CLINICAL INTERVENTIONS FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDER (HAND): A SYSTEMATIC REVIEW

A Thesis Presented to
the Faculty of the Graduate School
at the University of Missouri-Columbia

In Partial Fulfillment of the
Requirements for the Degree
Master of Science

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by
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DECEMBER 2020

The undersigned, appointed by the dean of the Graduate School, have examined the thesis entitled

CLINICAL INTERVENTIONS FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDER (HAND): A SYSTEMATIC REVIEW

Presented by Hannah Marie Mitchell,

A candidate for the degree of Master of Science

And hereby certify that, in their opinion, it is worthy of acceptance.

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ACKNOWLEDGEMENTS

It has been, and continues to be, a privilege to work alongside such talented researchers, clinicians, and teachers throughout my education at the University of Missouri. Completing this thesis and receiving this degree would not have been possible without the support of many dedicated faculty and staff across many departments who have guided and taught me throughout my journey.

Thank you to Dr. Erin Robinson – I truly would never have completed this project or degree without your incredible professional, academic, and personal support. Thank you for recognizing my potential and challenging me to see new perspectives, ask questions, and think critically. Thank you for believing in me before I knew that this goal was even achievable and for pushing me to take the first, intimidating steps toward making this dream a reality. More than anything, thank you for encouraging me every step of the way along the journey.

Thank you to my advisor, Dr. Dennis Miller, for supporting and encouraging me throughout this endeavor and my academic journey. Thank you for seeing potential in me and agreeing to step in as my adviser, even though I was an untraditional student and it certainly was not required of you. Thank you for you guidance and your support of all my academic endeavors.

Thank you to my other committee member, Dr. Todd Schachtman, for your insight, guidance, support, and dedication of your time. Thank you to Dr. Clark Peters who advocated for me to be able to pursue this degree and who provided guidance and support at the beginning and throughout my journey. Thank you to Allison Halt-Donehower, who provided excellent contributions to this project, and to my other former lab mates who supported me over the past five years. This project would not have been possible without your support.

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Abstract

Despite the widespread use of antiretroviral therapy, HIV-associated neurocognitive disorder (HAND) continues to be one of the most common central nervous system (CNS) complications of human immunodeficiency virus (HIV), with the prevalence of the disorder remaining stable at pre-cART levels. HAND ranges in severity from mild to severe and can greatly impact the lives of individuals living with the disorder, often leading to morbidity in severe cases. The prevalence and severity of HAND underscores the need for safe, effective therapies to mitigate or eliminate the impacts of the disorder in order to improve the quality of life of infected individuals. While extensive research has been conducted to investigate the effectiveness of various clinical interventions in treating HAND, no comprehensive systematic review of these studies exists. The purpose of the present study was to conduct and present a systematic review of the literature regarding experimental studies of clinical therapeutic interventions for HAND. In total, 4,269 articles were returned in the initial database search, 13 of which met the inclusion criteria and were selected for inclusion in the review. The 13 articles examined in the final review included experimental investigations of both pharmaceutical and cognitive therapies for HAND. This review presents the current evidence that exists regarding empirically investigated interventions for HAND and broadly discusses trends, limitations, and gaps in the literature.

Clinical Interventions for HIV-Associated Neurocognitive Disorder (HAND): A Systematic Review

Cognitive impairment and other central nervous system (CNS) complications have long been identified as complications of the human immunodeficiency virus (HIV) and/or acquired immunodeficiency syndrome (AIDS). In 1983, just two years after AIDS was first described clinically, encephalitis was recognized as being associated with AIDS. Three years later, in 1986, the AIDS dementia complex (ADC) was first identified and defined. This disorder, which described the neurologic manifestations of HIV infection, was characterized by abnormalities in cognition, motor performance, and behavior[1,2]. Over the next two decades, the terminology and nosology associated with the neurologic manifestations of HIV would continue to develop and change. Today, these neurocognitive complications of HIV infection are collectively known as HIV-associated neurocognitive disorder (HAND)[3].

Over the past twenty years, the advent and subsequent widespread use of combination antiretroviral therapy (cART) has drastically improved the lifespan and quality of life for individuals living with HIV and/or AIDS. Since the introduction of cART in 1996, HIV has largely shifted from being an acute, life-threatening disease to one that is chronic and manageable, with infected individuals now experiencing a near-normal lifespan and a dramatically decreased risk of opportunistic infections[2]. However, despite this improved prognosis for individuals living with HIV, HAND continues to be one of the most common CNS complications of HIV. Further, research suggests that the overall prevalence of HAND remains stable at approximately 30-50% today, virtually unchanged from the pre-cART era[4,5].

While HAND continues to be a highly prevalent CNS complication of HIV infection despite the widespread use of cART, there has been a shift in the epidemiology of HAND since

the introduction of cART. HAND refers to a spectrum of cognitive impairment with three defined stages: 1) asymptomatic neurocognitive impairment (ANI); 2) mild neurocognitive disorder (MND); and 3) HIV-associated dementia (HAD) – with ANI being the most mild form of the disorder and HAD being the most severe[3]. Prior to cART, the most common form of HAND was HAD, which was nearly always fatal[6]. However, the widespread use of cART has led to a significant decline in the prevalence of HAD, from 20% pre-cART to 5% post-cART[7,8]. Given this decrease in the prevalence of HAD but stability in the prevalence of HAND as a whole, it follows that the vast majority of HAND cases today are less severe forms of the condition. In fact, ANI now accounts for approximately 70% of cases of HAND[4].

Although the less severe and clinically asymptomatic forms of HAND are now more common than the most severe form, they are still clinically relevant. Individuals with ANI are two to six times more likely to develop a more severe form of HAND in their lifetime than individuals who are neurocognitively unimpaired[9]. Clinically, HAND can cause memory impairment, executive dysfunction, and significant disruption of attention, impulse control, judgment, and memory encoding and retrieval, as well as marked motor dysfunction, including bradykinesia, gait imbalance, and loss of coordination[10]. Despite overall prolonged lifespans for HIV+ individuals due to cART, those with HAND still experience a threefold increased mortality risk compared to those without HAND[11]. Unfortunately, severe cases of HAND remain a major cause of morbidity in HIV+ individuals[4]. Overall, HAND can lead to significant and sometimes devastating clinical outcomes for persons living with HIV. Together, the prevalence and severity of HAND underscores the need for safe, effective therapies to mitigate or eliminate the impacts of the disorder in order to improve the quality of life of infected individuals.

Although HAND persists despite the widespread use of cART, cART remains as the primary treatment for preventing and delaying the progression of HAND, with limited evidence regarding its effectiveness as an intervention[12]. In both the clinical and academic fields, there remains much debate regarding effective interventions for HAND, with a highly effective, reliable treatment yet to be widely accepted or utilized. A complete understanding of the current empirical evidence regarding interventions as well as the availability of this information is integral to the field's ability to move forward with identifying effective treatments for HAND. While extensive research has been conducted over the past thirty years to investigate the effectiveness of various clinical interventions in treating HAND, no comprehensive systematic review of these studies exists. Systematic reviews have been conducted regarding specific subsets or fragments of this issue, but they were limited in their scope and relevance. Joska et al.[13] conducted a systematic review examining the efficacy of highly active antiretroviral therapy (HAART) in improving neurocognitive function. However, this review is not generalizable beyond HAART interventions and does not specifically focus on interventions for HAND. Another review by Uthman and Abdulmalik[14] investigated adjunctive therapies for ADC. This study was limited in scope by only including pharmaceutical therapies given in conjunction with cART. To our knowledge, no study to date has systematically reviewed the entire body of empirical literature regarding interventions for HAND. A review of this type would establish a current, point-in-time baseline of evidence for future clinical and academic investigations to build on and would provide a comprehensive, overarching view of the current state of the literature regarding interventions for HAND. Based on these identified gaps in the current literature, the aims of the present study were to:

1) conduct a systematic review of controlled, experimental studies regarding interventions for HAND;
2) critically review the findings, with specific emphasis on overarching trends and limitations of the existing body of literature; and
3) guide clinicians and researchers towards a more complete understanding of the specific types of interventions for HAND that have been empirically investigated to date.

Materials and Methods

Inclusion and Exclusion Criteria

This systematic review includes controlled, prospective, experimental studies. It focuses on studies that investigate a given intervention's effects on the neurocognitive functioning of individuals diagnosed with HAND. To meet inclusion criteria, the articles must have specified the intervention's effects on the participants' neuropsychological performance, measured both pre- and post-intervention using a neuropsychological test battery.

As this systematic review focused on interventions for HAND rather than preventative treatments, studies were excluded if no participants had a diagnosis of HAND at baseline (or an equivalent diagnosis, as described below). Studies were included if either all or some of the participants had HAND at baseline. Additionally, due to the large amount of variability in study designs of the existing literature and to maintain reliability and consistency across studies and allow for greater comparison between studies in this review, only articles that utilized a controlled, prospective, experimental study design were selected for inclusion. Consequently, studies that utilized cross-sectional or prospective observational study designs were excluded. Importantly, due to the inconsistency in the diagnosis of HAND that is present in the existing literature and clinical practice, which makes between-studies comparisons difficult, articles were

only included in this review if the authors specified that the sample of study participants with cognitive impairment had a specific diagnosis of or met standardized diagnostic criteria for HAND, ADC, HIV-associated neurocognitive impairment (HNCI), or an equivalent, standardized diagnosis. For example, if the study simply stated that participants had neuropsychological complications or impairment, but no specific HAND, ADC, or HNCI diagnosis, the study was excluded. Finally, as an aim of this study was to present the existing literature regarding interventions for HAND for the purpose of informing clinical application and practice, articles were only included if they measured neuropsychological functioning in participants as an efficacy endpoint for the given intervention. Articles were excluded if their only outcome measurements assessed some indicator other than neuropsychological functioning – for example, neuroimaging or biological measurements. Studies were further excluded if they were written in a language other than English, were not published peer-reviewed original research articles, or if the study sample primarily included children under 18 years of age. These inclusion and exclusion criteria were applied at every level of the study selection process outlined in Figure 1.

Search Strategy

A keyword/title/abstract search of four electronic databases was conducted in December 2019. The databases searched included PsycINFO, SCOPUS, Ovid MEDLINE, and CINAHL. A general search string was created and used for the non-medical databases (PsycINFO and SCOPUS). An additional search string of MeSH terms was combined with the general search string and utilized for the two medical databases (Ovid MEDLINE and CINAHL). The search strings were as follows:

1) General: (AIDS Dementia OR AIDS Dementia Complex OR HIV Associated Neuro* OR HIV Associated Dementia OR HIV-Associated Neuro* OR HIV-Associated Dementia OR HIV-1 Associated Neurocognitive Disorder) AND (therap* OR treatment* OR intervention OR medication)
2) Combined (General search string and MeSH terms): (“AIDS Dementia Complex” [MH] OR "AIDS Dementia" [TIAB] OR "AIDS Dementia Complex" [TIAB] OR "HIV Associated Neuro*" [TIAB] OR "HIV Associated Dementia" [TIAB] OR "HIV-Associated Neuro*" [TIAB] OR "HIV-Associated Dementia" [TIAB] OR "HIV-1 Associated Neurocognitive Disorder" [TIAB]) AND (“therapeutics” [MH] OR “therap*” [TIAB] OR “treatment* [TIAB] OR "intervention" [TIAB] OR "medication" [TIAB])

Study Selection

A total of 4,269 articles were returned from the database search and exported into Mendeley, a reference management software. From there, the articles were exported into a Microsoft Excel worksheet using the JabRef conversion tool. This Excel worksheet was used to document each stage of the study selection process outlined in Figure 1.

The study selection process began with an initial title and abstract review, in which 4,237 articles were excluded due to being duplicates (n = 1,869) or not meeting inclusion criteria (n = 2,368). Next, a full text review of the remaining 32 articles was conducted and an additional 19 articles were excluded for not meeting inclusion criteria. A final sample of 13 articles met all inclusion criteria and were systematically reviewed and included in the data extraction process.

Results

Study Design and Characteristics

Table 1 outlines the descriptive variables of the studies included in this review. The majority of studies were conducted in the United States (n = 7), with the remaining studies being completed (one each) in South Africa, Australia, Italy, Uganda, and Switzerland. One study[15] did not specify the location in which it was conducted. Where reported, most studies were conducted in infectious disease clinics and/or in clinical research facilities associated with a hospital or clinic. Sample sizes of included studies range from 1 to 140, with a mean of 49.31 and a median of 32 participants. Most studies reported good participant completion rates, with only four studies with completion rates less than 70% – the lowest being 50%. Three studies reported completion rates of 100%, including the single study with one participant. While most studies reported education levels of participants in some manner, nearly half (n = 6) did not report and/or specify the mean completed years of education of participants. One study reported the median education level (13 years), but not the mean. The mean education level of the remaining six studies that reported on this variable was 13.03 years. The mean age of participants was fairly consistent across studies, ranging from 35.1 to 55.1 years, with a mean of 45.67 years. Most studies (n = 10) were majority male (ranging from 71% to 100% male), with two studies reporting majority female participants (10% and 12% male). Overall, the mean percentage of male participants was 76%.

All studies selected for this review utilized a controlled, prospective, experimental study design. There was some variance in the design and characteristics of the included studies, ranging from single-arm pilot studies to randomized, double-blind, placebo-controlled, multi-site trials (see Table 2). One study was a case study of an individual who participated in a related

clinical trial[16]. The case study was written on this participant due to their diagnosis of HAND and the participant's results were compared to that of sixteen other study participants. As this study followed a controlled experimental study design and met other inclusion criteria, it was selected for inclusion in this review. Additionally, five of the selected studies were pilot studies, six were placebo-controlled, and three were multi-site trials. Studies varied in how they assigned participants to experimental groups, as well. Most studies had a homogenous study sample of HIV+ individuals with HAND diagnoses and randomized participants into an experimental or placebo/control group. However, a few studies either were single-arm studies in which all participants received the same intervention or divided a clinically heterogeneous sample into experimental and control groups, conducting post-hoc analyses on the group differences between individuals with and without HAND. The length of included studies ranged from 12 to 60 weeks, with a mean length of 24.6 weeks.

Interventions

Twelve of the thirteen included studies investigated pharmaceutical interventions for HAND, while one study[17] investigated a cognitive rehabilitation protocol (see Table 2). Four of the twelve pharmaceutical studies investigated antiretroviral therapies (ART), a traditional treatment for HIV: didanosine[18], atevirdine[15], zidovudine[19], and cART of efavirenz, emtricitabine, and tenofovir[16]. The remaining eight pharmaceutical studies varied in intervention types and drug classes, including lithium[20,21], maraviroc[22], minocycline[23], memantine[24,25], selegiline[26], and rivastigmine[27]. Of these eight studies, all but the minocycline study tested their novel drug intervention as an adjunctive therapy to ART. The cognitive rehabilitation study[17] also tested its intervention adjunctive to ART. Just one[23] of the thirteen studies did not include ART in its experimental intervention; instead, participants only received the investigational drug.

Due to the variability in interventions tested, there was also great variability in the dose amounts and frequencies in the selected studies. Eleven of the twelve pharmaceutical interventions were given orally, while one[26] utilized a transdermal system. Most interventions were given once or twice daily, with adherence monitored via a self-report dosage log.

Neurocognitive Prevalence and Diagnosis

To be included in this review, studies must have specified that the sample of study participants with cognitive impairment had a specific diagnosis of or met standardized diagnostic criteria for HAND, ADC, or an equivalent, standardized diagnosis. Even with this specification, there was great variability not only with the clinical terminology used to establish cognitive impairment (i.e. HAND, ADC, etc.), but with the diagnostic assessment and/or criteria utilized to establish and measure the severity of a given diagnosis (i.e. baseline score on a standardized test battery, existing clinical diagnosis, etc.) (see Table 3). Six of the selected studies used ADC as their clinical terminology, all of which utilized a similar severity scale of 0 (no impairment) to 3 (severe impairment). Another six studies used HAND terminology, many of which utilized the Frascati criteria for HAND nosology[3] which includes asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), and HIV-associated dementia (HAD), while others utilized global deficit scores (GDS) to determine severity of cognitive impairment. One study[23] used the term HIV dementia for its nosology, referencing the HIV Dementia Scale and Memorial Sloan Kettering (MSK) dementia scale for assessment of cognitive impairment. In general, most studies included in this review that were published after 2007 (when the Frascati criteria were established[3]) referred to the disorder as HAND, while studies prior to 2007 used alternate terminology, such as ADC, HNCI, or HIV dementia.

Neuropsychological Testing Batteries

There was a large amount of variability in the neuropsychological test batteries utilized in the included studies. Most studies (11 of 13) did, however, specify the test batteries used in detail. The mean number of assessments in the testing battery was 10, with a range from 7 to 18. Most studies reported utilizing a diverse group of assessments to assess functioning of various neuropsychological domains, such as attention/working memory, psychomotor speed, learning and memory, verbal fluency, and abstraction/executive function. The most frequently utilized neuropsychological assessments among the selected articles include: grooved pegboard (n = 8), symbol digit (n = 4), timed gait (n = 6), and trail making test (n = 10). Some of the included studies utilized computerized neuropsychological test batteries such as the CogState (n = 1) or CalCAP (n = 2) systems. Table 3 further details the neuropsychological testing batteries utilized by each study included in this systematic review.

Neuropsychological Outcomes

The studies included in this review demonstrated significant variability in how neuropsychological outcomes and treatment efficacy were measured (see Table 3). In most studies (n = 7), a change in global neuropsychological z-scores based on population norms was used to assess treatment efficacy from baseline to study completion. Others (n = 4) measured efficacy by a change in global deficit score (GDS) or a similar global measurement of neuropsychological functioning. One study[15] measured efficacy by a change in clinical ADC diagnosis to below stage 1 and another[17] did not utilize a global measure of neuropsychological functioning and instead assessed each neuropsychological domain individually. Although the methods of establishing and measuring treatment efficacy varied greatly between each of the studies included in this review, overall, a slight majority of studies (n = 7) reported significant

improvement in neuropsychological functioning for study participants with HAND as a result of the given intervention (see Table 3).

Discussion

Despite the widespread use of cART over the past twenty-five years, HAND continues to be one of the most common neurocognitive complications of HIV, with the prevalence of the disorder remaining stable at pre-cART levels and affecting 30-50% of the HIV+ population[4,5]. The prevalence and severity of HAND emphasizes the need for safe, effective interventions for the disorder; however, such an intervention has yet to be identified. A thorough understanding of the interventions that have been investigated to date is integral to the ability of current and future researchers to make progress in identifying effective treatments for HAND. The present systematic review fills this gap in the literature; to our knowledge, this is the first systematic review of the literature regarding controlled, experimental investigations of clinical interventions for HAND.

Importantly, the purpose of this review was not to draw conclusions about the efficacy of the interventions for HAND investigated in the included studies, nor was it to conduct a meta-analysis of the aggregate data from these studies. Rather, the purpose of this study was to conduct and present a systematic review of the studies that have been conducted to date which investigate a given intervention's effects on the neuropsychological functioning of individuals with HAND. This review successfully accomplished this goal, with the primary finding of this review being that a total of thirteen such studies exist in the current body of literature. These studies were predominantly investigations of pharmaceutical interventions, ranging from ART to novel drug classes, with just one study investigating a non-pharmaceutical intervention – a cognitive rehabilitation protocol. Overall, seven of the thirteen studies reported significant

positive neuropsychological outcomes, as defined by a statistically significant improvement in neuropsychological functioning of study participants with HAND after intervention. However, it is important to acknowledge that studies were identified as achieving a positive neuropsychological outcome based on what was reported directly in the study; we did not identify a standard outcome measurement prior to reviewing the included studies that was then applied to each of the studies to determine if the outcome was met. As each study defined their own primary efficacy endpoints and interpreted reported on their own findings, the threshold for demonstrating significant results was different for each study. Taking this into consideration, the corresponding interventions that yielded significant positive neuropsychological outcomes were: cART of efavirenz, emtricitabine, and tenofovir[16], atevirdine (ART)[15], maraviroc (adjunctive to cART)[22], lithium (adjunctive to cART)[21], zidovudine (ART)[19], memantine[25], and a cognitive rehabilitation protocol (adjunctive to cART)[17].

Based on the data extracted from each of the studies, we are able to make further observations regarding the general state of the literature. Perhaps the most significant observation generated from the results of this review is that there is a great amount of variability present in practically every aspect of the studies investigating interventions for HAND. This variability and inconsistency makes any between-study comparisons or attempts to aggregate findings from studies difficult. In any review of experimental studies, some amount of variability is to be expected; however, the breadth of variability present across several aspects of the given studies combined with the relatively small sample of studies (n = 13) available on this topic makes the variability present in this selection of articles particularly significant. Some examples of this variability include the study design, diagnostic criteria, HAND nosology, testing battery, and outcomes measurement of included studies.

Of all these aspects, perhaps the most significant and concerning is the variability regarding the nosology, terminology, and subsequent diagnosis of HAND, as the use of universal, consistent diagnostic classification and terminology is key to accurate diagnosis and treatment[13]. In reviewing the literature, however, it is clear that this universal language or criteria does not yet exist or, at least, is not universally accepted and utilized. Within a historical context, the nosology and terminology related to neuropsychological complications of HIV have changed several times over the past thirty years, none of which were ever utilized universally. It was not until 2007 that the diagnosis and classification of HAND and the corresponding levels of impairment, ANI, MND, and HAD, were established[3]. Prior to this, previous nomenclature included HNCI (with subcategories of mild cognitive motor disorder [MCMD] and HAD), NeuroAIDS, ADC, and HIV dementia, among others. This review revealed that this variability in terminology is still present within the body of literature published after 2007, but even if this were not the case, between-study comparisons of studies pre- and post-2007 would be difficult due to these changes in terminology and nosology over time. While taking these historical changes into account, there still is not consistent language or diagnostic criteria used to identify, diagnose, and discuss cognitive impairment in HIV+ individuals. Further, this variability is only amplified cross-culturally, with studies varying in their nosology and terminology by country or region. The impacts of these inconsistencies reach beyond simply how those in the field refer to and classify HAND; they affect the diagnosis and treatment of HAND, underscoring the widespread importance and consequences of this issue. Because of this, establishing and implementing clear, consistent terminology, classification, and diagnostic criteria for HAND is imperative and should be a focus of future research efforts.

In terms of this review, the lack of clear, consistent language and diagnostic criteria for HAND resulted in many potentially relevant studies being excluded from analysis, as one of the inclusion criteria required that study participants had a specific diagnosis of or met standardized diagnostic criteria for HAND, ADC, HNCI, or an equivalent diagnosis. This, along with the lack of a controlled, experimental study design, was one of the primary reasons that otherwise relevant studies were excluded from inclusion in this review. The exclusion of potentially relevant studies is an unfortunate but necessary component of any systematic review, as clear inclusion and exclusion criteria are vital to the validity, reliability, and replicability of a systematic review[28]. Nonetheless, the specific inclusion criteria identified for this systematic review was a limitation of the present study. Further, of the 4,269 articles returned from the initial database search, only 13 met all inclusion criteria. This was largely attributable to the high number of duplicate studies that were returned from the four databases that were searched as well as the inherently broad nature of the search terms. An additional limitation of the study, which is present in all systematic reviews, is the potential selection bias in article selection. This potential bias was attenuated, however, by utilizing multiple reviewers, documenting and reviewing every decision related to article inclusion, and establishing clear, specific inclusion and exclusion criteria at the beginning of the article review process.

As the purpose of this study was to present the existing evidence, not to draw conclusions regarding efficacy of interventions for HAND, it is important not to take the findings of this study out of context or extend them beyond their specified purpose. In particular, it is important to acknowledge that this review only included findings and studies related to a given intervention's efficacy at improving neuropsychological functioning in individuals with HAND. The full picture of a given intervention's safety and tolerability, which are imperative clinical

considerations when identifying and prescribing any type of treatment, is not presented in this review. There are undoubtedly studies that describe further investigations into such questions for each of the thirteen studies included in this review but extended beyond the specific scope of the present study and were not included. Inevitably, there are also investigations into the efficacy of interventions for HAND that are not included in this review due to not meeting inclusion criteria for one reason or another, as mentioned above; however, we did make every effort to design this study in a way that would be inclusive and comprehensive, while remaining focused and ensuring the reliability and validity of our study design.

This systematic review identifies and discusses thirteen controlled, experimental studies that investigated the effects of a given intervention on the neuropsychological functioning of individuals with HAND. It is clear from the limited number of total studies identified in this review as well as the modest number that produced significant outcomes (n = 7) that future research on this topic is needed. However, a comprehensive understanding of the existing literature regarding interventions for HAND is an integral step towards identifying effective treatments, and this review provides a baseline from which to move forward.

References

1. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. Ann Neurol 1986;19:517-524.
2. Saylor D, Dickens AM, Sacktor N, et al. HIV-associated neurocognitive disorder: Pathogenesis and prospects for treatment. Nat Rev Neurol 2016;12:234-248.
3. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurol 2007;69:1789–1799.
4. Heaton R, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders (HAND) persist in the era of potent antiretroviral therapy: The CHARTER study. Neurol 2010;75-2087-2096.
5. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. AIDS 2007;21;1915-1921.
6. Ellis RJ, Deutsch R, Heaton RK, et al. Neurocognitive impairment is an independent risk factor for death in HIV infection. Arch Neurol 1997;54:416-424.
7. Becker JT, Kingsley LA, Molsberry S, et al. Cohort profile: Recruitment cohorts in the neuropsychological substudy of the Multicenter AIDS Cohort Study. Int J Epidemiol 2015;44:1506-1516.
8. McArthur JC, Hoover DR, Bacellar H, et al. Dementia in AIDS patients: incidence and risk factors. Neurol 1993;43:2245-2252.
9. Grant I, Franklin DR Jr, Deutsch R, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurol 2014:82:2055-2062.

10. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: Differences in rates, nature, and predictors. J Neurovirol 2011:17:3-16.
11. Vivithanaporn P, Heo G, Gamble J, et al. Neurologic disease burden in treated HIV/AIDS predicts survival: A population-based study. Neurol 2010;75:1150-1158.
12. Sacktor N. Changing clinical phenotypes of HIV-associated neurocognitive disorders. J Neurovirol 2018;24:141-145.
13. Joska JA, Gouse H, Paul RH, et al. Does highly active antiretroviral therapy improve neurocognitive function? A systematic review. J Neurovirol 2010;16:101-114.
14. Uthman OA, Abdulmalik JO. Adjunctive therapies for AIDS dementia complex. Cochrane Database Syst Rev 2008;3:CD006496.
15. Brew BJ, Dunbar N, Druett J-A, et al. Pilot study of the efficacy of atevirdine in the treatment of AIDS dementia complex. AIDS 1996;10:1357-1360.
16. Becker JT, Cuesta P, Fabrizio M, et al. Brain structural and functional recovery following initiation of combination anti-retroviral therapy. J Neurovirol 2012;18:423-427.
17. Livelli A, Orofino GC, Calcagno A, et al. Evaluation of a cognitive rehabilitation protocol in HIV patients with associated neurocognitive disorders: Efficacy and stability over time. Front Behav Neurosci 2015;9:306.
18. Kieburtz K, Price RW, Sidtis JJ, et al. Pilot study of didanosine in patients with HIV dementia. J NeuroAIDS 1996;1:1-5.
19. Sidtis JJ, Gatsonis C, Price RW, et al. Zidovudine treatment of the AIDS dementia complex: Results of a placebo-controlled trial. Ann Neurol 1993;33:343-349.

20. Decloedt EH, Freeman C, Howells F, et al. Moderate to severe HIV-associated neurocognitive impairment: A randomized placebo-controlled trial of lithium. Medicine 2016;95:e5401.
21. Letendre SL, Woods SP, Ellis RJ, et al. Lithium improves HIV-associated neurocognitive impairment. AIDS 2006;20:1885-1888.
22. Gates TM, Cysique LA, Siefried KJ, et al. Maraviroc-intensified combined antiretroviral therapy improves cognition in virally suppressed HIV-associated neurocognitive disorder. AIDS 2016;30:591-600.
23. Nakasujja N, Miyahara S, Evans S, et al. Randomized trial of minocycline in the treatment of HIV-associated cognitive impairment. Neurol 2013;80:196-202.
24. Schifitto G, Navia BA, Yiannoutsos CT, et al. Memantine and HIV-associated cognitive impairment: A neuropsychological and proton magnetic resonance spectroscopy study. AIDS 2007;21:1877-1886.
25. Zhao Y, Navia BA, Marra CM, et al. Memantine for AIDS dementia complex: Open-label report of ACTG 301. HIV Clin Trials 2010;11:59-67.
26. Schifitto G, Zhang J, Evans SR. A multicenter trial of selegiline transdermal system for HIV-associated cognitive impairment. Neurol 2007;69:1314-1321.
27. Simioni S, Cavassini M, Annoni J-M. Rivastigmine for HIV-associated neurocognitive disorders. Neurol 2013;80:553-560.
28. Rew L. The systematic review of literature: Synthesizing evidence for practice. J Spec Pediatr Nurs 2011;16:64-69

Appendix

Figure 1

Study selection process

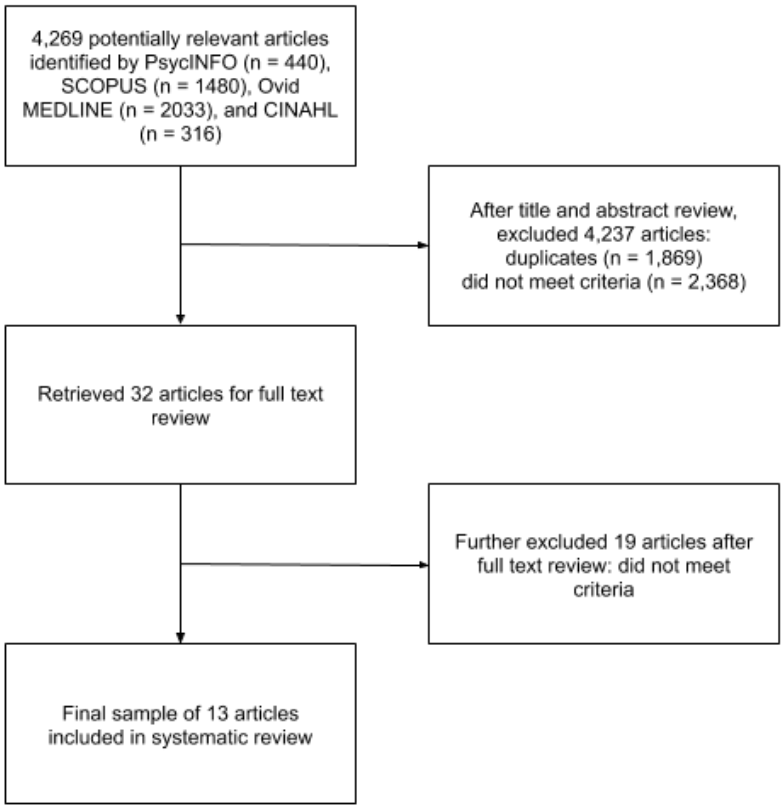

Table 1 Descriptive variables of studies examining therapeutic interventions for HAND

Author	Country	Setting	Sample size	Completion rate (%)	Mean education (years)	Mean age (years)	% Male
Becker 2012[16]	USA	HIV specialty clinic	1	100	13	54	100
Brew 1996[15]	Not reported	Not specified	10	50	Not reported	39.8	Not reported
Decloedt 2016[20]	South Africa	Public sector ART clinics and research clinic	66	92	Not specified	39.98	12
Gates 2016[22]	Australia	Hospital	17	82	12.05	54.99	100
Kieburtz 1997[18]	USA	Not specified	10	50	15.4	37.8	90
Letendre 2006[21]	USA	University-based tertiary care center	8	100	15.625	45.5	88
Livelli 2015[17]	Italy	Hospital infectious disease clinic	32	100	9.5	48.75	75
Nakasujja 2013[23]	Uganda	Outpatient HIV health clinic	73	71	Not specified	Not specified	10
Schifitto 2007[24]	USA	21 Adult AIDS Clinical Trial Group Centers	140	76	Not specified	43 (median)	90
Schifitto 2007[26]	USA	Not specified	128	Not reported	13 (median)	45 (median)	88
Sidtis 1993[19]	USA	Not specified	40	68	Not reported	35.1	98
Simioni 2013[27]	Switzerland	Hospital	17	71	12.6	55.1	71
Zhao 2010[25]	USA	21 Adult AIDS Clinical Trial Group Centers	99	63	Not specified	43 (median)	90

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Table 2 Characteristics of studies examining therapeutic interventions for HAND

Author	Intervention	Study design	Study length	Experimental groups	Neuro-cognitive prevalence	Dosage and treatment frequency	Relevant study objective
Becker 2012[16]	cART (efavirenz-emtricitabine-tenofovir)	Case study	6 months	cART (n = 1)	HAD	Daily	To assess the cognitive function of a treatment-naive patient presenting with HAD after 6 months of treatment with cART
Brew 1996[15]	Atevirdine	Single-arm, open label pilot study	12 weeks	Atevirdine (n = 12)	All participants had ADC stage 1 or 2	1800 mg daily in three divided doses	To determine the efficacy of the non-nucleoside reverse transcriptase inhibitor atevirdine in the treatment of ADC
Decloedt 2016[20]	Lithium (adjunctive to ART)	Randomized, placebo-controlled trial	24 weeks	Lithium (n = 34); Placebo (n = 32)	All participants had moderate to severe HAND (GDS >= 0.5)	250 mg lithium carbonate 12-hourly and matching placebo, titrated to achieve maintenance target plasma concentration of 0.6 to 1.0mmol/L	To evaluate the 24-week efficacy and safety of lithium in patients with moderate to severe HAND

Table 2 *(Continued)*

Author	Intervention	Study design	Study length	Experimental groups	Neuro-cognitive prevalence	Dosage and treatment frequency	Relevant study objective
Gates 2016[22]	Maraviroc (adjunctive to ART)	Double-blinded, open label pilot, randomized, controlled trial	12 months	cART only control (n = 8); maraviroc-intensification (n = 9)	All participants had HAND with symptom progression within the last 6 months noted by their primary physician	Oral maraviroc 150 mg/300 mg/600 mg twice daily	To investigate whether intensification of cART with the CC chemokine receptor type 5 (CCR5) entry inhibitor maraviroc leads to improvement in global neurocognitive functioning in virally suppressed men with HAND
Kieburtz 1997[18]	Didanosine	Single-arm, open label pilot study	16 weeks	Didanosine (n = 10)	All participants had ADC Stage 1-3	375 mg or 250 mg oral didanosine twice daily	To evaluate the effects of didanosine on NP functioning in individuals with ADC
Letendre 2006[21]	Lithium (adjunctive to ART)	Single-arm, open label pilot study	12 weeks	Lithium (n = 8)	All participants had HNCI subcategories of MCMD or HAD	Oral lithium initiated at 300 mg daily, titrated to maintain 12-h trough concentrations between 0.4 and 0.8 mEq/l	To determine the effects of low-dose oral lithium on the NP performance of individuals diagnosed with HAND

Table 2 *(Continued)*

Author	Intervention	Study design	Study length	Experimental groups	Neuro-cognitive prevalence	Dosage and treatment frequency	Relevant study objective
Livelli 2015[17]	Cognitive Rehabilitation Protocol (adjunctive to ART)	Prospective controlled experiment	4 months, with additional 6 months follow up for experimental group	Experimental group (receiving cognitive treatment) (n = 16); control group (receiving standard of care) (n = 16)	Half of the participants (n = 16) were diagnosed with HAND, half were not	36 50-minute sessions over 4 months	To examine the efficacy and durability of a cognitive rehabilitation treatment for HAND in HIV+ adults taking suppressive antiretroviral therapy
Nakasujja 2013[23]	Minocycline	Randomized, double-blind, placebo-controlled trial	24 weeks (plus additional 24 week open label phase)	Minocycline (n = 36); placebo (n = 37)	All participants had HIV dementia and scored <= 10 on the IHDS	100 mg minocycline or matching placebo orally every 12 hours	To evaluate the efficacy and safety of minocycline in the management of HIV-associated cognitive impairment
Schifitto 2007[24]	Memantine (adjunctive to ART)	Phase II randomized, double-blind, placebo-controlled, multi-site trial	20 weeks	Memantine (n = 70); placebo (n = 70)	All participants had mild to severe ADC (Stage 1 [n = 107], Stage 2/3 [n = 33])	Memantine initiated at 10 mg daily escalated to 40 mg daily or up to maximum tolerated dose or matching placebo	To assess the safety and efficacy of memantine as treatment of HIV-associated cognitive impairment
Schifitto 2007[26]	Selegiline Transdermal System (adjunctive to ART)	Placebo-controlled, multi-site, three-arm study	24 weeks	STS 3 mg (n = 42); STS 6 mg (n = 43); placebo (n = 43)	All participants had ADC Stages 0.5 (n = 44), 1 (n = 71), or 2 (n = 13)	STS 3 mg/24 hours, STS 6 mg/24 hours, or matching placebo patches daily	To assess the efficacy of STS for the treatment of HIV-associated cognitive impairment.

Table 2 *(Continued)*

Author	Intervention	Study design	Study length	Experimental groups	Neuro-cognitive prevalence	Dosage and treatment frequency	Relevant study objective
Sidtis 1993[19]	Zidovudine	Randomized, double-blind, placebo-controlled, multi-site trial	16 weeks	"Low-dose" 1,000 mg zidovudine (n = 12); "high-dose" 2,000 mg zidovudine (n = 13); placebo (n = 15)	All participants had mild to moderate ADC	200 or 400 mg zidovudine or matching placebo five times daily	To examine the efficacy of two doses of zidovudine for the treatment of ADC
Simioni 2013[27]	Rivastigmine (adjunctive to ART)	Randomized, double-blind, placebo-controlled, crossover pilot study	20 weeks on drug/off drug (with 6 week washout period in between, 46 weeks total)	Rivastigmine followed by placebo (n = 9); placebo followed by rivastigmine (n = 8)	All participants had HAND subcategories MND or HAD	1.5 mg/day increased over two weeks to 12 mg/day	To assess the efficacy of rivastigmine for the treatment of HAND in a cohort of long-lasting aviremic HIV-1 patients
Zhao 2010[25]	Memantine (adjunctive to ART)	Open label phase of larger clinical trial (following a double-blind phase)	60 weeks (initial 12-week open-label phase, followed by additional 48-week extension)	all participants received same treatment, but were grouped for analysis based on grouping in previous double-blind phase: Mem/O (n = 51); Placebo/O (n = 48)	All participants had ADC Stage 1 or greater and NP impairment, defined as at least 2 SD below mean on at least 2 NP tests	Up to 40 mg/day by week 12	To evaluate the long-term safety and efficacy of memantine use as treatment of HIV-associated cognitive impairment

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Table 3 Neuropsychological characteristics of studies examining therapeutic interventions for HAND

Author	Diagnostic assessment/criteria	Primary efficacy endpoint	NP testing battery	NP baseline	NP outcome
Becker 2012[16]*	Not reported	Change in domain and global impairment ratings ranging from 1 (superior) to 9 (severely impaired) from baseline to study completion	Letters and animals fluency, TMT-A/B, DSST, Block Design, HVLT-TR, HVLT-D, GP	Evidence of HAD; moderate to severe deficits in cognitive function	With the exception of memory and learning ratings, test performance improved from impaired to borderline and normal
Brew 1996[15]*	Price-Brew Scale	Price-Brew Scale score below ADC Stage 1 and improvement in NP performance from baseline to study completion	Price-Brew Scale; neurological and neuropsychological assessment score (testing battery not specified)	All participants had ADC Stage 1 or 2 and combined neurological and NP impairment score greater than 4 (normal <= 4)	4 out of 5 patients improved to below ADC Stage 1 (0 or 0.5); mean combined impairment score was 19.6 at baseline and 5.0 at week 12
Decloedt 2016[20]	GDS categories: normal (GDS <0.25); mild-moderate impairment (0.25 <= GDS <= 0.75); and severe impairment (GDS >= 0.75)	Change in GDS from baseline to study completion	MAT, DS, and PASAT (attention); HVLT (learning and memory); FT-D/ND and GP-D/ND (motor speed); TMT-A, CT-1, and DSC-W-III (psychomotor speed); CT-2, SCWT, and WCST (executive function); ROCF (visual learning and memory); animals and fruits and vegetables (verbal fluency).	All participants had a GDS >= 0.5	Adjunctive lithium in patients with HAND had no benefit on neurocognitive impairment compared with placebo when assessing NP test performance

Table 3 *(Continued)*

Author	Diagnostic assessment/criteria	Primary efficacy endpoint	NP testing battery	NP baseline	NP outcome
Gates 2016[22]*	HAND severity categorized as ANI, MND, or HAD; 2-step process to confirm HAND diagnosis at screening/baseline	Change in cognitive functioning across study time-points (baseline, 6 months, 12 months) as measured by a global NPZ	CogState brief computerized battery supplemented with written NP tests (CogState DET and IDN, TMT-A/B, DSC-W-III [speed of information processing]; CogState One-Back and Two-Back [attention and working memory]; GP [motor coordination]; CogState ISLT-L [verbal learning]; CogState ISLT-DR [verbal memory])	No significant differences in global NPZ scores between study arms at baseline	Medium to large effect sizes were observed favoring improved global NP functioning in maraviroc arm over control arm over time yielding a large between groups effect-size at 6 months and medium effect-size at 12 months
Kieburtz 1997[18]	Diagnosed with ADC stage 1-3	Change in global NPZ from baseline to study completion	TG, GP-D/ND, TMT-A/B, DSST, and FT-D/ND.	Group mean baseline z-score of -1.92 SD below the reference population	The change in the mean NPZ for the entire group, from baseline to the final visit, was not significant; trends towards improvement were observed for 5 participants
Letendre 2006[21]*	Clinical diagnosis of HAND – subcategories MCMD or HAD	Change in GDS from baseline to study completion	Not specified; "standard NP testing"	Not specified	NP performance improved in all participants after 12 weeks of lithium treatment

Table 3 *(Continued)*

Author	Diagnostic assessment/criteria	Primary efficacy endpoint	NP testing battery	NP baseline	NP outcome
Livelli 2015[17]*	Clinical diagnosis of HAND – subcategories ANI, MND, or HAD	Change in z-scores for each NP domain from baseline to study completion and 6-month follow-up; no global efficacy end point	MMSE and IHDS (screening); TMT-A and STROOP-T (speed information processing); RAVLT-IR, RAVLT-DR, and ROCF-DR (learning and memory); ToL, STROOP-E, TMT-B, FAB, and ROCF-C (abstraction/executive functioning); FAS and VS (verbal fluency); CORSI, DS, and TMT-B (attention/working memory); IADL (functional)	NP functioning of the two groups did not differ at baseline; both groups included participants who had HAND and participants who did not	Discordant clinical evolution in five out of eight domains in participants who received the intervention compared with those who did not: treated participants improved, untreated patients worsened
Nakasujja 2013[23]	IHDS, MSK scale	Change in U NP Sum z-score from baseline to study completion	U NP Sum z-score (including TG, GP-D/ND, CT-1/2, SD, WHO-UCLA VLT trial 5, WHO-UCLA VLT-DR, and DS-F/B) and MSK	Treatment arms were similar in baseline characteristics; 1 participant in minocycline arm had Stage 1 dementia (mild HAD) and the other 72 participants had stage 0.5 (equivocal or subclinical dementia)	Minocycline treatment of 100 mg given orally every 12 hours for 24 weeks did not improve HNCI among HIV+ individuals

Table 3 *(Continued)*

Author	Diagnostic assessment/criteria	Primary efficacy endpoint	NP testing battery	NP baseline	NP outcome
Schifitto 2007[24]	ADC stage was assessed according to MSK classification at each NP testing visit	Change in NPZ-8 from baseline to week 16; ½ of a SD in the summary score represents a clinically significant difference in ADC stage	TG, SD, GP-D/ND, TMT-A/B, two computerized reaction time tests (CalCAP system)	No significant differences in any NP measurement between the two study arms at baseline	Based on the NPZ-8, no significant difference was found between the memantine and placebo arms from baseline to week 16
Schifitto 2007[26]	Not specified	Change in NPZ-6 from baseline to study completion	NPZ-6 (RAVLT-TR/DR, GP-D/ND, and CalCAP (choice and sequential) tasks); NPZ-8 (TG, GP, TMT, SD, and CalCAP)	Baseline NPZ scores were comparable across the three groups with the exception of the TG task, where subjects assigned to placebo demonstrated significantly less deviation from the normative distribution than either STS group	Neither of the two STS arms showed improvement in primary or secondary cognitive outcomes compared with placebo
Sidtis 1993[19]*	Existing clinical diagnosis of mild to severe ADC based on presence of characteristic clinical symptoms and signs and affirmation of diagnosis with NP test battery	Clinical stabilization or improvement in performance on a battery of psychometric tests as measured by NPZ from baseline to study completion	VFT, TG, TMT-A/B, DSST, and FT-D/ND	No significant differences among the groups in ADC stage ($p=0.74$) or NPZ scores ($p=0.22$) at baseline	A significant improvement in NPZ was noted during the first 16 weeks of the study and the combined mean change for the participants in the two treatment arms was significantly different from the mean for the placebo group; however, among all pairwise comparisons, only the comparison between the 2,000-mg/day treatment group and the placebo group was significant

Table 3 *(Continued)*

Author	Diagnostic assessment/criteria	Primary efficacy endpoint	NP testing battery	NP baseline	NP outcome
Simioni 2013[27]	Frascati criteria	Improvement from baseline to week 20 (on drug) in ADAS-Cog score	ADAS-Cog examination (RT, TMT-A, and SD-W-III [information processing speed]; CANTAB RVP, CANTAB SWM error component, and DS-F/B [attention/working memory]; TMT-B, CANTAB SWM strategy component, and SOC [executive functioning]; RT motor component [motor skills]); HDS; IHDS	All participants had MND at baseline; baseline cognitive scores were equal in both treatment arms	No significant change was detected in the primary endpoint of change in improvement from baseline to week 20 (on drug) in ADAS-Cog score; one measure of processing speed (TMT-A) improved due to treatment effect
Zhao 2010[25]*	ADC stage was assessed according to MSK classification at each NP testing visit	Change in NPZ-8 from Week 20 (beginning of initial open-label phase) to week 32 (end of initial 12-week open-label study phase); one half of a SD in the summary score represents a clinically significant difference in ADC stage	TG, SD, GP-D/ND, TMT-A/B, CRT, and SRT	No statistically significant differences between groups Mem/O and Placebo/O were detected at baseline and Week 20	Participants in the Mem/O group had a marginally significant increase in NPZ-8 at Week 32 compared to Week 20, with a median increase of 0.14; the median NPZ-8 change at Week 32 in the Mem/O group was significantly higher than in the Placebo/O group

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Table 3 *(Continued)*

in study participants with HAND after intervention. Abbreviations used for neuropsychological tests: ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognitive subscale; CalCAP = California Computerized Assessment Package; CT-1/2 = Color Trails Test 1 or 2; CANTAB-RVP/SWM = Cambridge Neuropsychological Test Automated Battery Rapid Visual Information Processing/Spatial Working Memory; CORSI = Corsi's Block-Tapping Test; CRT = Choice reaction time; DET = Detection Task (CogState); DS-F/B = Digit Span forward/backward; DSC-W-III = Digit Symbol Coding subtest – WAIS III; DSST = Digit Symbol Substitution Test; FAB = Frontal Assessment Battery; FAS = Phonemic Fluency; FT-D/ND = Finger Tapping dominant hand/non-dominant hand; GP-D/ND = Grooved Pegboard dominant hand/non-dominant hand; HDS = HIV Dementia Scale; HVLT = Hopkins Verbal Learning Test; HVLT-D = Hopkins Verbal Learning Test Delay; HVLT-TR = Hopkins Verbal Learning Test Total Recall; IADL = Instrumental Activities of Daily Living; IDN = Identification Task (CogState); IHDS = International HIV Dementia Scale; ISLT-L/DR = International Shopping List Task learning/delayed recall; MAT = Mental Alternation Test; MMSE = Mini-Mental State Examination; MSK = Memorial Sloan-Kettering dementia scale; NP = neuropsychological; NPZ = neuropsychological z-score; PASAT = Paced Auditory Serial Addition Test; RAVLT-TR/IR/DR = Rey Auditory Verbal Learning Test total recall/immediate recall/delayed recall; ROCF-DR/C = Rey-Osterrieth Complex Figure delayed recall/copy; RT = Reaction time; SCWT = Stroop Color-Word Test; SD = Symbol Digit Test; SD-W-III = WAIS III Symbol Digit; SOC = Stockings of Cambridge test; SRT = Sequential reaction time; STROOP-E/T = Stroop Color Test errors/time; TG = Timed Gait; ToL = Tower of London; TMT-A/B = Trail Making Test A/B; U NP Sum = Uganda Neuropsychological Test Battery Summary Measure; VFT = Verbal Fluency Test; VS = Verbal Span; WCST = Wisconsin Card Sorting Test; WHO-UCLA VLT-DR = World Health Organization-University of California at Los Angeles Verbal Learning Test delayed recall