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The Veterans Aging Cohort Study (VACS) Index is associated with concurrent risk for neurocognitive impairment

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Abstract

Objective—The Veterans Aging Cohort Study (VACS) Index is predictive of mortality, and combines age, traditional HIV biomarkers (HIV-1 plasma RNA and current CD4 count) and non-HIV biomarkers (indicators of renal and liver function, anemia, and Hepatitis C co-infection). We examined the association between the VACS Index and HIV-associated neurocognitive impairment (NCI).

Design and Methods—Participants included 601 HIV-infected adults enrolled in cohort studies at the UCSD HIV Neurobehavioral Research Program (Ages: 18-76 years; 88% male; 63% White; Median current CD4=364; 63% on antiretroviral therapy; AIDS=64%). Biomarkers used in calculating the VACS Index were measured in prospectively collected blood samples using conventional laboratory methods. NCI was defined using global and seven domain deficit scores.

Results—Higher VACS Index scores were associated with concurrent risk for global NCI ($p < .001$; $OR=1.21$, $CI=1.12-1.32$), even when adjusting for psychiatric comorbidities. This relation was statistically significant for most cognitive domains in adjusted models. Furthermore, the VACS Index predicted concurrent NCI beyond nadir CD4 and estimated duration of infection. Older age, lower hemoglobin and lower CD4 counts were the VACS components most strongly linked to NCI.

Conclusions—The findings extend prior research on the potential usefulness of the VACS Index in predicting HIV-associated outcomes to include NCI. Although the effect size was relatively small, our findings suggest that demographic information, HIV-disease factors, and common comorbidities might each play important roles in the clinical manifestation of cognitive impairment among HIV-infected individuals. Additional research is needed to determine if a more sensitive and specific index can be developed.

Keywords

HIV; comorbidity; cognition; cohort study; aging; anemia

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Conflicts of Interest: None

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Introduction

Combination antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) infection into a chronic disease marked by multiple comorbid conditions. HIV-infected individuals are living longer and increasingly experiencing fewer AIDS-defining conditions and a wider range of non-AIDS diseases^{1, 2}. This has prompted the need for better methods to track the impact of comorbidities and multiple organ system dysfunctions on the health of people living with HIV.

The Veterans Aging Cohort Study (VACS) Index was developed as a step towards creating an integrated endpoint for research and a potentially useful risk index for clinical management^{3, 4}. One of the VACS Index hallmarks is that it combines age, along with traditional HIV biomarkers (i.e., HIV-1 plasma RNA and current CD4 count) and non-HIV biomarkers (i.e., indicators of renal [estimated glomerular filtration rate; eGFR] and liver [fibrosis index-4; FIB-4] function, anemia [hemoglobin], and Hepatitis C co-infection)^{4, 6}. By combining indicators of disease from multiple organs, it reflects the multisystem injury among people living with HIV disease. Importantly, its components are markers of disease that are routinely monitored by HIV healthcare providers^{3, 4}.

The VACS Index was developed and initially validated among HIV-infected veterans (mostly men) initiating ART, where it was found to be predictive of all cause mortality⁴, and deaths attributed to coronary heart disease⁷. More recently, it has been validated as a risk index for mortality (all cause and separately for both HIV and non-HIV deaths) in large and diverse patient groups with at least a year exposure to ART in North America and Europe^{5, 6}. In these prior studies, the VACS Index improved discrimination of all cause mortality as compared to HIV markers alone³⁻⁶. This improved discrimination was observed over a wide range of time on ART and length of follow-up⁵, and among subgroups by gender^{5, 6}, age (less than 50 and 50+ years)^{5, 6}, plasma RNA (<500 and >500 copies/mL)^{5, 6}, Hepatitis C Virus (HCV) status⁵, and race (Black and non-Black)⁶.

Despite its strong association with mortality, the discrimination of the VACS Index for other patient outcomes, such as neurocognitive impairment (NCI), has not been formally explored. NCI continues to be highly prevalent in the era of ART, with approximately half of HIV-infected persons experiencing some degree of NCI^{8, 9}. Moreover, NCI is associated with poorer everyday functioning in HIV, including unemployment, dependence in activities of daily living, driving problems, and medication nonadherence¹⁰⁻¹², as well as quality of life^{13, 14} and mortality^{15, 16}. The prevalence and real-world impact of HIV-associated NCI underscores the importance of neurocognition as a disease outcome in HIV, and highlights the need to identify persons at risk for NCI.

Several risk factors for HIV-associated NCI have been identified, including demographic variables, HIV-disease characteristics and comorbid conditions^{17, 18}. Some of these risk factors are part of the VACS Index, and have been separately associated with NCI, including age^{19, 20}, current CD4 counts²¹, plasma RNA²², anemia²³, and HCV²⁴⁻²⁶. Although there is little evidence on the association between eGFR and NCI among HIV-infected persons²⁷, it has been associated with NCI among HIV-uninfected persons²⁸. Similarly, there is scant evidence on FIB-4 and NCI in HIV, but compromised liver function is related to NCI in HIV-uninfected persons^{29, 30}. Yet, the combination of these factors, as they are represented and weighted in the VACS Index has not been evaluated for its relation to NCI.

The present study investigated the association between the VACS Index and NCI in a well-characterized, large cohort of persons with HIV. We hypothesized that higher VACS Index scores would be associated with higher rates of both global and domain-specific NCI.

Additionally, we examined which components of the VACS Index were most strongly associated with NCI.

Methods

Participants

Participants included 601 HIV-infected individuals enrolled in cohort studies at the University of California San Diego HIV Neurobehavioral Research Program from May 1st, 1999 to June 1st, 2012. Details of these studies have been described elsewhere³¹⁻³³. Inclusion criteria included: being HIV-infected; having laboratory data available to compute the VACS Index; having valid global neurocognitive scores based on evaluations undertaken within 2 months of laboratory data collection; and being primarily English-speaking, able to provide informed consent; and free of sensory or physical problems that would interfere with neurocognitive testing. For those participants who had data available on the VACS Index and neurocognition at more than one time point, data from the first date was used.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Materials and Procedures

Participants completed comprehensive neurocognitive, psychiatric, substance use, neuromedical, and laboratory evaluations.

Laboratory data—HIV infection was diagnosed by enzyme-linked immunosorbent assay with Western blot confirmation. Routine clinical chemistry panels, complete blood counts, rapid plasma reagin, HCV antibody, and CD4+ T cells (flow cytometry) were performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified, or CLIA equivalent, laboratory. HIV RNA levels in plasma were measured by reverse transcriptase polymerase chain reaction (Roche Amplicor, v. 1.5, lower limit of quantitation 50 copies per milliliter). The VACS Index was computed as previously described⁴ (see Table 2).

Neurocognitive evaluation—Neurocognitive data were obtained from the neuropsychological testing date closest to blood draw (interval number of days: *Mean*=1.44, *Standard Deviation*=5.19, range=0-49). The neurocognitive battery was constructed to maximize sensitivity to the frontal-subcortical deficits associated with HIV infection and was comprised of 15 measures covering seven neurocognitive domains, i.e., speed of information processing, verbal fluency, learning, recall, executive functions, attention/working memory and motor skills (see Cysique and colleagues³⁴ for a list of tests by domain).

Raw test scores were transformed into demographically-adjusted T-scores, including adjustments for age, education, gender and ethnicity^{35, 36}. Because some of our participants had undergone previous neurocognitive testing as part of their participation in our studies, we also adjusted scores for repeated testing when indicated following procedures described by Cysique and colleagues (2011)³⁴. The adjusted T-scores for each test were converted into deficit scores, ranging from 0 (T-score >39, no impairment) to 5 (T-score <20, severe impairment). Deficit scores for each test were then averaged to derive global and domain deficit scores^{32, 37}. Per previous studies, NCI was defined as global deficit scores $\geq .50$, and domain deficit scores $\geq .50$ ³⁷.

Psychiatric and Substance Use Characteristics—Current mood symptoms were assessed via the Beck Depression Inventory (BDI). Participants completed one of two versions of the BDI, the original³⁸ or version two³⁹. Both versions consist of 21 questions each scored on a scale of 0-3, with higher total scores indicating more severe depressive symptoms. The two versions of the scales have slightly different cutoff scores. We used the appropriate cutoff score to determine severity of depression symptoms (i.e. minimal, mild, moderate, or severe).

We obtained lifetime history of Substance Use and Major Depressive Disorder in a subset of our sample ($n=453$) using structured diagnostic interviews⁴⁰⁻⁴² which follow Diagnostic and Statistical Manual-Fourth Edition criteria⁴³. Presence of a “Substance Use Disorder” was defined as meeting either current or lifetime abuse or dependence criteria for any of the following substances: alcohol, cannabis, opioids, methamphetamine, cocaine, sedatives and hallucinogens.

Other Health Characteristics—Other common comorbidities associated with HIV, including diabetes, hypertension, hyperlipidemia, chronic pulmonary disease, and malignancy were ascertained based on self-report and medication regimen when available.

Statistical Analyses

To examine the relationship between the VACS Index and neurocognition we ran a series of logistic regressions on global and domain NCI, with VACS Index score as the predictor. To evaluate whether current mood symptoms explained the association between VACS Index scores and neurocognition, we ran a series of multivariable logistic regression models on NCI (global and domains) entering BDI and VACS Index scores as predictors. We conducted similar analyses on our subset of participants for whom we had obtained lifetime histories of a Substance Use Disorder and Major Depressive Disorder, entering these two variables along with the VACS Index as predictors.

Given that the VACS Index has been validated for mortality in patients initiating ART and on a wide range of time on ART, we examined whether ART status modified the relationship between the VACS Index and neurocognition. We divided our sample into those on ($n=375$) and off ($n=216$) ART, and conducted a logistic regression model on global NCI with VACS Index, ART status (on/off), and their interaction as predictors. To examine whether the VACS Index was associated with NCI beyond other traditional HIV-disease characteristics that are not part of the index but have been associated with NCI^{44, 45}, we ran a logistic regression models on global NCI with the VACS Index, nadir CD4 and estimated duration of infection as predictors. We did not include AIDS in this model given its association with nadir CD4. Odds ratios for all models including the total VACS Index score are reported per 10 units of VACS increase and with 95% confidence intervals. We also investigated the classification accuracy of the VACS Index for NCI and used receiver operating characteristic (ROC) curves to select a cutoff point that would maximize sensitivity.

To explore which components of the VACS Index might be most important in explaining its relation with neurocognition, we ran a stepwise logistic regression model on global NCI with the components of the VACS index as predictors, using a backward selection method and $p<.05$ as a stopping rule. We used specifications of these components as described in Justice and colleagues (2012) and weighted them accordingly.

Results

Demographics, HIV-disease and other health characteristics, and psychiatric conditions

Participants were between 18 and 76 years of age, and had between 6 and 20 years of education. As shown in Table 1, the majority were males and non-Hispanic White. Over half had AIDS and were on ART. Among those on ART, about half had a detectable plasma HIV RNA. Among participants off ART, approximately half were ART naïve and half were off ART at the time of the visit, but had been exposed to ART in the past. Rates of cardiovascular risk factors (diabetes, hypertension, hyperlipidemia) ranged from 5 to 20%. Approximately half of our sample reported at least mild current depressive symptoms and a lifetime history of Major Depressive, and close to three quarters were diagnosed with a lifetime Substance Abuse or Dependence Disorder (Table 1).

Descriptive statistics on the VACS Index and NCI

VACS Index scores in our sample ranged from 0-106 (*Median*=19, *IQR*=10, 35), with higher scores indicative of worse functioning. Approximately a third of participants had CD4 counts < 500 cells/mm³ (32%), half had HIV-1 RNA levels < 500 copies/mL (51%), 13% had hemoglobin levels < 12 g/dL, 3% had a fibrosis index consistent with fibrosis (FIB-4 > 3.25), 5% had some compromise in renal function (eGFR < 60), and 9% were co-infected with HCV (Table 2). Consistent with prior studies⁸, 40.6% of participants had global NCI (Table 3 shows rates of NCI by domain).

Association between the VACS Index and NCI

Higher VACS Index scores were significantly associated with higher rates of global NCI ($\chi^2=21.13$, $df=1$, $p<.001$, $OR=1.21$, $CI=1.12-1.32$), and across all neurocognitive domains (Table 3).

When current mood symptoms was added as a predictor, the overall model was significant ($\chi^2=33.89$, $df=4$, $p<.001$), and there continued to be a significant effect of the VACS Index ($\chi^2=16.53$, $p<.001$, $OR=1.20$, $CI=1.10-1.31$) on global NCI. Worse depressive symptoms were also significantly associated with global NCI ($\chi^2=14.43$, $p<.01$). Similarly, after adjusting for mood symptoms the VACS Index remained significantly associated with all domains (ps range $<.001$ to $.04$) except for verbal fluency ($p=.16$).

Analyses adjusting for lifetime Substance Use and Major Depressive Disorders also showed a significant association between the VACS Index and global NCI ($\chi^2=12.15$, $p<.001$, $OR=1.19$, $CI=1.08-1.32$), with neither lifetime history of a Substance Use Disorder ($p=.57$) or Major Depressive Disorder ($p=.44$) emerging as significant predictors. The VACS Index also continued to be significantly associated with all cognitive domains (ps ranged from $<.01$ to $.02$), except for learning ($p=.06$), when adjusting for Substance Use and Major Depressive Disorders.

Analyses examining the effect of ART status (on/off) showed that the overall model was significant ($\chi^2=27.75$, $df=3$, $p<.001$). Higher VACS Index scores and being on ART were associated with global NCI, but there was no significant interaction (Figure 1). In models including nadir CD4 and estimated duration of infection, the VACS Index was significantly associated with global NCI ($\chi^2=9.95$, $p<.01$, $OR=1.18$, $CI=1.06-1.30$), but neither of these other HIV-disease characteristics were ($ps>.13$). ROC analyses showed that a VACS Index cutoff point of 18 maximized sensitivity (60%) while not compromising specificity beyond chance levels (50%). A cutoff point of 10 resulted in increased sensitivity (82%) but very low specificity (26%). The odds ratios for a cutoff point of 18 and 10 were 1.54

($CI=1.11-2.14$) and 1.62 ($CI=1.08-2.44$), respectively. Association between the components of the VACS Index and Global NCI

Table 4 shows results from our multivariable stepwise regression on global NCI entering the VACS components as predictors. Our initial model including all VACS components showed that age was the only significant predictor. Plasma RNA, eGFR, FIB-4 and HCV were removed in that order given that they were not significantly associated with NCI (i.e., had the highest p values). Our final model showed that older age was the strongest predictor, and lower current CD4 count and hemoglobin were also significantly associated with NCI.

Follow-up analyses

To better characterize the association between the VACS Index and NCI, and because of the highly skewed distribution of the VACS Index, we divided our sample into three groups based on VACS Index scores (low VACS Index=lower quartile, $n=166$; high VACS Index=upper quartile, $n=150$; and medium VACS Index=between lower and upper quartile, $n=285$). Chi-Square tests showed that while there were no significant differences on rates of NCI between the low (34.3% NCI) and medium (35.4% NCI) VACS Index groups ($p=.81$), the high VACS Index group was significantly different from both the low and medium groups ($ps<.001$) and had nearly twice the frequency of NCI (57.3%) as the other groups. When adjusting these analyses for the same psychiatric and HIV-characteristics presented above, the high VACS Index group remained significantly different from the other groups.

Discussion

The VACS Index, which combines age, routinely obtained traditional HIV biomarkers and common biomarkers of multi-organ system dysfunction, is predictive of mortality among those infected with HIV³⁻⁶. The present study adds to the current literature by showing that higher VACS Index scores are significantly associated with concurrent NCI in a large, and well-characterized cohort of persons with HIV.

The association between the VACS Index and NCI was statistically significant for global cognition and all cognitive domains (i.e., speed of information processing, verbal fluency, learning, recall, working memory, executive functioning, and motor skills) using neurocognitive scores adjusted for demographic characteristics (i.e., age, education, gender, ethnicity). This relation remained after controlling for psychiatric comorbidities (i.e., current mood, and history of depression and substance use disorder) for global NCI and most cognitive domains. Further, ART status (on/off) did not significantly modify the association of the VACS Index with global NCI, and the VACS Index predicted NCI over and above other HIV-related characteristics (i.e., nadir CD4, and estimated duration of infection). The rates of global NCI were almost double in participants with VACS Index scores in the upper quartile of our sample, as compared to those in lower quartiles. Taken together, these findings suggest that the VACS Index might be helpful in tracking the impact of HIV on NCI.

Importantly, the strength of the association between the VACS Index and NCI as measured by some of the domains was not particularly strong, and its classification accuracy for NCI was poor, casting doubt as to the clinical significance of our findings. Other factors not included in the VACS Index might improve its predictive utility for NCI, such as demographic factors (e.g., ethnicity), non-HIV comorbidities (e.g., cardiovascular disease markers), and HIV-related factors (e.g., AIDS defining diagnoses). Furthermore, additional biomarkers might predict distinct cognitive outcomes and trajectories (e.g., incident impairment, decline, propensity for improvement). For instance, the accuracy of the VACS Index for NCI might improve with the addition of biomarkers of inflammation⁴⁶. The fibrin

degradation product, D-Dimer, is an indicator of inflammation and adds to the predictive accuracy of the VACS Index for mortality⁴, as does soluble CD14, which is a marker of lipopolysaccharide-mediated monocyte activation and has also been associated with neurocognitive function⁴⁷. While interleukin 6 (IL-6) might also be considered, it did not add to the predictive power of the VACS Index for mortality⁴.

The mechanism for the association between the VACS Index and NCI cannot be ascertained by our study, but our findings are consistent with the hypothesis that host factors (e.g., age of the patient), traditional indicators of HIV-disease severity and markers of chronic diseases that frequently co-occur among HIV-infected persons might each play important roles in the clinical manifestation of cognitive impairment among HIV-infected individuals.

Consistently, older age, lower hemoglobin levels and lower current CD4 counts were the better predictors of current NCI among all VACS components. Prior studies showed that separately all of these components are associated with HIV-associated NCI^{19-21, 23}.

Additionally, in a study on a diverse group of HIV-infected adults⁵, visual inspection of hazard ratios suggested that age, CD4 and hemoglobin were also the strongest predictors of mortality.

The fact that age showed the strongest association with NCI is consistent with prior findings^{19, 20}. Notably, neurocognitive scores in our study were corrected for age, which raises the question as to whether age is capturing the effects of another variable associated with aging and HIV, but not represented in the VACS Index, such as cerebrovascular disease. Alternatively, the normative corrections may not be optimal for this population or there may be interaction between aging and HIV that leads to worse neurocognitive outcomes. Consistent with prior research²³, anemia was also notably associated with NCI. Anemia is known to often reflect the impact of AIDS, immune activation and malnutrition on the bone marrow and on red cell growth factors, like erythropoietin, which is itself neuroprotective.

Our study has several limitations. Although we had a considerable range in VACS Index scores, we had a relatively small number of participants 65 years and older, with evidence of fibrosis, compromised renal function, and HCV co-infection. Moreover, most of our sample was male. Follow-up analyses showed that the association between the VACS Index and NCI was somewhat stronger in our subgroup of participants 50+ years ($n=108$, $p=.01$, $OR=1.36$, $CI=1.06-1.82$), suggesting studies including older samples with higher rates of comorbidities, might find stronger associations between the VACS Index and NCI. Further, they might yield other components of the VACS as more predictive of NCI. Given the cross-sectional and correlational nature of the present study, we cannot ascribe directionality to our findings. Longitudinal studies examining the predictive accuracy of the VACS Index for incident NCI would be better suited to address causality. Although ART status and current mood symptoms were associated with NCI when included as covariates in separate models with the VACS Index, caution is warranted in the interpretation of these findings, as our study was not designed to examine these associations. A strength of our study is our comprehensive neurocognitive battery that is adjusted for demographics, is validated in persons with HIV, and is particularly sensitive to the impairments seen in this population^{8, 37}. Furthermore, it measures cognitive domains with composite scores, which are more reliable and valid than using single tests for the assessment of neurocognitive deficits, and is being used internationally in studies of HIV⁴⁹.

Future studies examining whether other biomarkers not included in the VACS Index might enhance its relation to neurocognition would help improve the Index as a tool to track the clinical manifestation of neuroAIDS. Components in the current form of the VACS Index are weighted according to risk of all cause mortality. We chose to keep these weightings

because the purpose of our study was to evaluate the VACS Index in its current form and facilitate comparison with findings from other studies. Using a different weighting of VACS Index factors might strengthen its association with NCI. Given the documented association between NCI and real-world functional outcomes, an important next step will be to directly examine the relation between the VACS Index and everyday functioning outcomes relevant to HIV infection, such as medication adherence and employment.

Overall, we have found initial evidence linking the VACS Index with an important patient outcome in HIV, namely NCI. While using a single VACS Index cutoff point poorly classified individuals as neurocognitively impaired, participants with VACS Index scores in the highest quartile were nearly twice as likely to be impaired than those in the lower quartile. If replicated, the VACS Index may be a simple tool for helping HIV practitioners identify HIV-infected patients who are at high-risk for NCI and may warrant more comprehensive neurocognitive testing. Furthermore, as the VACS Index continues to be improved as a means of tracking disease burden in HIV, its relation to NCI might strengthen and further increase its utility in identifying individuals at risk for HIV-associated NCI.

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Figure 1.

Results from multivariable logistic regression model on neurocognitive impairment (NCI) showing that higher Veterans Administration Cohort Study (VACS) Index scores ($\chi^2=22.50$, $p<.001$, $OR=1.23$, $CI=1.13-1.34$) and being on ART were both associated with higher rates of global NCI ($\chi^2=6.10$, $p=.01$, $OR=1.56$, $CI=1.10-2.24$), but there was no significant VACS Index X ART status (on/off) interaction ($\chi^2=0.24$, $p=.62$). Subgroup of participants on ART: $n=375$; VACS Index: $M=22.9$, $SD=18.4$, Median=18, Interquartile Range=10,33; Global NCI: 44% Subgroup of participants off ART: $n=216$; VACS Index: $M=26.5$, $SD=22.0$, Median=20, Interquartile Range =10,40; Global NCI: 35%

Table 1Demographics, HIV-disease and other health characteristics, and psychiatric conditions ($N = 601$)

Variable	Descriptive statistic
Demographics	
Age (years, $M[SD]$)	41.6 (9.6)
Sex (% male)	88.2
Ethnicity (%)	
Non-Hispanic White	63.2
Non-Hispanic Black	19.0
Hispanic	13.0
Other	4.8
Education (years, $M[SD]$)	13.4 (2.5)
HIV disease characteristics	
Nadir CD4+ T-cell count (Median [IQR])	119.0 (20.0, 299.5)
Current CD4+ T-cell count (Median [IQR])	367.0 (164.0, 552.5)
ART status	
ART prescribed (% Yes)	63.5
Plasma HIV RNA (% Detectable) ^a	49.6
ART Naïve (%)	16.9
Currently off ART (%)	19.6
AIDS (% Yes)	64.2
Duration of infection (years, Median [IQR]) ^b	8.4 (3.3, 14.0)
Other Health Characteristics (% Yes) ^c	
Diabetes	5.3
Hypertension	19.5
Hyperlipidemia	14.0
Chronic Pulmonary Disease	14.8
Malignancy	4.7
Psychiatric Characteristics (%)	
Mood Symptoms (BDI) ^d	
Minimal	45.2
Mild	29.3
Moderate	18.3
Severe	7.2
Lifetime Major Depressive Disorder ^e	53.1
Lifetime Substance Use Disorder ^e	70.9

Note.

BDI = Beck Depression Inventory.

^a % detectable among those on antiretroviral therapy (ART)^b $n=523$

^cbased on self-report

^d
_{n=573}

^e
_{n=452}

Table 2

Components of the Veterans Administration Cohort Study (VACS) Index

VACS component		Points ^a	Frequencies ^b	
			n	%
Age				
	<50	0	493	82.0
	50-64	12	95	15.8
	65	27	13	2.2
CD4 count (cells/mm ³)				
	500	0	195	32.5
	350-499	6	115	19.1
	200-349	6	112	18.6
	100-199	10	89	14.8
	50-99	28	28	4.7
	<50	29	62	10.3
HIV-1 RNA (copies/mL)				
	<500	0	309	51.4
	500-1 X 10 ⁵	7	216	35.9
	1 X 10 ⁵	14	76	12.7
Hemoglobin (g/dL)				
	14	0	327	54.4
	12-13.9	10	197	32.8
	10-11.9	22	65	10.8
	<10	38	12	2.0
FIB-4				
	<1.45	0	454	75.5
	1.45-3.25	6	128	21.3
	>3.25	25	19	3.2
eGFR				
	60	0	569	94.7
	45-59.9	6	23	3.8
	30-44.9	8	5	0.8
	<30	26	4	0.7
HCV infection		5	55	9.2

Note.

eGFR = estimated glomerular filtration rate ($186.3 \times [\text{serum creatinine}^{-1.154}] \times [\text{age}^{-0.203}] \times [0.742 \text{ for women}] \times [1.21 \text{ if black}]$); FIB-4 = fibrosis index-4 ($[\text{years of age} \times \text{aspartate aminotransferase}] / [\text{platelets in } 10^9/\text{L} \times \text{square root of alanine aminotransferase}]$); HCV infection established by a positive antibody test or detectable virus.

^a Point values used to generate VACS Index scores as indicated by Justice et al. (2012).

^b Frequencies of the VACS Index components in our sample (n=601).

Rates of neurocognitive impairment (NCI) and association between the Veterans Administration Cohort Study (VACS) Index and NCI by cognitive domain

Table 3

SIP	Cognitive Domain					
	Verbal FL	Learning	Recall	Exec. Func.	Work. Mem.	Motor Skills
Rate of NCI	25.6%	26.4%	33.8%	33.3%	32.7%	30.9%
Multivariable models ^a						
χ^2	21.81	4.19	10.64	10.09	6.02	14.99
p	<.001	.04	<.01	<.01	.01	<.001
OR	1.23	1.10	1.15	1.15	1.11	1.19
CI	1.13-1.36	1.00-1.20	1.06-1.25	1.05-1.25	1.02-1.21	1.09-1.30
						1.12-1.34

Note.

Exec. Func. = Abstraction/Executive Function; SIP = Speed of Information Processing; Work. Mem. = Attention/Working Memory

^aResults from logistic regression models on NCI by domain with VACS Index total scores as predictor; OR (CI) per 10 units increase in the VACS Index. $\chi^2=1$ degree of freedom

Table 4

Association between the components of the Veterans Administration Cohort Study (VACS) Index and global neurocognitive impairment (NCI)

VACS component	Initial Model ^a		Final Model ^b	
	<i>p</i>	OR (CI)	<i>p</i>	OR (CI)
Age	<.01		<.001	
<50		1.00		1.00
50-64		1.82 (1.26-2.66)*		1.88 (1.32-2.70)*
65		3.86 (1.69-9.03)*		4.13 (1.87-9.37)*
CD4 count	.10		.03	
500		1.00		1.00
350-499		1.11 (0.98-1.26)		1.14 (1.01-1.27)*
200-349		1.11 (0.98-1.26)		1.14 (1.01-1.27)*
100-199		1.19 (0.96-1.46)		1.24 (1.02-1.50)*
50-99		1.62 (0.90-2.90)		1.81 (1.06-3.11)*
<50		1.65 (0.90-3.01)		1.85 (1.06-3.24)*
HIV-1 RNA	.82		---	
<500		1.00		---
500-1 X 10 ⁵		1.03 (0.79-1.34)		---
1 X 10 ⁵		1.06 (0.62-1.81)		---
Hemoglobin	.05		<.05	
14		1.00		1.00
12-13.9		1.23 (1.00-1.53)		1.24 (1.00-1.53)
10-11.9		1.59 (0.99-2.55)		1.59 (1.01-2.54)*
<10		2.22 (0.99-5.03)		2.24 (1.01-5.00)*
FIB-4	.15		---	
<1.45		1.00		---
1.45-3.25		1.17 (0.94-1.47)		---
>3.25		1.93 (0.78-4.95)		---
eGFR	.40		---	
60		1.00		---
45-59.9		0.83 (0.50-1.26)		---
30-44.9		0.78 (0.40-1.37)		---
<30		0.45 (0.05-2.75)		---
HCV infection	.12	1.59 (0.89-2.85)	---	---

Note.

^aResults from a multivariable logistic regression model on global NCI with all the VACS components as predictors ($\chi^2=30.24$, $df=7$, $p<.001$).

^bResults from a stepwise logistic regression model on global NCI with the VACS components as predictors, using a backward selection method and $p<.05$ stopping rule ($\chi^2=24.31$, $df=3$, $p<.001$)

*
p<.05