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The Utility of Olfactory Function in Distinguishing Early Stage Alzheimer's Disease from HIV-associated Neurocognitive Disorder

Running head: OLFACTION IN ALZHEIMER'S VERSUS HAND

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ABSTRACT

Objectives: Given the rising number of older people with HIV (PWH) and the overlap in cognitive dysfunction profiles in HIV-associated Neurocognitive Disorders (HAND) and Alzheimer's disease (AD) and its precursor, amnestic mild cognitive impairment (aMCI), methods are needed to distinguish aMCI/AD from HAND. As an early indicator of AD, we examined whether olfactory dysfunction could help to distinguish between aMCI/AD and HAND among PWH.

Design: Observational cohort study

Methods: Eighty-one older (• 50 years) PWH (83% male, 65% Caucasian) from the California NeuroAIDS Tissue Consortium completed the University of Pennsylvania Smell Identification Test (UPSIT; higher scores=better smell identification) and a comprehensive seven-domain neuropsychological test battery and neuromedical evaluation. HAND was classified via Frascati criteria. High aMCI risk was defined as impairment (>1.0 SD below normative mean) on two of four delayed recall or recognition outcomes (at-least one recognition impairment required) from the Hopkins Verbal Learning Test-Revised and the Brief Visuospatial Memory Test-Revised. We examined UPSIT scores in relation to: 1) aMCI risk and HAND status, and 2) continuous memory scores considering adjustments for demographics and relevant clinical or HIV disease characteristics.

Results: Fifty-seven participants were classified with HAND (70%) and 35 participants were classified as high aMCI risk (43%). UPSIT scores were lower (worse) in the high versus low aMCI risk group ($F(1,76)=10.04$, $p=.002$), but did not differ by HAND status ($F(1,76)=0.62$, $p=.43$). UPSIT scores positively correlated with all memory outcomes ($ps<.05$).

Conclusions: Olfactory assessments may help in detecting early aMCI/AD among PWH and allow for appropriate and early disease intervention.

Key words: Olfactory function, smell identification, Alzheimer's disease, HIV, HAND, aMCI

INTRODUCTION

Due to advances in antiretroviral therapies (ART), life expectancy among persons with HIV (PWH) is approaching that of the general population [1]. Presently, one-half of PWH in the U.S. are over age 50 [2]. Even in the post-ART era, 45% of PWH experience mostly mild neurocognitive complications, labeled HIV-associated neurocognitive disorders (HAND) [3], and rates of HAND tend to increase with age [4]. In addition to risk of HAND, older PWH, like members of the general population, are at risk for Alzheimer's disease (AD) and its precursor, amnestic mild cognitive impairment (aMCI). Given that episodic memory deficits define aMCI and are common in HAND, distinguishing between aMCI- versus HAND-related cognitive deficits is a major challenge for clinicians. It is possible that a proportion of older PWH are on the AD trajectory; however, their amnestic deficits are erroneously ascribed solely to HAND given their HIV-seropositive status. Developing strategies to identify aMCI amid a background of HAND has considerable public health impact given that the more progressive profile of aMCI requires early intervention in order to maximize the potential for delaying or altering the course of AD [5].

The overlap in memory impairment that can occur between HAND and aMCI makes it essential to compare and contrast multiple clinical factors to identify differences that can distinguish these two conditions. In a time when measurement of AD-specific pathological markers is limited by high cost, significant time burden and invasiveness (e.g., lumber puncture), the need for clinical diagnostic methods to disentangle aMCI versus HAND is crucial. Olfactory function represents a non-invasive and low-cost clinical measure with potential for identifying PWH at high risk for aMCI. Impairment in olfactory function is one of the earliest observable deficits in AD, likely due to the topography of AD-related pathology [6–9]. Amyloid-• plaques and neurofibrillary tangles occur initially in brain regions responsible for olfactory functioning, such as the entorhinal cortex and the orbital frontal cortex [7,10,11]. Indicative of the utility of olfactory dysfunction as an early marker of AD, olfactory deficits have been reported among individuals with aMCI [12] as well as cognitively normal older adults at-risk for AD by way of family history or the apolipoprotein E4 allele [13–15]. Furthermore, performance on odor identification tests related to AD biomarkers of positron emission tomography (PET) measured amyloid-• [16] and tau [17] pathology and hippocampal volume [18] in cognitively normal and aMCI samples. Also advantageous, is the relative specificity of olfactory deficits to aMCI versus other non-amnestic MCI [12,18].

Among PWH, there is evidence of mild olfactory impairments [19–22] and these impairments have been shown to relate to cognitive deficits including memory deficits [22,23]. It is unclear; however, whether these olfactory deficits are more reflective of aMCI- versus HAND-related cognitive deficits. In the present study, we leveraged previously-identified differences in the profile of memory impairment that typically characterizes aMCI versus HAND (i.e., recognition performance) [24–26] to determine whether olfactory deficits could signal aMCI/AD-specific risk. To do so, we took advantage of the established, neuropsychological Jak/Bondi criteria for MCI [27] that we previously adapted to identify aMCI risk amid a background of HAND among older PWH [28]. The adapted Jak/Bondi

criteria emphasizes recognition impairments that, in addition to recall deficits, are common in aMCI/AD [29], whereas recall, but not recognition, deficits are common in HAND [24–26]. Our earlier work found that high aMCI risk classification, as defined by the adapted criteria (either with or without HAND), was significantly associated with a higher likelihood of amyloid-• plaque pathology in frontal lobe brain tissue of older, HIV-seropositive post-mortem cases (N=74), whereas this relationship was not observed with HAND status [28]. These findings provide support for the ability of the adapted criteria to detect memory deficits related to underlying AD pathology among older PWH. Herein, both HAND and the adapted aMCI risk criteria were applied to a sample of older PWH that had neuropsychological testing in conjunction with the University of Pennsylvania Smell Identification Test (UPSIT). We examined performance on the UPSIT in relation to aMCI risk and HAND status as well as to continuous memory scores. We hypothesized that UPSIT scores would be significantly poorer among PWH classified as high versus low aMCI risk and would positively relate to memory performance. Conversely, UPSIT scores would not differ by HAND status.

METHODS

Participants

This study examined PWH that were enrolled in the California NeuroAIDS Tissue Network (CNTN), a site within the National NeuroAIDS Tissue Consortium (NNTC, www.nntc.org) [30], and participated in a NIH-funded Alzheimer's Disease-related supplemental study. Exclusion criteria for the parent CNTN study are minimal. In the present study, inclusion criteria included age • 50 years and availability of all study variables including aMCI classification and UPSIT scores. UCSD's Human Research Protections Program approved study procedures, and participants provided written informed consent. The final sample consisted of 81 PWH. Participants completed comprehensive neuromedical and neurobehavioral assessments during study visits in 2018-2019.

Neuropsychological Evaluation

Participants completed a standardized neurocognitive test battery of verbal fluency, working memory, processing speed, verbal and visual learning and delayed recall, executive function, and complex motor function. Specific tests are described elsewhere [31]. Raw test scores were transformed into age-, education-, sex-, and race/ethnicity-adjusted z-scores based on normative samples of HIV- participants [32,33].

HAND Classification

HAND classification was based on standard Frascati criteria [34] and required impairment in at-least two cognitive domains, defined by performance of at-least 1.0 standard deviation (SD) below the demographically-adjusted normative mean on neuropsychological tests. HAND status was further categorized as asymptomatic neurocognitive impairment (ANI; no interference in everyday function), mild neurocognitive disorder (MND; at-least mild interference in everyday function), and HIV-associated dementia (HAD; marked interference in everyday function). Due to limited statistical power resulting from small sample sizes within specific HAND diagnoses, our statistical comparisons were by overall HAND status although specific HAND diagnoses are provided for descriptive purposes.

aMCI Classification

aMCI was classified using a previously-adapted version [28] of the Jak/Bondi criteria, an established, neuropsychological method of classifying MCI [27]. The Jak/Bondi criteria for MCI requires two impaired neuropsychological tests (i.e., >1 SD below demographically-corrected mean) within a given domain. In order to capitalize on the retention deficit that is unique to aMCI/AD rather than the retrieval deficit that is common to both aMCI/AD and HAND, the Jak/Bondi MCI criteria was adapted to focus solely on the domain of episodic memory and, thus aMCI, and to require at least one of the two impaired memory tests be a recognition test. The memory outcomes used in these criteria were the demographically-adjusted z-scores of the Hopkins Verbal Learning Test – Revised (HVLT-R) [32] and the Brief Visuospatial Memory Test-Revised (BVMT-R) [33] delayed recall and recognition subtests. Participants were classified as "high aMCI risk" if they showed impaired performance (z-score<-1) on at-least two of the four measures with at-least one of the impaired scores being a recognition measure. Of important note, the HAND classification criteria used in this study and more generally in large scale studies (e.g., HIV Neurobehavioral Research Program, CHARTER) included BVMT-R and HVLT-R learning and delayed recall, but not recognition, scores to assess the memory domain.

Olfactory Test

Olfactory function was measured using the UPSIT [35]. The UPSIT involves scratching and sniffing 40 common odors embedded in microcapsules and then selecting the odor that was smelled among four multiple choice answers. Scores range from 0 (no odors identified) to 40 (all odors identified). The UPSIT is a well-validated test [35] that has shown utility in differentiating normal aging from aMCI and AD dementia [18,36].

Neuromedical Evaluation

Medical comorbidities were determined by self-report or self-reported medication records. The Composite International Diagnostic Interview (CIDI) [37], a computer-based, structured interview was administered to assess DSM-IV lifetime and current psychiatric disorders including Major Depressive Disorder (MDD) and substance use disorders (i.e., alcohol, amphetamine, cocaine, hallucinogen, inhalant, sedative, opioid, and PCP). Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II). HIV disease characteristics were determined via a combination of self-reports (i.e., estimated duration of HIV disease) and laboratory test results (e.g., CD4+ T-cell count). Nadir CD4+ T-cell count was the lowest lifetime value among self-report or study-obtained CD4+ T-cell counts and released medical records. CD4+ T-cell count was measured with flow cytometry. Plasma HIV-1 RNA level was measured by ultra-sensitive PCR (Amplicor, Roche Diagnostic System) in a CLIA-certified clinical laboratory. Concomitant Hepatitis C serostatus was measured via MedMira Multiplo rapid test (MedMira Inc.).

Statistical Analyses

We examined differences in sample characteristics (e.g., demographics, comorbidities, HIV disease variables) by HAND and aMCI risk status using chi-square tests for categorical variables, t-tests for normally-distributed continuous variables, and Kruskal-Wallis H-tests

for non-normally-distributed continuous variables as determined by the Shapiro-Wilk test. To avoid the multicollinearity resulting from the overlap in HAND and aMCI classifications, we used separate models of one-way analyses of covariance (ANCOVA) to examine mean differences in UPSIT scores between aMCI and HAND groups while adjusting for appropriate covariates. We used separate multivariable linear regressions to examine the relationship between continuous UPSIT and memory scores (i.e., HVLT-R and BVMT-R recall and recognition) across the overall sample. In the ANCOVA and regression analyses, considered covariates included demographics (age, education, race/ethnicity, sex), common comorbidities (history of substance abuse/dependence, major depressive disorder, BDI-II scores, Hepatitis C seropositivity) and HIV disease characteristics (nadir and current CD4+ T-cell count, estimated duration of HIV infection, log10 plasma viral load and ART use). Considered covariates that related to UPSIT scores or differed by aMCI or HAND status at p• .10 in univariate analyses were included in initial statistical models and retained in final models if significance level in the multivariable model was p• .15. Because older age is the strongest risk factor for aMCI/AD, analyses were repeated in a subset of participants at-least 60 years of age as a sensitivity analysis.

RESULTS

The sample (N=81) was 83% male, 65% Caucasian with a mean age of 63 years (SD=8.6). Thirty-five participants (43%) were classified as high aMCI risk and 57 participants (70%) as HAND. As expected, there was a higher rate of high aMCI risk classification among those classified as HAND (N=54%) versus non-HAND (N=17%), X^2=9.79, p=.002 (Table 1). Tables 2 and 3 displays sample characteristics by aMCI risk and HAND status, respectively. The HAND group had a significantly higher prevalence of a lifetime MDD diagnosis and higher mean BDI-II score compared to the no HAND group. Hepatitis C seropositivity was significantly more prevalent in the high versus low aMCI risk group. Other demographics, comorbidities and disease variables did not significantly differ by aMCI risk or HAND status although trends were present.

In ANCOVAs examining differences in mean UPSIT score by aMCI risk and HAND status, initial models covaried for age, education, sex, race/ethnicity, estimated duration of HIV infection and Hepatitis C serostatus due to either their difference between aMCI risk or HAND groups and/or their relationship with UPSIT scores at at-least trend level (p• .10). Age, sex and estimated duration of HIV disease were retained as covariates in the final model due to their significance level (p• .15) in the multivariable model. As hypothesized, UPSIT scores were significantly lower in the high aMCI risk versus the low aMCI risk group, F(1,76)=10.04, p=.002, Cohen's d=0.69; however, UPSIT scores did not differ by HAND status, F(1,76)=0.62, p=.43 (Figure 1A). Using published UPSIT demographically-adjusted normative data and performance cut-scores for mild, moderate and severe microsmia, or reduced ability to smell, and anosmia, or loss of smell, we compared performance across aMCI and HAND groups to healthy, normal performance by age and sex. We found that the mean UPSIT score for all aMCI and HAND groups was below the cut-score for mild microsmia (33 in men and 34 in women; 53% of sample fell below mild microsmia cut-score). However only the high aMCI risk group had a UPSIT mean that was below the cut-

score for moderate microsmia (29 in men and 30 in women). The proportion of participants below the moderate microsmia cut-point was 37% in the high aMCI risk group, 24% in the low aMCI risk group, 30% in the HAND group and 29% in the non-HAND group). A positive predictive value of 53% indicates that if the subject showed any evidence of microsmia (mild to severe) on the UPSIT, there is a 53% chance that they were categorized as high aMCI risk. A negative predictive value of 68% indicates that if the subject showed no evidence of microsmia (mild to severe) on the UPSIT, there is a 68% chance that they were categorized as low aMCI risk.

In separate linear regressions examining the relationship between UPSIT scores and individual memory outcomes, initial models included race/ethnicity, BDI-II scores, lifetime MDD diagnosis, and Hepatitis C serostatus as covariates due to their relationship with either UPSIT scores or any memory outcome (p• .10). BDI-II scores were retained in all final models due to its significance level in at-least one of the models (p• .15). Lower UPSIT scores related to lower scores on all memory outcomes (HVLT-R and BVMT-R Delayed Recall and Recognition), with the strongest relationship observed with HVLT-R Recognition scores (Figure 2).

In analyses limited to those aged • 60 years old (N=50, 34% high aMCI risk, 68% HAND), results were similar although the effect size of the lower (worse) UPSIT scores in the high versus low aMCI group was somewhat larger, F(1,45)=5.82, p=.02, Cohen's d=0.77 (Figure 1B). There continued to be no difference in UPSIT scores by HAND status, F(1,45)=0.05, p=.83. Whereas UPSIT scores no longer significantly related to BVMT-R Delay (B=0.07, • =0.25, SE=0.04, p=.08) or BVMT-R Recognition (B=0.03, • =0.09, SE=0.05, p=.55) in this subsample, lower UPSIT scores related more strongly to lower HVLT-R Delay (B=0.13, • =0.36, SE=0.05, p=.009) and HVLT-R Recognition (B=0.20, • =0.44, SE=0.06, p=.001) scores.

DISCUSSION

The present study evaluated whether the assessment of olfactory function may aid in disentangling aMCI from HAND among older PWH. As hypothesized, poorer UPSIT scores significantly related to poorer scores on all memory outcomes and UPSIT scores were significantly lower in the high versus low aMCI risk group. The poorer olfactory function in the high aMCI risk group further supports that these individuals may be on an AD-like trajectory. The difference in UPSIT scores by aMCI risk status was notably large when limiting to an older subsample (60+ years old) suggesting that the discriminative value of olfactory function becomes even more important as age and, in turn, aMCI/AD risk increase. Conversely, UPSIT performance did not discriminate between HAND groups suggesting that olfactory measures may help in disentangling aMCI from HAND among older PWH. High aMCI risk was classified based on demonstration of a memory impairment profile that was more characteristic of AD than HAND, i.e., presence of recognition impairment. In support of the utility of recognition scores in detecting a more AD-like memory deficit among PWH, UPSIT scores related most strongly to HVLT-R Recognition scores among the memory outcomes. The relationship between UPSIT scores and BVMT-R Recognition scores was weaker than that with HVLT-R Recognition and was no longer significant in the age 60+

subsample. This is likely due to the lower variability in BVMT-R, versus HVLT-R, Recognition scores (SD=15.3 versus 25.7) and a moderate ceiling effect with 66% of the sample reaching the maximum BVMT-R score.

Prior studies reported olfactory deficits in PWH compared to the general population [19–22] and showed that these deficits related to memory deficits [23]. Our results support these prior findings in that, across all aMCI and HAND groups, UPSIT means fell below the demographically-adjusted, normative cut-score for mild microsmia and significantly and positively correlated with our memory outcomes. However, only the high aMCI risk group had an UPSIT mean that fell below the cut-score for moderate microsmia. Our results suggest that, although mild olfactory deficits are prevalent among PWH, olfactory deficits associated with cognitive indicators of early-stage AD are more severe and, thus, can be detected amid a background of mild deficits among PWH.

In the post-ART era, HIV clinicians are faced with a new challenge of identifying older PWH who are most at-risk for or are on an AD trajectory. Olfactory assessment may represent a low-cost and non-invasive tool that can be utilized in-clinic as a screen for PWH most at-risk for aMCI/AD. The identification of aMCI among PWH is important for both experimental and clinical reasons. Experimentally, the identification of aMCI/AD among PWH will lead to more accurate assessments of prevalence rates, risk/protective factors and biomarker and genetic correlates of HAND and aMCI among PWH. Clinically, the more progressive profile of aMCI/AD requires different life planning and treatment options compared to HAND, which tends to be a more stable profile [5]. A delayed aMCI/AD diagnosis in PWH limits the opportunity to intervene early in the course of AD when interventions are most effective and life planning is better implemented. In parallel, the ability to identify aMCI/AD risk could also help allay fears of pending AD in PWH who have memory complaints but are not classified as high aMCI risk. In fact, when comparing positive and negative predictive values of the ability of UPSIT performance to predict aMCI risk status, the higher negative (68%) versus positive (53%) predictive value suggests that the absence of olfactory deficits may be even more informative in predicting a low likelihood that a PWH is on an AD trajectory compared to the presence of an olfactory deficit predicting high aMCI risk.

Our study has limitations and implications for future directions. The cross-sectional nature of analysis precludes us from examining the temporal pattern of results. A more definitive test of our hypothesis would be the examination of olfactory function in relation to cognitive decline or incident dementia over time. Ideally, we would have accounted for the frequency of nasal sinus disease in our sample since it is prevalent in HIV [38] and might predispose one to olfactory dysfunction and neurodegeneration in olfactory and memory processing areas; however, this data was unavailable. There is a cognitive component to the UPSIT that may influence the association between UPSIT performance and aMCI or HAND diagnoses; however, this component is minimized in that participants only need to recognize the correct odor among a list of options and not freely recall the odor. The current results suggest that further exploration with additional olfactory tasks that challenge different brain areas and networks that process olfactory information is warranted. The absence of data on AD-related biomarkers in study participants limits our ability to associate the observed olfactory and

memory deficits specifically with AD-related mechanisms. However, these findings suggest a common mechanism may underlie neurological dysfunction in AD and PWH with aMCI, which may provide therapeutic targets for both diseases. The generalizability of our results is limited by our sample being predominantly male and White. Lastly, our adapted aMCI criteria for PWH was specific to the amnestic subtype and, thus, we were unable to examine specificity of our results to this MCI subtype. Research is needed to identify differences in the cognitive profiles of HAND versus other MCI subtypes that we can leverage to expand analyses to comparisons with other MCI subtypes. However, research in the general population suggests that olfactory dysfunction is specific to aMCI versus non-amnestic MCI [12,18].

In summary, our results provide promise to the usefulness of olfactory assessment as an aid in disentangling aMCI from HAND in older PWH. Further research is needed to replicate these results in larger samples with longitudinal follow-up and to combine olfactory data with other AD-related biomarkers to further increase the ability to best identify aMCI in PWH.

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FIGURE LEGENDS

Figure 1. Differences in mean UPSIT scores when participants are classified by aMCI risk versus HAND status in the (A) total sample and (B) in a subsample of those aged at-least 60 years. Note. The left and right side of figures (dark and light bars) represent the same study sample except classified in two different ways (aMCI risk vs. HAND). Means and p-values adjusted for age, sex and duration of HIV infection in analysis of covariance. Higher UPSIT score indicate better smell identification. Because established UPSIT cut-scores for microsmia (reduced sense of smell) are age- and sex-specific, those indicated in Figure 1 are for men aged 50+ as this demographic group represents the majority of our sample. UPSIT cut-scores for women aged 50+ are one point higher than those represented in the Figure. aMCI = amnestic mild cognitive impairment. HAND = HIV-associated neurocognitive disorder. UPSIT = University of Pennsylvania Smell Identification Test.

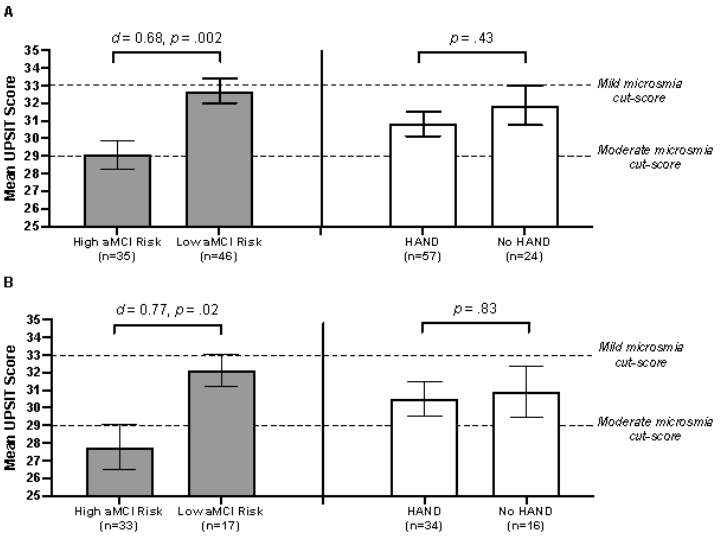

Figure 2. Lower UPSIT scores relate to poorer HVLT-R (panels A and C) and BVMT-R (panels B and D) z-scores. HVLT-R and BVMT-R z-scores are adjusted for age, sex, race and years of education based on a HIV-seronegative normative sample. Higher UPSIT score indicate better smell identification. Statistical results were derived from linear, multivariable regressions examining relationship between UPSIT scores and memory outcomes adjusting for BDI-II scores. UPSIT = University of Pennsylvania Smell Identification Test. HVLT = Hopkins Verbal Learning Test. BVMT = Brief Visuospatial Memory Test-Revised. B = unstandardized regression coefficient; • = standardized regression coefficient; SE = standard error.

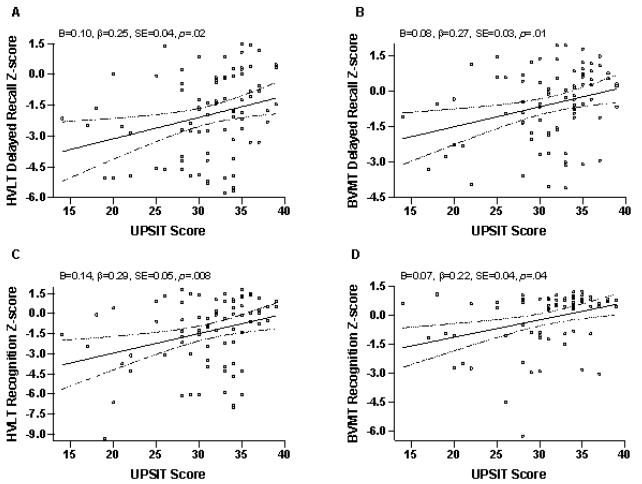

Table 1. Proportion of aMCI risk groups as a function of HAND status.

	High aMCI Risk	Low aMCI Risk
HAND	31 (38%)	26 (32%)
No HAND	4 (5%)	20 (25%)

Note. aMCI = amnestic mild cognitive impairment. HAND = HIV-associated neurocognitive disorders.

Table 2. Sample characteristics by aMCI risk classification.

	High aMCI Risk (N=35)	Low aMCI Risk (N=46)	p-value
Demographic/Clinical Factors			
Age, *mean (SD)*	61.0 (9.2)	64.6 (7.9)	.06
Education yrs, *mean (SD)*	14.8 (2.6)	14.5 (2.7)	.65
Sex, N (% male)	29 (83.8%)	38 (82.6%)	.98
Race/Ethnicity			.07
White, N (%)	19 (54.3%)	34 (73.9%)	
Black, N (%)	11 (31.4%)	5 (10.9%)	
Hispanic, N (%)	5 (14.3%)	7 (15.2%)	
HAND Diagnosis, N (%)			<.001
Normal	4 (11.4%)	20 (43.5%)	
ANI	21 (60.0%)	19 (41.3%)	
MND	3 (8.6%)	7 (15.2%)	
HAD	7 (20.0%)	0 (0%)	
Common Comorbidities			
History of Substance Disorder Diagnosis, N (%)	24 (68.6%)	33 (71.7%)	.76
History of Major Depressive Disorder, N (%)	23 (65.7%)	23 (50.0%)	.16
BDI-II score, *mean* (SD)	12.5 (11.4)	8.7 (8.0)	.08
Hepatitis C seropositivity, N (%)	15 (42.8%)	10 (21.7%)	.04
Disease Characteristics			
Nadir CD4+ T-cell Count (cells/µl), *mean (SD)*	123.5 (169.8)	100.2 (158.0)	.53
Current CD4+ T-cell Count (cells/µl), *mean (SD)*	478.3 (227.2)	593.0 (307.2)	.09
Detectable Plasma Viral Load (>50 copies/ml), N (%)	3 (9.7%)	6 (15.4%)	.48
Estimated Duration of HIV Disease, yrs, *mean (SD)*	23.5 (7.5)	23.8 (8.0)	.88
On ART regimen, N (%)	32 (91.4%)	42 (91.3%)	.47

Note. Sample characteristics were compared between aMCI risk groups using student t-test for continuous variable and chi-square tests for categorical variables. ART = antiretroviral therapy. aMCI = amnestic mild cognitive impairment. HAND = HIV-associated neurocognitive disorders. BDI-II = Beck Depression Inventory-II. ANI = asymptomatic neurocognitive impairment. MND = mild neurocognitive disorder. HAD = HIV-associated dementia.

Table 3. Sample characteristics by HAND classification.

	HAND (N=57)	No HAND (N=24)	p-value
Demographic/Clinical Factors			
Age, *mean (SD)*	62.6 (8.8)	64.1 (8.3)	.50
Education yrs, *mean (SD)*	15.0 (2.5)	13.7 (2.8)	.06
Sex, N (% male)	50 (87.7%)	17 (70.8%)	.07
Race/Ethnicity			.73
White, N (%)	38 (66.7%)	15 (62.5%)	
Black, N (%)	10 (17.5%)	6 (25.0%)	
Hispanic, N (%)	9 (15.8%)	3 (12.5%)	
HAND Diagnosis, N (%)			na
Normal	0 (0%)	24 (100%)	
ANI	40 (49.4%)	0 (0%)	
MND	10 (12.3%)	0 (0%)	
HAD	7 (8.6%)	0 (0%)	
Common Comorbidities			
History of Substance Disorder Diagnosis, N (%)	43 (75.4%)	14 (58.3%)	.12
History of Major Depressive Disorder, N (%)	37 (64.9%)	9 (37.5%)	.02
BDI-II score, mean (SD)	12.0 (10.9)	6.5 (4.5)	.02
Hepatitis C seropositivity, N (%)	19 (33.3%)	6 (25.0%)	.46
Disease Characteristics			
Nadir CD4+ T-cell Count (cells/µl), *mean (SD)*	121.4 (176.1)	83.0 (122.5)	.34
Current CD4+ T-cell Count (cells/µl), *mean (SD)*	545.3 (287.8)	536.9 (262.9)	.91
Detectable Plasma Viral Load (>50 copies/ml), N (%)	6 (12.2%)	3 (14.3%)	.81
Estimated Duration of HIV Disease, yrs, *mean (SD)*	23.0 (7.6)	25.2 (8.1)	.24
On ART regimen, N (%)	52 (91.2%)	22 (91.7%)	.22

Note. Sample characteristics were compared between HAND groups using student t-test for continuous variable and chi-square tests for categorical variables. ART = antiretroviral therapy. HAND = HIV-associated neurocognitive disorders. BDI-II = Beck Depression Inventory-II. ANI = asymptomatic neurocognitive impairment. MND = mild neurocognitive disorder. HAD = HIV-associated dementia.