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Journal

The Clinical Neuropsychologist, 35(2)

ISSN

1385-4046

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Publication Date

2021-02-17

DOI

10.1080/13854046.2019.1701084

Peer reviewed

HHS Public Access

Author manuscript

Clin Neuropsychol. Author manuscript; available in PMC 2022 February 01.

Published in final edited form as:

Clin Neuropsychol. 2021 February ; 35(2): 433–452. doi:10.1080/13854046.2019.1701084.

Neurocognitive Impairment in Spanish-speaking Latinos Living with HIV in the US: Application of the Neuropsychological Norms for the US-Mexico Border Region in Spanish (NP-NUMBRS)

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Abstract

Objective: Latinos in the US are at increased risk for HIV-associated neurocognitive impairment (NCI). Most studies of US Latinos living with HIV have included primarily English-speakers only. We investigated the rate, pattern, and correlates of HIV-associated NCI in native Spanish-speaking Latinos living in the US near the Mexican border.

Methods: Participants included 407 native Spanish-speaking Latinos (Age: M=37.65, SD=10.0; Education: M=10.75, SD=4.1; 53% male): 153 persons living with HIV (PLWH; 56% AIDS) and 254 healthy controls. All participants completed comprehensive neuropsychological assessments in Spanish. Raw neuropsychological test scores from seven domains were converted to demographically-adjusted T-scores using norms developed with healthy controls. Global and domain NCI were defined per established criteria. Among PLWH we applied norms developed for non-Hispanic (NH) Whites and Blacks, and investigated correlates of global NCI, including HIV disease characteristics and psychiatric comorbidities.

Results: Utilizing population specific norms, rates of global NCI were significantly higher among PLWH (39%) than healthy controls (17%), comparable to previously published rates. In contrast, rates of global NCI in the same group of PLWH were significantly different when NH White norms (63%, $p < 0.0001$) and NH Black norms were used (18%, $p < 0.0001$). Among

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PLWH without a history of lifetime substance use disorder, more years of antiretroviral exposure were significantly associated with decreased rates of global NCI.

Conclusions: Present findings lend support to the validity of newly developed norms for native Spanish-speakers living near the US-Mexico border, and underscore the importance of utilizing appropriate norms to accurately identify HIV-associated NCI.

Keywords

Hispanic/Latino; neuropsychological assessment; norms; HIV; cognition

Introduction

Advancements in the treatment of human immunodeficiency virus (HIV) over the past two decades have greatly improved the longevity and quality of life of people living with HIV (PLWH) (Saylor et al., 2016). However, HIV-associated neurocognitive impairment (NCI) remains prevalent, with NCI observed in approximately 40% of PLWH (Heaton et al., 2011). In addition, NCI remains problematic, contributing to impairments in everyday functioning that range from HIV care management (e.g., medication adherence; Hinkin et al., 2002; Thames et al., 2011) to basic daily tasks such as household and financial management (Heaton et al., 2004a).

In the United States, Hispanics/Latinx/Latinos/as, hereafter referred to as Latinos, are disproportionately affected by HIV as compared to non-Hispanic Whites (NH Whites) (Center for Disease Control and Prevention, 2016). Latinos have a three times higher risk for HIV infection than NH Whites (Centers for Disease Control and Prevention, 2016), and tend to present with worse HIV disease characteristics, such as higher rates of acquired immunodeficiency syndrome (AIDS) (Swindells et al., 2002). Moreover, substantial heterogeneity exists within Latinos, including differences in language, lifestyle, cultural norms, levels of acculturation and education, and shared values. These differences may impact the level of HIV knowledge and engagement with care, adherence, and positive health outcomes (Marquine et al., 2018b; Sheehan et al., 2015). The HIV care continuum and associated health outcomes can also differ between subgroups of Latinos based on their country of origin and place of residence within the United States (Marquine et al., 2018b; Sheehan et al., 2015; Chen et al., 2012). For example, Latinos born in Mexico and Puerto-Rico are respectively at particularly high risk for late HIV diagnosis and early mortality as compared to persons of Mexican and Puerto Rican descent born in mainland US (Sheehan et al., 2015). The diversity of this large minority group is indirectly overlooked due to methods of classification, further complicating the generalizability of research findings to HIV care among Latino communities around the nation.

Overall, Latino PLWH appear to be at increased risk for longitudinal neurocognitive decline (Heaton et al, 2015) and cross-sectional NCI (Marquine et al., 2018b; Rivera Mindt et al., 2004; 2008; 2014; Ryan et al., 2005). In addition, among PLWH in the mainland US, those of Puerto Rican origin/descent had significantly higher rates of global NCI than those of Mexican origin/descent (Marquine et al., 2018b). Yet, both of these subgroups of Latinos had increased rates of NCI compared to non-Latino Whites living in a similar geographic

region in the US, underscoring the complexity of factors underlying disparities in NCI among Latinos. (Marquine et al., 2018b). The majority of studies on NCI among Latino PLWH have only included individuals who are primarily English-speakers (Heaton et al., 2014; Marquine et al., 2018b; Rivera Mindt et al., 2004; 2008; Ryan et al., 2005). To date, a sole published study has investigated rates of NCI in native Spanish-speaking Latinos (Wojna et al., 2006). This study was conducted in women from Puerto Rico and neuropsychological scores of PLWH were compared to calculated z-scores from a small sample ($n = 34$) of matched healthy controls. This study reported NCI in 77.6% of the sample living with HIV. However, Wojna and colleagues (2006) specifically recruited women with low nadir CD4 cell counts (e.g. ≤ 500 cells/mm^3), a significant predictor of NCI (Ellis et al., 2011), thereby potentially inflating the reported prevalence rates of HIV-associated NCI among Spanish-speaking Latinos.

The focus on primarily English-speaking Latinos in neuropsychological research is likely multifactorial. It may be at least partly driven by practical considerations (e.g., limited study resources, lack of bilingual study personnel). It may also be a conscious choice made by investigators due to the limited availability of tests and normative data for Spanish-speakers living in the U.S. (Morlett-Paredes et al., 2019b, this issue; Rivera Mindt, Byrd, Saez, & Manly, 2010). The shortage of tests and norms for Spanish-speakers in the US impacts clinicians and researchers. Applying norms for English-speakers or norms collected among individuals living in Spanish-speaking countries (i.e. Mexico and Spain), to the Spanish-speaking U.S. Latino population is currently common clinical practice (Morlett-Paredes et al., 2019, this issue). However, this process does not consider the demographic differences between the normative sample and the individual, increasing the chances of misidentification of neurocognitive deficits, either over or under diagnosing impairment (Arango-Lasprilla, 2015; Casaletto & Heaton, 2017).

Demographic factors that are typically adjusted for in normative corrections (i.e. age, education, and sex) are known to impact cognitive performance in varying ways across racial/ethnic groups (Rivera Mindt et al., 2010; Gasquoine et al., 2007; Heaton, Miller, Taylor & Grant, 2004; Touradji, Manly, Jacobs & Stern, 2001). For example, Heaton, Miller, Taylor & Grant (2004) found that the percentage of variance accounted for by age on the Animals Category Fluency test was 20% for Caucasians and 12% for African Americans, with similar differential demographic effects between racial category found in other tests. Additionally, other background variables that are particularly relevant among Latinos living in the US (e.g. language spoken, level of bilingualism, acculturation, country where education was obtained) may impact cognitive test performances (Suarez et al., 2019 this issue, Flores et al., 2017; Echemendia & Harris, 2004; Gollan, Montoya & Werner, 2002). Similarly, not using regional and dialect specific Spanish words in test items and instructions may undermine the interpretability of an individual's true cognitive ability (Ardila, Rodriguez-Menéndez, & Rosselli, 2002). Thus, developing normative data for a specific population, is important for the accurate identification of underlying neurological dysfunction (e.g. HIV-associated NCI).

In the present study, we investigated NCI in native Spanish-speaking Latino PLWH from the U.S.-Mexico border, using a commonly administered neuropsychological test battery

sensitive to detecting HIV-associated NCI (Cysique et al., 2011, Dufour et al., 2018; Marcotte et al., 2013; Morgan et al., 2015). We then utilized normative corrections developed specifically for Spanish-speaking adults living in the U.S, with adjustments for age, sex, and education (Cherner, Marquine et al., this issue) in order to achieve the following aims: 1) determine the rate and pattern of NCI among Spanish-speaking Latino PLWH near the US Mexico border using these newly developed norms; 2) compare rates of global NCI and domain-specific functioning in this population against those in a sample of Spanish-speaking Latino healthy individuals; 3) compare rates of NCI against rates calculated using existing norms for English-speaking NH Whites and non-Hispanic African Americans/Blacks (hereafter referred to as NH Blacks) [we recognize that race-based normative groupings can be considered a short-hand method to account for sociodemographic differences in lived experiences and access to resources, rather than suggest that race itself is a predictive variable (Manly, 2005)]; and 4) determine predictors of NCI in our sample of Spanish-speaking Latino PLWH in the US. Based on findings in the normative sample presented in other NP-NUMBRS papers in this issue, we expected that using non-Hispanic norms would result in misclassification of NCI, and that the pattern of NCI observed with norms developed for NH Whites and NH Blacks would vary from the pattern of NCI observed when utilizing norms for Spanish-speakers. Additionally, we anticipated that the most common predictor of HIV-associated NCI among English-speaking Latinos of Mexican origin/descent, nadir CD4 count (Marquine et al., 2018b), would also predict NCI within our native Spanish-speaking, predominantly Latino population.

Materials and Methods

Participants

Participants included 407 native Spanish-speaking Latinos: 153 PLWH and 254 healthy controls. The group of PLWH included adults ages 20 and 65 years old with 0-20 years of education. PLWH were recruited from the greater San Diego area and enrolled in observational cohort studies aimed at investigating HIV-associated NCI at the University of California San Diego HIV Neurobehavioral Research Program (HNRP) from May, 1999 to September, 2017. Regulatory approval was obtained from the University of California San Diego Institutional Review Board. Descriptions of these studies can be found in prior reports (Heaton et al., 2011; Rippeth et al., 2004; Rivera Mindt et al., 2004). Inclusion/exclusion criteria were similar across parent studies: participants were excluded if they had a history of head injury with loss of consciousness greater than 30 min, other neuromedical comorbidities that may affect cognitive functioning (i.e. stroke, prior head injury, opportunistic infection), or significant sensory or physical issues that would interfere with neurocognitive testing. Inclusion criteria for these cross-sectional analyses was being infected with HIV, having neuropsychological data available at baseline and being native Spanish-speakers. Exclusion criteria for present analyses also included diagnosis of current any substance use disorder. Healthy controls were participants from the Neuropsychological Norms for the US-Mexico Border Region in Spanish (NP-NUMBRS) Project. Briefly, this project included adults ages 19 and 60 years old with 0-20 years of education, recruited from the US-Mexico border region in California and Arizona, who were free of a history of neurological, medical, and psychiatric conditions known to impact the central nervous

system or influence test performance (i.e. neurological/other medical conditions, significant injuries or disabilities, serious psychiatric conditions [e.g. psychosis, bipolar disorder, and severe symptoms of depression or anxiety], and any lifetime substance dependence; for further details see Cherner, Marquine et al., this issue).

Materials and Procedures

All participants completed comprehensive neuropsychological assessments, and PLWH completed neuromedical and substance use/psychiatric evaluations. Demographic information was collected via self-report. Country of origin was collected for a subset of the sample (n = 158) as well as information on whether individuals were foreign-born or US-born (n = 203). Assessments were administered by trained bilingual (English-Spanish) staff.

Neuropsychological assessment.—A comprehensive neuropsychological test battery assessed seven cognitive domains (i.e., verbal fluency, working memory, speed of information processing, executive functioning, learning, delayed recall, and fine motor skills) and was developed to be particularly sensitive to frontal-subcortical impairment commonly seen in HIV seropositive populations (Cysique et al., 2011, Heaton et al., 2011). Specific tests that comprise each of the seven domains are listed in Table 1. The process of adaptation, translation, and back translation of these tests from English to Spanish is available elsewhere (Cherner, Marquine et al., this issue). Raw test scores were calculated and converted to T-scores that adjusted for the effects of age, years of education, and sex using newly developed, region-specific norms based on our sample of healthy controls (Cherner, Marquine et al., this issue). T-scores from individual tests were also converted into deficit scores ranging from zero to five. Deficit scores were averaged across all tests in the battery to compute global deficit scores (GDS). Global NCI was defined as a GDS ≥ 0.5, which previous literature has established as the ideal cut-point that optimizes both sensitivity and specificity (Carey et al., 2004). Domain deficit scores (DDS) were also calculated by averaging deficit scores for tests in each domain and domains were categorized as impaired if the DDS > 0.5.

In order to examine how utilizing norms developed for other racial/ethnic groups may impact the classification of HIV-associated NCI, T-scores for PLWH were also calculated using previously published demographically-adjusted norms for NH Whites (Norman et al., 2011; Heaton, Miller, Taylor & Grant, 2004) and NH Blacks (Norman et al., 2011; Heaton, Taylor & Manly, 2003). GDS and DDS impairment based on these T-scores were also calculated using the same procedures described above.

Neuromedical assessments.—The following HIV disease characteristics were obtained via self-report in PLWH: AIDS diagnosis, estimated duration of infection, and antiretroviral therapy (ART) regimen. Nadir CD4+ T-cell count was estimated via a combination of self-report and medical records. Laboratory measurements consisted of routine blood and urine sample collection including clinical chemistry panels, complete blood counts, rapid plasma reagin, Hepatitis-C (HCV) antibody, CD4+ T cells (flow cytometry), and urine toxicology. Procedures were performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified, or CLIA-equivalent, laboratory. HIV infection was diagnosed by enzyme-linked

immunosorbent assay with Western blot confirmation. 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) in a CLIA-certified clinical laboratory.

The Veteran Aging Cohort Study (VACS) Index, a well-validated predictor of mortality, in PLWH (Justice et al., 2013) was computed using standard methods (Justice et al., 2012), which consist of a weighted approach of seven routine clinical variables (age, CD4 count (cells/mm), HIV-1 RNA (copies/mL), Hemoglobin (g/dL), Fibrosis-4 (an index of liver fibrosis), eGFR, and HCV infection). The VACS Index has been linked to HIV-associated NCI (Marquine et al., 2014), neurocognitive change (Marquine et al., 2016a) and poor functional outcomes (Marquine et al., 2018a); however, this association appears to be weaker among Latinos than other racial/ethnic minority groups (Marquine et al., 2016b).

Psychiatric/substance use assessments.—Current depressive symptoms were assessed using the Beck-Depression Inventory, 1st or 2nd Edition (BDI-I or BDI-II; Beck, Steer, & Brown, 1996), which consists of 21 items scored on a scale of zero to three, where higher total scores represent more severe depressive symptoms. Given that the two BDI versions have slightly different cutoff scores, we used respective cutoff scores for each scale to determine the presence of significant depression symptomatology.

A subset of our PLWH sample (n = 64) were also administered the Composite International Diagnostic Interview (CIDI version 2.1), a semi-structured clinical interview (Kessler & Ustun, 2004; Wittchen, 1994), which allowed for the assignment of current and lifetime histories of Diagnostic and Statistical Manual-Fourth Edition (DSM-IV) diagnoses for Major Depressive Disorder and Substance Use Disorders (abuse and/or dependence). Presence of current and lifetime Substance Use Disorder (SUD) was defined as meeting current or lifetime abuse or dependence criteria, respectively, for any of the following substances: alcohol, cannabis, opioids, methamphetamine, cocaine, sedatives and hallucinogens. Individuals meeting criteria for current SUD were excluded in subsequent analyses.

Statistical Analyses.—Assumptions for parametric methods were checked for the sample characteristics. Differences in demographic characteristics and rates of global NCI (based on Spanish-speaking normative corrections) were compared between PLWH and healthy controls using independent sample t-tests and Chi^2 tests. Comparisons of categorical variables with low frequency were analyzed using Fisher's exact test.

In order to compare domain specific cognitive performance between PLWH and healthy controls, independent sample t-tests were conducted using domain T-scores. Effect sizes were calculated using Cohen's d (0.20=small; 0.50=medium; 0.80=large; Cohen, 1988). Within PLWH, McNemar's tests were used to compare rates of global and domain NCI utilizing current Spanish-speaking Latino norms and previously published norms for NH Whites and NH Blacks. In order to investigate correlates of HIV-associated NCI within Spanish-speakers, two-sample t-tests and Chi^2 tests were used to examine the univariable association between NCI (i.e., impaired using GDS cutoff of ≥0.5) and participant characteristics, including demographic factors (e.g., age, years of education, and sex), HIV

disease characteristics (e.g., estimated duration of infection, nadir CD4, viral load), and psychiatric characteristics (e.g., total BDI score). In order to build a final multivariable model examining correlates of NCI, we 1) selected variables that were univariably associated with GDS impairment at $\alpha = .10$; 2) examined the two-way interactive effects among these variables on NCI, and 3) removed any interaction terms that were not significantly associated with NCI at $p < .05$. JMP version 13.0.0 and $\alpha < .05$ were used for all analyses, R version 3.5.0 was used to create Figure 3.

Results

Demographic characteristics

Table 2 demonstrates the participants' demographic characteristics by group. There were no significant differences between PLWH and healthy controls on age (p=0.36) and years of education (p=0.61), and there were more males in the group of PLWH than the healthy control group (p< 0.0001). Among participants with available country of origin and place of birth data, the large majority of the sample reported being of Mexican origin/descent (PLWH, 96.6%; healthy controls: 93%), and foreign born (PLWH, 94.6%; healthy controls: 82%).

HIV disease characteristics and psychiatric conditions among PLWH

As shown in Table 3, approximately half of our sample of PLWH reported a historical diagnosis of AIDS. The average estimated duration of HIV infection was approximately six years. Most of this sample was currently on ART, with about 1.7 median years of ART exposure. Among those on ART, approximately one-third had detectable plasma viral load (≥50), and a small percent had a detectable CSF viral load (≥50). HCV co-infection was reported in a small percent of this sample. Approximately half of those individuals with available psychiatric and substance use data endorsed a lifetime history of MDD, while 39% were diagnosed with a lifetime Substance Use Disorder (Table 3).

Rates of global neurocognitive impairment and differences in domain functioning in PLWH and healthy controls

Figure 1 depicts the rates of global NCI among Spanish-speaking PLWH and healthy controls. Using normative corrections developed in the group of Spanish-speaking healthy controls, the rate of global NCI in our sample of PLWH was 39.2% (n = 60). As expected, the rate for healthy controls was 16.5% (n = 42*).* Using Chi^2 test, the rate of global NCI was significantly higher among PLWH than healthy controls (χ^2 = 25.55, df =1, p < .0001).

Significant differences in domain functioning using presented Spanish-speaking norms between PLWH and healthy controls were found for all domains (ps < .001) except verbal fluency (p=.08) and fine motor skills (p=.10). Figure 2 depicts all effect sizes, which were small to medium (0.36 – 0.52) for the significant domains of executive functioning, speed of information processing, learning, recall and working memory (Figure 2).

Rates of global and domain NCI among PLWH utilizing different sets of norms

As shown in Figure 3, the rate of global NCI in our sample of PLWH was 39.2% ($n = 60$) after applying the normative corrections for Spanish speakers in the US (Cherner, Marquine et al., this issue). In contrast, the rate of global NCI in the same sample of PLWH was significantly higher when NH White norms for English-speakers were applied ($p < 0.0001$), and significantly lower when NH Black norms for English-speakers were applied ($p < 0.0001$). These group differences were evident across most neurocognitive domains, except that there were no significant differences (relative to Spanish-speaking norms) in verbal fluency and fine motor skills when applying NH White norms, and in delayed recall memory when applying NH Black norms (Figure 3).

When using norms for Spanish-speakers in the US, the most impaired individual cognitive domains were executive functioning, speed of information processing, learning, and working memory (collectively between 25-35% impairment). Using NH White normative adjustments, executive functioning was impacted at a much higher rate (64%) compared to the remaining domains of learning, working memory, and speed of information processing (between 39-45%). Using NH Black normative corrections, the impairment was most commonly present in executive functioning and speed of information processing (21-25%). Rates of impairment in other domains were present in approximately 16% of the sample, aside from learning and fine motor skills, which showed impairment in 4-9% of the sample, which was substantially lower than expected in a sample of PLWH. (Figure 3).

In post hoc analyses, we applied normative corrections for English-speaking Latinos (Taylor & Heaton, 2001) that are available for three subtests of the Weschler Adult Intelligence Scale – 3rd Edition (WAIS-III): Digit Symbol, Symbol Search, and Letter Number Sequencing (Weschler, 1997) to our PLWH sample. We compared the rates of impairment between these English-speaking adjustments (Taylor & Heaton, 2001) to normative corrections for Spanish speakers living in the US (Cherner, Marquine et al., this issue). Impairment was categorized as T-score <40. The rate of impairment using English-speaking adjustments for Latinos was 32.9%for Digit Symbol, 27.9% for Symbol Search, and 24.0% for Letter Number Sequencing. Using newly developed norms for Spanish-speakers, the rate of impairment was 30.7% for Digit Symbol, 27.9% for Symbol Search, and 31.0% for Letter Number Sequencing. Using McNemar's test, these differences in rates of impairment across normative type for PLWH were only statistically significant for Letter Number Sequencing ($p = .007$), but not Digit Symbol or Symbol Search ($p > .05$).

Correlates of global NCI

Univariable analyses between demographic variables and Spanish-speaking normative corrections showed that age, years of education, and sex were not significantly associated with NCI. Univariable analyses of HIV disease and psychiatric/substance use characteristics with NCI showed that years exposure to ART, AIDS status, and lifetime SUD were each significantly associated with NCI at $\alpha < .10$ (Table 3). Contrary to our hypothesis, nadir CD4 was not a significant univariable predictor of NCI ($p = .13$). The final multivariable logistic regression model included factors that were significantly associated with NCI in univariable analyses ($\chi^2 = 9.71$, df =4, $p = .046$), and revealed a significant interaction (p

= .04) between lifetime history of any SUD and years of exposure to ART, after adjusting for AIDS status (Figure 4). Within the subset of the sample with available current and lifetime psychiatric and substance use diagnosis data (n = 61), the participants who did not meet criteria for a lifetime substance use disorder (n = 39) had approximately 40% decreased concurrent risk for NCI with every additional year of exposure to ART (odds ratio (OR) = 0.61, 95% confidence interval (CI) = 0.34 – 0.93; p = .04), while those who did meet criteria for a lifetime substance use disorder (n = 25) had no significant association between years of exposure to ART and risk for NCI (OR = 1.02; 95% CI = 0.81 – 1.31; p = .70) (Figure 4).

Discussion

Our study examined rates and pattern of NCI in a sample of native Spanish-speaking PLWH living in southern California (U.S.), utilizing recently developed neuropsychological normative adjustments for Spanish-speaking adults living near the U.S.-Mexico border. We found that the rate and pattern of NCI in our cohort of PLWH was similar to that observed in other studies in this illness population (Marquine et al., 2018b; Heaton et al., 2011). Furthermore, the level of global and domain impairment was significantly higher than in a group of healthy controls, also consistent with prior research. These findings lend support to the validity of the newly developed normative adjustments, by indicating that these norms allow for the detection of HIV-associated NCI in the population for which they were developed.

Applying published norms for NH Whites and NH Blacks resulted in significantly higher (63%) and lower (18%) rates of global NCI, respectively, compared to those based on norms for Spanish-speakers. These results suggest that using normative corrections most appropriate for NH Whites and NH Blacks either over or underestimated global NCI in our sample. Additionally, the pattern of deficit varied drastically depending on the correction used, an indication that applying inaccurate normative adjustments may result in differential diagnostic conclusions for this Spanish-speaking population. These findings underscore the importance of clinicians and researchers carefully considering the norming adjustments and tests used when diagnosing HIV-associated NCI.

Applying the most suitable demographic adjustments to neuropsychological data for specific populations of interest is crucial when hoping to make proper interpretations and comparisons of cognitive functioning (Casaletto & Heaton, 2017); particularly for participants with clinical conditions. Our results show that using NH White based norms for this population, a common clinical practice, inflates rates of HIV-associated NCI. This inadvertent inflation, when compared against an ethnic/linguistic majority group, may be interpreted as a seemingly large disparity. Conversely, applying norms developed for another minority group within the United States, in the hopes of adjusting for the overestimation of impairment using majority group-based data, results in the opposite categorization bias. NH Black norms would not be appropriate for Spanish-speaking Latinos, as applying them would perhaps lead to incorrect conclusions surrounding the presence of a culturally related protective mechanism against HIV-associated NCI.

With the exception of one prior study in Puerto Rican women with advanced HIV disease (Wojna et al., 2006), previous studies of Latinos with HIV have included only native English-speaking Latinos. Our findings showing that the obtained rate of global NCI in Spanish-speaking PLWH in the US (39%) using newly created normative corrections is consistent with prior research in primarily English-speaking Latino PLWH of Mexican origin/descent when English-speaking normative corrections were applied (Marquine et al., 2018b). Our results also found that individuals without a lifetime history of any substance use disorder had a lower risk of neurocognitive impairment as their years of exposure to ART increased, compared to those who did have a lifetime history of any substance use disorder. This may point to differences in health behaviors among those with and without any lifetime substance use disorder that may influence delivery of initial treatment and/or adherence to medication over time. However, these analyses were conducted only on a subset of participants who had substance use disorder data available. Furthermore, we excluded individuals with current substance use disorder from our sample, which might further impact these findings. While this exclusion was done in an effort to avoid confounding the potential impact of HIV with the presence of comorbidities, future studies with individuals who have current substance use disorder may help improve the generalizability of our results to this population.

Contrary to our hypothesis, nadir CD4 did not predict NCI in this population. This may be due to mean nadir CD4 counts in our sample being low, with limited range, perhaps indicative of Spanish-speaking PLWH delayed treatment engagement. Also, two-thirds of our sample provided their nadir CD4 count via self-report rather than objective lab measurements. While this type of ascertainment of nadir CD4 is common and has been predictive of NCI in past studies (Ellis et al., 2011), it might be more accurate to obtain objective evidence of nadir CD4 via access to medical records or direct laboratory assessment in samples at risk for lower health literacy.

Making proper comparisons across different populations with appropriately validated instruments and norms for each group of interest (Casaletto & Heaton, 2017) is a vital component of health disparity research and should be a priority for future disparity work. With this in mind, our study mainly analyzed data from Spanish-speaking Latinos of mostly Mexican origin/descent living near the U.S.-Mexico border. As Latinos living in the US are a highly heterogenous group, caution should be taken when extending reported rates of impairment to other subgroups of Spanish-speaking Latino PLWH within or outside the United States. Furthermore, Marquine et al., (2018b) found that compared to NH Whites living in the same geographic location of the US, rates of NCI for Mexican and Puerto Rican subgroups of Latinos living with HIV were found to be elevated, and Latinos of Puerto Rican origin/descent were reported to have significantly higher rates of NCI compared with those of Mexican origin/descent.

Additionally, not only were our rates comparable to impairment seen in NH White PLWH using NH White based norms, using English and Spanish corrections available for specific available tests demonstrated significant differences in rate of impairment only in WAIS-III Letter Number Sequencing. This may indicate that perhaps the effect of preferred language on detecting cognitive impairment may be salient using only certain tests (for specific details

on the development of adjustments for Digit Symbol and Symbol Search see Rivera Mindt et al., 2019a this issue, and for Letter Number Sequencing, see Gooding et al., 2019 this issue). Ongoing studies by our group are investigating whether rates of HIV-associated NCI differ among predominantly English-speaking and Spanish-speaking Latinos on a battery of tests. Moreover, as differences exist in rates of impairment and related health outcomes across subgroups of Latinos (Marquine et al., 2018a; Sheehan et al., 2015; Chen et al., 2012), future studies should analyze the application of these developed normative data to various groups of Spanish-speakers, healthy and clinical populations, across the United States.

The application of neuropsychological normative corrections for Spanish-speakers in this population who may be seen at a variety of clinical settings will result in more accurate diagnostic conclusions. Practically, clinicians must choose which normative data to apply to their clients on a regular basis when providing a diagnosis. Understanding the normative sample, factors considered when creating the norms, and if their individual patients' information fits with what adjustments are available is crucial. For this purpose, clinicians can refer to the methodology of the normative data development (Cherner, Marquine et al, this issue) for detailed educational, social, and language characteristics of the normative sample. Applying these norms to other illness populations of Spanish-speaking Latinos living near the U.S.-Mexico border would provide further details on their applicability and potentially expand their reach. Improved diagnostic accuracy for this population may have additional downstream implications such as treatment planning and decision-making, engagement with relevant services, and other far-reaching health outcomes (Cherner et al., 2007). Further discussion on the future directions of these norms can be found in Rivera Mindt et al., 2019a, this issue.

While our study is a meaningful beginning to the usage of these population-specific norms for Spanish-speakers residing in the U.S., future directions might focus on validating these norms in individuals with other neurological conditions, such as early Alzheimer's disease and traumatic brain injury, among others. Data from native Spanish-speaking Latinos might also be compared with data from primarily English-speaking Latinos, NH Whites, and NH Blacks to identify any true disparities in rates of HIV-associated NCI, to then begin answering questions about the mechanisms and pathways of any reported differences. Further additional analyses of functional outcomes and performance-based measures may bring specific insight as to how HIV-associated NCI in Spanish-speakers may be impacting their daily functioning and quality of life.

There are several limitations to our study. While we investigated the associations of demographic characteristics on the current Spanish-speaking normative data, we lacked data on several measures of cultural factors, such as socioeconomic status and income, as well as measures of acculturation such as language use history, level of bilingualism, and time living in and being educated in the United States. These factors, as well as health literacy and access to healthcare, are important to include in future studies investigating cognition within Spanish-speaking individuals, as they may partially account for any reported differences in NCI across groups (Marquine et al., 2018b; Sheehan et al., 2015). Finally, our study was cross-sectional in design, and causal predictions of impairment from sample characteristics cannot be inferred. Previous longitudinal data have indicated that Latino ethnicity is an

independent predictor of HIV-associated neurocognitive decline (Heaton et al., 2015) and investigations using valid normative corrections on longitudinal cognitive data for Spanish-speakers would further clarify this significant association.

In summary, the present study lends support to the validity of newly developed normative neuropsychological data for Spanish-speaking Latinos living near the U.S.-Mexico border. It also shows the impact that applying different sets of norms might have on rates of HIV-associated NCI, and underscores the need for population-specific norms. Applying the new normative standards in clinical settings serving Spanish-speakers of similar characteristics to the participants in our study will enhance clinicians' ability to characterize neurocognitive performance more accurately in this population, and facilitate diagnosis and decision-making regarding care. Present findings highlight the importance of proper methodologies in the effort to understand and reduce neurocognitive and health disparities in the United States.

Acknowledgements

This work was supported by grants from the National Institutes of Health (The HIV Neurobehavioral Research Center (HNRC): P30MH62512, R01MH57266, K23MH105297, P30AG059299, T32MH019934, P01DA012065) and the UCSD Hispanic Center of Excellence.

The HIV Neurobehavioral Research Center (HNRC) is supported by Center award P30MH062512 from NIMH. The San Diego HIV Neurobehavioral Research Center [HNRC] group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the Veterans Affairs San Diego Healthcare System, and includes: Director: Robert K. Heaton, Ph.D., Co-Director: Igor Grant, M.D.; Associate Directors: J. Hampton Atkinson, M.D., Ronald J. Ellis, M.D., Ph.D., and Scott Letendre, M.D.; Center Manager: Jennifer Iudicello, Ph.D.; Donald Franklin, Jr.; Melanie Sherman; NeuroAssessment Core: Ronald J. Ellis, M.D., Ph.D. (P.I.), Scott Letendre, M.D., Thomas D. Marcotte, Ph.D, Christine Fennema-Notestine, Ph.D., Debra Rosario, M.P.H., Matthew Dawson; NeuroBiology Core: Cristian Achim, M.D., Ph.D. (P.I.), Ana Sanchez, Ph.D., Adam Fields, Ph.D.; NeuroGerm Core: Sara Gianella Weibel, M.D. (P.I.), David M. Smith, M.D., Rob Knight, Ph.D., Scott Peterson, Ph.D.; Developmental Core: Scott Letendre, M.D. (P.I.), J. Allen McCutchan; Participant Accrual and Retention Unit: J. Hampton Atkinson, M.D. (P.I.) Susan Little, M.D., Jennifer Marquie-Beck, M.P.H.; Data Management and Information Systems Unit: Lucila Ohno-Machado, Ph.D. (P.I.), Clint Cushman; Statistics Unit: Ian Abramson, Ph.D. (P.I.), Florin Vaida, Ph.D. (Co-PI),, Anya Umlauf, M.S., Bin Tang, M.S.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

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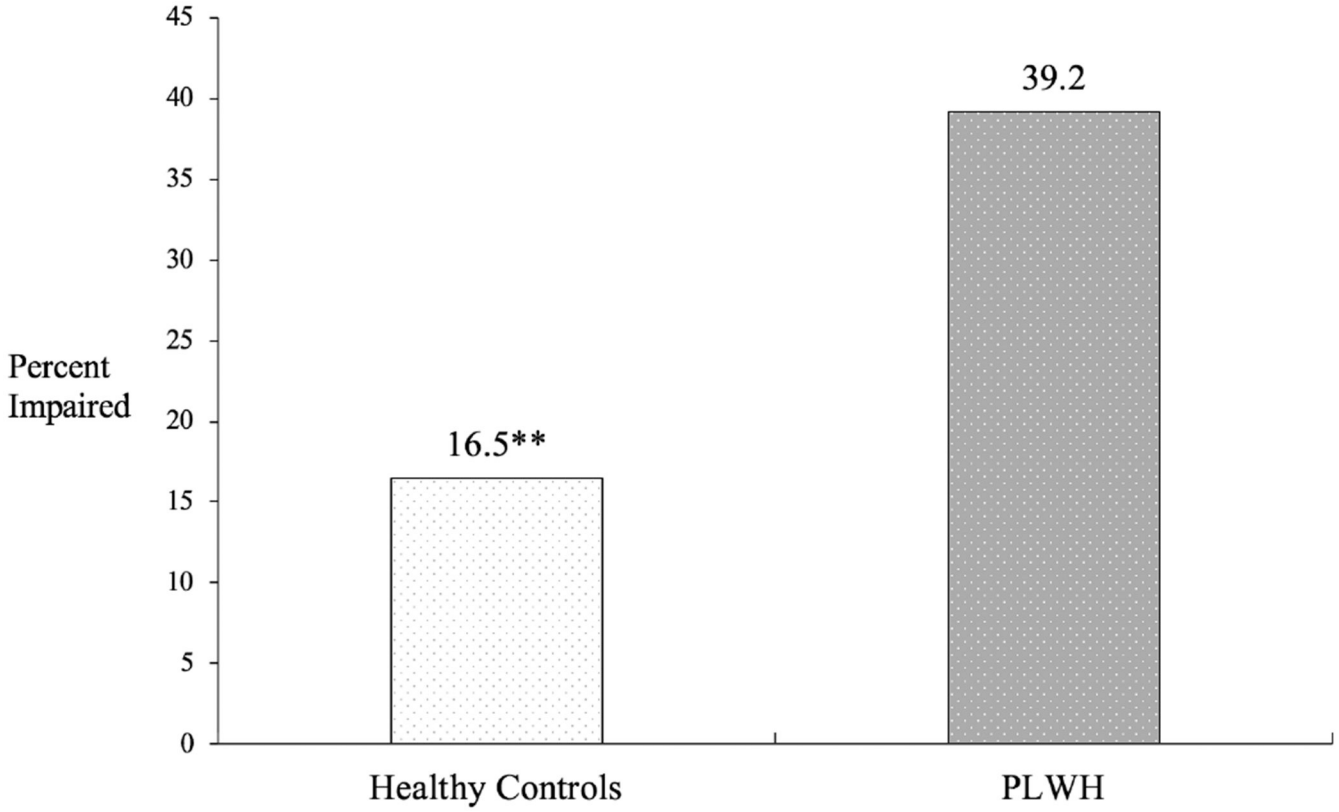

Figure 1.

Rates of global neurocognitive impairment (NCI) in healthy controls and PLWH.

** Significantly different at $p < .0001$ based on Chi^2 test

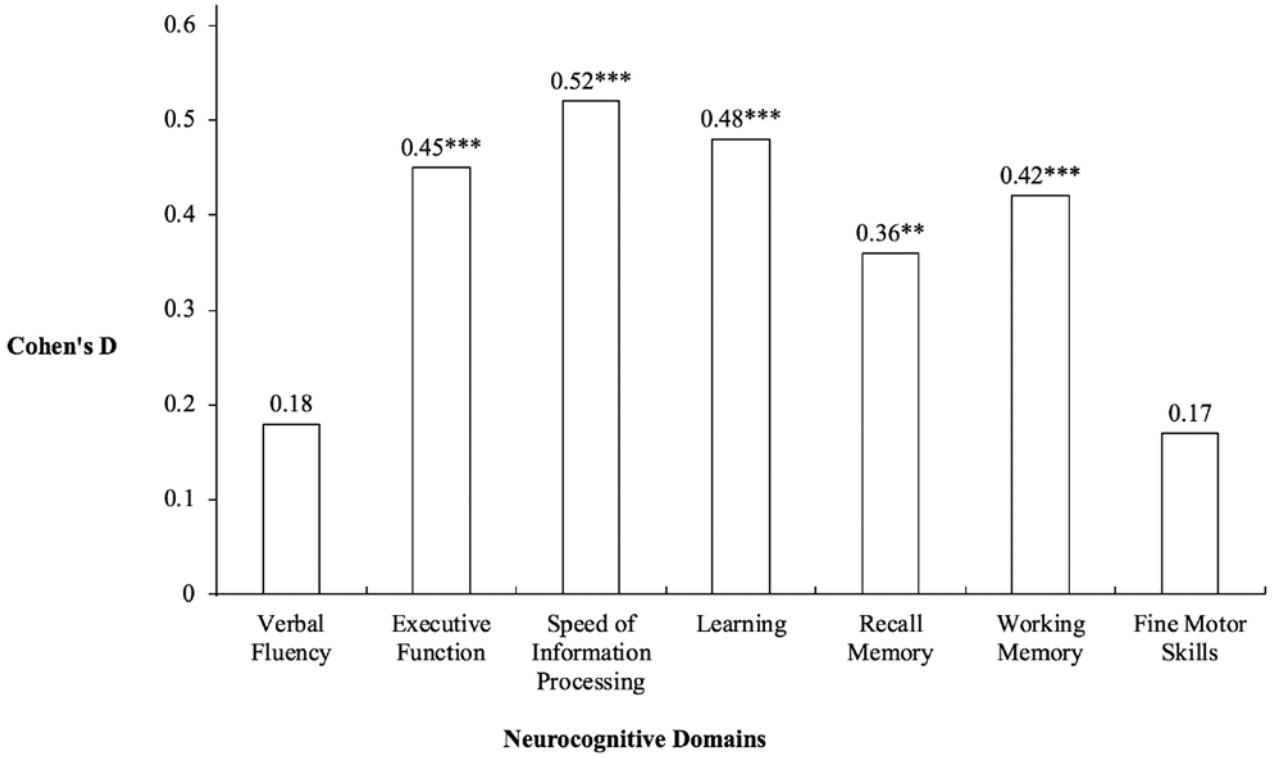

Figure 2.

Effect sizes on domain neurocognitive function (T-scores) between PLWH and healthy controls. Asterisks denote significant differences between PLWH and healthy controls based on independent sample t-tests, ** p <.001; *** p < .0001. Positive effect sizes indicate worse performance among PLWH. Effect sizes: .20 = small; .50 = medium; .80 = large (Cohen, 1988).

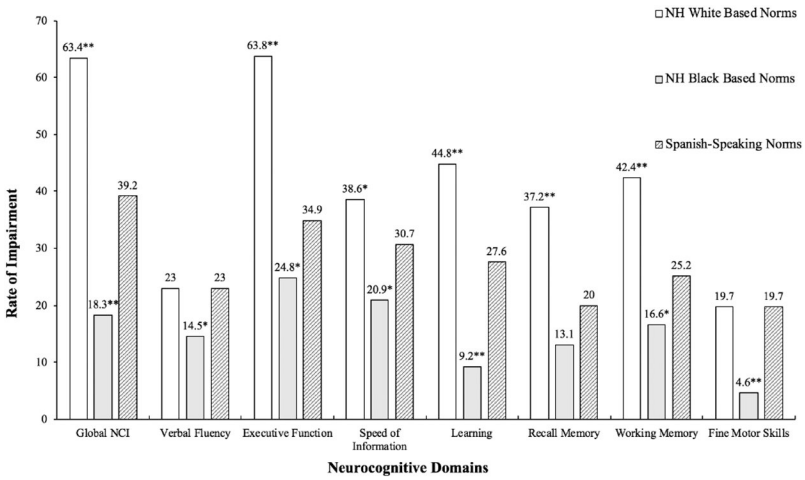

Figure 3.

HIV-associated neurocognitive impairment (NCI) across available normative data. Asterisks denote significant difference based on McNemar's tests compared to rate of NCI based on Spanish-speaking norms *p <.01; **p < .0001

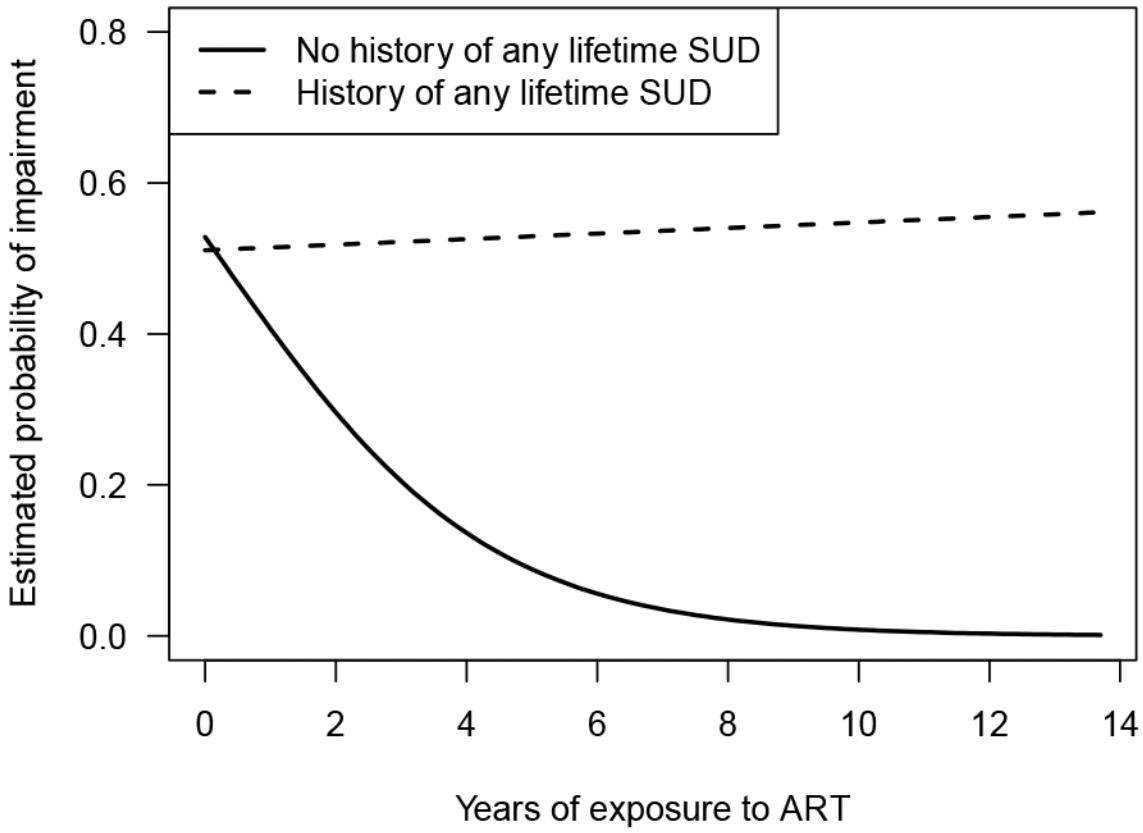

Figure 4.
Interaction of years of exposure to ART and any lifetime Substance Use Disorder on estimated probability of global neurocognitive impairment (NCI) in PLWH (n = 61)

Table 1.

Comprehensive Neuropsychological Test Battery with References to Normative Adjustments

Domain	NH White Norms	NH Black Norms	NP-NUMBRS
Fine Motor Skills (*n* = 152) Grooved Pegboard: Dominant & non-dominant hand (Klove, 1963)	Heaton et al., 2004b	Heaton et al., 2004b	Heaton et al., 2019, this issue
Working Memory (*n* = 151) PASAT-50 (Gronwall, 1977) WAIS-III L-N Sequencing (Weschler, 1997)	Diehr, Heaton & Miller, 1998 Heaton, Taylor & Manly, 2003	Diehr, Heaton & Miller, 1998 Heaton, Taylor & Manly, 2003	Gooding et al., 2019, this issue
Speed of Information Processing (*n* = 153) Trail Making Test A (Army Individual Test Battery, 1944) WAIS-III Digit Symbol (Weschler, 1997) WAIS-III Symbol Search (Weschler, 1997)	Heaton et al., 2004b Heaton, Taylor & Manly, 2003	Heaton et al., 2004b Heaton, Taylor & Manly, 2003	Suarez et al., 2019, this issue Rivera Mindt et al., 2019a, this issue
Verbal Fluency (*n* = 152) Animal Fluency (Benton, Hamsher & Sivan, 1994) Letter Fluency (Benton, Hamsher & Sivan, 1994)	Heaton et al., 2004b Gladsjo et al., 1999	Heaton et al., 2004b Gladsjo et al., 1999	Marquine et al., 2019a, this issue
Executive Functioning (*n* = 152) WCST-64 Perseverative Responses (Kongs, Thompson, Iverson, & Heaton, 2000) Trail Making Test B (Army Individual Test Battery, 1944)	Norman et al., 2011 Heaton et al., 2004b	Norman et al., 2011 Heaton et al., 2004b	Marquine et al., 2019b, this issue Suarez et al., 2019, this issue
learning (*n* = 153, 145 for NH Black norms only) Hopkins Verbal Learning Test-Revised: Total Learning (Brandt & Benedict, 2001) Brief Visuospatial Memory Test – Revised: Total Learning (Benedict, 1997)	Norman et al., 2011	Norman et al., 2011	Cherner et al., 2019, this issue
Delayed Recall (*n* = 153, 145 for NH Black norms only) Hopkins Verbal Learning Test-Revised: Delayed Recall (Brandt & Benedict, 2001) Brief Visuospatial Memory Test-Revised: Delayed Recall (Benedict, 1997)	Norman et al., 2011	Norman et al., 2011	Cherner et al., 2019, this issue

Table 2.

Participant demographics (N = 407)

	Mean (SD), Median (IQR), or Count (%)		Group Comparisons	
Demographics	**PLWH (*n* = 153)**	**Healthy Controls (*n* = 254)**	**p-value**	**Pairwise**
Age	38.2 (9.66)	37.3 (10.2)	0.36	--
Education	10.89 (3.74)	10.67 (4.34)	0.61	--
Male	112 (73.2%)	105 (41.3%)	< 0.0001	PLWH > HC
Mexican[a]	80 (93%)	71 (98.6%)	0.40	--
Foreign-Born[b]	124 (94.6%)	59 (82%)	0.07	--

Note: Group comparisons based on Fisher's exact test or Chi^2 test.

a: Only available for a subsample of participants (*n*=158).

b: Only available for a subsample of participants (*n* = 203).

Table 3.

HIV-disease and psychiatric variables for PLWH (n = 153)

	Mean (SD), Median [IQR], or Count (%)	p*	Directionality*
HIV-disease characteristics			
AIDS Status	86 (56.2%)	0.06	non-AIDS > AIDS
Estimated years of infection	6.00 (5.08)		--
Current CD4 count	357.5 [193.5, 533.8]		--
Nadir CD4 count	190.0 [73.0, 290.0]		--
Antiretroviral Therapy (ART)	92 (62.6%)		--
Plasma viral load detectable [a]	28 (30.8%)		--
CSF viral load detectable [a]	4 (8.0%)		--
Years exposure to ART	1.7 [0.3, 4.2]	0.08	(−)
Years not on ART while infected	1.7 [0.3, 5.1]		--
VACS Index	16.0 (10.0, 28.0)		--
HCV co-infection	11 (7.3%)		--
Psychiatric Conditions			--
Current Major Depressive Disorder [b]	4 (6.3%)		--
Lifetime Major Depressive Disorder [b]	31 (48.4%)		--
Any Lifetime Substance Use Disorder [b]	25 (39.1%)	0.06	Yes (+), No (ns)
Lifetime alcohol Substance Use Disorder [b]	20 (31.3%)		--
Lifetime cannabis Substance Use Disorder [b]	5 (7.8%)		--
Urine Toxicology [c]	2 (1.4%)		--
BDI, n (%) depressed	54 (47%)		--

Note: IQR=interquartile range; HCV=Hepatitis C virus; VACS=Veterans Aging Cohort Study;

*: Significant univariable association with NCI classification, $p < 0.10$.

a: Among those on ART

b: Only available for a subset of sample (n = 64)

c: Positive for any substance