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Gender-related risk factors improve mortality predictive ability of VACS Index among HIV-infected women

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Abstract

Background—Adding gender-related modifiable characteristics or behaviors to the Veterans Aging Cohort Study (VACS) Index might improve the accuracy of predicting mortality among HIV-infected women on treatment. We evaluated the VACS Index in women with HIV, determined whether additional variables would improve mortality prediction, and quantified the potential for improved survival associated with reduction in these additional risk factors.

Methods—The VACS Index (based on age, CD4 count, HIV-1 RNA, hemoglobin, AST, ALT, platelets, creatinine and Hepatitis C status) was validated in HIV-infected women in the Women's Interagency HIV Study (WIHS) who initiated antiretroviral therapy (ART) between January 1996

and December 2007. Models were constructed adding race, depression, abuse, smoking, substance use, transactional sex, and comorbidities to determine whether predictability improved. Population attributable fractions were calculated.

Results—The VACS Index accurately predicted 5-year mortality in 1057 WIHS women with 1 year on HAART with c-index 0.83 (95% CI 0.79–0.87). In multivariate analysis, the VACS Index score (adjusted hazard ratio [aHR] for 5-point increment 1.30; 95% CI 1.25–1.35), depressive symptoms (aHR 1.73; 95% CI 1.17–2.56) and history of transactional sex (aHR 1.93; 95% CI 1.33–1.82) were independent statistically significant predictors of mortality.

Conclusions—Including depression and transactional sex significantly improved the performance of the VACS Index in predicting mortality among HIV-infected women. Providing treatment for depression and addressing economic and psychosocial instability in HIV infected women would improve health and perhaps point to a broader public health approach to reducing HIV mortality.

Keywords

HIV; Women; Mortality; Depression; Transactional Sex

Developing a reliable, simple prognostic tool to identify patients with HIV at highest risk for dying is a priority for both providers and patients. The Veterans Aging Cohort Study (VACS) Index has been demonstrated to be such a tool, primarily in male cohorts. Using readily available laboratory and clinical data reflecting target organ injury and comorbidities common in treated HIV infected patients, the VACS Index provides a more accurate prediction of mortality and prognosis than models restricted to CD4 and HIV-1 RNA [1, 2]. Additional modifiable characteristics or behaviors might improve the accuracy of this index and be relevant to particular groups of patients, such as women with HIV.

Although antiretroviral therapy has brought overall declines in HIV deaths and promises of longevity similar to uninfected persons, sex disparities in HIV disease and mortality burden continue [3]. Using the VACS index, VA investigators found that women had less improvement in overall disease burden after 1 year of HIV treatment compared to men [4]. Further, gender inequalities resulting in inadequate HIV care continue to be documented, particularly among poor and marginalized groups of women [5]. Women with HIV had higher rates of hospitalization for opportunistic infections than men with HIV in a nationwide report, reflecting less access to antiretroviral therapy [6]. In a study comparing trends between 1993–1995 and 2005–2007, HIV mortality declined for most men and women, but rates were unchanged for black women with fewer years of education [7].

The intersection of gender, race, and poverty contribute to this disparity by increasing the likelihood of vulnerability due to substance use, incarceration, gender based violence, and mental illness, which may result in reduced access to care, worse adherence, poor prognosis and mortality in women with HIV [8–10].

Evaluating the VACS Index in a longitudinal cohort of women provides an opportunity to consider additional factors that disproportionately affect women and might contribute to mortality. In this study we identified and validated predictors of woman specific mortality

amassed through two decades of study of U.S. women with and at risk for HIV in the Women's Interagency HIV Study (WIHS) [11–14]. Variables of particular interest are those that disproportionately impact women, including depression, history of childhood sexual abuse, domestic violence, as well as high risk behaviors related to HIV, which can be routinely identified and addressed as part of clinical care.

The goals of this analysis are to 1) evaluate the performance of the VACS Index in women with HIV, 2) determine whether inclusion of additional gender informed variables to the VACS Index would significantly improve mortality prediction in women, and 3) quantify the potential for improved survival associated with reduction in these additional risk factors.

Methods

The WIHS is an ongoing representative longitudinal cohort study of HIV-infected and uninfected women in Chicago, San Francisco, Brooklyn, the Bronx, Washington, DC and Los Angeles initiated in 1994. Cohort recruitment, methods, and characteristics, have been previously described [15, 16]. Women are seen semiannually for a structured interview, physical exam and collection of specimens. Written informed consent was obtained from all participants after approval by institutional review boards at each participating institution.

This analysis was restricted to women with HIV infection who initiated HAART between January 1996 and December 2007, but follow up continued through December 31, 2011. National Death Index (NDI) Registry matches completed in 2013 confirmed deaths through December 31, 2011. All WIHS deaths are reviewed by 2 clinicians and classified as AIDS, non-AIDS, pneumonia, or indeterminate. HIV seroconverters were excluded (n=24). HAART was defined per contemporaneous Department of Health and Human Services Guidelines.

VACS Index score was calculated by summing points for age, CD4 count, HIV viral load, hemoglobin, Fibrosis Index (FIB)-4, estimated glomerular filtration rate (eGFR), and HCV serostatus and categorized into quartiles. Continuous scores were also considered in 5-point increments [1]. The visit closest (within -90 to 180 days) to the one year anniversary of first reported HAART use was the visit at which VACS index was calculated and follow up began, herein referred to as the anchoring visit.

Additional predictors included race/ethnicity (White non-Hispanic, Black non-Hispanic, Hispanic, Other non-Hispanic, and as Black vs. non-Black), history of transactional sex ("ever had sex for drugs, money, or shelter?"), childhood (<17 years of age) sexual abuse, and history of adult abuse (sexual, physical, or emotional/domestic abuse) and anchoring visit current smoking, recent (since last visit) harmful drinking per NIAAA definition, recent and ever use of crack, cocaine, or heroin, clinically significant depressive symptoms defined as ≥ 16 on the Center for Epidemiologic Study CES-D [17], recent (in past year) adult abuse, current hypertension defined as having SBP ≥ 140 , DBP ≥ 90 or self-reported use of anti-hypertensives, and diabetes determined by self-report or use of anti-diabetic medications, fasting glucose ≥ 126 or HgbA1C $\geq 6.5\%$.

We examined the association between VACS index score (primary explanatory variable) and time to all-cause mortality over 5 years of follow-up using Cox proportional hazards regression. Person-time in years was calculated from the anchoring date to death, last WIHS visit, or 5 years from the anchoring point. Cumulative mortality was calculated using Kaplan-Meier methods. VACS Index scores and expanded variables were treated as fixed exposures at the one-year anchoring point. We calculated univariable hazard ratios and VACS-adjusted hazard ratios for each exposure. Variables with $p < 0.2$ in univariable analysis and others based on a-priori hypotheses were entered in multivariable Cox regression models. Model building used an iterative stepwise selection process with $p < 0.05$ as the cutoff for retention in the final models. Improvement in model fit was assessed using likelihood ratio testing, Akaike's Information Criterion (AIC), and Bayes Information Criterion (BIC) fit indices. Model calibration and discrimination were assessed by comparing observed vs. expected survival curves and Harrell's C-index for survival data [18]. The C-index is a measure of how well a model discriminates between responses; i.e. whether "high" values are classified as high by the model and "low" values are classified as low. A value of 0.5 indicates no additional predictive value over that expected due to chance; a value of $> .7$ is considered good, and > 0.8 is considered excellent.

We calculated optimism-adjusted c-statistics by bootstrapping using 200 replicates and compared c-statistics for models with VACS Index only and with VACS Index plus the additional predictors, entered one at a time and in combination with one another. The proportional hazards assumption for the Cox models was assessed graphically by examining log-log survival curves for each exposure, and by statistical testing for non-zero slope of scaled Schoenfeld residuals on functions of time [19]. Standard errors were calculated using robust variance estimation.

We calculated population attributable fractions (PAFs) to determine the relative contribution of final model predictors to 5-year mortality using the STATA *punafcc* program [20]. The adjusted PAF represents the proportion of deaths attributable to the exposure controlling for other variables in the model and potential mortality reduction [21].

We conducted multiple imputation using established methods [22, 23], implemented with the MI procedure in SAS version 9.3, assuming multivariate normality and non-monotone missingness. Markov-Chain Monte Carlo methods were used to create 30 replicate datasets, with Cox models refitted in the imputed datasets and estimates combined to obtain summary effect measures [22,23]. The complete case and imputed analyses yielded the same final models with similar relative magnitude, direction, and significance of effects. Thus, results from the complete case analysis are presented. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) and STATA version 13.1 (StataCorp, College Station, TX).

Results

Of 3067 women with HIV infection, 1430 initiated HAART between January 1997 and December 2007 and had a visit within -90 to +180 days of the one-year anniversary of HAART initiation. Of these, 1057 women had at least 1 visit with non-missing VACS (Table 1). Over 80% of the women were African American or Latina, under 50 years of age,

with a CD4 cell count >200 cells/ μ l and 50% had HIV-1 RNA levels<500 copies/ml. The participants were poor and over one had not finished high school. One third of the population was anemic, one third was co-infected with HCV and one fourth had liver abnormalities. Less than 6% had renal abnormalities by eGFR. VACS scores were low at the first anchoring visit with a median of 27 (range 0–115). During the first 5 years of follow-up 113 deaths occurred over 4771.6 person-years of observation, yielding a mortality rate of 2.37 (95% CI 1.97–2.85) per 100 person-years. Causes of death (n=113) during the first 5 years were classified as AIDS (46/41%), non-AIDS (50/44%), pneumonia (15/13%) and indeterminate 2 (2%).

Cumulative mortality increased substantially with increasing quartiles of VACS score, from 0.71 (95% CI 0.48–1.06) to 18.8 (95% CI 12.6–28.1) per 100 person-years in the lowest and highest quartiles respectively (Figure 1a). Comparison of observed mortality and VACS Index score predicted mortality (Figure 1b) showed close agreement, indicating good model calibration. We found a 30% increase in mortality with every additional 5 point increase in VACS Index score at 1 year post-HAART initiation. Discrimination was good for models with both the categorical (c-index 0.79; 95% CI 0.75–0.83) and continuous (c-index 0.83; 95% CI 0.79–0.87) versions of VACS Index score with higher VACS scores associated with significantly higher hazard ratios. (Table 2) We calculated annually updated VACS Index scores at 2,3,4, and 5 years post-HAART initiation to determine changes in index performance with increasing time on HAART, and found stable (c-index range 0.79–0.83) discriminatory power (data not shown).

Associations between VACS Index scores, expanded variables, and 5-year mortality are shown in Table 3. In univariable analysis, depressive symptoms, smoking, history of transactional sex, history of injection drug use, ever and recent use of crack, cocaine, or heroin (CCH), hypertension, income and Black race were statistically significant predictors of 5 year mortality. Adjusted for VACS Index score, depressive symptoms, smoking, CCH use, and transactional sex history remained statistically significant. In the final multivariable model, the VACS Index score (adjusted hazard ratio [aHR] for 5-point increment 1.30; 95% CI 1.25–1.35), depressive symptoms (aHR 1.73; 95% CI 1.17–2.56) and history of transactional sex (aHR 1.93; 95% CI 1.33–1.82) were statistically significant predictors of mortality.

Table 4 shows comparative fit indices for models including VACS Index and other exposures. Transactional sex and depression had a substantial effect on mortality independent of the VACS Index. Expanding the VACS Index to include these variables yielded statistically significant likelihood ratio tests and reductions in AIC and BIC values, indicating improvements in model fit. There were only small changes in c-indices from 0.83 for the VACS model to 0.85 for the expanded model with VACS, depression, and transactional sex history. While the expanded model does result in a small increase in the c-index over that of the VACS index, c-statistics have been shown to be insensitive to small improvements in model fit, particularly when the value of the initial c-index is above 0.8. The statistically significant effects of depression and transactional sex, independently of the effects of the VACS index suggest that these factors are important predictors of mortality

over and above that explained by the VACS index, despite the small improvements in c-statistics.

In terms of the relative contribution of these exposures to overall mortality, VACS Index contributed the most by PAF (0.69; 95% CI 0.56–0.78), followed by depressive symptoms (0.30; 95% CI 0.11–0.45) and history of transactional sex (0.25; 0.08–0.39).

Discussion

In this study, the VACS Index accurately predicted mortality over 5 years of follow up in women in WIHS with 1 year of HAART exposure. We expected the VACS Index to perform well within the WIHS, as it was developed on HIV populations which were primarily African American, poor and with substantial prevalence of HCV and liver disease [1]. The VACS index performed similarly among women in our study as in other predominantly male cohorts, indicated by the similar c-statistics and relative magnitude of association with mortality in our study as compared to other studies. In our study we found c-statistics of approximately 0.8 or higher, similar to the other VACS Index papers, in which c-statistics ranged from 0.78–0.81 in various predominantly male populations, including male veterans.

However since the VACS was based on and validated in cohorts that were majority male, we investigated whether other variables specifically related to women's HIV prognosis would also be predictive when added to the VACS [1, 2]. We identified two conditions that predicted mortality in WIHS women independently of the VACS index: depressive symptoms and a history of engaging in transactional sex. Both variables were highly statistically significant ($p < 0.01$) in a model including VACS. Adding these variables to the model resulted in small improvement in the c-index, probably reflecting the insensitivity of C-statistics to small improvements in model fit, even when new variables are statistically significant, and limited room for improvement when the c-index of the base model is > 0.8 . [24,25]

In addition to finding an 80% increased risk of death (1.8–1.9) associated with depression and transactional sex, the high prevalence of these exposures in our population (44% for depression and 36% for history of transactional sex) makes them important potential candidates for interventions in this population. The PAFs suggest that even if VACS were held constant, mitigation or elimination of depression could reduce mortality up to 30%.

The magnitude of the correlation between transactional sex and current depressive symptoms, though statistically significant, was quite low (Spearman $r = 0.13$), and though the association of each variable was somewhat attenuated in models with both exposures (Table 3), each exposure was independently associated with mortality when controlling for the other, suggesting that the effect of these exposures on mortality operate via distinct pathways.

Depression and transactional sex represent significant predictors that have not previously been considered in constructing the VACS Index, probably because this data is not routinely collected in male HIV cohorts. Why might these two variables add predictive accuracy to

identify those at highest mortality and what is their relevance in caring for HIV-infected patients? Depression contributes to increased mortality in cardiovascular, cerebrovascular and peripheral vascular diseases, hypertension, neurocognitive decline, and cancer through several mechanisms [26–29]. Depressive symptoms often emerge from the psychosocial stress of being diagnosed, may reduce medication adherence, and are associated with significant behavioral risk factors like lower educational level, obesity, reduced physical activity, alcohol abuse, unhealthy diet, and smoking. Depression in patients with coronary heart disease and cancer can cause an increase in proinflammatory and a decrease in anti-inflammatory cytokines, as well as dysregulation of cortisol production which might increase cardiac events and promote metastasis. [29]

These psychosocial and inflammatory responses of depression are also evident in HIV disease. Depression is common in persons with HIV and is associated with stigma, chronic stress and trauma, isolation, poverty and poor social support which can reduce engagement in care and medication adherence [30]. Depression in HIV also directly and indirectly affects immune function by stimulating production of pro-inflammatory cytokines, shifting from Th1 to Th2 response, reducing NK cell cytotoxicity, suppressing cell mediated response to antigen, and accelerating HIV disease progression and mortality through activation of stress response systems [31–33].

Trading sex for money, drugs or shelter is an under-recognized but serious public health problem. Women living in poverty, often with drug or alcohol problems are at high risk for sexually transmitted diseases including HIV, unwanted pregnancies, abortions, discrimination, criminalization and abuse when engaging in transactional sex [34]. Studies from an urban emergency room and family planning clinic found that 8% of women reported recently trading sex for money [35, 36]. Although trading sex for drugs or money is most often discussed in the context of sex workers, poverty and economic insecurity can motivate sexual decision making and risk taking in general. Dunkle et al found that economic needs motivated relationships and transactional sex and these behaviors were associated with HIV risk behaviors [37].

In our study, transactional sex may represent the intersection of vulnerabilities that predict mortality in HIV infected women above and beyond the VACS Index. Sex work is often equated with acquiring and using drugs, but this is probably accounted for in the VACS by the surrogate markers of HCV and liver function. Women reporting a history of transactional sex face multiple social stressors and difficult life circumstances including poverty, lack of social support, criminalization, social isolation, disempowerment, abuse and possibly psychiatric comorbidities. Transactional sex might be a marker in this analysis for women with the most vulnerable economic and social situations [34].

The VACS index and the additional criteria suggested by this study are important because they can help prioritize interventions that might change prognosis and reduce disease progression and mortality. Providers are trained to use the most effective antiretroviral regimen to sustain undetectable viral load, one of the components of the VACS score. As HCV treatment becomes accessible and affordable, we might see less liver disease and HCV

induced inflammation and better HIV outcomes, and this too will be reflected in improved VACS scores.

Similarly if providers screen for depressive symptoms, there would be opportunity to discuss and treat depression and thereby influence HIV prognosis. Treatment of depression could lead to better quality of life, an improvement in underlying inflammation, and better outcomes for HIV and other related comorbidities, also affected by depression [38, 39]. Use of antidepressants in women with HIV on antiretroviral therapy was associated with a 29% higher rate of being employed [40]. Nonetheless, Cook et al recently reported that less than half of HIV infected women in WIHS with depressive symptoms actually received appropriate treatment [41]. Efforts to diagnose and treat depression will have direct health and economic benefits for women with HIV, which could be expected to improve their prognosis.

Asking women with HIV if they have a history of or are currently trading sex for money, drugs or other needs could be accomplished easily at a clinic visit. Primary prevention of the vulnerabilities that may be driving this association will likely include efforts to address gender inequalities and economic dependence of women, including support groups and vocational training. In addition, referrals to community empowerment models in which sex workers implement programs to address barriers to their overall health and human rights can help women with HIV have better outcomes. [42] Recently described trauma-informed primary care models may be applicable to care for sex workers in providing onsite and community based programs after screening and creating safe, non-discriminatory and empowering environments for both patients and providers. [43]

Several limitations are noted. First, exposures were self-reported, though WIHS validation studies of self-report demonstrate high correlation with objective measures [44]. Second, missing data rates were high but consistent with clinical practice and large longitudinal studies including those using the VACS Index. We addressed missing data effectively using robust imputation methods with minimal loss of precision, and imputed and complete case analyses yielded similar results. Third, our prediction models are based on relatively early post-HAART anchoring points and may not reflect recent improvements in clinical and public health knowledge and practice related to infectious (HIV, HCV), non-infectious (CVD, metabolic) and mental health (depression) conditions that influence mortality risk. Our ongoing longitudinal data and cohort expansion will allow us to assess the impact of contemporaneous treatment and effects of increased duration of illness and time on therapy.

In conclusion, the VACS Index performed well in WIHS but including two gender related factors further improved its performance in HIV infected women. The finding that these two factors contributed substantially to improving the predictive power of the Index can lead to a model more inclusive of biologic, psychological and sociocultural factors which may be relevant for other high risk populations, especially the growing number of young black men who have sex with men. A depressive symptom screen and transactional sex query are relatively easy to implement in routine clinical care visits. Patients and providers could use the expanded index to better determine prognosis and to address these modifiable risk factors in an attempt to reduce mortality in HIV patients. Providing treatment for depression

and addressing economic and psychosocial instability and empowerment in women with HIV would improve health and perhaps be part of a broader public health approach to reducing HIV mortality.

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FIGURE 1.

Table 1

Distribution of VACS Index Components in the WIHS Cohort after 1 year on HAART, 1997–2007

	Points Assigned	n (%)
Total n	–	1057
Age in years		
<50	0	936 (88.6)
50–64	12	116 (11.0)
65	27	5 (0.5)
CD4 (cells/mm³)		
500	0	352 (33.3)
350–499	6	217 (20.5)
200–349	6	264 (25.0)
100–199	10	139 (13.2)
50–99	28	33 (3.1)
<50	29	52 (4.9)
HIV RNA (copies/mL)		
<500	0	526 (49.8)
500–99,999	7	463 (43.8)
100,000	14	68 (6.4)
Hemoglobin (g/dL)		
14	0	144 (13.6)
12–13.9	10	559 (52.9)
10–11.9	22	302 (28.6)
<10	38	52 (4.9)
FIB-4^a		
<1.45	0	773 (73.1)
1.45–3.25	6	236 (22.3)
>3.25	25	48 (4.5)
eGFR (mL/min)^b		
60	0	996 (94.2)
45–59.9	6	36 (3.4)
30–44.9	8	10 (0.9)
<30	26	15 (1.4)
HCV co-infection	5	369 (34.9)
Year of HAART initiation		
1995–1996		150 (14.2)
1997–1999		492 (46.6)
2000–2006		415 (39.3)
Race/Ethnicity		
White		149 (14.1)
Black		615 (58.2)
Hispanic		264 (25.0)

	Points Assigned	n (%)
Other		29 (2.7)
Educational attainment		
Less than high school		396 (37.5)
High school or equivalent		314 (29.7)
Some college or more		346 (32.8)
Annual income		
<\$18,000		713 (67.5)
\$18,000		323 (30.6)
Median VACS Score (IQR);		27 (17–39)
Range		0–115

Abbreviations: HCV, Hepatitis C virus; IQR, interquartile range; eGFR, Estimated Glomerular Filtration Rate, FIB-4, Fibrosis Index-4; HAART, highly active antiretroviral therapy

^a Fibrosis Index-4 (FIB-4) is a validated marker of hepatic fibrosis based on age, aspartate and alanine aminotransferase (AST and ALT), and platelet count [FIB-4 = (age in years AST)/(platelet*sqrt(ALT))].

Sterling RK, Lissen E, Clumeck N et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006; 43: 1317–1325.

^b Estimated glomerular filtration rate (eGFR) is calculated based on the Modification of Diet in Renal Disease (MDRD) Study. [eGFR = $186 \times (\text{serum creatinine} - 1.154) \times (\text{age} - 0.203) \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$].

Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function-measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 354: 2473–2483.

Table 2

Hazard ratios and C-Index associated with Composite VACS Score: 5 year Mortality after 1 year on HAART, 1997–2007

	HR (95% CI)	c-index (95% CI)
VACS Index score, continuous^a	1.30 (1.26–1.34) **	0.83 (0.79–0.87)
VACS Index score, categorical^b		0.79 (0.75–0.83)
0–34	1.0 (Ref)	
35–49	4.32 (2.49–7.50) **	
50–69	13.2 (7.93–22.1) **	
70	27.9 (16.0–48.7) **	

Abbreviations: HR, hazard ratio, CI, confidence interval

^a Per 5-point increase

^b By approximate quartiles of outcome.

**
p<0.01

Table 3

Univariable and Multivariable Hazard Ratios for Predictors of 5-Year Mortality among Patients with Complete VACS at One year

	Univariable HR (95% CI)	p-value	VACS-adjusted HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
VACS score, per 5-point increase	1.30 (1.26–1.34)	<0.001	–	–	1.30 (1.25–1.35)	<0.001
CESD 16	2.37 (1.61–3.47)	<0.001	1.93 (1.31–2.83)	<0.001	1.73 (1.17–2.56)	0.006
History of childhood sexual abuse	1.12 (0.66–1.89)	0.668	0.90 (0.52–1.53)	0.685	–	–
History of adult abuse	1.22 (0.72–2.06)	0.469	1.23 (0.72–2.09)	0.444	–	–
Recent abuse	1.32 (0.61–2.89)	0.483	1.73 (0.79–3.79)	0.174	–	–
Current smoking	2.11 (1.43–3.11)	<0.001	1.69 (1.14–2.49)	0.008	–	–
Hazardous alcohol use	0.64 (0.32–1.26)	0.193	0.63 (0.32–1.25)	0.189	–	–
Transactional sex ever	2.18 (1.50–3.15)	<0.001	2.12 (1.46–3.07)	<0.001	1.93 (1.33–2.82)	<0.001
IDU ever	2.52 (1.74–3.64)	<0.001	1.31 (0.89–1.94)	0.173	–	–
CCH ever	2.56 (1.63–4.02)	<0.001	1.68 (1.06–2.66)	0.028	–	–
CCH use, recent	1.99 (1.25–3.17)	0.004	1.61 (1.01–2.57)	0.046	–	–
Hypertension, current	1.97 (1.35–2.87)	<0.001	1.35 (0.91–1.99)	0.133	–	–
Diabetes history	0.74 (0.45–1.23)	0.246	0.71 (0.43–1.18)	0.183	–	–
Black race	2.05 (1.35–3.11)	<0.001	1.37 (0.90–2.10)	0.142	–	–
Educational attainment	1.06 (0.73–1.54)	0.770	1.26 (0.86–1.84)	0.230	–	–
Less than high school	1.0 (Ref)		1.0 (Ref)			
High school graduate	1.11 (0.72–1.72)	0.626	0.95 (0.61–1.48)	0.835	–	–
Some college/degree	0.80 (0.50–1.26)	0.331	0.63 (0.41–1.04)	0.072	–	–
Annual income < \$18,000	2.61 (1.56–4.38)	<0.001	1.62 (0.96–2.76)	0.073	–	–

Abbreviations: CESD, Center for Epidemiological Studies-Depression; CCH, crack, cocaine, and/or heroin use; CI, confidence interval; HR, hazard ratio; IDU, injection drug use.

VACS-adjusted hazard ratios are adjusted for the VACS index score only. Multivariable hazard ratios are adjusted for all variables for which estimates are presented.

Table 4

Attributable Fractions from Final Multivariable Model, N=1052

	Exposure	Prevalence (%)	aHR (95% CI) ^a	p-value	PAF (95% CI) ^a	p-value
VACS Index score						
0–34		67.1	1.00 (Ref)	<0.001	0.69 (0.56, 0.78)	<0.001
35–49		18.4	3.94 (2.25–6.90)			
50–69		10.4	11.8 (6.97–20.0)			
70		4.1	27.0 (15.7–46.7)			
CESD 16		43.8	1.88 (1.27–2.79)	0.002	0.30 (0.11, 0.45)	0.004
Transactional sex ever		36.0	1.85 (1.26–2.71)	0.002	0.25 (0.08, 0.39)	0.005

Abbreviations: CESD, Center for Epidemiological Studies-Depression; CI, confidence interval; aHR, adjusted hazard ratio; PAF, population attributable fraction

^a Hazard ratios and population attributable fractions are adjusted for all variables for which estimates are presented.