054	0.216	0.188	0.291

Conditions refers to unhealthy alcohol use, cigarette smoking, and depressive symptoms

Table 3

Hazard ratios (95% CI) for interactive effect of HIV status and syndemic conditions on incident cardiovascular disease

HIV-uninfected			HIV-infected			Pairwise comparison	
Number of conditions	HR (95% CI)	p-value	Number of conditions	HR (95% CI)	p-value	HR (95% CI)	p-value
HIV-/0 conditions	1·0 (ref)	–	HIV +/0 conditions	1.31 (1.05, 1.63)	0.015		
HIV-/1 condition	1.44 (1.17, 1.78)	0.001	HIV +/1 condition	1.66 (1.34, 2.06)	< 0.001	1.15 (0.95, 1.39)	0.160
HIV-/ 2 conditions	1.70 (1.35, 2.13)	< 0.001	HIV + / 2 conditions	1.87 (1.47, 2.38)	< 0.001	1.10 (0.89–1.37)	0.380

HIV – HIV-uninfected, *HIV +* HIV-infected, *HR* hazard ratio, *CI* confidence interval, Conditions refer to unhealthy alcohol use, cigarette smoking, and depressive symptoms

Adjusted for age, race/ethnicity, education, cardiovascular disease risk factors (hypertension, diabetes, LDL cholesterol, HDL cholesterol, triglycerides, and obesity), Hepatitis C infection, hemoglobin, eGFR, PTSD, illicit drug use and OUD

Table 4

Adjusted hazard ratios (95% CI) for association between syndemic conditions and incident cardiovascular disease by HIV status

Total sample

Number of conditions	Age-adjusted incidence rate	HR (95% CI)	p
0 Conditions	18.2 (16.2, 20.2)	1·0 (ref)	
1 Condition	23.6 (21.4, 25.8)	1.34 (1.16, 1.55)	< 0.001
2 Conditions	25.2 (22.5, 27.8)	1.55 (1.32, 1.83)	< 0.001

HIV-uninfected

Number of conditions	Age-adjusted incidence rate	HR (95% CI)	p
0 Conditions	14.8 (12.3, 17.3)	1·0 (ref)	
1 Condition	21.1 (18.1, 24)	1.48 (1.2, 1.83)	< 0.001
2 Conditions	24.1 (20.6, 27.7)	1.82 (1.43, 2.33)	< 0.001

HIV-infected

Number of conditions	Age-adjusted incidence rate	HR (95% CI) With baseline viral load and CD4 count	p	HR (95% CI) With time-updated viral load	p
0 Conditions	21.7 (18.5, 24.8)	1·0 (ref)		1·0 (ref)	
1 Condition	26.0 (22.6, 29.3)	1.22 (1.00, 1.48)	0.048	1.21 (1.00, 1.48)	0.054
2 Conditions	26.2 (22.2, 30.1)	1.37 (1.09, 1.72)	0.007	1.34 (1.07, 1.68)	0.012

CI confidence interval, *%* percentage, *HR* hazards ratio, *ref* reference, Conditions refers to unhealthy alcohol use, cigarette smoking, and depressive symptoms

Incidence rates per 1000 person-years

All models adjusted for baseline age, race/ethnicity, education, cardiovascular disease risk factors (hypertension, diabetes, LDL cholesterol, HDL cholesterol, triglycerides, and obesity), Hepatitis C infection, hemoglobin, eGFR, PTSD, illicit drug use, and OUD. In models with the full sample, HIV status was included for adjustment. In models with only HIV-infected patients, HIV-1 RNA viral load and CD4 + T-cell count were included for adjustment