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The impact of ethnicity/race on the association between the Veterans Aging Cohort Study (VACS) Index and neurocognitive function among HIV-infected persons

M. J. Marquine[1], **M. Sakamoto**[1], **C. Dufour**[2], **A. Rooney**[1], **P. Fazeli**[3], **A. Umlauf**[1], **B. Gouaux**[1], **D. Franklin**[1], **R. Ellis**[4], **S. Letendre**[2], **M. Cherner**[1], **R. K. Heaton**[1], **I. Grant**[1], **D. J. Moore**[1], and **HNRP Group**

M. J. Marquine: mmarquine@ucsd.edu

[1]Department of Psychiatry, University of California, San Diego, CA, USA

[2]Department of Medicine, University of California, San Diego, CA, USA

[3]Psychology Department, University of Alabama, Birmingham, CA, USA

[4]Department of Neurosciences, University of California, San Diego, CA, USA

Abstract

The Veterans Aging Cohort Study (VACS) Index was developed as a risk index for health outcomes in HIV, and it has been consistently associated with mortality. It shows a significant, yet relatively weak, association with neurocognitive impairment, and little is known about its utility among ethnic/racial minority groups. We examined whether the association between the VACS Index and neurocognition differed by ethnic/racial group. Participants included 674 HIV-infected individuals (369 non-Hispanic whites, 111 non-Hispanic blacks, and 194 Hispanics). Neurocognitive function was assessed via a comprehensive battery. Scaled scores for each neurocognitive test were averaged to calculate domain and global neurocognitive scores. Models adjusting for demographics and HIV disease characteristics not included in the VACS Index showed that higher VACS Index scores (indicating poorer health) were significantly associated with worse global neurocognition among non-Hispanic whites. This association was comparable in non-Hispanic blacks, but nonsignificant among Hispanics (with similar results for English and Spanish speaking). We obtained comparable findings in analyses adjusting for other covariates (psychiatric and medical comorbidities and lifestyle factors). Analyses of individual neurocognitive domains showed similar results in learning and delayed recall. For other domains, there was an effect of the VACS Index and no significant interactions with race/ethnicity. Different components of the VACS Index were associated with global neurocognition by race/ethnicity. In conclusion, the association between the VACS Index and neurocognitive function differs by ethnic/racial group. Identifying key indicators of HIV-associated neurocognitive impairment by ethnic/

Correspondence to: M. J. Marquine, mmarquine@ucsd.edu.

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Compliance with ethical standards

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racial group might play an important role in furthering our understanding of the biomarkers of neuroAIDS.

Keywords

HIV; Cognition; Comorbidity; Latino; African American

Introduction

Hispanics and non-Hispanic (NH) blacks/African-Americans represent the largest minority groups in the USA. While there is considerable heterogeneity within ethnic/racial groups, persons from these underserved segments of the population tend to be disproportionally affected by HIV/AIDS. As a group, Hispanics and NH blacks have higher rates of infection than NH whites in the USA (Centers for Disease Control and Prevention 2013) and tend to be tested for HIV and engage in care later in the course of the disease (Chen et al. 2012; Dennis et al. 2011; Shapiro et al. 1999; Turner et al. 2000). Thus, not surprisingly, they tend to present with worse HIV disease characteristics as compared to NH whites (Swindells et al. 2002).

HIV-infected Hispanics and NH blacks also appear to be at increased risk for worse neurocognitive outcomes than HIV-infected NH whites (Durvasula et al. 2001; Heaton et al. 2014; Manly et al. 1998; Mindt et al. 2008; Ryan et al. 2005; Wojna et al. 2006). Despite the availability of more effective combination antiretroviral treatment (cART), neurocognitive impairment (NCI) continues to be common and impactful in HIV. It is observed in approximately half of HIV-infected persons overall (Heaton et al. 2011), with elevated rates of impairment in minority groups, and is associated with worse everyday functioning, such as medication nonadherence and driving problems (Heaton et al. 2004; Marcotte et al. 1999). The reasons for ethnic/racial differences in neurocognitive performance are not fully understood. There are likely multiple variables associated with race/ethnicity, both psychosocial and biomedical, which impact the expression of NCI in HIV-infected persons of diverse backgrounds. Most biomedical factors underlying NCI are likely to occur across ethnic groups, yet they might be differentially prevalent and impactful. Bidirectional associations and complex interactions among the various risk factors may lead to them having a differential impact among ethnic/racial groups with varying vulnerabilities.

Both biomarkers of HIV disease burden and common co-morbidities have been related to HIV-associated NCI (Cysique et al. 2010; Heaton et al. 2014; McCutchan et al. 2012). Furthermore, examination of a large diverse cohort of HIV-infected persons showed that non-white ethnic/racial groups had higher rates of comorbid conditions that contribute to NCI in HIV (Heaton et al. 2010). Thus, an index of disease status that incorporates both traditional HIV disease characteristics and biomarkers of common comorbidities, such as the Veterans Aging Cohort Study (VACS) Index, might prove to be a particularly good marker of neurocognitive status among minority groups. The VACS Index was developed as a tool to monitor the impact of dysfunction involving multiple organs commonly affected in HIV, using objective measures that are collected routinely in HIV clinics (Justice et al. 2010,

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2012, 2013; Tate et al. 2013). It includes 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 coinfection). The VACS Index has been consistently validated for estimating risk for mortality among HIV-infected persons, including in diverse cohorts (Justice et al. 2010, 2012, 2013; Tate et al. 2013). There is one published study showing a significant, yet weak, association with NCI (Marquine et al. 2014), suggesting that other factors not considered in the VACS Index may play important roles. Race/ethnicity might prove to be a key one. As described above, racial/ethnic identity is associated with multiple biomedical (e.g., genetics) and psychosocial factors (e.g., educational exposure and healthcare access), which interact with one another resulting in their impact being greater than the sum of its parts, and potentially leading to varying influences on VACS Index scores by ethnic/racial group.

The main purpose of the present study was to examine whether the association between the VACS Index and neurocognitive function differed among ethnic/racial groups. In order to do so, we examined this association in large and well-characterized cohorts of HIV-infected NH whites, NH blacks, and Hispanics living in the US-Mexico border region. We hypothesized that, by incorporating both “traditional” HIV markers and biomarkers of common comorbidities, the VACS Index might better capture the complexity of factors leading to NCI in HIV-infected persons from minority groups, and thus be more strongly associated with neurocognitive function in these groups than in NH whites. We were also interested in exploring whether the components of the VACS Index might be differentially associated with neurocognitive function by ethnic/racial group.

Methods

Participants

Six hundred and seventy-four HIV-infected individuals (369 NH whites, 111 NH blacks, and 194 Hispanics) enrolled in NIH-funded observational studies at the University of California San Diego HIV Neurobehavioral Research Program from May 1, 1999, to June 1, 2012, participated in the current study. Details on these studies have been published previously (Heaton et al. 1995; Rippeth et al. 2004; Woods et al. 2004). Participants were excluded if they had a history of head injury with loss of consciousness greater than 30 min, a neurologic or psychiatric illness that may affect cognitive functioning (e.g., stroke and schizophrenia), or significant sensory or physical problems that would interfere with neurocognitive testing. Inclusion criteria for the present study were as follows: (1) presence of HIV infection as determined by enzyme-linked immunosorbent assays (ELISA) with Western blot confirmatory test; (2) having laboratory data available to calculate the VACS Index; (3) completing neurocognitive testing within 2 months of laboratory data collection; (4) self-identification as Hispanic/Latino, NH white, or NH black/African American; and (5) proficiency in English or Spanish.

Materials and procedures

Study procedures were in accordance with the institutional and national ethical standards of the responsible committee on human experimentation. After providing written informed

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consent, participants completed comprehensive neuromedical, neurocognitive, psychiatric, and substance use assessments, consistent with our previous research on the VACS Index and NCI (Marquine et al. 2014). Evaluations were conducted in English or Spanish. For participants who reported some degree of bilingualism, language of evaluation was determined via participant's report of preferred language and performance-based fluency in English and Spanish (Cherner et al. 2007).

Neuromedical evaluation—Neuromedical evaluations included a medical history, structured neurological and medical examination, and collection of blood and urine samples. Laboratory measurement included routine clinical chemistry panels, complete blood counts, rapid plasma reagin, HCV antibody, and CD4+ T cells (flow cytometry) 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). We calculated the VACS Index as previously described (Justice et al. 2012). We assessed via self-report whether participants had a history of hypertension, hyperlipidemia, and diabetes.

Neurocognitive evaluation—Neurocognitive scores from the neuropsychological testing date closest to blood draw were used for the present analysis (interval number of days: mean = 1.31, SD = 4.79, range = 0–49). Participants completed a standardized neurocognitive test battery covering seven domains: learning, recall, verbal fluency, speed of information processing, executive function, working memory, and fine motor skills (see Cysique and colleagues for a list of specific tests (Cysique et al. 2011)). For participants who had previously completed neurocognitive testing during their participation in studies at our center, raw test scores were transformed into practice-adjusted scaled scores (SS), using published norms for change (Cysique et al. 2011). SS for tests comprising each domain were averaged to obtain domain scores. Global neurocognitive function represented the average of SS for all tests. We also computed rates of overall NCI (including scores from all tests) based on previously published standard regression-based models. In addition to adjusting for the effects of repeated testing when appropriate, overall NCI rates adjusted for the effects of age, education, gender, and race/ethnicity (Cysique et al. 2011).

The development of the Spanish language neurocognitive battery has been described elsewhere (Artiola i Fortuny et al. 1999; Cherner et al. 2007). Briefly, it included already existing translated test versions where appropriate and adaptation of other tests into Spanish. This adaptation was done through back translation and group consensus in order to obtain a neutral Spanish language and culturally relevant version of the neurocognitive tests, while preserving their comparability to the English version.

Psychiatric and substance use characteristics—We obtained past and current history of substance use and major depressive disorder in a portion of our sample (n = 493) via structured interviews with available English and Spanish versions (First et al. 2002; Hasin et al. 1996; World Health Organization 1997) and which follow Diagnostic and Statistical Manual-Fourth Edition criteria (American Psychiatric Association 1994). A substance use disorder was determined to be present if participants met criteria for either abuse or dependence for the following substances: alcohol, cannabis, opioids,

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methamphetamine, cocaine, sedatives, and/or hallucinogens. Current mood was assessed with the English and Spanish versions of the Beck Depression Inventory (BDI) versions one and two (Beck et al. 1961, 1996a, b; Beck and Steer 1993), using cutpoints appropriate for the version administered.

Lifestyle factors—Participants underwent urine drug screen (UDS) for the following drugs: marijuana, cocaine, opiates, barbiturate, benzodiazepines, phencyclidine (PCP), methamphetamine, and other amphetamines. We assessed history of smoking (lifetime and current) via self-report. We also evaluated participants' adherence to their ART regimen by asking them to indicate the percent ART doses that they took as prescribed over the past 4 weeks. We considered a self-report of greater than 95 % of ART doses taken as prescribed as "adherent."

Statistical analyses

Ethnic/racial group differences on demographic factors, HIV disease characteristics, psychiatric and medical comorbidities, lifestyle factors, global and domain neurocognitive scores, overall NCI, and VACS Index (overall score and individual components) were assessed via analyses of variance (ANOVA) and follow-up pairwise comparisons with Tukey's correction (or nonparametric equivalent) and chi-squared tests. To examine the association between the VACS Index and neurocognitive function, we ran separate multivariable linear regression models in the overall sample on global and domain SS with NH whites as the reference group. These models adjusted for demographic characteristics (age, education, gender) and HIV disease characteristics that differed across groups, and included terms for the interaction between the VACS Index and race/ethnicity. For models with a significant interaction, we then ran separate analyses by ethnic/racial group adjusting for the same variables and examined the impact of language use within our Hispanic sample. To explore which VACS Index components might be more strongly associated with neurocognitive function by ethnic/racial group, we ran separate linear regression models on global SS with the VACS Index components as predictors. We used standard specifications and weightings of these components (Justice et al. 2012). We adjusted for education and gender in these models given the known effect of demographics on neurocognition. In initial analyses, we did not adjust for age, however, because age (as a categorical variable) is a component of the VACS Index, and we were interested in evaluating its effect as a component of the index.

All analyses on global SS were performed on rates of NCI using logistic regression methods. The global NCI score adjusts for demographics (age, education, gender, race/ethnicity) as well as a correction for repeated exposures to the individual neuropsychological tests (Cysique et al. 2011). We chose to make the primary focus of the manuscript on analyses using the SS approach given that results based on these scores are easier to interpret in the context of investigating the impact of race/ethnicity on the association between the VACS Index and neurocognitive functioning. In order to facilitate comparisons with prior relevant findings (e.g., Marquine et al. 2014), we also report results on overall NCI. For all models including the VACS Index overall score, estimates are provided per 10-unit change in this index.

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Results

Demographic factors, HIV disease characteristics, and neurocognitive function by ethnic/racial group

NH whites were older, better educated, had a lower proportion of women, and had longer estimated duration of infection than NH blacks and Hispanics. They also were less likely to be on cART than NH blacks. The ethnic/racial groups differed on various aspects of neurocognitive function in analyses unadjusted for demographics (Table 1). Analyses on NCI (this type of score includes adjustments for demographic factors including race/ethnicity) indicated overall ethnic/racial group differences in NCI ($p = 0.03$), such that rates of NCI were higher in Hispanics (46 %) than blacks (31 %; $p < 0.01$), with no significant differences between NH whites (40 %) and NH blacks ($p = 0.08$) or NH whites and Hispanics ($p = 0.17$). Among Hispanic participants, 44 % reported being born in Mexico, 30 % in the USA, 2 % in Central America, and 1 % in South America (23 % data missing on this variable), and 60 % were primarily Spanish speaking.

VACS Index scores and its components by ethnic/racial group

VACS Index scores were higher in NH blacks than NH whites ($p = 0.03$) and Hispanics ($p = 0.04$), with no significant differences between NH whites and Hispanics (Table 1). Follow-up analyses adjusting for age and gender demonstrated comparable findings.

Among the VACS Index components (Table 2), ethnic/ racial groups were comparable on traditional HIV biomarkers and HCV coinfection and differed significantly on indicators of anemia (hemoglobin), liver function (fibrosis index-4 (FIB-4)), and renal function (estimated glomerular filtration rate (eGFR)).

Association of the VACS Index to neurocognitive function by ethnic/racial group

Multivariable analyses predicting global neurocognition with NH whites as the reference group showed a significant main effect of the VACS Index ($p < 0.001$), indicating a significant association in NH whites (Fig. 1). There was also a significant VACS Index × Hispanic interaction ($p = 0.04$) but no significant interaction for NH blacks ($p = 0.74$), indicating that the strength of the association between the VACS Index and neurocognition was significantly weaker in Hispanics than NH whites, but comparable between NH blacks and whites. Follow-up analyses stratified by race/ethnicity showed that higher VACS Index scores (worse health) were significantly associated with worse global neurocognitive function in NH whites (estimate = −0.32, SE = 0.06, $p < 0.001$, semi-partial $R^2 = 0.07$) and NH blacks (estimate = −0.24, SE = 0.08, $p < 0.01$, semi-partial $R^2 = 0.06$), but not in Hispanics (estimate = −0.09, SE = 0.07, $p = 0.21$, semi-partial $R^2 = 0.01$). We obtained similar results in comparable analyses on NCI, including a significant VACS Index × Hispanic interaction ($p = 0.02$), but no significant VACS Index × NH black interaction ($p = 0.16$). In stratified analyses, higher VACS Index scores were associated with increased NCI in NH whites (OR = 1.29, CI = 1.15–1.47, $p = 0.02$) and NH blacks (OR = 1.41, CI = 1.15–1.75, $p = 0.03$), but not in Hispanics (OR = 1.08, CI = 0.94–1.24, $p = 0.29$).

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Analyses of the overall sample on the seven neurocognitive domains with NH whites as the reference group showed a main effect of the VACS Index for all domains (all *ps*< 0.01). There were no significant VACS Index × NH black interactions for any of the domains (*ps* > 0.25). The VACS Index × Hispanics terms were significant for learning ($p = 0.01$; Fig. 2a) and recall ($p = 0.02$; Fig. 2b), and there was a nonsignificant trend for verbal fluency ($p = 0.08$), with this interaction term being non-significant for other domains (*ps* > 0.26). Follow-up analyses showed that higher VACS Index scores were associated with worse learning and recall in NH whites ($p < 0.001$ for both domains) and NH blacks ($p = 0.03$ and $p = 0.02$, respectively), but not in Hispanics ($p = 0.94$ and 0.84, respectively). Separate analyses on verbal and visual learning and memory tests showed comparable findings.

Analyses examining the association between the VACS Index components and global neurocognitive function (Table 3), showed that age (as weighted in the VACS Index) was a significant predictor in all ethnic/racial groups, while the other components varied by group. FIB-4 and hemoglobin were significant predictors for NH whites, CD4 cell counts for NH blacks, and HCV status for Hispanics. We obtained similar results in comparable analyses on NCI.

The impact of psychiatric and medical comorbidities and lifestyle factors— Considering that VACS Index scores may be impacted by lifestyle factors and psychiatric and other medical comorbidities, we evaluated the potential contribution of these factors to the different associations found between the VACS Index and neurocognition among ethnic/racial groups. The groups did not differ significantly on most psychiatric and substance use comorbidities, except Hispanics were less likely to have a positive UDS. Hispanics were also less likely to report a history of smoking (lifetime and current) than both NH groups, and NH blacks reported reduced ART adherence compared to NH whites and Hispanics. The ethnic/racial groups also reported varying rates of medical comorbidities (Table 4).

Of the comorbidities and lifestyle factors that differed across ethnic/racial groups, positive UDS (all tested substances except marijuana), hypertension, and medication adherence were significantly associated with global SS (*ps* < 0.05). We ran a linear regression model on global SS similar to the one in the original analyses (adjusting for demographics and ART status, and including terms for the VACS Index, race/ethnicity, and the interaction of these two latter factors) and also including terms for UDS status and hypertension. Results from this model showed similar results to those reported above, including a main effect of the VACS Index ($p < 0.001$), a nonsignificant VACS × NH black interaction ($p = 0.52$), and a significant VACS Index × Hispanic interaction ($p = 0.04$). We obtained comparable findings on NCI.

Within our group of patients on ART, we ran a comparable linear regression adjusting for demographics and medication adherence (NH whites: $n = 203$; NH blacks, $n = 66$; and Hispanics, $n = 111$). Results from this analysis showed a main effect of the VACS Index, but no significant VACS Index × race/ethnicity interactions. Because our smaller sample might have precluded us from finding a significant interaction, we ran separate models by ethnic/racial groups. Results from these analyses showed a pattern consistent with our larger sample size analyses, where the VACS Index was significantly associated with global

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neurocognition in NH whites (estimate = −0.31, SE = 0.09, $p < 0.001$) and NH blacks (estimate = −0.30, SE = 0.11, $p < 0.01$), but not in Hispanics (estimate = −0.16, SE = 0.09, $p = 0.08$). We obtained similar findings in NCI (NH whites: OR = 1.31, CI = 1.08–1.61, $p = 0.005$; NH blacks: OR = 1.48, CI = 1.15–1.98, $p = 0.002$; Hispanics: OR = 1.05, CI = 0.87–1.30, $p = 0.63$).

Follow-up subgroup analyses

Age- and gender-matched samples of NH whites and Hispanics—Given significant differences in demographic factors among ethnic groups, we selected (blinded to all nondemographic data) a subset of NH white participants ($n = 194$), comparable in age ($M = 38.04$; SD = 8.37) and gender (85 % male) to our total group of Hispanics ($n = 194$; see Table 1 for descriptive characteristics). We also made efforts to have years of education be equivalent, but there continued to be significant ethnic differences (NH whites education: $M = 12.63$, SD = 2.10; $p < 0.001$). We excluded NH blacks from these analyses given the smaller size of this group. Hispanics and the selected subgroup of NH whites did not differ significantly on the VACS Index (NH whites: median = 18, IQR = 10, 33), but NH whites had higher nadir CD4 (median = 194, IQR = 39, 333; $p < 0.001$), were less likely to be currently on ART (53 %; $p < 0.01$) and were more likely to have detectable plasma RNA (67 %; $p = 0.02$). The groups were comparable on other HIV disease characteristics.

Consistent with findings of analyses with the overall sample, multivariable analyses with this subset of participants on global SS adjusting for demographics and HIV disease characteristics that differed significantly between groups (education, nadir CD4, ART status, detectable plasma RNA) and including the VACS Index and its interaction with ethnicity (with NH whites as the reference group) showed a main effect of the VACS Index ($p<0.0001$) and a significant VACS Index × Hispanic interaction ($p = 0.02$). Within our subset of NH whites, the VACS Index was significantly associated with global neurocognition (estimate = −0.43, SE = 0.08, $p < 0.001$, semi-partial $R^2 = 0.10$). We obtained similar findings in analyses adjusting for comorbidities and lifestyle factors that differed between groups (i.e., hypertension, smoking, marijuana-positive UDS; NH whites: estimate =−0.38, SE= 0.09, $p <0.001$), and when we used NCI as the outcome (NH whites: OR = 1.23, CI = 1.01–1.51, $p = 0.04$). Comparable analyses on neurocognitive domains yielded largely similar results to those in the larger sample including all NH whites. Analyses investigating the VACS Index components most predictive of global neurocognitive function in the subset of NH whites also yielded similar results to those of the larger NH white sample.

The effect of language use among Hispanics—Table 5 presents characteristics of Hispanics by language use. To explore whether language modified the association between the VACS Index and neurocognition, we ran a multivariable model on global SS within our Hispanic sample, adjusting for age, gender, education, and including a VACS Index and language (English/Spanish) interaction term. Results showed there was not a significant main effect of the VACS Index ($p = 0.82$) or VACS Index × language interaction ($p = 0.50$). Comparable analyses also adjusting for current and lifetime substance use disorder yielded similar findings. We also obtained similar results on rates of NCI.

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Discussion

Previous findings showed a significant, yet relatively weak, association between higher VACS Index scores and increased concurrent risk for NCI (Marquine et al. 2014). Results from the present study extend these prior findings by showing that the strength of the association between the VACS Index and global neurocognition differed by ethnic/ racial groups. In contrast to our primary hypothesis, however, higher VACS Index scores were significantly associated with worse global neurocognition among NH whites and blacks, but this association was notably weaker and nonsignificant among Hispanics.

The reasons for these ethnic/racial differences are likely to be varied. Results from our study suggest that they cannot be fully explained by group differences in demographic factors (age, gender, education, language background), HIV disease characteristics that are not part of the VACS Index, psychiatric and medical comorbidities, or certain lifestyle factors (smoking, ART adherence). These differences in global neurocognitive function seem to be primarily driven by differential associations of the VACS Index to learning and recall domains across ethnic/racial groups. These neurocognitive domains are among the most affected in HIV infection in the cART era (Heaton et al. 2011) and are key predictors of functional outcomes in HIV (Heaton et al. 2004), highlighting their relevance among HIV-infected persons. Learning and memory tend to be mediated by medial temporal lobe structures and underlying subcortical pathways, indicating that disease processes primarily impacting these brain regions among HIV-infected Hispanics might not be fully captured in the VACS Index. While there are a number of diseases that lead to problems in learning and memory and our cohort was fairly young, studies in older non-HIV infected samples have shown an increased risk for mild cognitive impairment and dementia, including Alzheimer's disease, among Hispanics (Manly et al. 2008; Tang et al. 2001), and an earlier onset of dementia symptoms in Hispanics (Clark et al. 2005). The identification of optimal biomarkers of these disease processes in older age is underway, and there is likely much to be gained by incorporating such biomarkers in the development of indexes for persons aging with HIV.

Components of the VACS Index were differentially associated with global neurocognition among ethnic/racial groups. Among NH whites biomarkers not specific to HIV disease (hemoglobin and FIB-4) were more strongly associated with neurocognition, whereas markers of infectious diseases were more relevant in minority groups; detectable plasma RNA for NH blacks and HCV coinfection for Hispanics. Poor or late treatment for infectious diseases among minority groups might be one of the factors explaining these findings. The biomarkers that were most important for a given ethnic/ racial group were not necessarily more severe or problematic in that group. This is in line with the notion that other factors not included in the index, such as biomarkers of inflammation or host genetic influences, may be particularly important for neurocognition, especially among HIV-infected Hispanics. Interactions between these factors and those that are part of the VACS Index might also result in the various biomarkers having a differential effect on neurocognitive function across ethnic/racial groups. It might also be that the components of the index need to be weighted differently across ethnic groups, at least when considering its association with neurocognition. Age, as a component in the VACS Index, was an important predictor of

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neurocognition in all groups. This is not surprising given the known effect of age on neurocognitive function in the general population. Age as a component of the VACS Index might also be capturing the effect of other factors associated with neurocognitive function in aging with HIV that are not included in the index (Marquine et al. 2014).

It is also possible that there are “protective” factors among Hispanics that were not assessed in the current study that attenuate the association between poor health, as measured in the VACS Index, and neurocognitive function. We assessed a limited number of comorbidity and lifetime factors that were more favorable among Hispanics in the present study (positive UDS, hypertension, hyperlipidemia, smoking, medication adherence). None of these factors seemed to explain the lack of a significant association between the VACS Index and neurocognition among Hispanics. Yet, our assessment of these factors was fairly limited (e.g., medication adherence was assessed by participant-report on a single assessment question, medical comorbidities were assessed via self-report), There are many other culturally relevant factors that warrant examination (e.g., increased social support, genetic factors), and could explain, at least in part, the current findings suggesting a weaker association between the VACS Index and neurocognition among Hispanics.

While we did not find an association between the VACS Index and neurocognitive function in Hispanics, work from the North American AIDS Cohort Collaboration Study (NA-ACCORD) showed that the VACS Index was predictive of mortality in a diverse cohort, including Hispanics, NH whites, and NH blacks (Justice et al. 2013). In addition to the difference in outcomes between this past study and ours, the NA-ACCORD study did not investigate interactions between race/ ethnicity and the VACS Index. Furthermore, the present sample of Hispanics (residing in the US-Mexico border region) likely differed in various ways from that of the NA-ACCORD study (which included sites across the USA and Canada). There is great heterogeneity *within* all ethnic/racial groups, particularly Hispanics, and regional differences may influence adherence to specific cultural norms. Thus, caution is warranted in generalizing present findings to other subgroups not included in our sample. Hispanics are highly diverse, comprising multiple national origins, racial groups, patterns of immigration, educational backgrounds, and language use, which have implications for health care use and outcomes (Guarnaccia et al. 2007). Nonetheless, there are also notable cultural aspects that are shared by many Hispanics (Anez et al. 2005; Guarnaccia and Rodriguez 1996). In the present study, we focus on Hispanics living in the US-Mexico border, which are primarily of Mexican origin/ descent. Importantly, Mexican Americans represent the majority (63 %) of the total US Hispanic population (9 % Puerto Ricans; 4 % Cubans, 3 % Dominican, 8 % Central American, 6 % South American, and 7 % other).

One limitation of the present study is that our cohort, particularly the NH black and Hispanic groups, were relatively young, and rates of severe comorbidities were fairly low across all groups (partly due to our exclusion criteria). Future studies including older HIV-infected persons, particularly members of minority groups, are a vital next step. Importantly, though, present findings indicate that the differential association between the VACS Index and neurocognitive function across ethnic/racial groups, cannot be explained by group differences in age, or severity of the index or its individual components. Other than language spoken and country of birth, we had limited data regarding culturally relevant characteristics

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of our group of Hispanics (e.g., years in the USA, ancestry). Future studies might investigate potential differences among subgroups of Hispanics, particularly given prior findings on the association between the VACS Index and mortality (Justice et al. 2013). The cross-sectional nature of the present study precludes ascribing directionality to our findings and highlights the need for future longitudinal studies in this area. The main strengths of our study include having a relatively large, diverse, and well-characterized group of HIV-infected adults, and the use of a comprehensive neurocognitive test battery that is sensitive to HIV-associated NCI and is used in both national and international HIV studies (Heaton et al. 2008, 2010).

Overall, results from the present study indicate that the association between the VACS Index and neurocognitive function differs by ethnic/racial group. In its current form the index does not appear to be an optimal indicator of risk for NCI, particularly among Hispanics. Thus, caution is warranted when utilizing the index as an indicator of NCI in this group. More broadly, present findings highlight the importance of examining the role of race/ethnicity when studying the association of HIV and non-HIV biomarkers to neurocognitive function. Identification of the key factors leading to NCI among different ethnic/racial groups of HIV-infected persons might prove to be an important step in developing tailored interventional approaches and furthering our understanding of biomarkers of neuroAIDS.

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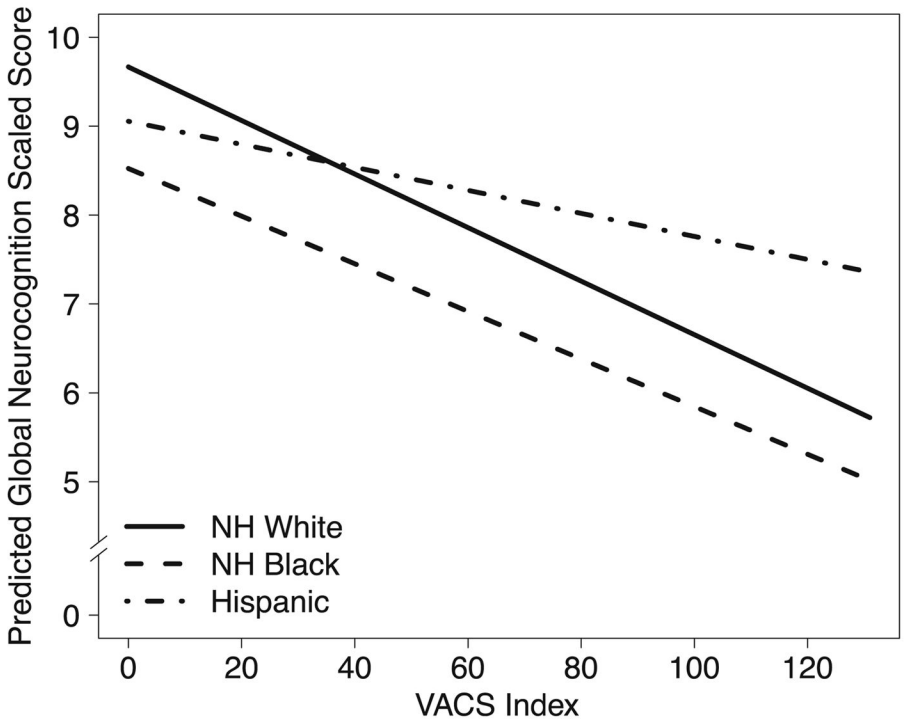

Fig. 1.

Results from multivariable models on global neurocognitive function adjusting for covariates (age, education, gender, ART status) and predictors being VACS Index and terms for the interaction of this index with race/ethnicity

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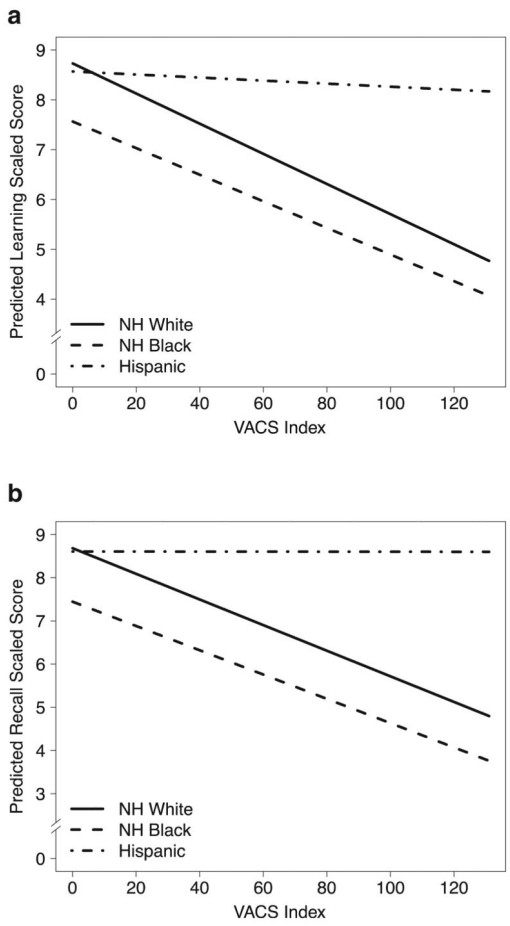

Fig. 2.

Results from multivariable models on learning (**a**) and recall (**b**) neurocognitive domains adjusting for covariates (age, education, gender, ART status) and predictors being VACS Index and terms for the interaction of this index with race/ethnicity

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Table 1

Demographic factors, HIV disease characteristics, neurocognitive function, and VACS Index by study group

Term	NH whites (W), *n* = 369	NH blacks (B), *n* = 111	Hispanics (H), *n* = 194	Group comparisons	
				p value[a]	Pairwise[b]
Demographic factors					
Age, *M*(SD); range	43.08 (9.64); 20–76	39.71 (8.52); 18–63	37.84 (9.51); 20–66	<0.001	W > B, W > H
Education, *M*(SD); range	13.85 (2.52); 6–20	12.66 (2.00); 7–20	11.36 (3.36); 4–20	<0.001	W > B > H
Male gender	91 %	79 %	79 %	<0.001	W > B, W > H
HIV disease characteristics					
Nadir CD4	140 (26, 300)	159 (10, 300)	88 (18, 264)	0.39	
Current CD4 count (cells/mm^3)	388 (184, 585)	349 (163, 536)	339 (161, 547)	0.39	
ART prescribed	60 %	72 %	68 %	0.02	W < B
Detectable plasma RNA	59 %	59 %	56 %	0.68	
AIDS	64 %	61 %	64 %	0.87	
EDI (years)	10 (4, 14)[c]	7 (2, 13)[d]	6 (2, 11)[e]	<0.001	W > B, W > H
Neurocognitive performance (SS), *M*(SD)					
Global	9.36 (2.14)	8.04 (2.13)	8.81 (2.04)	<0.001	W > H > B
Learning	8.49 (2.71)	7.10 (2.58)	8.53 (2.65)	<0.001	W > B, H > B
Recall	8.53 (3.13)	7.01 (2.84)	8.69 (2.92)	<0.001	W > B, H > B
Verbal fluency	10.28 (2.53)	9.64 (2.53)	9.60 (2.55)	<0.01	W > H
Speed of information	9.96 (2.56)	8.43 (2.61)	9.02 (2.69)	<0.001	W > B, W > H
Executive function	9.79 (2.72)	8.40 (2.71)	8.56 (2.64)	<0.001	W > B, W > H
Working memory	9.75 (2.69)	7.95 (2.76)	8.06 (2.55)	<0.001	W > B, W > H
Fine motor skills	8.64 (2.75)	7.84 (2.94)	9.31 (2.96)	<0.001	H > W > B
VACS Index	18 (10, 33)	23 (10, 45)	17 (7, 34)	0.02	B > W, B > H

Values represent median (IQR) unless otherwise noted

ART antiretroviral therapy, *EDI* estimated duration of infection, *NH* non-Hispanic, *VACS* Veterans Aging Cohort Study

[a] Results from analyses of variance (ANOVAs) and chi-squared tests

[b] Indicates significant group differences ($p < 0.05$) based on results from follow-up pairwise comparisons with Tukey's correction and chi-squared tests

[c] Forty-two missing

[d] Thirteen missing

[e] Twenty-seven missing

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Table 2

Components of the Veterans Aging Cohort Study (VACS) Index by group

VACS component	Pts[a]	NH whites (*n* = 369), *n* (%)	NH blacks (*n* = 111), *n* (%)	Hispanics (*n* = 194), *n* (%)	Group comparison[b]	
					p value	Pairwise
Age						
<50	0	287 (78 %)	100 (90 %)	173 (89 %)	<0.01	W > B, W > H
50–64	12	71 (19 %)	11 (10 %)	18 (9 %)		
≥65	27	11 (3 %)	0 (0 %)	3 (2 %)		
CD4 count (cells/mm^3)						
≥500	0	125 (34 %)	37 (33 %)	60 (31 %)	0.24	
350–499	6	73 (20 %)	18 (16 %)	33 (17 %)		
200–349	6	71 (19 %)	22 (20 %)	33 (17 %)		
100–199	10	54 (15 %)	14 (13 %)	35 (18 %)		
50–99	28	14 (4 %)	3 (3 %)	16 (8 %)		
<50	29	32 (9 %)	17 (15 %)	17 (9 %)		
HIV-1 RNA (copies/mL)						
<500	0	187 (51 %)	60 (54 %)	110 (57 %)	0.48	–
500–1 × 10^5	7	135 (37 %)	36 (32 %)	67 (35 %)		
≥1 × 10^5	14	47 (13 %)	15 (14 %)	17 (9 %)		
Hemoglobin (g/dL)						
≥14	0	224 (61 %)	38 (34 %)	109 (56 %)	<0.001	W > H > B
12–13.9	10	121 (33 %)	41 (37 %)	53 (27 %)		
10–11.9	22	21 (6 %)	28 (25 %)	28 (14 %)		
<10	38	3 (1 %)	4 (4 %)	4 (2 %)		
FIB-4						
<1.45	0	265 (72 %)	85 (77 %)	169 (87 %)	<0.001	H < W
1.45–3.25	6	92 (25 %)	20 (18 %)	20 (10 %)		
>3.25	25	12 (3 %)	6 (5 %)	5 (3 %)		
eGFR						
≥60	0	346 (94 %)	106 (95 %)	187 (96 %)	<0.01	W > B, H > B
45–59.9	6	20 (6 %)	0 (0 %)	6 (3 %)		

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VACS component	Pts[a]	NH whites (*n* = 369), *n* (%)	NH blacks (*n* = 111), *n* (%)	Hispanics (*n* = 194), *n* (%)	Group comparison[b]	
					p value	Pairwise
30–44.9	8	2 (1 %)	2 (2 %)	1 (1 %)		
<30	26	1 (0 %)	3 (3 %)	0 (0 %)		
HCV infection	5	27 (7 %)	12 (11 %)	19 (10 %)	0.35	–

Fibrosis index (FIB-4) = (years of age × AST) / (platelets in 109/L × square root of ALT); estimated glomerular filtration rate (eGFR) = 186.3 × (serum creatinine – 1.154) × (age – 0.203) × (0.742 for women) × (1.21 if black)

ALT alanine transaminase, *AST* aspartate transaminase

[a] Points assigned as indicated by Justice et al. (2012)

[b] Group comparisons based on chi-squared or Fisher's exact tests

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Table 3

Association between the components of the VACS Index and global neurocognitive function by ethnic/racial group

	NH white		NH black		Hispanic	
	p	**Estimate[a]**	***p***	**Estimate[a]**	***p***	**Estimate[a]**
Age	<0.001	–	<0.001	–	0.008	–
<50		Reference		Reference		Reference
50–64		−1.25		−2.27		−0.96
≥65		−2.81		−5.10		−2.16
CD4 count	0.17	–	0.003	–	0.61	–
HIV-1 RNA	0.59	–	0.33	–	0.17	–
Hemoglobin	0.004	–	0.52	–	0.21	–
≥14		Reference		–		–
12–13.9		−0.47		–		–
10–11.9		−1.03		–		–
<10		−1.79		–		–
FIB-4	0.004	–	0.27	–	0.73	–
<1.45		Reference		–		–
1.45–3.25		−0.37		–		–
>3.25		−1.53		–		–
eGFR	0.44	–	0.99	–	0.62	–
HCV	0.68	–	0.21	–	0.03	−0.77

Represents results from three separate multivariable linear regression models on global neurocognitive function (scaled scores) by ethnic/racial group with predictors being the components of the VACS Index and adjusting for years of education and gender

[a]Estimates are given for levels of significant predictors only

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Table 4

Psychiatric and medical comorbidities and lifestyle factors among the three ethnic/racial groups

Term	NH whites (W), *n* = 369	NH blacks (B), *n* = 111	Hispanics (H), *n* = 194	Group comparisons	
				p^a	Pairwise[b]
Psychiatric comorbidities					
Current major depressive disorder	21 %[c]	17 %[d]	17 %[e]	0.58	
Lifetime major depressive disorder	54 %[c]	51 %[d]	48 %[e]	0.60	
Current substance use disorder	16 %[c]	13 %[d]	11 %[e]	0.32	
Lifetime substance use disorder	69 %[c]	66 %[d]	61 %[e]	0.26	
Current depressed mood (BDI)	56 %	56 %	51 %	0.53	
Medical comorbidities					
Hypertension	22 %	17 %	10 %	0.001	W > H
Hyperlipidemia	18 %	6 %	12 %	<0.001	W > B, W > H
Diabetes	7 %	2 %	5 %	0.10	
Lifestyle factors					
UDS+ (all drugs except marijuana)	17 %	22 %	9 %	<0.01	W > H, B > H
UDS+ for marijuana	21 %	25 %	13 %	0.02	W > H, B > H
Current smoking (%)	24 %	29 %	12 %	<0.001	W > H, B > H
Ever smoked	27 %	31 %	14 %	<0.001	W > H, B > H
ART adherence	77 %	57 %	80 %	0.003	W > H, H > B

ART antiretroviral therapy, *BDI* Beck Depression Inventory, *NH* non-Hispanic, *UDS+* positive urine drug screen

[a] Results from chi-squared tests

[b] Indicates significant group differences ($p < 0.05$) based on results from follow-up pairwise chi-squared tests

[c] Ninety-five missing

[d] Twenty-nine missing

[e] Eighty-two missing

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Table 5

Characteristics of Hispanics (n = 194) by language background

Term	Spanish speakers, n = 116	English speakers, n = 78	p value[a]
Demographic factors			
Age, M (SD); range	38.30 (9.74)	37.14 (9.19)	0.40
Education, M (SD); range	10.49 (3.60)	12.64 (2.49)	<0.001
Male gender	74 %	87 %	0.02
HIV disease characteristics			
Nadir CD4	77 (17, 230)	111 (19, 501)	0.33
Current CD4 count (cells/mm^3)	329 (152, 534)	386 (161, 563)	0.37
ART prescribed	30 %	36 %	0.32
Detectable plasma RNA	54 %	58 %	0.64
AIDS	67 %	61 %	0.43
EDI (years)	6 (2, 10)[b]	5 (1, 12)[c]	0.84
Psychiatric comorbidities			
Current major depression	15 %[d]	19 %[e]	0.56
Lifetime major depression	46 %[d]	50 %[e]	0.66
Current substance use disorder	2 %[d]	17 %[e]	<0.01
Lifetime substance use disorder	31 %[d]	83 %[e]	<0.001
Current depressed mood (BDI)	52 %	50 %	0.80
Medical comorbidities			
Hypertension	8 %	14 %	0.16
Hyperlipidemia	14 %	8 %	0.18
Diabetes	6 %	3 %	0.31
Lifestyle factors			
UDS+ (all drugs except marijuana)	8 %	9 %	0.76
UDS+ for marijuana	11 %	16 %	0.29
Current smoking	8 %	16 %	0.10
Ever smoked	11 %	18 %	0.13
ART adherence	80 %	79 %	0.83
Global SS, M (SD)	8.84 (2.13)	8.77 (1.91)	0.81
VACS Index	17 (10, 35)	17 (6, 27)	0.43

Values represent median (IQR) unless otherwise noted

ART antiretroviral therapy, *BDI* Beck Depression Inventory, *EDI* estimated duration of infection, *NH* non-Hispanic, *UDS+* positive urine drug screen, *VACS* Veterans Aging Cohort Study

[a] Results from independent sample t tests (or Wilcoxon rank-sum test) and chi-squared tests

[b] Fifteen missing

[c] Twelve missing

[d] Sixty-eight missing

[e] Fourteen missing

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