Published in final edited form as:

Res Nurs Health. 2018 February ; 41(1): 11–18. doi:10.1002/nur.21841.

Can Computerized Cognitive Training Reverse the Diagnosis of HIV-Associated Neurocognitive Disorder? A Research Protocol

David E. Vance [Professor and Director of Research and Scholarly Development],

School of Nursing, University of Alabama at Birmingham, Birmingham, Alabama, USA

Pariya L. Fazeli [Assistant Professor],

School of Nursing, University of Alabama at Birmingham, Birmingham, Alabama, USA

Andres Azuero [Associate Professor],

School of Nursing, University of Alabama at Birmingham, Birmingham, Alabama, USA

Virginia G. Wadley [Professor],

School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

Michael Jensen [Program Manager], and

School of Nursing, University of Alabama at Birmingham, Birmingham, Alabama, USA

James L. Raper [Professor and Director of the 1917 (HIV/AIDS) Clinic]

School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

Abstract

Nearly 50% of adults with HIV have some form of HIV-associated neurocognitive disorder (HAND), ranging from subtle to symptoms that interfere with everyday functioning and quality of life. HAND is diagnosed when a person performs more than 1 standard deviation below his or her normative mean on standardized measures in two or more cognitive domains (e.g., attention, speed of processing, verbal memory, executive functioning). As adults age with HIV, they are more likely to develop comorbidities such as cardiovascular disease, hypertension, and insulin resistance that may further contribute to poorer cognitive functioning and HAND. Certain computerized cognitive training programs may be able to improve specific cognitive domains in those with HIV. Such programs may be effective in changing the diagnosis of HAND in cognitively vulnerable adults. In this article we describe the design and methods of TOPS – the Training On Purpose Study. In this on-going experimental study, 146 older adults (50+) with HAND are randomized to either: 1) an Individualized-targeted cognitive training group, or 2) a no-contact control group. This study targets those cognitive domains in which participants experience a deficit and trains participants with the corresponding computerized cognitive training program for that domain. An individualized targeted cognitive training approach using cognitive-domain-specific cognitive training programs may offer symptom relief to those individuals diagnosed with HAND, which may actually reverse this diagnosis. Given that these cognitive training programs are commercially

Corresponding Author: David E. Vance, PhD, MGS, Professor, 1701 University Boulevard, School of Nursing, University of Alabama at Birmingham, Birmingham, AL 35294-1210, (o) 205-934-7589, devance@uab.edu.

Disclosures:

Dr. David Vance was a one-time consultant for Posit Science, Inc. in November, 2014. The software discussed in this article is developed and marketed by the same company.

available, this approach represents a potential paradigm shift in how HAND is considered and treated.

Keywords

brain fitness; cognitive reserve; cognitive training; HIV-Associated Neurocognitive Disorder; neuroplasticity; speed of processing

Approximately 50% of people with HIV experience some form of HIV-associated neurocognitive disorder (HAND), which may affect medication adherence and other instrumental activities of daily living (IADLs), mood, and quality of life (Vance, Cody, & Moneyham, 2017). These cognitive deficits are observed in several cognitive domains, including memory, learning, executive functioning, and attention. By 2020, 70% of adults with HIV in the United States will be 50 and older (United States Senate Special Committee on Aging, 2013). When comparing cognitive functioning of older and younger adults with and without HIV, older adults with HIV perform the worst; in fact, with increasing age with HIV, cognitive deficits can become more common and severe (Vance, Fazeli, & Gakumo, 2013).

Using Frascati criteria, a consensus-derived neuropsychiatric algorithm used extensively in the study of neuroAIDS, HAND is diagnosed when a person performs at least 1 to 2 *SD* below his or her age and educational (and gender and ethnicity when norms are available) normative means, on measures of two or more cognitive domains (e.g., verbal memory, speed of processing). Many individuals may be only a fraction of a *SD* below the cut off (Vance, Cody, & Moneyham, 2017). Unfortunately, pharmacological cognitive interventions have short-lived effects, if any, and can produce adverse side effects in a clinical population already prone to multiple comorbidities and polypharmacy (Vance, Mugavero, Willig, Raper, & Saag, 2011). Fortunately, computerized cognitive training interventions have been shown to improve or maintain cognition without adverse side effects (Lampit, Hallock & Valenzuela, 2014).

Mitigating the cognitive symptoms of HIV (i.e., HAND) is vital. First, HIV produces a form of accentuated or accelerated aging, including cognitive aging that can produce deficits across cognitive domains (Vance, Cody et al., 2017). Second, cognitive deficits in HIV are related to poorer everyday functioning and quality of life (Vance, Cody et al., 2017). Third, improvement in individual cognitive domains resulting from cognitive training translate into improved performance on everyday functioning and quality of life (Edwards et al., 2009).

Only four types of computerized cognitive training interventions have been studied in adults with HIV (Vance, Cody, et al., 2017; Weber, Blackstone, & Woods, 2013). First, Becker and colleagues partially randomized 60 adults with and without HIV to engage in 14 computerized targeted modules (e.g., knowledge, memory) over 24 weeks. No significant effects were found; however, adherence was poor. Second, Vance and colleagues (2012) randomized 46 older adults with HIV to either a speed of processing training group (10 hours of training) or a no-contact control group. Adherence was excellent, and improvements were observed on this cognitive domain that transferred to a timed laboratory

measure of instrumental activities of daily living. Third, Towe and colleagues (2017) randomized 21 adults with HIV to either a working memory training group (12 sessions over 10 weeks) or an attention-control group. Adherence was excellent, and improvements in working memory were observed in the active intervention group.

Fourth, in a pre/post case comparison study, Hossain and colleagues (2017) randomized three older adults with HAND to receive either 10 hours of speed of processing training, 20 hours of speed of processing training, or 10 hours of a sham internet training in which the participant engaged in normal internet activities on the computer that were not considered to have any therapeutic cognitive benefit. After training, it was observed that the participant who received 20 hours of speed of processing training improved on measures of speed of processing and more importantly, no longer met the cognitive hallmarks of HAND. This was the first study to suggest that a diagnosis of HAND may be reversed by using computerized cognitive training.

With only a handful of cognitive training studies in HIV, it is difficult to determine their clinical utility in this population. Yet, studies in older adults without HIV have shown their efficacy in improving specific cognitive abilities, some as much as 1 to 1.5 standard deviations (*SD*) above baseline performance or age/education-based norms (Lampit et al., 2014). In a meta-analysis of 52 cognitive training studies, the average cognitive improvement following cognitive training was 0.22 *SD* (Lampit et al., 2014). Although this seems to be a small to moderate effect size, such cognitive training programs may be effective in changing the diagnosis of HAND for some, by improving cognitive performance in specific domains to within acceptable performance norms. By targeting domain-specific cognitive deficits in those with HAND, the corresponding domain-specific computerized cognitive training may be able to improve cognitive functioning and reduce the severity of HAND or even reverse the diagnosis of HAND.

In an ongoing large randomized trial called Think Fast, we are focusing on an intervention to improve one cognitive skill in people with HAND: speed of processing (Vance, Fazeli et al., 2017). Participants are randomized to receive either 10 or 20 hours of speed of processing training or 10 hours of a sham Internet training. Speed of processing training has been shown in the cognitive aging literature to improve not only this cognitive ability but also to benefit other areas, such as better everyday functioning and safer on-the-road driving and driving simulator performance, protection against depression, and improved locus of control, self-rated health, and health-related quality of life (e.g., Ball & Vance, 2007; Vance, 2009; Vance, Dawson et al., 2007). As mentioned above, in the case comparison study by Hossain and colleagues (2017), the participant who received 20 hours of speed of processing training no longer met the cognitive criteria required for a HAND diagnosis. Although the Think Fast study was not designed to investigate if this intervention was effective in reversing HAND, it is encouraging that cognitive training may produce such an effect.

The current study, Training On Purpose Study or TOPS, extends this work by specifically targeting a broader range of cognitive deficits that contribute to HAND. This focus is important because cognitive deficits vary, and some people have more deficits in verbal memory and spatial ability than in speed of processing, and all these cognitive deficits can

negatively affect everyday functioning and quality of life (Vance, Cody et al., 2017). The TOPS study is designed to provide individualized treatment targeting the cognitive deficits that contribute specifically to each person's HAND diagnosis.

The purpose of this article is to describe the methodology of the TOPS study, funded through a R21 mechanism by the National Institute on Nursing Research. This protocol is designed to enroll older adults with HAND, assess which cognitive deficits they are experiencing, and target these cognitive domains with domain-specific cognitive training, referred to as Individualized-Targeted Cognitive Training. A tailored, patient-centered approach to standard cognitive training programs may offer symptom relief to those individuals diagnosed with HAND. The results may support a paradigm shift, in that HAND may not be a static "progressive" diagnosis.

Rationale and Background of Study Aims

In this simple two-group pretest-posttest experimental design, one primary study aim and two exploratory aims are examined. The primary aim is to compare older adults with HAND who receive Individualized-Targeted Cognitive Training to those who do not, in order to determine whether a change in HAND prevalence and severity occurs between groups. It is hypothesized that those who receive Individualized-Targeted Cognitive Training will experience a greater reduction in the prevalence and severity of HAND compared to those in the no-contact control group.

Exploratory Aim 1 is to compare adults who receive Individualized-Targeted Cognitive Training to those who do not in order to determine whether this improves everyday functioning (e.g., IADLs). Exploratory Aim 2 is to determine whether improvements in HAND and/or everyday functioning over time are associated with improvement in quality of life (e.g., depression, health-related quality of life). These aims are based upon the neuroscience literature on cognitive training in older adults.

Methods

To provide the context in which the intervention is administered, the following study characteristics are briefly reviewed: 1) overview; 2) participant characteristics; 3) measures; and 4) data analysis. Then, given the novelty of the intervention approach, this intervention is described more thoroughly in a separate section.

Study Overview

This TOPS Study utilizes a two-group pretest-posttest experimental design (Figure 1). After participants are recruited, a baseline (pretest) assessment is administered to participants during a ~2-hour visit. After the baseline assessment, participants' data are examined to determine a HAND diagnosis (see the Intervention Protocol section). Only participants with HAND are invited to continue with the study, at which point they are randomized to one of two groups: 1) 20 hours of Individualized-Targeted Cognitive Training group, or 2) no-contact control group. Stratified random assignment ensures an equal number of participants

are in each group by gender and minority status. After the Individualized-Targeted Cognitive Training is completed, participants are scheduled for their immediate posttest assessment.

Participants' Characteristics

Participants are recruited from HIV/AIDS and community clinics using flyers and other recruitment materials. Participants are instructed to call the research office for more information, at which point they are screened over the phone to determine whether they meet basic eligibility criteria. Participants must be 50 and older, diagnosed with HIV for at least a year, and English-speaking, as the assessments and computerized training programs are delivered in English. Those with significant neuromedical comorbidities (e.g., multiple sclerosis, mental retardation) are excluded. Other conditions (e.g., legally blind or deaf, currently undergoing radiation or chemotherapy, a history of brain trauma) that could affect cognitive assessment and cognitive training also necessitate exclusion (Vance et al., 2013).

Measures

The measures in Table 1 are used to diagnose HAND and assess the primary and exploratory aims. The normative data from these measures are essential to establish a HAND diagnosis. These cognitive measures are commonly used to make a clinical diagnosis of HAND and have good psychometric properties; many also have alternative versions to preclude practice effects (Blackstone et al., 2012).

Data Analysis

For Aim 1, HAND diagnosis is re-assessed at post-intervention to determine the proportions of participants who no longer meet HAND criteria. For each neurocognitive measure (see Table 1), repeated measures ANOVA will be used to examine changes by treatment group over time. If necessary, the models will be adjusted for baseline covariates found to be imbalanced at baseline or associated with attrition. Similar analyses will be used for Exploratory Aims 1 and 2.

Intervention Protocol

Participants are randomized to either the active intervention or a no-contact control group. The commercially available computer training programs can target a variety of cognitive domains. To understand how the active intervention was developed, it is necessary to understand the nuances of diagnosing HAND. From this understanding, a framework for selecting which cognitive domains to target for training is provided along with treatment fidelity considerations.

Diagnostic Classification

The Individualized-Targeted Cognitive Training protocol is based upon results of the HAND diagnostic process. Using a norms-based cognitive assessment measuring several cognitive domains, the severity of HAND is determined using the following Frascati criteria, a neuropsychological algorithm (Gandhi et al., 2010; Heaton et al., 2010). If a participant scores below 1 *SD* for their age/education (and gender and ethnicity when norms are available) in any 2 cognitive domains, they are defined as having the form of HAND referred

to as Asymptomatic Neurocognitive Impairment (ANI), which affects approximately 33% of people with HIV. If these cognitive deficits also influence everyday functioning, then they have the form of HAND referred to as Mild Neurocognitive Disorder, which affects 12% of people with HIV. If a participant scores 2 *SD* below normative levels in any 2 cognitive domains, then the level of HAND is referred to as HIV-Associated Dementia, which is rare and affects 2% of those with HIV.

Given the higher prevalence of ANI, we enroll participants in our study with at least ANI (whether or not they also meet criteria for more severe HAND classifications that involve everyday impairment). The effect of the intervention on daily outcomes will be assessed using the same laboratory-based everyday functioning measures. Although a clinician would go on to rule out potential causes of cognitive deficits beyond HIV, such as comorbid conditions (e.g., diabetes, depression, substance abuse), but given the prevalence of such conditions in the HIV population, clinicians and researchers generally diagnose HAND in the presence of these comorbidities. Our rigorous exclusion criteria eliminate those with severe conditions precluding a HAND diagnosis (e.g., history of brain trauma).

Figure 2 provides an example of a participant who was administered a normed-based cognitive assessment in six cognitive domains. This participant has HAND (in this case, ANI) because she scored below 1 *SD* on speed of processing and executive functioning and performed below 2 *SD* on verbal memory (Vance, Cody, et al., 2017). If she had performed slightly worse on speed of processing, such that her score was below 2 *SD*, then a diagnosis of HIV-Associated Dementia would be satisfied. (Typically, this also requires an evaluation of whether such cognitive problems contribute to difficulty with everyday functioning, but that is not taken into consideration here). Regardless, this participant would qualify for the study, but because there are three cognitive domains impaired, a decision must be made as to which cognitive domains to target for her individualized cognitive training plan.

Matching Cognitive Deficits to Domain-Specific Cognitive Training

In results of a meta-analysis of 52 domain-specific computerized cognitive training studies on healthy older adults, many studies employ between 10 and 20 hours of domain-specific cognitive training. There appeared to be a U-shaped dosage-therapeutic response, in which additional hours of training often resulted in fatigue and less cognitive gain (Lampit et al., 2014). If a participant has three or more cognitive domain deficits (e.g., speed of processing, executive function, and verbal memory), applying 10 hours of training to each cognitive domain would represent a significant burden of cost, time, and participant fatigue. Therefore, it behooves clinicians and researchers to be selective in the domains targeted for training.

A practical strategy is to allocate 10 hours to each of two domains (20 hours total). In this example (Figure 2), speed of processing, executive function, and verbal memory all contribute to an official diagnosis of HAND. Verbal memory (greater than 2 *SD*) could be targeted for cognitive intervention because that is the most severe cognitive deficit, but the domain-specific cognitive training in verbal memory may not be effective enough to create such a change, and the other two cognitive areas also require remediation, so a framework is needed to guide which domain-specific cognitive domains are to be targeted for treatment.

A hierarchy based upon Wicken's Model of Information Processing and the Diminished Speed of Processing Theory was developed to decide which cognitive domains are targeted for cognitive training. According to Wicken's Model of Information Processing, attentional processes underlie other basic cognitive processes including executive functioning, verbal learning, etc. Therefore, cognitive training that targets strengthening attention should be a primary candidate for intervention and remediation (Wickens, Hollands, Bandbury, & Parasuraman, 2013).

Likewise, according to the Diminished Speed of Processing Theory (Salthouse, 1996), the rate at which adults mentally process information slows with age. Speed of processing declines can occur at all stages of information processing, from initial encoding of a stimulus to the execution of a response (Cerella, 1994). This reduction in speed of processing places demands on other cognitive systems. In 186 adults with HIV, speed of processing "fully mediated the effects of age on learning, memory, and executive functioning and partially mediated the effect of major depressive disorder on learning and memory" (Fellows, Byrd, & Morgello, 2014, p.806). Others have shown that increasing age affects speed of processing (effect size = -.69) to a greater degree than memory (effect size = -.25) or executive functioning/reasoning (effect size = -.27), which reinforces a focus on speed of processing (Fristoe, Salthouse, & Woodard, 1997). Obviously, speed of processing is further compromised by the combination of aging with HIV.

Based on these two cognitive models and the algorithm with which HAND is diagnosed, the Individualized-Targeted Cognitive Training Framework was developed (Figure 3). If cognitive deficits are observed in speed of processing or attention, domain-specific cognitive training exercises designed to improve them will be selected over training in other cognitive domains. The underlying cognitive processes of attention and speed of processing may singularly or in combination translate to improvement in other cognitive domains. If either speed of processing or attention does not fall within 1 *SD* below the participant's normative mean, then the least compromised (1.5 *SD* versus 1.7 *SD* below the normative mean) cognitive domain closest to 1 *SD* below the normed mean is targeted for cognitive training. The rationale for this is: 1) there are more cognitive resources for that domain to benefit from training; and 2) even slight improvement in this cognitive domain may reverse the diagnosis of HAND and improve everyday function and quality of life.

Although only two cognitive domains are targeted for training (10 hours of training each), within a cognitive domain (e.g., Spatial Ability), two or more cognitive training exercises may be employed (e.g., Mental Maps, True North; Table 2). These exercises have been selected based on the cognitive domain being targeted for improvement. These exercises provide immediate feedback as well as intermittent summary feedback and are logarithmically customized to the participants' individual ability; the rate, difficulty, and/or complexity of each game are systematically decreased or increased based on participants' performance, so as to always be challenging but not impossible.

Treatment Adherence

A treatment adherence checklist is used to review with participants the amount of time that they have engaged in training. The software monitors the amount of time participants spend

engaged in each exercise. In the meta-analysis described earlier, Lampit and colleagues (2014) found optimal therapeutic effects occurred when training sessions lasted 60 minutes or less and were administered 1-3 times per week. These dosage parameters were incorporated in the TOPS Study protocol. Furthermore, as in the ACTIVE Study, participants are considered to be trained in each cognitive domain when they successfully complete 8 to 10 hours of training in each domain (Ball et al., 2002). This completers-only analysis is appropriate for use when examining the actual potential of the cognitive training. To include participants who do not complete training, the data can be examined using an intent-to-treat analysis as well.

Discussion

Collectively, past cognitive training studies have provided extensive evidence that such cognitive training programs improve cognition in normal older adults; likewise, early studies in adults with HIV provide increasing support for such findings (Vance, Cody, et al., 2017). Given the overwhelming work on cognitive training already accomplished, the TOPS Study will advance the treatment of HAND. This R21 proof of concept study translates noninvasive, commercially-available computerized cognitive training exercises to improve cognition and reduce the prevalence/severity of HAND as well as improve everyday function and quality of life in adults aging with HIV. Furthermore, a methodological enhancement is incorporated – a selection framework for targeting which cognitive domain should be trained.

To date, no other study team is known to have attempted to specifically reverse a HAND diagnosis. Although the causes of HAND and impact of HAND have been widely studied, few behavioral interventions have actually been attempted to ameliorate the effects of HAND or even reverse it. If the TOPS Study successfully produces a therapeutic benefit and can reverse the diagnosis of HAND, this behavioral approach represents a significant strategy in which to help facilitate successful cognitive aging in this population. Nurses, particularly psychiatric and mental health nurses and clinicians, can then incorporate cognitive training within their treatment regimens. Furthermore, this intervention may be paired with other cognitive interventions that may generate synergistic benefits for patients as they age with HIV.

Acknowledgments

This study was funded by an NIH/NINR R21-award (1R21NR016632-01; ClinicalTrials.gov (NCT03122288); Vance, Principal Investigator) titled “Individualized-Targeted Cognitive Training in Older Adults with HAND” and by an NIH/NIMH R01-award (1R01MH106366-01A1; ClinicalTrials.gov (NCT02758093); Vance, Principal Investigator) titled “An RCT of Speed of Processing Training in Middle-aged and Older Adults with HIV”. Physical support for the study was provided by an NIH grant for the Edward R. Roybal Center for Translational Research in Aging and Mobility (P30 AG022838).

References

- Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Vital Elderly Study, G. Effects of cognitive training interventions with older adults: A randomized controlled trial. *Journal of the American Medical Association*. 2002; 288:2271–2281. [PubMed: 12425704]

- Becker BW, Thames AD, Woo E, Castellon SA, Hinkin CH. Longitudinal change in cognitive function and medication adherence in HIV-infected adults. *AIDS and Behavior*. 2011; 15:1888–1894. DOI: 10.1007/s10461-011-9924-z [PubMed: 21437726]
- Blackstone K, Moore DJ, Franklin DR, Clifford DB, Collier AC, Marra CM, Heaton RK, et al. Defining neurocognitive impairment in HIV: Deficit scores versus clinical ratings. *Clinical Neuropsychologist*. 2012; 26:894–908. DOI: 10.1080/13854046.2012.694479 [PubMed: 22708483]
- Cerella J. Generalized slowing in Brinley plots. *Journal of Gerontology*. 1994; 49:P65–P71. <https://doi.org/10.1093/geronj/49.2.P65>. [PubMed: 8126361]
- Edwards JD, Myers C, Ross LA, Roenker DL, Cissell GM, McLaughlin AM, Ball KK. The longitudinal impact of cognitive speed of processing training on driving mobility. *Gerontologist*. 2009; 49:485–494. DOI: 10.1093/geront/gnp042 [PubMed: 19491362]
- Fellows RP, Byrd DA, Morgello S. Effects of information processing speed on learning, memory, and executive functioning in people living with HIV/AIDS. *Journal of Clinical and Experimental Neuropsychology*. 2014; 36:806–817. DOI: 10.1080/13803395.2014.943696 [PubMed: 25111120]
- Fristoe NM, Salthouse TA, Woodard JL. Examination of age-related deficits on the Wisconsin Card Sorting Test. *Neuropsychology*. 1997; 11:428–436. [PubMed: 9223147]
- Gandhi NS, Moxley RT, Creighton J, Roosa HV, Skolasky RL, Selnes OA, Sacktor N, et al. Comparison of scales to evaluate the progression of HIV-associated neurocognitive disorder. *HIV Therapy*. 2010; 4:371–379. DOI: 10.2217/hiv.10.23 [PubMed: 20824119]
- Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, et al. Group, C. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010; 75:2087–2096. DOI: 10.1212/WNL.0b013e318200d727 [PubMed: 21135382]
- Hossain S, Fazeli PL, Tende F, Bradley B, McKie P, Vance DE. The potential of computerized cognitive training on HIV-associated neurocognitive disorder: A case comparison study. *Journal of the Association of Nurses in AIDS Care*. 2017; 28:971–976. [PubMed: 28784586]
- Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: A systematic review and meta-analysis of effect modifiers. *PLoS Medicine*. 2014; 11(11):e1001756.doi: 10.1371/journal.pmed.1001756 [PubMed: 25405755]
- Salthouse TA. Constraints on theories of cognitive aging. *Psychonomic Bulletin and Review*. 1996; 3:287–299. DOI: 10.3758/BF03210753 [PubMed: 24213930]
- Towe SL, Patel P, Meade CS. The acceptability and potential utility of cognitive training to improve working memory in persons living with HIV: A preliminary randomized trial. *Journal of the Association of Nurses in AIDS Care*. 2017; 28:633–643. DOI: 10.1016/j.jana.2017.03.007 [PubMed: 28442186]
- United States Senate Special Committee on Aging. Older Americans: The changing face of HIV/AIDS in America; Washington, DC. One Hundred Thirteenth Congress, Hearing, First Session; 2013.
- Vance DE, Cody SL, Moneyham L. Remediating HIV-associated neurocognitive disorders via cognitive training: A perspective on neurocognitive aging. *Interdisciplinary Topics in Gerontology and Geriatrics*. 2017; 42:173–186. DOI: 10.1159/000448562 [PubMed: 27875832]
- Vance DE, Fazeli PL, Gakumo CA. The impact of neuropsychological performance on everyday functioning between older and younger adults with and without HIV. *Journal of the Association of Nurses in AIDS Care*. 2013; 24:112–125. DOI: 10.1016/j.jana.2012.05.002 [PubMed: 22943982]
- Vance DE, Fazeli PL, Ross LA, Wadley VG, Ball KK. Speed of processing training with middle-age and older adults with HIV: A pilot study. *Journal of the Association of Nurses in AIDS Care*. 2012; 23:500–510. DOI: 10.1016/j.jana.2012.01.005 [PubMed: 22579081]
- Vance D, Fazeli P, Shacka J, Nicholson W, McKie P, Raper J, Ball K, et al. Testing a computerized cognitive training protocol in adults aging with HIV-associated neurocognitive disorder: An RCT in the Southern United States. *Journal of Medical Internet Research: Research Protocols*. 2017; 6(4):e68.doi: 10.2196/resprot.6625
- Vance DE, Mugavero M, Willig J, Raper JL, Saag MS. Aging with HIV: A cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. *Journal of the Association of Nurses in AIDS Care*. 2011; 22:17–25. DOI: 10.1016/j.jana.2010.04.002 [PubMed: 20471864]

- Weber E, Blackstone K, Woods SP. Cognitive neurorehabilitation of HIV- associated neurocognitive disorders: A qualitative review and call to action. *Journal of NeuroVirology*. 2013; 19:65–74. DOI: 10.1007/s11065-013-9225-6 [PubMed: 23250704]
- Wickens, CD., Hollands, JG., Bandbury, S., Parasuraman, R. *Engineering psychology and human performance*. Upper Saddle River, NJ: Pearson; 2013.
- Wolinsky FD, Mahncke H, Vander Weg MW, Martin R, Unverzagt FW, Ball KK, Tennstedt SL, et al. Speed of processing training protects self-rated health in older adults: Enduring effects observed in the multi-site ACTIVE randomized controlled trial. *International Psychogeriatrics*. 2010; 22:470–478. DOI: 10.1017/S1041610209991281 [PubMed: 20003628]
- Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Stoddard A, Tennstedt SL. The ACTIVE cognitive training trial and health-related quality of life: protection that lasts for 5 years. *Journals of Gerontology Series A, Biological Sciences and Medical Sciences*. 2006; 61:1324–1329.
- Wolinsky FD, Vander Weg MW, Martin R, Unverzagt FW, Ball KK, Jones RN, Tennstedt SL. The effect of speed-of-processing training on depressive symptoms in ACTIVE. *Journals of Gerontology Series A, Biological Sciences and Medical Sciences*. 2009; 64:468–472. DOI: 10.1093/gerona/gln044
- Wolinsky FD, Vander Weg MW, Martin R, Unverzagt FW, Willis SL, Marsiske M, Tennstedt SL, et al. Does cognitive training improve internal locus of control among older adults? *Journals of Gerontology Series B, Psychological Sciences and Social Sciences*. 2010; 65:591–598. DOI: 10.1093/geronb/gbp117

Figure 1.
Study Methodological Flowchart.

Figure 2. Example of Diagnosing HAND and Targeting Domain-Specific Cognitive Training

In this example, the participant performed more than 1 standard deviation (*SD*) below her age and education normed mean on speed of processing and executive functioning, and more than 2 *SD* below her age and the education-normed mean on verbal memory. Using the framework (Figure 3) of targeting speed of processing and attention deficits for training, speed of processing is one of the domains selected for training for this participant because this deficit is observed. In other cases, the cognitive domain that is more than 1 *SD* below the normed mean but closest to 1 *SD* below the mean is selected for training because such a deficit may be improved enough to establish a normal cognitive profile.

Figure 3.
Individualized-Targeted Cognitive Training Framework.

Table 1

Study Measures That Correspond to Study Aims

Demographic, Background, and Covariate Measures	Aim 1: HAND Diagnosis and Cognitive Functioning	Exploratory Aim 1: Everyday Functioning	Exploratory Aim 2: Quality of Life
Demographic questionnaire	Speed of Processing (i.e., Trails Making Test A) Attention (i.e., Paced Auditory Serial Attention Test)	Timed Instrumental Activities of Daily Living	Centers for Epidemiological Studies – Depression (CES-D)
Wide Range Achievement Test – 4 (Educational Quality)	Verbal Learning (i.e., HVLT-R) Delayed Verbal Memory (i.e., HVLT-R Delayed Recall)	Medication Adherence	Locus of Control
Addiction Severity Index	Spatial Learning (i.e., BVMT-R)		Self-rated Health and Health- related Quality of Life
HIV History and Status	Delayed Spatial Memory (i.e., BVMT-R Delayed Recall)		
Medical Records	Executive Functioning (i.e., Trails Making Test B)		Cognitive Failures Questionnaire

Notes. BVMT-R = Benton Visuospatial Memory Test – Revised; HVLT-R = Hopkins Verbal Learning Test – Revised.

Table 2**Deficits in Cognitive Domains That Are Matched to Specific Cognitive Training**

Cognitive Domain Assessed for HAND	Cognitive Training Exercises Matching the Cognitive Domain Being Measured ^a
<p>Attention – Focusing one’s thoughts on a particular activity while ignoring distractors is an essential component of encoding information needed for other cognitive domains.</p>	<p>Divided Attention – This exercise requires one to react to particular details (e.g., shapes, colors) while ignoring other information.</p>
<p>Speed of Processing – A 2014 study of 186 adults with HIV found that speed of processing “fully mediated the effects of age on learning, memory, and executive functioning and partially mediated the effect of major depressive disorder on learning and memory” (Fellows et al., 2014, p. 806).</p>	<p>Target Tracker – This exercise requires one to visually scan and keep track of circular objects that move on the screen; this has target features similar to the Trails A test.</p> <p>Double Decision – This exercise is designed specifically to improve visual speed of processing. The task adapts by increasingly presenting targeted stimuli faster as participants become faster in detecting the type and location of such stimuli.</p> <p>Hawkeye – This exercise requires one to quickly notice which specific birds are within one’s peripheral view, specifically honing visual speed of processing and precision.</p>
<p>Verbal Ability (Verbal Learning or Delayed Verbal Memory) – These exercises are designed to help one attend to word sounds and practice committing them to memory, tasks similar to the cognitive measures of verbal learning and memory.</p>	<p>Visual Sweeps – This exercise requires one to notice whether two spatial frequency sweeps (movements bars) are swept out or in at very rapid presentation speeds.</p> <p>Memory Grid – This exercise requires one to match cards that have certain syllable sounds. Thus, it is designed to also improve auditory processing which is important for verbal learning and memory as measured by the HVLTL.</p>
<p>Spatial Ability (Spatial Learning or Delay Spatial Memory) – These exercises are designed to utilize one’s mental rotation, navigation, and sequentially remember presentation of landmarks in a virtual environment.</p>	<p>Syllable Stacks – Using the same syllables in the Memory Grid exercises, this “serial memory-span” exercise requires one to “listen to a series of syllables and then repeat them in order” over increasingly challenging conditions which is important for encoding needed for verbal learning and verbal memory.</p> <p>Mental Maps – This exercise requires one to use landmarks to develop a mental map and “remember the relative locations of important objects”.</p> <p>True North – This exercise requires one to use cardinal directions to find one’s way in a city, thus utilizing spatial memory and navigational skills.</p>

^a for more detail, please see POSIT Science at www.brainhq.com.