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Assessing and Treating Forgetfulness and Cognitive Problems in Adults with HIV

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Abstract

In addition to the immune system, HIV affects the nervous system and the brain producing neurological sequelae, often resulting in forgetfulness and cognitive problems. These problems can compromise medication adherence, interfere with instrumental activities of daily living such as driving and managing finances, increase dependency, and decrease quality of life. Cognitive problems emerge due to a variety of reasons; likewise, several evidence-based methods to mitigate causes and compensate for cognitive problems can be used alone or in combination. This article focuses on non-pathological, non-dementia forgetfulness and cognitive problems. However, dementia must be considered and assessed as measured by marked cognitive decline over time. Methods for assessing and measuring forgetfulness and cognitive problems are provided. In addition, methods of treating non-pathological cognitive problems are provided ranging from Recommended for Practice to Not Recommended for Practice. A case study is presented to demonstrate how to implement recommended treatment options.

Keywords

aging; cognitive remediation; co-morbidity; forgetfulness; HIV; speed of processing

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Problem

Active antiretroviral therapy (ART) has dramatically reduced the incidence and prevalence of HIV-related dementia, yet memory and other cognitive problems persist. Such neuropsychological impairments present themselves as cognitive problems that interfere with everyday functioning. Declines in memory (i.e., forgetfulness) are usually the hallmark of such cognitive problems. In fact, forgetfulness tends to be the more salient feature of cognition that patients complain about the most because it is more obvious and noticeable to the individual and his or her family, friends, and coworkers (Simioni et al., 2010). Memory is but one of many cognitive domains adversely affected by HIV, including executive functioning (i.e., reasoning), speed of processing, attention, psychomotor ability, and language (Hardy & Vance, 2009; Reger, Welsch, Razani, Martin, & Boone, 2002). Declines in one domain such as speed of processing may adversely affect another domain such as memory. This means that if there is a cognitive problem in one area, a more subtle and less obvious decline in another cognitive domain may be likely (Vance, Graham, Fazeli, Heaton, & Moneyham, 2012). Likewise, studies have suggested that while some people living with HIV (PLWH) can give an accurate account of their cognitive problems, others experience an inability to monitor and accurately recognize problems in cognition. This cognitive ability is referred to as metacognition (i.e., thinking about thinking; Vance, Ross, & Downs, 2008). Therefore, relying solely on self-report of cognition from patients may not always yield a valid assessment.

In a cross-sectional study of 1,555 adult PLWH from six university clinics in the United States, 52% experienced measureable neuropsychological impairment (33% asymptomatic neurocognitive impairment, 5% confounded cases of neurocognitive impairment, 12% mild neurocognitive disorder, and 2% HIV-associated dementia; Heaton et al., 2010). In HIV, cognitive problems can manifest quickly, gradually, or not at all depending on a variety of factors such as disease severity or existing cognitive resources. For example, changes in brain metabolism and cognition have been detected in many adults just 1 year after diagnosis (Basso & Bornstein, 2000; Bornstein et al., 1993; Lentz et al., 2011); yet there remains a high degree of variability, with some individuals being more resistant to such cognitive problems than others. Bornstein and colleagues (1993) found that those already performing poorly at baseline were more likely to exhibit more cognitive declines 1 year later; likewise, Basso and Bornstein (2000) found that those with better pre-morbid intelligence experienced fewer cognitive declines.

In an 8-year longitudinal study, Baldewicz and colleagues (2004) compared adults with and without HIV on several measures of cognition. Compared to uninfected adults, those with HIV experienced significant declines in fine motor speed and speed of processing, especially for those who progressed to AIDS. Studies show that AIDS (as indicated by CD4+ T lymphocyte counts < 200 cells/mm³) reduces cognitive functioning, with the lowest ever CD4+ T lymphocyte count (or CD4+ T lymphocyte count nadir) being predictive of current cognitive status (Heaton et al., 2010; Valcour et al., 2006). Therefore, it is important to monitor this cognitively vulnerable population, especially as they age and experience other cognitive impairing problems such as medical co-morbidities, such as diabetes, heart disease, substance use, depression, insomnia, and fatigue (Vance, Eagerton, Harnish, McKie-Bell, & Fazeli, 2011).

In this article, the definition and incidence of forgetfulness and cognitive problems are provided. Procedures for monitoring and assessing such cognitive problems are explained along with some clinical suggestions for addressing such problems. Following this, based upon the extant literature, interventions and clinical suggestions are discussed including both recommended and non-recommended strategies. As a note of caution, despite the well-

documented cognitive problems found in this clinical population, few studies have attempted to improve or maintain cognitive functioning or compensate for and adapt to such cognitive problems. Many of the recommendations in the current article have been garnered from the cognitive aging literature where several evidence-based approaches have demonstrated some success in ameliorating cognitive functioning in uninfected normal older adults. Although not tested in PLWH, such approaches are likely effective. Finally, a case study is provided to exemplify how to assess and provide treatment to adult PLWH who experience cognitive problems.

Definition of Symptoms

Forgetfulness and other cognitive problems can be identified subjectively (i.e., self-reported) and objectively (i.e., as observed by caregivers and/or clinician). Because forgetfulness is a common cognitive complaint, it will be defined separately but in tandem with other cognitive problems. In this article, *subjective forgetfulness* is defined as self-reported persistent failure to remember information that interferes with daily functioning and vocational pursuits, conversation and socializing, and instrumental activities of daily living such that it creates frustration or concern for the individual. Further, forgetfulness is reported as a common reason for non-adherence with medication regimes (Harzke et al., 2004). Likewise, *subjective cognitive problems* are defined as self-reported persistent failure to perform mental operations required to perform daily functioning and vocational pursuits, conversation and socializing, and instrumental activities of daily living such that it creates frustration or concern for the individual. For example, a patient may express concerns about overdrawing a checking account due to emerging difficulty balancing his or her checkbook. Because some adults with HIV also experience concurrent metacognitive dysfunction, they may be unaware of such forgetfulness or cognitive problems. Reliance on self-report of such problems should be approached with caution (Vance, Farr, & Struzick, 2008); observations during clinic visits should also be considered to assess *objective forgetfulness* and *objective cognitive problems*.

Incidence

The incidence of forgetfulness and cognitive problems varies and may increase by age, certain types of comorbidities (e.g., hepatitis C), substance use, and mood disturbances (Vance, Ross et al., 2008; Woods et al., 2007). Incidence varies by how forgetfulness and cognitive problems are defined and measured. There is no clear diagnosis or cut-point for forgetfulness or cognitive problems. Yet, comparisons between adults with and without HIV do show that PLWH consistently report more cognitive problems. Using the 16-item Prospective and Retrospective Memory Questionnaire (Crawford, Smith, Maylor, Sala, & Logie, 2003) with items such as *How often do you forget something that you were told a few minutes ago?*, Woods and colleagues (2007) found that adult PLWH reported significantly more cognitive problems in self-cued prospective memory and retrospective memory. In another study, Simioni and colleagues (2010) asked 200 relatively healthy adults with HIV (e.g., undetectable viral load; no major depression, current use of intravenous drugs, or history of a major central nervous system opportunistic infection within the past 3 years) three *yes/no* questions about cognitive problems (e.g., *Do you feel that you are slower when reasoning, planning activities, or solving problems?*); 27% reported at least one problem with memory (18%), mental slowing (16%), or attention (9%).

Assessment

Figure 1 provides a flowchart (Vance, Farr et al., 2008) that outlines the steps necessary to clinically evaluate patients for cognitive problems, forgetfulness, and cognitive complaints. In general, such assessments begin by listening to patients, asking questions about any

cognitive problems they are experiencing, and observing patients' reactions to questions. Possible questions can include, *How often are you forgetting to take your medication?*, *How often are you having trouble concentrating on reading a book or watching a movie?* or *How often has your partner mentioned concerns about your memory?* If cognitive problems are reported or there are suspicions of cognitive problems, this can be validated with one of many brief cognitive screeners (e.g., Mini-Mental Status Exam [MMSE]; Folstein, Folstein, & McHugh, 1975). If observable cognitive problems are detected with such screeners over time, possible treatable causes (e.g., poor sleep hygiene) can be determined and addressed. If alternative causes are successfully treated and cognitive problems are abated, no further action is necessary. On the other hand, if cognitive problems persist, comprehensive neuropsychological evaluation and treatment may be needed. Importantly, trajectory of cognitive functioning should be monitored as this may indicate more serious problems such as the development of mild cognitive impairment, HIV-associated neurocognitive disorders, or early stage dementia such as Alzheimer's disease or HIV-associated dementia.

Clinical Measurement Tools

A variety of tools can subjectively assess forgetfulness and cognitive problems and objectively assess cognitive functioning. Subjective assessment can indicate the impact of symptoms on a patient's quality of life and everyday functioning. Likewise, objective assessment allows the clinician to determine to what degree and in which cognitive domain(s) functioning is compromised. By assessing cognition both subjectively and objectively, the clinician can determine whether incongruence exists (e.g., a patient does not report any cognitive complaints but performs poorly on an objective tool of cognitive functioning), and incongruence can indicate a problem with metacognitive abilities.

Subjective Forgetfulness and Cognitive Complaint Tools

There are several subjective cognitive functioning measures including the Cognitive Failures Questionnaire (Broadbent, Cooper, FitzGerald, & Parkes, 1982) and the Prospective and Retrospective Memory Questionnaire (Crawford et al., 2003). Although questionnaires can be helpful in quantifying the subjective severity of forgetfulness and cognitive problems, they do not always predict objective cognitive functioning (Vance, Ross et al., 2008).

Objective Cognitive Functioning Tools

Many cognitive functioning screening tools can objectively measure cognition. While none of these tools are superior to a full neuropsychological evaluation, which commonly takes several hours and measures cognitive functioning in a variety of domains, they are useful for assessing global cognition in a few minutes within the clinical setting. The MMSE and the Montreal Cognitive Assessment are the recommended gold standards. Most clinicians are familiar with the MMSE, which takes about 10 minutes to administer and has a range from 0 to 30 with higher scores indicating better cognitive functioning. A score of 24 or less is generally used as a cut-off to indicate possible mild cognitive impairment or early stage dementia (Folstein et al., 1975). The cut-off can vary according to the education level of the individual (Toglia, Fitzgerald, O'Dell, Mastrogiovanni, & Lin, 2011).

In the past few years, the Montreal Cognitive Assessment has been recognized as being comparable to the MMSE and perhaps superior in sensitivity and specificity for classifying people with cognitive impairment (Sweet et al., 2011; Toglia et al., 2011). In addition, the Montreal Cognitive Assessment can be used in a variety of clinical populations including geriatric (Sweet et al., 2011), stroke (Cumming, Bernhardt, & Linden, 2011), and heart failure (Athilingam et al., 2011). The score sheet and instructions for the Montreal Cognitive Assessment are freely available on line (www.mocatest.org; See Figure 2). The Montreal Cognitive Assessment takes about 10 minutes to administer and scores range from 0 to 30;

scores 26 and higher are considered normal for global cognition. The Montreal Cognitive Assessment represents an easy and face valid tool that can be used to detect global cognitive functioning in adult PLWH (Koski et al., 2011).

Which Interventions are Effective for Preventing and Treating Forgetfulness and Cognitive Problems in People with HIV?

Interventions for addressing non-pathological forgetfulness and cognitive problems generally fall into two strategies: (a) restoring or improving existing cognitive functioning and (b) compensating for a loss in cognitive functioning. These strategies may be employed together to improve cognition as much as possible and compensate for any remaining deficits. Given the multifaceted causes of cognitive problems associated with this clinical population, a basic understanding of cognitive reserve hypothesis is needed (Figure 3).

Cognitive reserve refers to the amount of damage the brain and nervous system can absorb before cognitive problems emerge. The brain is composed of 100 billion neurons with countless interconnections (Fields, 2009). With prolonged inflammation, oxidative stress, social isolation, substance abuse, cortisol toxicity from stress, depression, and anxiety, as well as a host of other factors known to impact brain health, neurons and their connections to each other are damaged (Figure 3). Although connections between neurons are severed, other connections can compensate and maintain cognitive functioning. Unfortunately, when the connections become too severe, communication between neurons becomes compromised and cognitive problems emerge (Vance, Graham et al., 2012). The area of the brain where these connections are compromised also influences the type of cognitive problems that emerge such as forgetfulness or inability to sustain attention (Vance, Graham et al., 2012). Fortunately, many strategies and lifestyle changes can promote neuronal health and connectivity.

Although the neurological sequelae and subsequent cognitive problems that occur with HIV are well documented (i.e., Heaton et al., 2010), few studies have investigated strategies for restoring or improving cognitive functioning through promoting neuronal health and increasing cognitive reserve in PLWH. Likewise, few studies have tested strategies to compensate for a loss in cognitive functioning. Fortunately, many strategies developed and tested in normal geriatric populations are likely to be effective in PLWH; however, such strategies cannot be recommended with confidence until they have been tested in the HIV population.

Recommended for Practice

Antiretroviral Therapy

Given the negative effects that HIV exerts on the brain and cognition, reducing the amount of HIV in the body is by far the most effective strategy to mitigate forgetfulness and cognitive problems. Strict adherence to ART remains the most effective approach to preventing problems and even to improving cognitive functioning. In a review of the literature, Al-Khindi, Zakzanis, and van Gorp (2011) reviewed 23 studies and found that ART was associated with modest improvements in motor function, attention, and executive function. Yet the evidence did not find that ART improved verbal memory, visual memory, visuospatial function, and language. There was an observed improvement in cognitive functioning significantly correlated to the increase in CD4+ T lymphocyte count associated with ART, reflecting a connection between the nervous system and the immune system. In a typical study of ART and cognition, Parsons, Braaten, Hall, and Robertson (2006) performed a 6-month longitudinal study of 59 adult PLWH who were either ART naïve or were about to change an ART regimen due to its failure to suppress the plasma viral load. At baseline, the participants were administered neuropsychological measures and a

psychological evaluation. Participants who experienced successful treatment exhibited statistically better performance on measures of mental speed of processing compared to those who experienced failure of ART. Furthermore, those who experienced treatment failure also reported more cognitive problems. This study and others (e.g., Koopmans, Ellis, Best, & Letendre, 2009) have demonstrated that ART is effective in protecting and improving cognition.

Given the effectiveness of treatment in restoring cognitive functioning, it has been suggested that ART be targeted for higher central nervous system penetration to more effectively reduce the amount of HIV in the cerebrospinal fluid and, thereby, protect the brain (Koopmans et al., 2009). Letendre and colleagues (2008) developed a schema whereby nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors were classified as having lower, intermediate, or higher central nervous system penetration. For nucleoside reverse transcriptase inhibitors, didanosine, tenofovir, and zalcitabine had lower penetration; emtricitabine, lamivudine, and stavudine had intermediate penetration; and, abacavir and zidovudine had higher penetration. For non-nucleoside reverse transcriptase inhibitors, efavirenz had intermediate penetration and delavirdine and nevirapine had higher penetration. For protease inhibitors, nelfinavir, ritonavir, saquinavir, saquinavir (with ritonavir), and tipranavir (with ritonavir) had lower penetration; amprenavir, atazanavir, atazanavir (with ritonavir), and indinavir had intermediate penetration; and amprenavir (with ritonavir), indinavir (with ritonavir), and lopinavir (with ritonavir) had higher penetration. For fusion inhibitors, enfuvirtide had lower penetration. Furthermore, indinavir has been shown to be particularly effective in ameliorating induced cognitive deficits in mice (Sharma, Singh, Singh, & Jaggi, 2008). Additional research in humans is warranted.

Three caveats of using ART to address forgetfulness and cognitive problems should be considered. First, medication adherence of 95% or greater is highly recommended for adequate viral suppression to occur and to avoid viral mutation and drug resistance (Howard et al., 2002). Unfortunately, studies have shown that adults with forgetfulness and cognitive problems tend to be less adherent to ART. Non-adherence to ART can further exacerbate cognitive problems, which can also lead to lower levels of medication adherence (Becker, Thames, Woo, Castellon, & Hinkin, 2011). Therefore, strategies to improve medication adherence must be incorporated into the patient care plan. Second, although efavirenz is an effective non-nucleoside reverse transcriptase inhibitor, it has been found to increase the risk for cognitive impairment (Ciccarelli et al., 2011). The reason for this possible neurotoxic risk is not well understood (Koopmans et al., 2009). Some suggest that non-nucleoside reverse transcriptase inhibitors may exert a deleterious effect on brain mitochondria and metabolism (Schweinsburg et al., 2005). Although studies are ongoing, no conclusive results have shown other antiretroviral medications possessing a similar neurotoxic risk (Koopmans et al., 2009). Third, ART can create metabolic syndromes such as hypertension, diabetes, heart disease, and hypercholesterolemia that, over time, can contribute to poorer cognitive functioning (Vance, Mugavero, Willig, Raper, & Saag, 2011). Therefore, these syndromes must be monitored and treated to avoid the onset or exacerbation of forgetfulness and cognitive problems.

Spaced retrieval

Spaced retrieval is a memory technique to help people freely recall specific information over progressively longer periods of time until it is successfully consolidated into one's long-term memory (Vance, Struzick, & Farr, 2010). Quite simply, information to be remembered, such as a phone number, is presented and then immediately recalled. Then in a stair-step manner, the information is recalled (without cues) after 30 seconds, 1 minute, 2 minutes, 4 minutes, 8 minutes, and 16 minutes. If the information cannot be recalled correctly at any time point,

say 8 minutes, the information is presented again and then attempted to be recalled at the previous time point, 4 minutes, in which there was a successful recall. This back and forth recall is performed until the information can be freely recalled after 16 minutes. Once the information can be freely recalled up to 16 minutes, it is fully consolidated into long-term memory. This memory technique has been used effectively in those with early stage dementia and brain injury (Vance, Struzick et al., 2010) and is likely effective in PLWH.

In a pilot study of 10 older adult PLWH experiencing memory and executive functioning problems, Neundorfer and colleagues (2004) used spaced retrieval in combination with external memory aids to assist participants with two tasks (e.g., remembering clinic appointments and remembering to take medications). The intervention was conducted in eight 30-minute sessions over a 4-week period. Overall, participants found the intervention to be effective in achieving their tasks. Given the ease of this memory technique, it is likely that motivated patients can incorporate it into their own self-care regimens.

Likely to Be Effective

Cognitive remediation programs

Cognitive remediation programs have been used in several clinical populations (e.g., geriatric, traumatic brain injury) to improve specific cognition domains (i.e., memory, reasoning, speed of processing) and global cognition (Vance, Graham et al., 2012). These programs use non-invasive therapeutic techniques that are easy to use and understand (Vance, Graham et al., 2012). In a typical study, Vance and colleagues (2007) randomized older adults ($N = 159$) to either a speed of processing cognitive remediation therapy or a social-contact Internet control group. Participants assigned to the speed of processing group received as many as 10 hours of computerized training exercises. Specifically, participants engaged in tasks whereby they were to detect the presence of certain objects in the middle of the computer screen while also locating a stimulus object on the periphery of the screen. The exercises were made easier or more difficult by altering colors and presentation times of the stimuli. Exercises were also designed to allow participants to engage in tasks that were near their perceptual and cognitive threshold, thus making it challenging. The goal of training was to improve the speed and accuracy of detecting objects. This intervention was specifically designed to improve one's Useful Field of View (UFOV[®]; a cognitive measure shown to be related to driving and automobile accidents). Those in the speed of processing group significantly improved on measures of speed of processing (UFOV[®] and Starry Night). Moreover, even after only 10 hours of training, cognitive gains were robust over a 2-year period.

The study by Vance and colleagues (2007) has relevance for PLWH. As mentioned, UFOV[®] has been shown to be related to driving safety. In a sample of 68 adult PLWH, Marcotte and colleagues (1999) found that half of the sample experienced impairment in UFOV[®]. Impairment was also observed to be related to more accidents in a simulation of city driving. Thus, there is concern that as adults age with HIV, UFOV[®] impairments may translate into poorer driving safety.

In a pilot study of 46 middle-age and older adult PLWH ($M_{\text{age}} = 51.55$; range 40.7 – 70.6) using a pre-post experimental design, Vance, Fazeli, Ross, Wadley, and Ball (in press) randomized participants to either a speed of processing protocol as previously mentioned ($n = 22$) or to a no-contact control group ($n = 24$). Those in the speed of processing group received as many as 10 hours of training over a 4- to 6-week period. Participants in the active condition improved on the UFOV[®] measure compared to those in the control group. Overall, improvement in speed of processing translated into significant improvements in a

laboratory measure of everyday functioning called the Timed Instrumental Activities of Daily Living Test.

Cognitive remediation has great potential for improving cognitive functioning in PLWH. Generally, such programs are fun and enjoyable, can be used in the privacy of one's home, and are fairly inexpensive (Vance, Graham et al., 2012). The training effects have been found to generalize to instrumental activities of daily living and driving. Yet not all cognitive remediation programs are the same. Cognitive remediation programs are commercially available but some may not be properly designed to produce a clinically meaningful and sustained cognitive benefit. Therefore, clinicians recommending these programs need to contact the manufacturer and ask for published scientific articles that validate the use of their products. Also, some programs are designed to improve global cognition while others are designed specifically to improve a specific cognitive ability such as visual speed of processing. It is important to pick the correct cognitive remediation program that will address the specific cognitive problems (e.g., memory, speed of processing, global cognition) being treated.

Depression and anxiety treatment

In a sample of 1,478 adult PLWH, Vance, Mugavero, and colleagues (2011) found the prevalences of depression (40%) and anxiety (20%) were fairly consistent across each decade of life. Forgetfulness and cognitive problems have often been associated with depression, anxiety, and other mood disorders (Vance, Larsen, Eagerton, & Wright, 2011). Thames and colleagues (2011) found that adult PLWH with higher levels of depression were more likely to report forgetfulness and cognitive problems and tended to over-report cognitive problems. Those experiencing actual cognitive dysfunction tended to under-report cognitive problems. This incongruence indicates that patients who present self-reported forgetfulness and cognitive problems should also be screened for depression. Those who do not report any cognitive problems may still be experiencing them but may be under-reporting their incidence.

Given the interconnection between negative affect and cognition, it has been suggested that treatment of depression and anxiety through medication and cognitive-behavioral therapy may also relieve cognitive problems. For example, in a sample of 75 adult PLWH with depression, Claypoole and colleagues (1998) treated participants with antidepressants over a 12-week period. They found that as depressive symptomatology abated, forgetfulness and cognitive complaints also abated. In addition, neuropsychological performance scores increased. Because treatment of depression and anxiety should be considered part of HIV treatment, this approach is an obvious way to address forgetfulness and cognitive problems.

Methylphenidate and psychostimulants

Methylphenidate (Ritalin) is a psychostimulant dopamine agonist. Few studies have examined its effectiveness in treating forgetfulness and cognitive problems in PLWH. In a double-blind crossover, placebo-controlled study, van Dyck and colleagues (1997) used sustained release methylphenidate in eight adult PLWH undergoing inpatient methadone treatment. Using a variety of neuropsychological measures to form a composite of cognitive functioning, methylphenidate was found to be effective in improving functioning. Likewise, Hinkin and colleagues (2001) used a single-blind crossover, placebo-controlled study of methylphenidate (once daily 30 mg dose) in 16 adult PLWH. They found that those at baseline with greater cognitive slowing and depressive symptomatology exhibited better functioning on computerized neuropsychological measures of dual-task reaction time and choice in response to methylphenidate. Compared to placebo, those without any measurable cognitive slowing at baseline did not show any cognitive improvement with

methylphenidate. Hinkin and colleagues (2001) also investigated whether depressive symptomatology may have attenuated the improvement in cognitive functioning. Compared to placebo, methylphenidate did not abate depressive symptomatology. Overall, Hinkin and colleagues (2001) concluded that methylphenidate could be used effectively to treat cognitive slowing in adult PLWH.

Physiological data also support the use of methylphenidate for adult PLWH experiencing cognitive problems. Studies have suggested that some adult PLWH may experience dopaminergic dysfunction. In cerebrospinal fluid samples of adult PLWH, reduced levels of dopamine and a dopamine metabolite, homovanillic acid, have been observed (Berger, Kumar, Kumar, Fernandez, & Levin, 1994). Therefore, increasing the amount of dopamine in the brain through methylphenidate may be a viable solution. Further studies have also determined that too much or too little dopamine can negatively affect working memory (Williams & Goldman-Rakic, 1995).

Unfortunately, no large randomized clinical trials have investigated the use of methylphenidate in PLWH, but several studies have found that methylphenidate improved cognitive functioning in those with attention deficit disorder (Julien, 1998), multiple sclerosis (Harel, Appleboim, Lavie, & Achiron, 2009), and normal healthy adults (Tomasi et al., 2011). Given its use in the treatment of fatigue (Mar Fan et al., 2008), which affects approximately 50% of PLWH (Leserman, Barroso, Pence, Salahuddin, & Harmon, 2008), in general methylphenidate is considered safe for chronic use. Recent evidence suggests that methylphenidate may also be effective in reducing total cholesterol, low-density lipoprotein cholesterol, and triglycerides (Charach, Kaysar, Grosskopf, Rabinovich, & Weintraub, 2009); this is an added advantage since approximately 38% of adult PLWH tend to have elevated lipids (e.g., hypercholesterolemia; Vance, Mugavero et al., 2011).

Other psychostimulants, such as modafinil, have also been used to support cognitive functioning and mitigate the effects of fatigue. Traditionally, modafinil has been shown to enhance cognition in adults with attention deficit/hyperactivity disorder (Turner, Clark, Dowson, Robbins, & Sahakian, 2004). In a placebo-controlled study, McElhiney, Rabkin, van Gorp, and Rabkin (2010) randomized adult PLWH to either a modafinil group ($n = 59$) or a placebo control group ($n = 44$) and monitored them over a 4-week period. The study utilized a heterogeneous sample whereby 51% had a history of drug use, 40% had DSM-IV diagnosis of depression, 29% were taking antidepressants, and 20% had hepatitis C, which reflected the general HIV population (Vance, Mugavero et al., 2011). McElhiney and colleagues (2010) found that participants who were administered modafinil exhibited improved global cognitive functioning compared to the placebo-control group. Those in the modafinil group also scored significantly lower on the Cognitive Failures Questionnaire (Broadbent et al., 1982) and experienced fewer subjective cognitive problems. No adverse effects were reported.

In general, the use of psychostimulants such as methylphenidate and modafinil appears to be well tolerated and efficacious in treating forgetfulness and cognitive problems associated with HIV. Psychostimulants may also help to reduce hypercholesterolemia and treat fatigue; they appear to be safe for chronic use, even in those with hepatitis C. Unfortunately, psychostimulants can be abused (Volkow & Swanson, 2008) and patients with a propensity for substance abuse should be monitored closely when psychostimulants are employed.

Mnemonic techniques

Numerous mnemonic techniques have been used successfully in aging populations. As previously mentioned, spaced retrieval is a useful technique to consolidate specific information into long-term memory. Vance, Webb, and colleagues (2008) reviewed a

variety of other mnemonic techniques such as chunking (i.e., memorizing chunks of information and then putting the chunks together such as the prefix and suffix of a phone number), levels of processing (i.e., thinking about information to be remembered at a deeper, more sophisticated way in order to make such information more salient to recall), method of loci (i.e., recalling sequential information visualized along a familiar route or path), and external memory aids (i.e., calendars, notes on the refrigerator, lists). These techniques have been found to be easy to incorporate into practice, simple to use, and pose no adverse events.

Lifestyle factors

Lifestyle factors that benefit the body tend to also benefit the brain and cognition. Although it is beyond the scope of this article to discuss such factors in detail, the general consensus is that physical activity, good sleep hygiene, avoidance of substance use (i.e., opiates), social interaction, and intellectual exercise are beneficial in promoting good cognitive health and avoiding forgetfulness and cognitive problems by reducing oxidative stress and neuro-inflammation and producing brain-derived neurotrophic factor (Atkins et al., 2010; Foster, Rosenblatt, & Kulji, 2011; Malaspina et al., 2011). Studies have shown that cessation of substance use such as methamphetamine results in improved speed of processing and motor abilities after approximately 1 year (Iudicello et al., 2010). Encouraging these positive lifestyle behaviors can be a cornerstone of good general, mental, and cognitive health.

Benefits Balanced with Harms

Inflammation treatment

Although HIV does not directly infect neurons, it does infect microglia and macrophages that produce inflammatory molecules such as cytokines and quinolic acid that create oxidative stress, which collectively are damaging to neurons (Eggert et al., 2010; Fields, 2009). Neuro-inflammation occurs even when ART has effectively reduced the plasma viral load and stabilized the immune system (Harezlak et al., 2011). In a comparison of 26 adult PLWH taking ART, magnetic resonance imaging scans revealed cortical thinning in prefrontal parietal cortices compared to 14 adults without HIV (Thompson et al., 2005). In fact, in rare cases (0.9%) a condition known as immune reconstitution inflammatory syndrome (IRIS) has been associated with ART. IRIS is characterized by more acute cognitive problems (McCombe et al., 2009).

Because neuro-inflammation may be the driving mechanism leading to forgetfulness and cognitive problems, it has been suggested that reducing neuro-inflammation could alleviate these cognitive problems while also contributing a neuro-protective dimension (Malaspina et al., 2011). Antioxidants and polyphenols may be effective in reducing neuro-inflammation. Rapo and colleagues (2009) found green tea to be effective in reducing astrogliosis in HIV-1 Tat transgenic mice. Although not tested in humans, such an approach may be effective in adult PLWH. Others have suggested that non-steroidal anti-inflammatory medications may possess neuro-protective properties in adult PLWH (Eggert et al., 2010; McCombe et al., 2009). Unfortunately, the effectiveness of anti-inflammatory medications has not been established nor can all patients tolerate them, but neuro-protective benefits may be achieved when antiinflammatory medications are prescribed for other co-morbid conditions (e.g., arthritis).

Treatment of co-morbidities

As mentioned, co-morbidities associated with HIV such as heart disease, hypertension, diabetes, and hepatitis C can also interfere with cognitive functioning. Some co-morbidities can be the unintended consequences associated with effective ART (Malaspina et al., 2011;

Vance, Mugavero et al., 2011). Therefore, treating such comorbidities is also the standard of care for preventing forgetfulness and cognitive problems and improving overall cognition (Vance, Larsen et al., 2011). For example, in a study of 41 middle age adults with type 2 diabetes and 47 age-, gender-, and education-matched adults without diabetes, Bruehl and colleagues (2009) found that those with diabetes exhibited poorer cognitive functioning and decreased volume in the hippocampi (the brain structures necessary for memory consolidation) and the prefrontal cortex (the brain structure instrumental in executive functioning). Furthermore, they found that poorer glycemic control was statistically associated with decreased volume in the prefrontal cortex. This finding suggested that by improving medical management of diabetes, cognitive functioning might also be improved. Studies of co-morbidities such as hypertension and heart disease have revealed similar patterns of cognitive problems when poorly treated (Vance, Larsen et al., 2011).

In treating co-morbidities, it is also important to evaluate polypharmacy and medication side effects. Studies have indicated that polypharmacy can negatively impact cognitive functioning, especially in medically vulnerable individuals such as those who are older or those with AIDS (Malaspina et al., 2011). Medications such as opiates, benzodiazepines, and anticholinergics can exert a detrimental effect on cognitive function (Julien, 1998). Patients prescribed such medications should be monitored closely for any change in cognitive functioning that may impair driving and medication adherence.

Effectiveness Unlikely

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors (e.g., donepezil) are used to improve cognition for people suffering from Alzheimer's disease and related dementias; however, studies of their use in treating non-pathological cognitive problems are limited. The use of neurotropic medications has not been established for PLWH. Yesavage and colleagues (2008) examined the use of donepezil and cognitive training over a 1-year period in 168 nondemented community-dwelling older adults with memory complaints. They found that, although cognitive training improved cognitive performance, donepezil produced the same level of cognitive improvement as a placebo. Although some studies have shown a brief boost in cognition with donepezil, the effects are short-lived. Yesavage and colleagues (2008) posited that physiological tolerance could occur over time with chronic donepezil use. Given this, it is unlikely that such cognitive enhancing medications would be effective in the long-term for PLWH experiencing non-demented forgetfulness and cognitive problems. Because PLWH already have a heavy medication burden and are more likely to experience liver and renal disease compared to the general population (Vance, Mugavero et al., 2011), the addition of yet another medication is not warranted, especially when it is unlikely to be effective in producing long-term cognitive benefits.

Not Recommended for Practice

Herbal and alternative supplements—It has been suggested that some herbal and alternative supplements such as ginkgo biloba, ginseng, omega-3 fatty acids, and phosphatidylserine improve memory and cognitive functioning. Unfortunately, research does not support the use of such supplements to protect or improve cognitive functioning (e.g., Serby, Burns, & Roane, 2011). In a longitudinal randomized trial of 3,069 cognitively-normal, community-dwelling older adults from six medical centers across the United States, Snitz and colleagues (2009) randomized participants to receive either twice-daily 120-mg extract dose of ginkgo biloba ($n = 1,545$) or an identical-looking placebo ($n = 1,524$). With a median follow-up of 6.1 years, changes over time did not differ between the two groups on global cognition nor in individual domains of memory, attention, language, visuospatial

abilities, and executive function. Some have speculated that ginkgo biloba produces cognitive benefits by reducing blood pressure and the incidence of hypertension; in this same study, however, no such benefit was observed (Brinkley et al., 2010).

Cognitive studies investigating the effects of other supplements (e.g., ginseng, omega-3 fatty acids, and phosphatidylserine) have found similar findings to that of ginkgo biloba. In general, findings have been inconclusive. Much of this may be due to small sample sizes, quality of the supplements, and various measurement techniques (Gorby, Brownawell, & Falk, 2010; Serby et al., 2011). More controlled randomized clinical trials are needed before considering the use of these supplements in clinical practice.

Furthermore, PLWH should be counseled about the potential dangers of herbal and alternative supplements to improve cognitive functioning. First, the quality of such supplements is not regulated and could contain cadaverous materials that may be harmful. Likewise, potential side effects may not be listed on the product packaging (Serby, Yhap, & Landron, 2010). For example, ginkgo biloba has been associated with seizures. Ginkgo biloba induces CYP2C19 and thus speeds omeprazol breakdown in patients treated with this proton pump inhibitor. It has been speculated that ginkgo biloba may increase the breakdown of antiepileptic drugs in a similar manner, thus allowing seizure breakthrough (Leistner & Drewke, 2010). Second, pill burden is a concern for PLWH (Vance, Mugavero et al., 2011). Third, studies have indicated that people who use alternative therapies tend to be less adherent to prescribed medications and medical advice (Raper, 2010). Finally, for many patients who have few financial resources, the cost associated with supplements is not warranted given their lack of efficacy in protecting or improving cognitive functioning.

Hormone replacement therapy—Estrogen replacement therapy has been touted as a possible treatment for forgetfulness and cognitive problems, as well as being neuro-protective against Alzheimer's disease in normal older adults. Estrogen is known to promote cholinergic activity and growth of cholinergic neurons, and to inhibit the formation of amyloid precursor protein, the protein associated with Alzheimer's disease (Janicki & Schupf, 2010). Despite these positive characteristics, the efficacy of estrogen replacement therapy on cognition has been inconsistent. In one meta-analysis of 29 cohort studies and randomized controlled trials, Leblanc, Chan, and Nelson (2002) found evidence of cognitive improvement with estrogen replacement therapy. Specifically, women with menopausal symptoms tended to benefit cognitively. In another meta-analysis of 36 randomized controlled trials, Hogervorst and Bandelow (2010) concluded that estrogen replacement therapy was not effective in improving cognition. Negative effects on cognition have also been observed (Gibbs, 2010). The Women's Health Initiative Memory Study found approximately a 2-fold increase in dementia with the use of estrogen replacement therapy (Shumaker et al., 2003). Given the inconsistent findings, estrogen replacement therapy is not recommended at this time.

Testosterone replacement therapy has also been touted as a possible treatment for forgetfulness and cognitive problems (Sharma & Perros, 2009). As seen with estrogen replacement therapy, the efficacy of testosterone on improving cognition has not been well established (Mitsiades, Correa, Gross, Hurria, & Slovin, 2008). Although testosterone replacement therapy is used in adult PLWH to prevent or treat weight loss and muscle wasting (Choi et al., 2005), to use it as a treatment for forgetfulness and cognitive problems cannot be recommended. In fact, testosterone replacement therapy is not without risk. It may predispose some men to prostate cancer, liver disease, heart failure, erythrocytosis, hyperviscosity, prostatic hypertrophy, and untreated sleep apnea (Bassil & Morley, 2010).

Expert Opinion

In confronting cognitive issues in HIV, a holistic, long-term approach is encouraged to: (a) prevent forgetfulness and cognitive problems and (b) promote brain health and cognitive reserve (Malaspina et al., 2011). A combination approach should be sought because there are different mechanisms for preventing and restoring cognition. As seen in Figure 4, Ms. D and Mr. C have similar clinical characteristics (e.g., age, CD4+ T lymphocyte count). Ms. D is prescribed ART, treated for insomnia and depression, prescribed methylphenidate for fatigue, and engages in a physical exercise regimen. All of these are associated with better cognitive functioning over a period of time. Mr. C experiences a brief cognitive benefit from being prescribed ART and being treated for depression. Unfortunately, with a relapse into alcoholism, experiencing symptoms of fatigue, and having a co-morbid diagnosis of hepatitis C, his cognitive functioning declines over time.

Although these are simple examples, they demonstrate that forgetfulness and cognitive problems associated with HIV emerge from multiple causes. Prevention and treatment for such problems will likely emerge from multiple interventions. Recently, Vance, Eagerton, and colleagues (2011) developed a rubric whereby many of these factors can be incorporated within a single, individualized cognitive prescription. Cognitive prescriptions address potential causes of forgetfulness and cognitive problems with specific and individually tailored instructions. For example, a person may experience insomnia, depression, and withdrawal from social situations but remain involved with certain intellectual pursuits. In this case, the cognitive prescription would have very specific behavioral goals designed to improve sleep (i.e., exercise 15 minutes every day), treat depression (i.e., take a selective serotonin reuptake inhibitor daily), improve socialization (e.g., attend a support group and go out to dinner with a friend once a week), and maintain intellectual pursuits (e.g., read 1 book a week). With specific behavioral goals developed from motivational interviewing techniques, the individualized cognitive prescription would be a holistic tool for improving cognitive functioning. Although untested, based upon learning theory and standard behavior management techniques, this approach could be one way of integrating and delivering treatment to address forgetfulness and cognitive problems in adult PLWH, which could potentially result in better quality of life.

Case Study—This case study is provided as an example of the clinical decision making involved in determining appropriate evidence-based treatments and recommendations for treating and preventing cognitive problems in patients with HIV infection. It is presented in standard SOAP (Subjective, Objective, Assessment/Plan) guidelines. Whereas HIV affects people from varied backgrounds, some patients will have more cognitive reserve and other resources to compensate for forgetfulness and cognitive problems than others. Although it is beyond the scope of this article to go into specific details, considerations must be made on a case-by-case basis.

Case Description

Subjective notes: Mr. A is a 49-year-old African American man who recently moved to the area and is seeking HIV treatment. He mentioned that with the move to take a job as a manager of a grocery store, he seems a little more confused than normal and is having trouble navigating his way around town. After completing a standard patient assessment, Mr. A reported that he contracted HIV through a former partner but is currently single. He was diagnosed with HIV 12 years ago and suspects he was infected 3 years prior to his diagnosis. He initially started zidovudine and emtricitabine/tenofovir but later was switched to efavirenz/emtricitabine/tenofovir and has successfully been on this regimen for the past 8 years. Mr. A reported that his CD4+ T lymphocyte count has hovered around 400 cells/mm³ and his viral load has been consistently undetectable. When asked about medication

adherence, he mentioned that with the recent move, he has missed a dose “here and there” but is otherwise “very religious about taking my medication on time, every time.” Likewise, he reported that he has never had an opportunistic infection or AIDS. Mr. A reported no medical conditions other than borderline hypertension and diabetes for which he is not taking medication. After some reluctance, he reported that he had been a recovering alcoholic for 5 years and 2 months. He has smoked half a pack of cigarettes per day since high school.

Objective notes: Mr. A is alert and oriented. He was 5' 9", weighed 167 pounds with a normal body mass index, 24.7. His blood pressure was 135/85 mm/Hg (borderline high). His general appearance reflected an overall good state of health (clear skin and eyes and no noticeable odors). Fasting blood draw results indicated: CD4+ T cell count, 450 cells/mm³; HIV viral load < 20 copies/mL; triglycerides, 259 mg/dL (high); high-density lipoproteins, 40 mg/dL (low); glucose, 115 mg/dL (high); and glycated hemoglobin (A1c), at 6.0%. All other laboratory results for liver and renal function were well within normal parameters.

Assessment/plan notes: For this section of the SOAP notes, assessment and plan will be integrated together for didactic purposes. Succinctly, the assessment was that, even with Mr. A's general good health, his recent move had resulted in significant stress. The cognitive problems he reported were probably stress induced and were likely to subside as he acclimated to his new environment. The plan was to monitor whether his cognitive problems persisted over time while also addressing his borderline hypertension and diabetes as possible risk factors for cognitive problems. If the cognitive problems persisted, further action would be necessary to assess these cognitive problems in more detail using an objective cognitive screener and looking for progression in cognitive declines. In addition, a more thorough interview would be conducted to assess plausible causes of Mr. A's cognitive problems if they persisted.

3-month follow-up: Mr. A returned to the clinic seeking relief from flu-like symptoms. Upon a brief interview, he reported he was still having some cognitive problems such as forgetfulness and inability to pay attention to details. He also mentioned that he was having trouble meeting people, socializing, and was experiencing financial concerns over selling his former residence. His laboratory values/blood work appeared about the same as his first visit, but it seemed that the cognitive problems had persisted and may have gotten a little worse. The Montreal Cognitive Assessment (Nasreddine, 2010) was administered and he received a score of 28, indicating that he was functioning normally. After talking with Mr. A further, it was clear that he was under a great deal of stress and might have been experiencing depression and/or anxiety. He said that he was treated for depression several years ago and that paroxetine was very helpful. A brief depression screener indicated that that he had elevated depressive symptomatology. Mr. A seemed receptive to restarting paroxetine but was too busy to go to counseling. He agreed to call the clinic for a status report in 4–6 weeks and return in 3 months for his standard HIV care and to review his symptoms of forgetfulness and depression.

6-month follow-up: Mr. A returned to the clinic 1 month later than previously scheduled. His laboratory values were essentially unchanged. Close examination revealed that he was no longer experiencing cognitive problems and that his attention to detail was improved. He remarked that he had been very busy lately, had met someone special, and had missed his previously planned clinic appointment because the two of them had gone out of town together. His mood seemed much brighter. The depression screener revealed a much lower level of depressive symptomatology. He said he would like to continue taking paroxetine for the rest of the year until he is more acclimated to the area. He denied any paroxetine-related

side effects. The forgetfulness and cognitive problems seemed to have emerged from the stress and depression of moving to a new area and readjusting to his new surroundings. Education brochures on smoking, hypertension, and pre-diabetes were given to Mr. A with a promise that this would be a topic of conversation at his next visit in 6 months. He agreed to read the literature and consider the information.

Future Directions—Methods for treating forgetfulness and cognitive problems continue to be developed. Lindl, Marks, Kolson, and Jordan-Sciutto (2010) recently reported some very interesting vectors of research investigating promising therapies. Although such therapies cannot be recommended at the moment, they are worth mentioning for future consideration.

First, memantine, which reduces glutamate excitotoxicity in HIV mice models and adults with Alzheimer's disease, may be neuro-protective for PLWH. A preliminary study demonstrated that adult PLWH did not experience any significant neuropsychological benefit from taking this medication. However, magnetic resonance spectroscopy revealed that 16-week exposure to memantine may be protective of the parietal cortex and frontal white matter (Schifitto et al., 2007).

Second, minocycline, a second-generation tetracycline antibiotic derivative, is considered an excellent anti-inflammatory that can also cross the blood-brain barrier. It possesses unique properties that reduce immune cell infiltration in the brain that can lead to encephalitis. A study (ACTG5235) is currently underway investigating the potential of this drug in treating HIV-associated neurocognitive disorders (Lindl et al., 2010).

Third, selegiline, a monamine oxidase type B inhibitor, has been considered as a possible treatment for HIV-associated dementia. Selegiline is also a neurotropic antioxidant. Studies have shown that transdermal administration of selegiline can be safely administered. Although it cannot be recommended at this time, it may prove to be effective in the future (Lindl et al., 2010).

Fourth, intranasal delivery of insulin-like growth factor-1, insulin, and neurotrophin has shown potential for ameliorating the effects of neural damage due to HIV-associated neurocognitive disorders, Alzheimer's disease, stroke, and diabetes. Preliminary studies suggest that it may not only improve short-term and long-term memory, it may also improve odor detection and mood. The delivery system appears to be easy to use with no adverse side effects such as damage to the olfactory bulb or olfactory epithelium (Lindl et al., 2010).

Fifth, Letendre and colleagues (2006) investigated the use of lithium on HIV-associated neurocognitive impairment. Using an open-label, single-arm, 12-week pilot study of eight adults with neurocognitive impairment, researchers found that cognitive functioning improved in all subjects. Although lithium is clearly not appropriate for everyone, additional research may suggest ways that it can be used to improve cognitive functioning in PLWH experiencing cognitive problems.

Finally, researchers are considering ways of assisting ART to penetrate the blood-brain barrier in order to deliver antiretrovirals to where they are needed. Dou and colleagues (2009) are working on nanoparticle delivery of ART. Therefore, if ART could more easily penetrate the brain, the medications would better protect the brain from HIV (Lindl et al., 2010).

Conclusion

We have provided some general guidelines for protecting against forgetfulness and cognitive problems and improving cognition in PLWH. By 2015, nearly half of PLWH in developed countries will be ages 50 and older (Kirk & Goetz, 2009). With adults aging with HIV, the combination of age-related cognitive declines and HIV-related cognitive declines will merge. Thus, those aging with HIV will be more vulnerable to cognitive declines and possibly mild cognitive impairment and dementia (Hardy & Vance, 2009). In general, successful cognitive aging is an important component of successful aging. Optimal cognition is important to adhering to medication and clinic appointments as well as to driving and managing finances (Vance, Graham et al., 2012). Although there may be some methods to promote good cognitive health (e.g., physical exercise, good sleep hygiene, avoidance of substance use/abuse, medication adherence, intellectual stimulation), it is essential to encourage maintenance of these health behaviors over a long period of time to maximize their benefit. HIV is a chronic disease that impacts development across the lifespan. As PLWH age, the behaviors they engage in today will likely have a cumulative impact on their cognitive health in years to come.

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References

- Al-Khindi T, Zakzanis KK, van Gorp WG. Does antiretroviral therapy improve HIV-associated cognitive impairment? A quantitative review of the literature. *Journal of the International Neuropsychological Society*. 2011; 17:1–14. [PubMed: 21083962]
- Athilingam P, King KB, Burgin SW, Ackerman M, Cushman LA, Chen L. Montreal Cognitive Assessment and Mini-Mental Status Examination compared as cognitive screening tools in heart failure. *Heart and Lung: The Journal of Acute and Critical Care*. 2011 [Epub ahead of print].
- Atkins JH, Rubenstein SL, Sota TL, Rueda S, Fenta H, Bacon J, Rourke SB. Impact of social support on cognitive symptom burden in HIV/AIDS. *AIDS Care*. 2010; 22(7):793–802. [PubMed: 20635243]
- Baldewicz TT, Leserman J, Silva SG, Petitto JM, Golden RN, Perkins DO, Evans DL. Changes in neuropsychological functioning with progression of HIV-1 infection: Results of an 8-year longitudinal investigation. *AIDS and Behavior*. 2004; 8(3):345–355. [PubMed: 15475681]
- Bassil N, Morley JE. Late-life onset hypogonadism: A review. *Clinics in Geriatric Medicine*. 2010; 26(2):197–222. [PubMed: 20497841]
- Basso MR, Bornstein RA. Estimated premorbid intelligence mediates neurobehavioral change in individuals infected with HIV across 12 months. *Journal of Clinical & Experimental Neuropsychology*. 2000; 22(2):208–218. [PubMed: 10779835]
- Becker BW, Thames AD, Woo E, Castellon SA, Hinkin CA. Longitudinal change in cognitive function and medication adherence in HIV-infected adults. *AIDS Behavior*. 2011 [Epub ahead of print].
- Berger JR, Kumar M, Kumar A, Fernandez JB, Levin B. Cerebrospinal fluid dopamine in HIV-1 infection. *AIDS*. 1994; 8(1):67–71. [PubMed: 8011238]
- Bornstein RA, Nasrallah HA, Para MF, Whitacre CC, Rosenberger P, Fass RJ. Neuropsychological performance in symptomatic and asymptomatic HIV infection. *AIDS*. 1993; 7(4):519–524. [PubMed: 8507418]

- Brinkley TE, Lovato JF, Arnold AM, Furberg CD, Kuller LH, Burke GL, Williamson JD. Effect of ginkgo biloba on blood pressure and incidence of hypertension in elderly men and women. *American Journal of Hypertension*. 2010; 23(5):528–533. [PubMed: 20168306]
- Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology*. 1982; 21(1):1–16. [PubMed: 7126941]
- Bruehl H, Wolf OT, Sweat V, Tirsi A, Richardson S, Convit A. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. *Brain Research*. 2009; 1280:186–194. [PubMed: 19463794]
- Charach G, Kaysar N, Grosskopf I, Rabinovich A, Weintraub M. Methylphenidate has positive hypocholesterolemic and hypotriglyceridemic effects: New data. *Journal of Clinical Pharmacology*. 2009; 49(7):848–851. [PubMed: 19553406]
- Choi HH, Gray PB, Storer TW, Calof OM, Woodhouse L, Singh AB, Bhasin S. Effects of testosterone replacement in human immunodeficiency virus-infected women with weight loss. *Journal of Clinical Endocrinology & Metabolism*. 2005; 90(3):1531–1541. [PubMed: 15613414]
- Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, Baldonero E, Bracciale L, Silveri MC. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology*. 2011; 76(16):1403–1409. [PubMed: 21502598]
- Claypoole KH, Elliott AJ, Uldall KK, Russo J, Dugbartey AT, Bergam K, Roy-Byrne PP. Cognitive functions and complaints in HIV-1 individuals treated for depression. *Applied Neuropsychology*. 1998; 5(2):74–84. [PubMed: 16318457]
- Crawford JR, Smith G, Maylor EA, Sala SD, Logie RH. The Prospective and Retrospective Memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. *Memory*. 2003; 11(3):261–275. [PubMed: 12908675]
- Cumming TB, Bernhardt J, Linden T. The Montreal Cognitive Assessment: Short cognitive evaluation in a large stroke trial. *Stroke*. 2011; 42:2642–2644. [PubMed: 21757673]
- Dou H, Grotepas, McMillan JM, Destache CJ, Chaubal M, Werling J, Gendelman HE. Macrophage delivery of nanoformulated antiretroviral drug to the brain in a murine model of neuroAIDS. *Journal of Immunology*. 2009; 183(1):661–669.
- Eggert D, Dash PK, Gorantla S, Dou H, Schifitto G, Maggirwar SB, Gendelman HE. Neuroprotective activities of CEP-1347 in models of neuroAIDS. *Journal of Immunology*. 2010; 184(2):746–756.
- Fields, RD. *The other brain*. New York: NY: Simon & Schuster; 2009.
- Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 1975; 12(3):189–198. [PubMed: 1202204]
- Foster PP, Rosenblatt KP, Kuljiš RO. Exercise-induced cognitive plasticity, implications for mild cognitive impairment and Alzheimer's disease. *Frontiers in Neurology*. 2011; 2(28):1–15. [PubMed: 21331281]
- Gibbs RB. Does short-term estrogen therapy produce lasting benefits to the brain? *Endocrinology*. 2010; 151(3):843–845. [PubMed: 20172970]
- Gorby HE, Brownawell AM, Falk MC. Do specific dietary constituents and supplements affect mental energy? Review of the evidence. *Nutrition Reviews*. 2010; 68(12):697–718. [PubMed: 21091914]
- Hardy D, Vance D. The neuropsychology of HIV/AIDS in older adults. *Neuropsychology Review*. 2009; 19(2):263–272. [PubMed: 19247836]
- Harel Y, Appleboim N, Lavie M, Achiron A. Single dose of methylphenidate improves cognitive performance in multiple sclerosis patients with impaired attention process. *Journal of Neurological Science*. 2009; 276(1–2):38–40.
- Harezlak J, Buchthal S, Taylor M, Schifitto G, Zhong J, Darr E, Navia B. Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral therapy. *AIDS*. 2011; 25(5):625–633. [PubMed: 21297425]
- Harzke AJ, Williams ML, Nilsson-Schonnesson L, Ross MW, Timpson S, Keel KB. Psychosocial factors associated with adherence to antiretroviral medications in a sample of HIV-positive African American drug users. *AIDS Care*. 2004; 16(4):458–470. [PubMed: 15203414]

- Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, Grant I. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy (CHARTER Study). *American Academy of Neurology*. 2010; 75:2087–2096.
- Hinkin CH, Castellon SA, Hardy DJ, Farinpour R, Newton T, Singer E. Methylphenidate improves HIV-1-associated cognitive slowing. *Journal of Neuropsychiatry & Clinical Neuroscience*. 2001; 113(2):248–254.
- Hogervorst E, Bandelow S. Sex steroids to maintain cognitive function in women after the menopause: A meta-analysis of treatment trials. *Maturitas*. 2010; 66(1):56–71. [PubMed: 20202765]
- Howard AA, Arnsten JH, Lo Y, Vlahov D, Rich JD, Schuman P, Schoenbaum EE. A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS*. 2002; 16:2175–2182. [PubMed: 12409739]
- Iudicello JE, Woods SP, Vigil O, Scott JC, Cherner M, Heaton RK, Grant I. Longer term improvement in neurocognitive functioning and affective distress among methamphetamine users who achieve stable abstinence. *Journal of Clinical & Experimental Neuropsychology*. 2010; 32(7):704–718. [PubMed: 20198527]
- Janicki SC, Schupf N. Hormonal influences on cognition and risk for Alzheimer's disease. *Current Neurology and Neuroscience Reports*. 2010; 10:359–366. [PubMed: 20535591]
- Julien, RM. A primer of drug action. New York, NY: W.H. Freeman and Company; 1998.
- Kirk JB, Goetz MB. Human immunodeficiency virus in an aging population, a complication of success. *Journal of the American Geriatrics Society*. 2009; 57(11):2129–2138. [PubMed: 19793157]
- Koopmans PP, Ellis R, Best BM, Letendre S. Should antiretroviral therapy for HIV infection be tailored for intracerebral penetration? *The Netherlands Journal of Medicine*. 2009; 67(6):206–211.
- Koski L, Brouillette M-J, Lalonde R, Hello B, Wong E, Tsuchida A, Fellows LK. Computerized testing augments pencil-and-paper tasks in measuring HIV-associated mild cognitive impairment. *HIV Medicine*. 2011; 12:472–480. [PubMed: 21395965]
- Leblanc, E.; Chan, B.; Nelson, HD. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2002. Hormone replacement therapy and cognition.
- Leistner E, Drewke C. Ginkgo biloba and ginkgotoxin. *Journal of Natural Products*. 2010; 73:86–92. [PubMed: 20041670]
- Lentz MR, Kim WK, Kim H, Soulas C, Lee V, Venna N, González RG. Alterations in brain metabolism during the first year of HIV infection. *Journal of Neurovirology*. 2011; 17(3):220–229. [PubMed: 21494901]
- Leserman J, Barroso J, Pence B, Salahuddin N, Harmon J. Trauma, stressful life events and depression predict HIV-related fatigue. *AIDS Care*. 2008; 20:1258–1265. [PubMed: 18608079]
- Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, Ellis RJ. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Archives of Neurology*. 2008; 65(1):65–70. [PubMed: 18195140]
- Letendre S, Woods SP, Ellis RJ, Atkinson JH, Masliah E, van den Brande G. HNRC Group. Lithium improves HIV-associated neurocognitive impairment. *AIDS*. 2006; 20(14):1885–1888. [PubMed: 16954730]
- Lindl KA, Marks DA, Kolson DL, Jordan-Sciutto KL. HIV-associated neurocognitive disorder: Pathogenesis and therapeutic opportunities. *Journal of Neuroimmune Pharmacology*. 2010; 5:294–309. [PubMed: 20396973]
- Malaspina L, Woods SP, Moore DJ, Depp C, Letendre SL, Jeste D, Grant I. Successful cognitive aging in persons living with HIV infection. *Journal of Neurovirology*. 2011; 17:110–119. [PubMed: 21165783]
- Mar Fan HG, Clemons M, Xu W, Chemerynsky I, Breunis H, Braganza S, Tannock IF. A randomised, placebo-controlled, double-blind trial of the effects of *d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. *Support Care Cancer*. 2008; 16(6):577–583. [PubMed: 17972110]

- Marcotte TD, Heaton RK, Wolfson T, Taylor MJ, Alhassoon O, Arfaa K, Grant I. The impact of HIV-related neuropsychological dysfunction on driving behavior. *Journal of the International Neuropsychological Society*. 1999; 5:579–592. [PubMed: 10645701]
- McCombe JA, Auer RN, Maingat FG, Houston S, Gill MJ, Power C. Neurologic immune reconstitution inflammatory syndrome in HIV/AIDS: Outcomes and epidemiology. *Neurology*. 2009; 72(9):835–841. [PubMed: 19255411]
- McElhiney M, Rabkin J, van Gorp W, Rabkin R. Modafinil effects on cognitive function in HIV+ patients treated for fatigue: A placebo controlled study. *Journal of Clinical and Experimental Neuropsychology*. 2010; 32(5):474–480. [PubMed: 19937504]
- Mitsiades N, Correa D, Gross CP, Hurria A, Slovin SF. Cognitive effects of hormonal therapy in older adults. *Seminars in Oncology*. 2008; 35(6):569–581. [PubMed: 19027461]
- Nasreddine Z. Montreal Cognitive Assessment (MoCA): Administration and scoring instructions. 2010 Aug 18. Retrieved from www.mocatest.org.
- Neundorfer MM, Camp CJ, Lee MM, Skrajner MJ, Malone ML, Carr JR. Compensating for cognitive deficits in persons aged 50 and over with HIV/AIDS: A pilot study of a cognitive intervention. *Journal of HIV/AIDS & Social Services*. 2004; 3(1):79–98.
- Parsons TD, Braaten AJ, Hall CD, Robertson KR. Better quality of life with neuropsychological improvement on HAART. *Health and Quality of Life Outcomes*. 2006; 4:11. [PubMed: 16504114]
- Raper, JL. The medical management of HIV disease. In: Durham, JD.; Lashley, FR., editors. *The person with HIV/AIDS: Nursing perspective*. 4th ed.. New York, NY: Springer Publishing Company; 2010. p. 221-291.
- Reger M, Welsch R, Razani J, Martin DJ, Boone KB. A meta-analysis of the neuropsychological sequelae of HIV infection. *Journal of the International Neuropsychological Society*. 2002; 8(3): 410–424. [PubMed: 11939699]
- Rapo E, Zhu Y, Tian J, Hou H, Smith A, Fernandez F, Giunta B. Green tea-EGCG reduces GFAP associated neuronal loss in HIV-1 tat transgenic mice. *American Journal of Translational Research*. 2009; 1(1):72–79. [PubMed: 19966940]
- Schifitto G, Navia BA, Yiannoutsos CT, Marra CM, Chang L, Ernst T, Lipton SA. Memantine and HIV-associated cognitive impairment: A neuropsychological and proton magnetic resonance spectroscopy study. *AIDS*. 2007; 21(14):1877–1886. [PubMed: 17721095]
- Schweinsburg BC, Taylor MJ, Alhassoon OM, Gonzalez R, Brown GG, Ellis RJ, Grant I. Brain mitochondrial injury in human immunodeficiency virus-seropositive individuals taking nucleoside reverse transcriptase inhibitors. *Journal of Neurovirology*. 2005; 11:356–364. [PubMed: 16206458]
- Serby MJ, Burns SJ, Roane DM. Treatment of memory loss with herbal remedies. *Current Treatment Options in Neurology*. 2011 [Epub ahead of print].
- Serby MJ, Yhap C, Landron EY. A study of herbal remedies for memory complaints. *Journal of Clinical Neuropsychiatry and Clinical Neuroscience*. 2010; 22(3):345–347.
- Sharma V, Perros P. The management of hypogonadism in aging male patients. *Postgraduate Medicine*. 2009; 121(1):113–121. [PubMed: 19179819]
- Sharma B, Singh N, Singh M, Jaggi AS. Exploitation of HIV protease inhibitor Indinavir as a memory restorative agent in experimental dementia. *Pharmacology, Biochemistry and Behavior*. 2008; 89:535–545.
- Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Wactawski-Wende J. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. *Journal of the American Medical Association*. 2003; 289:2651–2662. [PubMed: 12771112]
- Simioni S, Cavassini M, Annoni JM, Abraham AR, Bourquin I, Schiffer V, Du Pasquier RA. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*. 2010; 24:1243–1250. [PubMed: 19996937]
- Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, DeKosky ST. Ginkgo biloba for preventing cognitive decline in older adults: A randomized trial. *Journal of the American Medical Association*. 2009; 302(24):2663–2670. [PubMed: 20040554]

- Sweet L, Van Adel M, Metcalf V, Wright L, Harley A, Leiva R, Taler V. The Montreal Cognitive Assessment (MoCA) in geriatric rehabilitation: Psychometric properties and association with rehabilitation. *International Psychogeriatrics*. 2011 [Epub ahead of print].
- Thames AD, Becker BW, Marcotte TD, Hines LJ, Foley JM, Ramezani A, Hinkin CH. Depression, cognition, and self-appraisal of functional abilities in HIV: An examination of subjective appraisal versus objective performance. *Clinical Neuropsychology*. 2011; 25(2):224–243.
- Thompson PM, Dutton RA, Hayashi KM, Toga AW, Lopez OL, Aizenstein HJ, Becker JT. Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. *Proceedings of the National Academy of Science*. 2005; 102(43):15647–15652.
- Toglia J, Fitzgerald KA, O'Dell MW, Mastrogianni AR, Lin CD. The Mini-Mental State Examination and Montreal Cognitive Assessment in persons with mild subacute stroke: Relationship to functional outcome. *Archives of Physical and Medical Rehabilitation*. 2011; 92:792–798.
- Tomasi D, Volkow ND, Wang GJ, Wang R, Telang F, Caparelli EC, Fowler JS. Methylphenidate enhances brain activation response to visual attention and working memory tasks in healthy controls. *Neuroimage*. 2011; 54:3101–3110. [PubMed: 21029780]
- Turner DC, Clark L, Dowson J, Robbins TW, Sahakian BJ. Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2004; 55(10):1031–1040. [PubMed: 15121488]
- Valcour V, Yee P, Williams AE, Shiramizu B, Watters M, Selenes O, Sacktor N. Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection – The Hawaii Aging with HIV Cohort. *Journal of Neurovirology*. 2006; 12(5):387–391. [PubMed: 17065131]
- van Dyck CH, McMahon TJ, Rosen MI, O'Malley SS, O'Connor PG, Lin CH, Kosten TR. Sustained-release methylphenidate for cognitive impairment in HIV-1-infected drug abusers: A pilot study. *Journal of Neuropsychiatry and Clinical Neuroscience*. 1997; 9:29–36.
- Vance DE, Dawson J, Wadley VG, Edwards JD, Roenker DL, Rizzo M, Ball KK. The Accelerate Study: The longitudinal effect of speed of processing training on cognitive performance of older adults. *Rehabilitation Psychology*. 2007; 51(1):89–96.
- Vance DE, Eagerton G, Harnish B, McKie-Bell P, Fazeli P. Cognitive prescription across the lifespan: A nursing approach to increasing cognitive reserve. *Journal of Gerontological Nursing*. 2011; 37(4):22–29. [PubMed: 21175110]
- Vance DE, Farr K, Struzick TC. Assessing the clinical value of cognitive appraisal in adults aging with HIV. *Journal of Gerontological Nursing*. 2008; 34(1):36–41. [PubMed: 18274303]
- Vance DE, Fazeli PL, Ross L, Wadley VG, Ball KK. Speed of processing training with middle-aged and older adults with HIV: A pilot study. *Journal of the Association of Nurses in AIDS Care*. (in press).
- Vance DE, Graham MA, Fazeli PL, Heaton K, Moneyham L. An overview of non-pathological geroneuropsychology: Implications for nursing practice and research. *Journal of Neuroscience Nursing*. 2012; 44(1) [Epub ahead of print].
- Vance DE, Larsen KI, Eagerton G, Wright MA. Comorbidities and cognitive functioning: Implications for nursing practice and research. *Journal of Neuroscience Nursing*. 2011; 43(4):215–224. [PubMed: 21796044]
- Vance DE, Mugavero M, Willig J, Raper JL, Saag MS. Aging with HIV: A cross-sectional study of co-morbidity prevalence and clinical characteristics across decades of life. *Journal of the Association of Nurses in AIDS Care*. 2011; 22(1):17–25. [PubMed: 20471864]
- Vance DE, Ross LA, Downs CA. Self-reported cognitive ability and global cognitive performance in adults with HIV. *Journal of Neuroscience Nursing*. 2008; 40(1):6–13. [PubMed: 18330405]
- Vance DE, Struzick TC, Farr K. Spaced retrieval technique – A cognitive tool for social workers and their clients. *Journal of Gerontological Social Work*. 2010; 52(2):148–158. [PubMed: 20094934]
- Vance DE, Webb N, Marceaux J, Viamonte S, Foote A, Ball KK. Mental stimulation, neural plasticity, and aging: Directions for nursing practice and research. *Journal of Neuroscience Nursing*. 2008; 40(4):241–249. [PubMed: 18727340]

- Volkow N, Swanson J. The action of enhancers can lead to addiction. *Nature*. 2008; 451:520. [PubMed: 18235477]
- Williams CG, Goldman-Rakic PS. Modulation of memory fields by dopamine D1 receptors in the prefrontal cortex. *Nature*. 1995; 376:572–575. [PubMed: 7637804]
- Woods SP, Carey CL, Morgan LM, Dawson MS, Letendre SL, Grant I. Frequency and predictors of self-reported prospective memory complaints in individuals with HIV. *Archives of Clinical Neuropsychology*. 2007; 22:187–195. [PubMed: 17289343]
- Yesavage JA, Friedman L, Ashford JW, Kraemer HC, Mumenthaler MS, Noda A, Hoblyn J. Acetylcholinesterase inhibitor in combination with cognitive training in older adults. *Journal of Gerontology: Psychological Science*. 2008; 63(5):P288–P294.

Clinical Considerations

When working with HIV-infected adults who are experiencing forgetfulness or cognitive problems, consider the following:

- Measureable neuropsychological impairments, including asymptomatic neurocognitive impairment, confounded cases of neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia are common.
- Forgetfulness and other cognitive problems can be identified subjectively (i.e., self-reported) and objectively (i.e., as observed by caregivers and/or clinician).
- Many cognitive functioning screening tools objectively measure cognition. While none of these tools are superior to a full neuropsychological evaluation, which commonly takes several hours, they are useful for assessing global cognition in a few minutes within the clinical setting.
- Interventions for addressing non-pathological forgetfulness and cognitive problems generally fall into two strategies: (a) restoring or improving existing cognitive functioning and (b) compensating for a loss in cognitive functioning. These strategies may be employed together to improve cognition as much as possible and to compensate for any remaining deficits.
- Given the negative effects that HIV exerts on the brain and cognition, reducing the amount of HIV in the body is the most effective strategy to mitigate forgetfulness and cognitive problems.
- Mnemonic techniques and cognitive strategies such as spaced retrieval and cognitive remediation programs, treating depression and anxiety, prescribing methylphenidate and psychostimulants, reducing inflammation, treating co-morbid conditions, and encouraging a healthy lifestyle will most likely ameliorate cognitive functioning in this clinical population.
- Using acetylcholinesterase inhibitors, herbal and alternative supplements, and hormone replacement therapy to treat forgetfulness and cognitive problems are not encouraged.

Figure 1.

Assessment flow chart. Reprinted with permission from SLACK Incorporated: Vance, D. E., Farr, K., & Struzick, T. C. (2008). Assessing the clinical value of cognitive appraisal in adults aging with HIV. *Journal of Gerontological Nursing*, 34(1), 36–41. doi: 10.3928/00989134-20080101-11

Note. IADLS = Instrumental activities of daily living.

MONTREAL COGNITIVE ASSESSMENT (MOCA) Version 7.1 Original Version				NAME : Education : Sex :	Date of birth : DATE :			
VISUOSPATIAL / EXECUTIVE			Copy cube [] []	Draw CLOCK (Ten past eleven) (3 points) [] [] [] [] [] [] [] [] [] []	POINTS ____/5			
NAMING					[] [] [] ____/3			
MEMORY		Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.			No points			
		FACE	VELVET	CHURCH	DAISY	RED		
		1st trial	2nd trial	1st trial	2nd trial	1st trial		
ATTENTION		Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [] 2 1 8 5 4 Subject has to repeat them in the backward order [] 7 4 2			____/2			
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [] FBACMNAAJKLBAFAKDEAAAJAMOFAB					____/1			
Serial 7 subtraction starting at 100 [] 93 [] 86 [] 79 [] 72 [] 65 4 or 5 correct subtractions: 3 pts. 2 or 3 correct: 2 pts. 1 correct: 1 pt. 0 correct: 0 pt					____/3			
LANGUAGE		Repeat : I only know that John is the one to help today. [] The cat always hid under the couch when dogs were in the room. []			____/2			
Fluency / Name maximum number of words in one minute that begin with the letter F [] ____ (N ≥ 11 words)					____/1			
ABSTRACTION		Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler			____/2			
DELAYED RECALL		Has to recall words WITH NO CUE []	FACE []	VELVET []	CHURCH []	DAISY []	RED []	Points for UNCUEd recall only ____/5
Optional		Category cue						
Multiple choice cue								
ORIENTATION		[] Date	[] Month	[] Year	[] Day	[] Place	[] City	____/6
© Z.Nasreddine MD		www.mocatest.org		Normal ≥ 26 / 30		TOTAL		____/30
Administered by: _____						Add 1 point if ≤ 12 yr edu		

Figure 2. Montreal cognitive assessment. Copyright Z. Nasreddine, MD. Reproduced with permission. Copies are available at www.mocatest.org

Figure 3.
Factors that positively or negatively affect cognitive reserve.

Figure 4.

Co-morbidities, treatment, and lifestyle factors affect cognition over time.

Note. ART = antiretroviral therapy.