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Neurocognitive Impairment is Associated with Lower Health Literacy Among Persons Living with HIV Infection

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Abstract

This study sought to determine the effects of HIV-associated neurocognitive disorders (HAND) on health literacy, which encompasses the ability to access, understand, appraise, and apply health-related information. Participants included 56 HIV seropositive individuals, 24 of whom met Frascati criteria for HAND, and 24 seronegative subjects who were comparable on age, education, ethnicity, and oral word reading. Each participant was administered a brief battery of well-validated measures of health literacy, including the Expanded Numeracy Scale (ENS), Newest Vital Sign (NVS), Rapid Estimate of Adult Literacy in Medicine (REALM), and Brief Health Literacy Screen (BHLS). Results revealed significant omnibus differences on the ENS and NVS, which were driven by poorer performance in the HAND group. There were no significant differences on the REALM or the BHLS by HAND status. Among individuals with HAND, lower scores on the NVS were associated with greater severity of neurocognitive dysfunction (e.g.,

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working memory and verbal fluency) and self-reported dependence in activities of daily living. These preliminary findings suggest that HAND hinders both fundamental (i.e., basic knowledge, such as numeracy) and critical (i.e., comprehension and application of healthcare information) health literacy capacities, and therefore may be an important factor in the prevalence of health illiteracy. Health literacy-focused intervention may play an important role in the treatment and health trajectories among persons living with HIV infection.

Keywords

HIV-associated neurocognitive disorders; Neuropsychology; Disability; Health literacy

Health literacy has been broadly defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions [1].” A recent systematic review by Berkman et al. [2] found considerable evidence that lower health literacy increases risk of suboptimal health outcomes, including more hospitalizations, reduced utilization of preventative medicine, and non-adherence to prescribed medications. Health literacy may play a particularly important role in health outcomes for underserved populations with chronic medical conditions, such as HIV disease [3]. It is estimated that between 20 and 40 % of persons infected with HIV have low health literacy [4], usually defined as self-reported difficulties with understanding healthcare materials or poor performance on validated measures of medical word knowledge or comprehension (e.g., Rapid Estimates of Adult Literacy in Medicine (REALM)). Specifically, HIV-related low health literacy is associated with limited knowledge of HIV disease [5] and refusal of HIV testing [6]. In the setting of HIV disease, low health literacy is particularly prevalent among ethnic and racial minorities and persons with lower levels of educational attainment [7]. HIV-infected persons with lower health literacy are at greater risk for psychosocial difficulties, such as stigma and depression [7], as well as non-adherence to antiretroviral therapies [ART; 8, cf. 9].

There are both practical and theoretical reasons to believe that neurocognitive functions might contribute to many dimensions of health literacy in HIV. At the level of theory, Sorensen’s [10] integrative model provides a suitable framework within which to investigate the contribution of neurocognitive functions to health literacy [11]. Sorensen and colleagues posited the existence of two competencies central to health literacy: (1) fundamental competencies, including knowledge, competence, and motivation; and (2) critical competencies, which utilize the core fundamental competencies to access, understand, appraise, and apply health information. The model suggests that both fundamental and critical health literacy competencies are supported by specific neurocognitive abilities, like memory (e.g., the ability to acquire, retain, and retrieve information and events), information processing speed, attention and working memory (e.g., the ability to hold and manipulate information), verbal fluency and the various executive functions, including initiation, persistence, cognitive flexibility, problem-solving, planning, and decision-making. At the practical level, an individual’s ability to obtain, understand, and use complex health-related information would affect their health outcomes; for example, an individual with deficits in memory may miss healthcare appointments, readily forget or misremember the details of a conversation with their provider, and fail to properly adhere to prescribed medication regimens [12]. To date, a handful of prior studies in older adults support the notion that health literacy is indeed dependent upon the integrity of these types of higher-order neurocognitive functions [13].

Yet we know very little about the influence of HIV-associated neurocognitive disorders (HAND) on health literacy. HIV is neurovirulent, crossing the blood brain barrier early in the course of infection and adversely impacting the structure and function of the prefrontal and temporolimbic neural systems [14]. Approximately half of persons living with HIV infection meet criteria for HAND [15], the prevalence of which has grown among persons with less advanced HIV disease in the era of effective antiretroviral therapies [16]. The profile of HAND includes deficits in neurocognitive domains that may support health literacy, including memory, attention/working memory, verbal fluency, executive functions, and information processing speed [17]. Although such neurocognitive deficits tend to be mild-to-moderate in severity [18], they nevertheless increase risk of suboptimal real-world outcomes, including declines in instrumental activities of daily living (e.g., financial management; [19]), unemployment [20], and lower health-related quality of life [21]. HAND also exerts a negative impact on HIV-related health behaviors, including medication management capacity [22] and combined antiretroviral therapy (cART) adherence [23]. There is also emerging evidence suggesting that HAND may relate to non-traditional measures of other real-world abilities, including social-emotional skills known as social cognition [24]. Given that health care decisions are often made in social contexts involving interactions between the patient and family, friends, and a variety of health care providers, it is possible that HAND-related social cognition deficits may also negatively impact health literacy [3].

As such, it is plausible that HIV-associated neurocognitive impairments may adversely impact health literacy among persons living with HIV disease. The literature provides a few additional hints that neurocognitive functions may be critical to optimal health literacy in HIV. Kalichman and colleagues [7] found that HIV-infected persons with low health literacy were moderately inaccurate in recalling their recent viral loads (but not their CD4 cell counts), suggesting the possible influence of HIV-associated memory impairment on personal healthcare knowledge. More recently, Waldrop-Valverde et al. [25] reported that measures of health literacy comprehension and numeracy were uniquely associated with performance on standardized clinical measures of visual memory, attention, and complex visuomotor sequencing in 191 HIV-infected persons prescribed ART. With this background in mind, the present study aimed to test the hypothesis that individuals with HAND are at higher risk for low health literacy than both neurocognitively normal persons living with HIV infection and HIV-seronegative individuals.

Methods

Participants

This pilot study assessed 80 subjects consecutively enrolled in various NIH-funded projects at the University of California, San Diego HIV Neurobehavioral Research Program (HNRP), who had been recruited from the San Diego community and local HIV clinics. The sample included 56 subjects with HIV infection and 24 seronegative comparisons as determined by a point-of-care test (MedMira Inc., Nova Scotia, Canada). Twenty-four participants in the HIV+ group met criteria for HIV-associated Neurocognitive Disorder (HAND) according to Frascati guidelines [26] on the basis of a comprehensive neuropsychological and neuromedical research evaluation (see below). This resulted in a three-group design that included 24 HIV+ participants with HAND ("HAND+"), 32 HIV+ participants without HAND ("HAND-") and 24 HIV seronegative ("HIV-") participants. Participants were excluded if they had any major neurological (e.g., seizure, stroke) or psychiatric (e.g., psychosis) conditions, or a positive urine toxicology screen for illicit drugs or Breathalyzer test for alcohol on the day of evaluation.

Demographic, medical, psychiatric, and HIV disease and treatment characteristics for the three study groups (HIV−, HAND−, and HAND+) are presented in Table 1. The groups were comparable (i.e., p values for group differences [0.10) across many of these characteristics, including education level and oral word reading as indexed by the Wide Range Achievement Test—3rd edition (WRAT-3; [27]), as well as age, ethnicity, and proportions of current diagnoses of Major Depressive disorder and history of substance use disorders (all $p > 0.10$). The HAND+ group had significantly fewer females and a greater proportion of individuals who met criteria for lifetime major depressive disorder ($p < 0.05$). The two HIV+ groups were comparable for proportion with hepatitis C infection and most HIV disease and treatment characteristics ($p > 0.10$), though the HAND+ group had lower nadir and current CD4 counts relative to the HAND− group ($p < 0.05$).

Materials and Procedures

The parent studies were approved by UCSD's human research protections program. Each participant provided written, informed consent and was administered a brief battery of health literacy measures alongside a comprehensive medical, psychiatric, neurocognitive, and functional assessment.

Health Literacy Assessment

Rapid Estimate of Adult Literacy in Medicine (REALM; [28])—The REALM is a 66-item word recognition screening tool designed to measure an individual's fundamental competency to recognize and read common medical terminology related to anatomy or illnesses (e.g., anemia, antibiotics). It is scored on a scale ranging from 0 (no words pronounced correctly) to 66 (all words pronounced correctly), with higher scores indicating better literacy.

The Brief Health Literacy Screen (BHLS; [29])—The BHLS is a screening tool designed to assess an individual's perceived fundamental competency to perform health literacy related tasks such as reading hospital materials, learning about his/her medical condition, and filling out forms. Specifically, the BHLS consists of three questions: [1] "How often do you have someone [like a family member, friend, hospital/clinic worker or caregiver] help you read hospital materials?"; [2] "How often do you have problems learning about your medical condition because you have difficulty understanding written information?"; and [3] "How confident are you filling out forms by yourself?". For each question, individuals rate themselves on a scale of 0–4, and their scores are summed (range 0–12), with higher scores indicating a need for more assistance with their health information.

The Expanded Numeracy Scale (ENS; [30])—The ENS is a 7-item task assessing the fundamental competency with mathematical concepts (e.g., basic probability) in the context of perceived health risks health (e.g., "Which of the following numbers represents the biggest risk of getting a disease: 1 in 10, 1 in 100, or 1 in 1,000?"). The total items correct served as the outcome variable (range 0–7).

The Newest Vital Sign (NVS; [31])—The NVS consists of six questions designed to assess an individual's critical competency to read, interpret, and act on information contained on a nutrition label for ice cream. It assesses both literacy (e.g., "Pretend that you are allergic to the following substances: Penicillin, peanuts, latex gloves, and bee stings. Is it safe for you to eat this ice cream?") and numeracy (e.g., "If you eat 2,500 calories in a day, what percentage of your daily value of calories will you be eating if you eat one serving?"). The total number of correct responses was used as the outcome variable for analyses (range = 0–7).

Medical and Psychiatric Evaluation

The neuromedical evaluation consisted of a blood draw and detailed assessment of comorbid medical conditions and current medications. Current and lifetime depression and substance use disorder diagnoses were determined using the Composite International Diagnostic Interview version 2.1 (CIDI version 2.1; [32]).

Neuropsychological (NP) Assessment

Battery Composition—Each participant was administered a comprehensive NP evaluation which included an estimate of premorbid intellectual functioning (i.e., WRAT-3) alongside a comprehensive clinical battery that assessed seven cognitive ability domains commonly affected in HAND [15]. The domains and the tests that comprised them were as follows: 1. Verbal Fluency: Controlled Oral Word Association Test (COWAT-FAS; [33, 34]) and semantic verbal fluency (animals; [34]); 2. Speed of Information Processing: Trail Making Test-Part A (TMT-A; [35, 36]), Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Symbol and Symbol Search [37, 38]; Stroop Color-Word Test Color Trial [39]; 3. *Attention/Working Memory*: Paced Auditory Serial Addition Test (PASAT; [40, 41]), Wechsler Adult Intelligence Scale-III (WAIS-III) Letter-Number Sequencing [37, 39]; 4. *Executive Functions*: Halstead Category Test [35, 36]; Wisconsin Card Sorting Test-64 Card Version Perseverative Responses (WCST-64; [42]), Trail Making Test Part B (TMT-B; [35, 36]), Stroop Color-Word Test Interference Ratio [38]; 5. Learning: Hopkins Verbal Learning Test-Revised (HVLT-R; [43, 44]) and Brief Visuospatial Memory Test-Revised (BVMT-R; [44, 45]) Total Trials 1–3 Recall; 6. *Memory*: HVLT-R and BVMT-R [43–45] Delayed Recall Trials; 7. *Motor*: Grooved Pegboard Dominant and Non-dominant hand [35, 46].

HAND Diagnosis—To assign HIV+ participants a HAND status (i.e., HAND+ versus HAND−), an empirically-supported procedure described by Carey et al. [47] was utilized to summarize neurocognitive performance across the comprehensive battery by weighting impaired performance to enhance sensitivity. First, individual raw scores were demographically-adjusted using the best available normative data [35, 44, 48] and the resulting T-scores were converted into deficit scores that range from 0 (T > 40) to 5 (T < 20). Individual test deficit scores were then averaged to create a Global Deficit Score (GDS) that defined the HAND+ group using a well-validated cutpoint of ≥0.5 (higher scores indicate greater impairment).

Correlational Analyses within the HAND+ Group—In contrast to the demographically-adjusted methods use to assign HAND status, unadjusted neurocognitive scores were used in correlational analyses conducted within the HAND+ group. This approach was chosen because the use of scaled scores places all of the measures on the same scale, and it maintains consistency with the health literacy outcome variables, which do not have normative data available and therefore must be analyzed as unadjusted scores. Moreover, it has been argued that unadjusted scores are more appropriate and meaningful when examining relationships with functional outcomes. Specifically, raw scores on the neurocognitive tests were converted to uncorrected, normalized scaled scores from the test manuals (i.e., a scale transformation with a resulting mean of 10 and standard deviation of 3), which were subsequently averaged to derive mean scaled scores for each neurocognitive domain. In addition to the domain summary scores from the traditional battery, participants also completed the Social-Emotional Cognition Test (SECT), which is a subtest of a computerized test package entitled CogState (www.cogstate.com; [49]). The SECT involves a brief practice trial and one 7-min test trial in which participants view an array of pictures on the computer screen, one of which differs from the others on some emotional dimension (e.g., three angry faces and one fearful face). Participants are instructed to identify the “odd one out” as quickly as possible. The primary outcome variable is arcsine proportion correct, which is provided by the scoring program.

Everyday Functioning Assessment

Activities of daily living were assessed using a modified version of the Lawton and Brody Activities of Daily Living (ADL) Scale [50], which asks participants to rate their current and best level of functioning with regard to basic (e.g., laundry) and instrumental ADLs (e.g., medication management). Participants were classified as ADL dependent if they reported decline (i.e., current functioning rated lower than best level) in two or more ADLs [19]. Everyday cognitive symptoms were determined using the Patient’s Assessment of Own Functioning Inventory (PAOFI; [51]), which is a 41-item self-report measure in which the participant is asked to report the frequency of cognitive problems in their daily lives. Items endorsed as a 1. (“Almost Always”), 2. (“Very Often”), or 3. (“Fairly Often”) were counted as a “significant symptoms”; three “significant symptoms” or greater was considered elevated [52].

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Results

Association Between HAND and Health Literacy

Descriptive data for the health literacy measures across the three study groups are displayed in Table 1. A series of separate multivariable regressions were conducted with HAND group status (i.e., HIV−, HAND−, and HAND+) as the primary predictor and the indices of health literacy as the criterion variables. As stated previously, the groups were largely comparable across demographic, psychiatric, and medical characteristics that could influence health literacy performance with the exception of gender and lifetime MDD diagnosis. The broad comparability of the groups allowed us to keep the number of covariates to a minimum as only these latter variables were included in each of the models as covariates, which was beneficial in the context of a relatively small sample size.

The models predicting the REALM and the BHLS were not significant (*ps* > 0.10). However, the models predicting the ENS [*Model:* Adjusted $R^2 = 0.08$, $F(4, 73) = 2.78$, $p = 0.033$] and the NVS [*Model:* Adjusted $R^2 = 0.12$, $F(4, 63) = 3.31$, $p = 0.016$] were significant, as shown in Table 2. In both of these significant models, there was a strong main effect of HAND group status (ENS: $F = 4.30$, $p = 0.017$; NVS: $F = 5.97$, $p = 0.004$). In the model predicting the ENS, the HAND group performed significantly lower than the HIV+ individuals without HAND ($b = 1.18$, $p = 0.016$) and the HIV seronegative group ($b = 1.47$, $p = 0.007$), but the two comparison groups did not differ from each other ($b = -0.04$, $p = 0.886$). Similarly, in the model predicting the NVS the HAND group's performance was significantly worse than that of the HIV+ individuals without HAND ($b = 1.59$, $p = 0.003$) and the HIV seronegative group ($b = 1.63$, $p = 0.003$), while the two latter groups were comparable ($b = -0.13$, $p = 0.660$).

Clinical Correlates of Health Literacy in HAND

Given that significant associations with HAND group status were observed only for the ENS and NVS, examination of the clinical correlates of poor health literacy performance within the HAND group was restricted to these measures using Spearman's *rho* correlations or Wilcoxon ranked-sums tests, as appropriate.

Displayed in Fig. 1, the associations between health literacy measures and domain-specific neurocognitive functions were examined in order to determine whether the relationship between HAND and health literacy was driven by specific ability areas. The ENS was significantly associated with the learning domain ($p = 0.035$), but not any other cognitive functions (ps > 0.05). A post hoc analysis of the measures that comprise the learning domain revealed that this association was driven by visual learning ($\rho = 0.448$, $p = .032$) and not verbal learning ($\rho = 0.280$, $p = .120$). The NVS was moderately to strongly correlated with WRAT-3 and all domain-level scores (*ps* < .05), with the strongest relationships observed on the verbal fluency and working memory domains (based on *rho* effect sizes). SECT accuracy correlated significantly with the NVS ($p = .017$) but not ENS ($p = .403$).

Demographic and clinical correlates of health literacy performance were also explored in the HAND group. Non-Caucasian participants performed worse relative to Caucasians on the ENS ($Z = -2.341$, $p = .018$), but not the NVS ($Z = -1.577$, $p = .107$). Education was not significantly associated with the ENS (ρ = 0.255, $p = .240$) but a significant association was observed for the NVS (ρ = 0.56, $p = .007$). There were no significant associations with age or gender for either measure (*ps* > .10). Regarding the HIV disease characteristics reported in Table 1, no associations with the ENS or NVS were observed (*ps* > .05). Psychiatric factors were not associated with either of the health literacy measures, including lifetime histories of MDD diagnosis and substance use disorders (*ps* > .10).

Finally, we examined the everyday functioning correlates of health literacy performance in the HAND group with logistic regressions controlling for lifetime history of MDD, which is among the strongest predictors of self-reported real-world outcomes in HIV [53]. The ENS was not associated with PAOFI or ADL status (*ps* >.10). The NVS was not associated with PAOFI Total Score ($p > .10$), but it was associated with ADL status [Model:$\chi^2 = 9.75$, $p = .008$; NVS $\chi^2 = 5.58$, $p = .018$). Each one-unit increase in NVS score was associated with 5 times greater likelihood of being ADL independent (95 % CI = 1.29, 36.44).

Discussion

The present study is the first to demonstrate an association between HAND and health literacy, which is an ability that has important implications for many aspects of heath care management among individuals with HIV. This finding suggests that poor health literacy in HIV-infected individuals may be exacerbated among those with HIV-associated neurocognitive impairment. One interpretation of the observed pattern of HAND-associated health literacy deficits suggests that HAND can affect components of both higher-level fundamental and critical health competencies as described by the Sorensen model [10]. Notably, the magnitude of lower health literacy performance among individuals with HAND was medium-to-large, suggesting that this deficit may be of clinical relevance. Furthermore, the association between HAND and health literacy was not better explained by demographic factors, basic literacy, or comorbid conditions such as Major Depressive disorder and Substance Dependence disorder.

As defined by the Sorensen model [10] of health literacy, the fundamental aspects of health literacy include knowledge, motivation, and competence. The present study evaluated the association between HAND status and the knowledge and competence components of fundamental health literacy, which can be conceptualized as healthcare-related skills (e.g., numeracy and language as applied to healthcare topics) and self-perceived ability in use of those skills. In other words, these are the “building blocks” that may facilitate the process of working with health care information. The association with HAND was observed solely for numeracy (i.e., ENS), but neither medical word recognition (i.e., REALM) nor health-related self-efficacy (i.e., BHLS) differed by HAND status. It is possible that both groups of HIV-infected participants have sufficient exposure to medical information (e.g., hospital materials, HIV-specific information, and medical forms) through regular visits with various providers and infectious disease specialists that their recognition of medical terminology and comfort in dealing with health information is bolstered and therefore not vulnerable to HAND. In support of this idea, the HIV groups were comparable in terms of their health care involvement, as indexed by cART status. Moreover, the groups did not differ in terms of educational attainment and non-medical oral word reading, which might partly account for the lack of HAND differences on these measures. In contrast, numeracy, or the ability to relate mathematical concepts to perceived health risks, may not necessarily improve with simple exposure based on its reliance on mathematical ability in combination with the complexity of utilizing that ability to gauge perception of health risk, which is arguably more complex. Of note, basic mathematical ability is not assessed by the ENS, so the relationship between HAND and basic numeracy remains to be determined. A complementary explanation might be that word reading, perhaps regardless of content, is a "crystallized" cognitive ability that is often used to index premorbid verbal intellectual functioning and tends to be resistant to subsequent neurological insult [54], whereas mathematical problem-solving is a more "fluid" domain that may be relatively more vulnerable to the neurological impact of HIV. In either case, the result is an adverse impact of HAND on health numeracy abilities.

The Sorensen model [10] states that critical competences draw on the fundamental competences in the process of working with health information, which involves accessing, understanding, appraising, and applying health information. In the present study, we observed an association between HAND and performance on a measure of critical competency, the NVS, which requires an individual to read an ice cream label, perform calculations related to serving size and calorie count, and make decisions about health risks posed by the ice cream based on a broader health context (e.g., food allergies). The applied nature of the NVS task suggests that HAND interferes with understanding, appraisal, and application of health information. In measuring a critical competency, the task draws upon fundamental competencies (as supported by a modest association with ENS, $\rho = 0.368$) but introduces complexity by requiring them to be applied in the context of a health choice or decision. This deceptively simple task requires that the individual utilize the fundamental competencies of recognizing health-related words (e.g., literacy for words such as "allergic" and "penicillin") and numeracy (e.g., comparing calorie counts per serving to daily calorie intake) to make health-related decisions about how to act based on the information on a nutrition label. In other words, fundamental competencies are necessary, but not sufficient for critical competencies. In the context of HAND, it appears that although some fundamental competencies are intact (i.e., medical word reading), others are not (i.e., advanced numeracy), which may be contributing to critical competency deficits.

It was expected that different aspects of cognitive ability may relate to specific aspects of health literacy performance, as suggested by the Sorensen model [10]. Given that the prototypical cognitive profile of HAND is variable and "spotty," the pattern of cognitive correlates with the health literacy measures provides some insight into the contribution of the cognitive features of HAND to the expression of deficient health literacy. For example, numeracy, a fundamental competency, was exclusively associated with the learning domain summary score. Further analysis of the measures that comprise the learning domain revealed that this association was driven by visual learning and not verbal learning. This finding is consistent with prior work showing that the performance of HIV+ individuals was significantly slower and more error-prone on both visuospatial and number processing tasks (which were positively correlated) relative to that of HIV− individuals, and that the spatial representation of numerical distance, or a "mental number line," was disrupted among individuals with HIV [55]. Interestingly, this finding also dovetails with literature suggesting that one possible mechanism of dyscalculia is difficulty with numeric-spatial representations due to poor spatial working memory, including "mental number line" conceptualization [56], which interfere with the ability to comprehend and apply mathematical concepts, likely including the types of percentages and ratios involved in health-related information. This finding has implications for approaches to compensating for deficient numeracy. On one hand, it may be important for numeric medical information to be presented to patients visually, which may better enable them to relate that information to perceived health risk as part of medical decision-making. Building on this idea, remediation strategies may take the form of visual exercises that increase an individual's familiarity with the skill of numeracy. With regard to critical competency, the NVS was robustly associated with a broader ranger of neurocognitive domains. This may reflect the fact that critical competencies are more cognitively complex and demanding, requiring multiple abilities for applied health literacy tasks. Although the small samples did not allow for statistical comparison of the effect sizes, the strongest associations were observed for the verbal fluency and working memory domains, each of which has an underlying executive component. The ability to rapidly search and retrieve stored information (i.e., verbal fluency) and hold information in mind in order to act on it (i.e., working memory) are both conceptually important for health literacy. For example, during a doctor's appointment at which a new medication is being added to a patient's regimen, the patient needs to listen to the risks and benefits of the new medication (e.g., side effect profile), integrate this potential new medication with the his/her current regimen and lifestyle demands, and recognize when he/she has questions or concerns in the context of a brief visit in order to make a decision about whether to agree to the medication. To do this effectively, intact working memory is engaged, as has been demonstrated in non-medical decision-making tasks [57].

Highlighting its real-world relevance, critical competency as measured by the NVS was correlated with social-emotional cognition skills and everyday functioning ability, whereas numeracy was not. Social cognitive abilities may interfere with the applied nature of critical competencies at various points in the Sorensen model [10], ranging from accessing information (e.g., doctor-patient communication), processing and understanding information (e.g., emotion dysregulation may interfere with this process), and applying information toward appropriate health decisions (e.g., failure to account for outcome expectancies and implications of health choices, many of which are social in nature). Future targeted investigations may reveal such relationships within the multifaceted constructs of social cognition and health literacy, which may then inform augmented interventions. Interestingly, better performance on the critical competency component of the health literacy assessment, but not the fundamental competency, was also associated with five times greater likelihood of being independent with activities of daily living. This association may be indicative of the fact that the more complex critical competency better approximates good health management and disease outcomes facilitating independence, and illustrates the potential everyday implications of health literacy in HAND. As such, health literacy-focused remediation may be an appropriate target for disabled individuals with HAND.

The largely absent associations between health literacy and HIV disease factors in the HAND group are not definitive but do provide some context for the present findings. Specifically, the fact that there was no effect of nadir or current CD4 count suggest that the relationship of HAND to health literacy was not driven by a subset of individuals with more severe historical or current HIV disease; in other words, HAND-related health literacy deficits are not solely a non-specific function of greater illness. On the other hand, the inverse relationship between numeracy performance and plasma viral load that approached significance may reflect better disease management with better health literacy performance, which is an important future direction for exploration. Furthermore, given that substance dependence increases risk of HAND and functional dependence [58], it is possible that synergistic effects on health literacy could emerge in future studies with larger samples.

As mentioned above, a limitation of our study is the small sample size. We have attempted to balance our risks of type I and type II error by maintaining a critical alpha of .05 and using effect sizes to enhance interpretation, and we have limited our examination of the correlates of health literacy to only those measures of health literacy outcomes that demonstrated an association with our primary independent variable, HAND group status. The small sample size is particularly pronounced for female participants, which may limit the generalizability given that the performance of women with and without HAND on health literacy tasks (as well as the relationship between these tasks and neurocognitive domain performance) is not adequately represented. Given the longstanding association between gender and numerical skills, a possible interaction between HIV and gender on these aspects of health literacy may be relevant for future studies. In summary, the present sample size did not allow for thorough investigation of additive and/or synergistic effects of HAND and other factors on health literacy, and therefore studies that expand on our findings to explore these possibilities and extend our investigation of correlates of poor health literacy performance are suggested. Another limitation of this study is the psychometric properties of the REALM and 3-Brief in a sample of relatively well-educated individuals, which resulted in a 27 % ceiling effect on the REALM and 74 % floor effect on the 3-Brief. However, the rates of ceiling and floor effects did not differ across groups, and the pattern of our findings was unchanged when the regression models for these outcome variables used dichotomous versions of the variables based on a median split instead of continuous outcomes.

There are many possible directions for future work that could build on the present findings. For example, future work may explore potential additive or synergistic effects of HAND in combination with demographic factors (e.g., age) and psychiatric disorders such as Major Depressive disorder and substance use disorders. Along those lines, while the present study reported proportions of individuals who met current (i.e., last 30 days) criteria for Major Depressive disorder, a measure of current depressive symptoms was not included. Given that the performance one the NVS has been show to be associated with depression, a measure of affective distress and/or depressive symptoms may be informative in future studies. Furthermore, extended characterization of the cognitive correlates of health literacy in HAND could include prospective memory [59], and decision-making [60], and expanded measures of social cognition, which may be particularly important correlates of critical competencies and would not only serve to better characterize health literacy in HAND but also could inform remediation targets. Future studies may then package remediation strategies at both levels of competency, such as visual aids for fundamental competency, and cognitive trainings for skills involved in critical competency (e.g., semantic cueing for verbal fluency; [61]). Additionally, it may be important to investigate the underlying neuropathological changes associated with health literacy deficits through biomarker techniques such as neuroimaging and assays (e.g., neuro-inflammatory biomarkers) in order to identify the neural mechanisms driving these impairments. To further examine the real-world relevance of health literacy performance to health behavior in HAND, investigation of outcomes such as medication adherence, compliance with medical appointments and instructions, and skills with everyday health activities such as web-based medical records and pharmacy interfaces should be examined. The relationship of health literacy to HIV transmission risk behavior may reveal additional targets for prevention, and could serve to illuminate the relative roles of pre-existing health literacy deficits in contracting HIV and acquired health literacy deficits in difficulty with managing HIV disease.

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Appendix

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: Thomas D. Marcotte, Ph.D.; Jennifer Marquie-Beck, M.P.H.; Melanie Sherman; Neuromedical Component: Ronald J. Ellis, M.D., Ph.D. (P.I.), Scott Letendre, M.D., J. Allen McCutchan, M.D., Brookie Best, Pharm.D., Rachel Schrier, Ph.D., Terry Alexander, R.N., Debra Rosario, M.P.H.; Neurobehavioral Component: Robert K. Heaton, Ph.D. (P.I.), J. Hampton Atkinson, M.D., Steven Paul Woods, Psy.D., Thomas D. Marcotte, Ph.D., Mariana Cherner, Ph.D., David J. Moore, Ph.D., Matthew Dawson; Neuroimaging Component: Christine Fennema-Notestine, Ph.D. (P.I.), Terry Jernigan, Ph.D., Monte S. Buchsbaum, M.D., John Hesselink, M.D., Sarah L. Archibald, M.A., Gregory Brown, Ph.D., Richard Buxton, Ph.D., Anders Dale, Ph.D., Thomas Liu, Ph.D.; Neurobiology.

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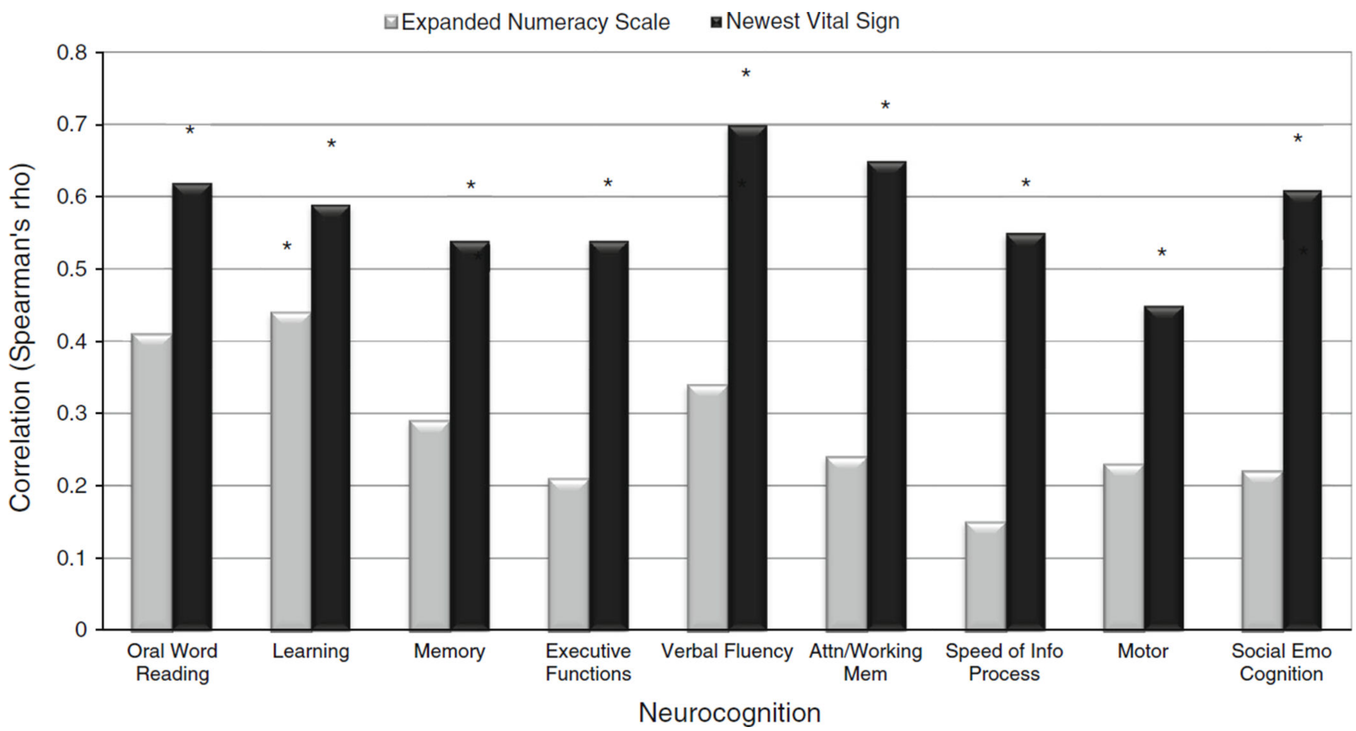

Fig. 1.

The pattern of neurocognitive correlates of health literacy performance are displayed, showing that critical competency (as measured by the Newest Vital Sign) was significantly correlated with each of the domains, which may reflect the multidimensional complexity of this aspect of health literacy. In contrast, fundamental competency (as measured by the Expanded Numeracy Scale) was significantly associated with only the learning domain, possibly indicating greater neurocognitive specificity for fundamental competencies. Correlates of Health Literacy in HAND. *Note*: For consistency in visual presentation, the absolute value of all correlations has been displayed; * $p < .05$; *Attn/Working Mem* attention/working memory, *Speed of Info Process* speed of information processing, *Social Emo Cognition* social emotional cognition test

Table 1

Demographic, medical, psychiatric, and substance use characteristics of the study groups

	HIV− (n = 24)	**HAND− (n = 32)**	**HAND+ (n = 24)**	***p***	**Group differences[k]**
Demographic variables					
Age (years)	53.1 (18.6)	54.3 (7.6)	52.1 (9.1)	0.721	–
Education (years)	14.4 (2.3)	13.8 (2.8)	13.2 (2.9)	0.218	–
Gender (% female)	25.0 %	25.0 %	4.7 %	0.052	HAND+ < HAND−, HIV−
Ethnicity (% Caucasian)	62.5 %	65.6 %	66.7 %	0.951	–
Oral Word Reading[a]	100.9 (15.6)	99.8 (14.9)	94.3 (16.0)	0.398	–
Psychiatric/substance use variables					
Current MDD (%)	4.2 %	3.1 %	12.5 %	0.349	–
LT MDD (%)	29.2 %	46.9 %	79.2 %	0.001	HAND+ > HAND−
LT alcohol dependence (%)	25.0 %	43.8 %	20.8 %	0.138	–
LT non-alcohol substance dependence (%)	41.7 %	50.0 %	54.2 %	0.675	–
Medical/HIV disease characteristics					
HCV (%)	–	4.0 %	15.0 %	0.194	–
Duration of HIV Infection (months)[b]	–	198.5 (139.6, 252.8)	154.8 (69.4, 289.4)	0.639	–
AIDS Status (%)	–	62.5 %	75.0 %	0.318	–
cART Status (% prescribed)	–	90.6 %	83.3 %	0.210	–
Nadir CD4 (cells/μl)[b]	–	115.0 (42.5, 287.5)	49.5 (4.0, 195.0)	0.046	HAND+ < HAND−
Current CD4 (cells/μl)[b]	–	542.0 (434.3, 825.0)	366.0 (146.5, 778.8)	0.029	HAND+ < HAND−
Plasma Viral Load (% detectable)	–	16.1 %	21.7 %	0.601	–
Health literacy variables[b]					
REALM (total correct of 66)	65.0 (64.0, 66.0)	65.0 (63.0, 66.0)[c]	65.0 (61.0, 65.0)[d]	0.228	–
Brief Health Literacy Screen (total; range 0–12[k])	0.0 (0.0, 0.8)	0.0 (0.0, 0.0)	0.0 (0.0, 3.0)	0.299	–
Expanded Numeracy Scale (total correct of 7)	6.0 (4.3, 6.0)	5.0 (4.0, 7.0)[c]	4.0 (3.0, 5.0)[d]	0.033	HAND+ < HAND−[g], HIV[h]
Newest Vital Sign (total correct of 7)	4.0 (3.0, 6.0)[e]	4.0 (3.0, 5.8)[f]	3.0 (2.0, 4.0)[e]	0.007	HAND+ <HAND−[i], HIV−[j]

Values represent means (standard deviation) unless otherwise noted.

* $p < 0.05$

NS nonsignificant, $p > 0.10$. HAND = HIV-associated neurocognitive disorder. *LT* lifetime, *MDD* major depressive disorder, *HCV* hepatitis C virus, AIDS acquired immune deficiency syndrome, *cART* combination antiretroviral therapy, CD4 cluster of differentiation 4, REALM Rapid Estimate of Adult Literacy in Medicine

[a] As determined by the Wide Range Achievement Test—3rd edition (WRAT-3)

[b] Median (interquartile range)

[c] n = 31;

[d] n = 23;

[e] n = 22;

[f] n = 24

Cohen's d effect sizes: ENS:

[g] HAND+ < HAND− = −0.47,

[h] HAND+ <HIV−= −0.69; *NVS*:

[i] HAND+ <HAND− = −0.70,

[j] HAND+ <HIV+ = −0.76

[k] Higher scores indicate worse health literacy

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Table 2

Regression analyses reveal an association between HAND status and health literacy

Outcome	Model statistics			Predictor statistics	
Predictor	Adjusted R^2	F ratio	*p* value	Estimate	*p* value
ENS	0.08	2.78	0.03	–	–
Gender	–	–	–	0.85	0.09
LT MDD	–	–	–	−0.01	0.98
HAND+ vs. HIV−	–	–	–	1.47	0.007
HAND+ vs. HAND−	–	–	–	1.18	0.02
NVS	0.12	3.31	0.02	–	–
Gender	–	–	–	0.82	0.13
LT MDD	–	–	–	−0.24	0.58
HAND+ vs. HIV−	–	–	–	1.63	0.003
HAND+ vs. HAND−	–	–	–	1.60	0.003
REALM	−0.02	0.70	.59	–	–
Gender	–	–	–	−0.17	0.58
LT MDD	–	–	–	0.13	0.61
HAND+ vs. HIV−	–	–	–	−0.19	0.49
HAND+ vs. HAND−	–	–	–	−0.35	0.28
3-Brief	0.02	1.44	0.22	–	–
Gender	–	–	–	−0.47	0.11
LT MDD	–	–	–	−0.01	0.98
HAND+ vs. HIV−	–	–	–	−0.01	0.96
HAND+ vs. HAND−	–	–	–	−0.34	0.29

ENS Expanded Numeracy Scale, *NVS* Newest Vital Sign, *REALM* Rapid Estimate of Adult Literacy in Medicine, LT *MDD* Lifetime Major Depressive Disorder