The Veterans Aging Cohort Study (VACS) Index Predicts Mortality in a Community-recruited Cohort of People With Human Immunodeficiency Virus (HIV) Who Use Illicit Drugs

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The Veterans Aging Cohort Study (VACS) index combines commonly collected clinical biomarkers to estimate human immunodeficiency virus (HIV) disease severity. Among a prospective cohort of people living with HIV who use illicit drugs (PWUD) ($n = 948$), we found that the VACS index was significantly associated with mortality over a 20-year study period.

Keywords. VACS index; mortality; HIV; people who use drugs; Restricted Index.

INTRODUCTION

People living with human immunodeficiency virus (HIV) have increased inflammation and immune activation that persists even while receiving antiretroviral therapy (ART), which are strongly associated with morbidity and mortality [1]. The Veterans Aging Cohort Study (VACS) index was developed

as a predictor of all-cause mortality among people living with HIV [2, 3]. Highly correlated with measures of systemic inflammation, the VACS index is composed of measures of HIV mortality risk and indicators of comorbidity and organ system dysfunction [2–4].

HIV-positive people who use illicit drugs (PWUD) have not benefited equally from HIV treatment advancements. The inflammatory effects of illicit substance use may contribute to increased morbidity and mortality among this population [5]. Existing measures of HIV disease progression (eg, CD4+ cell count) suffer from well-known limitations. Employing the VACS index to evaluate mortality risk among HIV-positive PWUD may provide important information for research and clinical practice [3, 4]. Although substance use is a crucial risk factor for HIV disease progression, we are unaware of any study that has specifically examined the application of the VACS index among HIV-positive PWUD. In light of these knowledge gaps and need to improve outcomes for people living with HIV who use illicit drugs, we sought to: (1) evaluate the association between the VACS index with rates of mortality among a prospective cohort of HIV-positive PWUD; and (2) compare its discriminative power to the restricted index [4].

METHODS

The data for this investigation were collected from a prospective cohort of people living with HIV and who use illicit drugs in Vancouver, Canada: The AIDS Care Cohort to Evaluate exposure to Survival Services (ACCESS) [6]. Individuals were eligible for ACCESS if they were: aged ≥ 18 years, HIV seropositive, report using illicit drugs other than or in addition to cannabis (a controlled substance during the study period), resided in the Greater Vancouver Regional District, and provided informed consent at study enrollment.

At baseline and every 6 months thereafter, participants provided blood samples for hepatitis C virus (HCV) serology and HIV clinical monitoring (human immunodeficiency virus type 1 [HIV-1] RNA plasma viral load [VL], CD4+ cell counts) and completed an interviewer-administered questionnaire that elicited sociodemographic information, substance use patterns, engagement with health and social services, and other related exposures. The University of British Columbia/ Providence Health Care Research Ethics Board approved the ACCESS study.

Through a confidential data linkage with the Drug Treatment Program of the British Columbia Centre for Excellence in HIV/AIDS, we accessed retrospective and prospective data for all ACCESS participants on: HIV-related measures (e.g., HIV VL, CD4+ cell counts) and other biological measures collected

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during regular clinical care necessary to calculate the VACS index, as well as records of ART dispensation.

The analytical sample for this analysis included all ACCESS participants receiving ART who completed at least 2 study visits between May 1996 and May 2018. For each death, dates and primary causes of death were accessed through a confidential linkage with the British Columbia Vital Statistics Agency that recorded causes of death based on the International Classification of Diseases and Related Health Problems–10th Revision codes used in medical records. The primary outcomes of interest were all-cause mortality and nonaccidental mortality, which was defined as HIV-related, liver-related, and other nonaccidental mortality. The primary explanatory variable of interest was the VACS index, which is a cumulative measure that combines indicators of HIV-specific mortality (eg, age, CD4+ cell count, HIV VL), with composite measures of liver and renal injury (eg, fibrosis [FIB]-4, estimated glomerular filtration rate [eGFR]) and HCV antibody status [4]. Missing values for the components of the VACS and restricted index were imputed using a single imputation regression approach based on multilayer perception [7]. The analysis of the association between the VACS index (time-varying) and mortality also included a range of potential confounders hypothesized to confound the association (Table 1). Random intercepts were included in the models to account for the clustering of observations within participants. We also calculated the Restricted Index using age, CD4+ cell count, and HIV VL.

The crude associations between each explanatory variable and mortality over follow-up were analyzed using extended Cox regression models with time-varying covariates. Next, an a priori confounding model building protocol was applied to a Cox regression model. Beginning with a full multivariable model including the VACS index and all covariates, reduced models were fit by removing 1 covariate at a time that produced the smallest relative change in the VACS index coefficient. This process was repeated in a stepwise manner until the minimum change in the VACS index coefficient exceeded 5%. We also performed this analysis among complete cases to determine if the imputation procedure influenced the findings.

The association between the traditional Restricted Index and mortality was also analyzed using the same model building protocol. Harrell's C-statistics were used to compare the ability of the VACS index and Restricted Index (at baseline) to predict mortality over the study period. All statistical analyses were conducted using SAS version 9.4 (SAS, Cary, NC, USA) and all *P* values were 2-sided with a significance threshold of .05.

RESULTS

A total of 948 individuals were included in this analysis and the baseline characteristics of the study sample are presented in [Supplementary Tables 1 and 2](#). The median VACS index and

Restricted Index values at baseline were 18 (interquartile range [IQR] = 12–25) and 21 (IQR = 11–33), respectively. A total of 242 deaths occurred over follow-up for a crude mortality rate of 3.75 (95% confidence interval [CI] = 3.23–4.26) per 100 person-years.

In the adjusted analysis of the VACS index, only unstable housing (AHR = 1.96, 95% CI = 1.36–2.82) and the VACS index (AHR=1.03, 95% CI = 1.02–1.04) were significantly associated with all-cause mortality (Table 1). In the adjusted analysis of the Restricted Index, only unstable housing (AHR = 1.97, 95% CI = 1.36–2.84) and the Restricted Index (AHR = 1.02, 95% CI = 1.01–1.03) were significantly associated with all-cause mortality. Based on the C statistic, the VACS index provided a more accurate predictor of all-cause mortality at each 5-year interval of follow-up. When using only baseline values, the VACS index provided a better discriminatory measure of all-cause mortality than the Restricted Index over the entire study period (C statistic: 0.60 vs 0.56).

DISCUSSION

In the present study, higher VACS index scores were a significant predictor of all-cause mortality among a cohort of HIV-positive PWUD over a 20-year study period. The VACS index provided a more discriminative prediction of all-cause mortality compared to the Restricted Index over the entire study period and at each 5-year study interval.

In addition to predicting all-cause mortality, the VACS index has been shown to predict HIV-associated mortality, cardiovascular mortality, and long-term mortality among HIV-negative individuals [3, 8, 9]. VACS index scores are also highly responsive to ART initiation, adherence, and interruption and are strongly predictive of mortality among ART-naïve individuals, ART-exposed individuals, and individuals with varying degrees of HIV VL suppression [3, 4, 10].

The VACS values and mortality rate we observed were similar to those observed in previous studies although the discrimination of the VACS index in our study (C statistic: 0.60) is considered “fair” (0.60–0.69), which was lower than values estimated in previous studies (C statistic: 0.77) [3, 4]. This may be attributed to the inflammatory effects of different substances used by this population, comorbid health conditions, or the risk of overdose among PWUD in this setting [11]. Nevertheless, the VACS index may have important clinical and research advantages compared to the Restricted Index among PWUD based on the ability to predict all-cause, HIV, and cardiovascular mortality, correlations with frailty, and responsiveness to ART [4, 8–10]. Clinically, calculation of the VACS index could assist with case management to identify vulnerable patients who are in need of intensive care or referral to additional health services [4]. Providing a single summary measure that is

Table 1. Unadjusted and Adjusted Cox Regression Analyses of Factors Associated With Mortality Among People With Human Immunodeficiency Virus (HIV) Who Use Illicit Drugs

Unadjusted		Adjusted	
All-cause Mortality		All-cause Mortality	Non-accidental Mortality
Hazard Ratio (95% CI, <i>P</i> -value)		Hazard Ratio (95% CI, <i>P</i> -value)	Hazard Ratio (95% CI, <i>P</i> -value)
Characteristic		Characteristic	VACS Index Analysis ^b
VACS index		VACS index	
(per 1 unit increase)	1.03 (1.02 – 1.04, <.001)	(per 1 unit increase)	1.03 (1.02 – 1.04, <.001)
Restricted index		Unstable housing^a	
(per 1 unit increase)	1.02 (1.01 – 1.03, <.001)	(yes vs no)	1.96 (1.36 – 2.82, <.001)
Age			
(per year older)	1.05 (1.03 – 1.07, <.001)		Restricted Index Analysis ^c
Sex		Restricted index	
(male vs nonmale)	1.42 (1.04 – 1.93, .027)	(per 1 unit increase)	1.02 (1.01 – 1.03, <.001)
Ethnicity		Unstable housing^a	
(White vs non-white)	.86 (.64 – 1.15, .309)	(yes vs no)	1.97 (1.36 – 2.84, .024)
Unstable housing^a			2.26 (1.39–3.70, .001)
(yes vs no)	1.87 (1.34 – 2.61, <.001)		
Injection heroin use^a			
(≥daily vs <daily)	.79 (.51 – 1.24, .302)		
Injection cocaine use^a			
(≥daily vs <daily)	.64 (.36 – 1.15, .137)		
Injection prescription opioid use^a			
(≥daily vs <daily)	.97 (.40 – 2.35, .941)		
Injection speedball use^a			
(≥daily vs <daily)	1.13 (.57 – 2.23, .731)		
Injection methamphetamine use^a			
(≥daily vs <daily)	1.22 (.59 – 2.50, .595)		
Non-injection crack use^a			
(≥daily vs <daily)	.93 (.67 – 1.30, .691)		
Cannabis use^a			
(≥daily vs <daily)	.98 (.69 – 1.41, .930)		
Alcohol use^a			
(≥daily vs <daily)	1.31 (.88 – 1.94, .185)		
Incarceration^a			
(yes vs no)	.62 (.34 – 1.12, .116)		
Opioid agonist therapy^a			
(yes vs no)	.85 (.63– 1.14, .281)		
Drug or alcohol addiction treatment^a			
(yes vs no)	.70 (.36 – 1.37, .299)		
Sex work^a			
(yes vs no)	.61 (.32– 1.13, .117)		
Binge drug use^a			
(yes vs no)	.94 (.70– 1.27, .679)		

Abbreviations: CI, confidence interval; VACS, Veterans Aging Cohort Study.

^aRefers to activities in the 6 months prior to the follow-up interview; variables excluded from the table were not retained in the multivariable model building protocol.

^bRefers to the multivariable model including all variables with the exception of the Restricted Index. ^cRefers to the multivariable model including all variables with the exception of the VACS index.

responsive to treatment and behavioural changes may also facilitate tracking progress in mortality risk and response to ART or medications for substance use disorder (eg, opioid agonist therapy) over time [4]. The VACS index has also been proposed as a method of balancing study arms for prognostic factors in randomized controlled trials or being applied as a propensity score in observational research [4].

Further analysis of other significant predictors of mortality, such as unstable housing, may also improve mortality risk assessments among PWUD. Finally, substance use has been shown to induce changes in immune and inflammatory markers; further evaluation of these effects, and how they interact with immune responses caused by ART, is warranted in future studies [11].

Limitations of this study include the nonrandom recruitment of participants and measuring substance use behaviours by self-report. The VACS index was recently updated to include albumin, body mass index, and white blood cell count, but these data were not available in our sample.

In summary, we observed that the VACS index was an independent predictor of mortality among PWUD after adjustment for a range of sociodemographic, clinical, and behavioral confounders. Applying the VACS index to PWUD may have important implications for clinical care and research by facilitating investigations of the immune and inflammatory responses associated with specific types of substance use among people living with HIV.

Notes

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