Published in final edited form as:

J Neurosci Nurs. 2013 October ; 45(5): 306–316. doi:10.1097/JNN.0b013e31829d8b29.

The Role of Neuroplasticity and Cognitive Reserve in Aging with HIV: Recommendations for Protection and Rehabilitation

David E. Vance, PhD, MGS [Associate Professor],

The University of Alabama School of Nursing, Room 456, 1701 University Boulevard, University of Alabama at Birmingham (UAB), Birmingham, AL 35294-1210, Office: 205-934-7589, Fax: 205-996-7183

Pariya L. Fazeli, BA, MA [Doctoral Student],

Department of Psychology & Center for Research in Applied Gerontology, Holly Mears Building, 924 19th Street South, University of Alabama at Birmingham, Birmingham, AL 35294, Office: 205-975-2292

Joan S. Grant, DSN, RN [Professor],

1701 University Boulevard, NB Room 556, University of Alabama School of Nursing, 1530 3rd Ave. South, Birmingham, Alabama 35205-1210, Office: 205-934-6527; Fax: 205-996-9165

Larry Z. Slater, PhD, RN-BC, CCRN [Post-Doctoral Scholar], and

University of Alabama School of Nursing, University of Alabama at Birmingham, 1701 University Boulevard, NB 1020P, Birmingham, AL 35294-1210, USA, Office: 205-934-6164, Fax: 205-996-9165

James L. Raper, DSN, CRNP, JD [Director]

1917 Clinic, Associate Professor, University of Alabama at Birmingham; School of Medicine, Department of Medicine, Division of Infectious Diseases; Birmingham, Alabama 35294-2050; Office: 205-975-7732; Fax: 205-934-8490

David E. Vance: devance@uab.edu; Pariya L. Fazeli: plfazeli@uab.edu; Joan S. Grant: grantj@uab.edu; Larry Z. Slater: lzslater@uab.edu; James L. Raper: jimraper@uab.edu

By 2015, nearly half of people with HIV in developed countries will be 50 years or older (Kirk & Goetz, 2009). This demographic change is due largely to three factors: 1) Highly Active Antiretroviral Therapy (HAART) that is extending the quantity and quality of life for those with HIV, 2) the aging of the population in general, and 3) later life (50 and older) infections which account for 15% of all new diagnoses (Centers for Disease Control [CDC] and Prevention, 2008; Kirk & Goetz). With the aging of this clinical population, concerns remain that HIV, HIV-associated co-morbidities, and inflammation may accelerate the aging process which may detrimentally impact everyday functioning via declines in cognitive functioning (Vance, Bayless, Kempf, Keltner, & Fazeli, 2011).

Although the incidence and prevalence of HIV-related dementia decreased significantly due in large part to HAART, cognitive problems continue to persist in many adults with HIV (Simioni et al., 2010). In as little as one year post diagnosis, alterations in brain metabolism and cognition are commonly observed (Basso & Bornstein, 2000; Lentz et al., 2011). Based upon a cross-sectional sample of 1,555 adults with HIV assessed from six university clinics

Correspondence to: David E. Vance, devance@uab.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

across the United States, 52% exhibited neuropsychological deficits; 33% presented asymptomatic neuropsychological deficits, 12% presented mild neuropsychological deficits, and 2% presented HIV-related dementia (Heaton et al., 2010). Baldewicz and colleagues (2004) followed a group of adults with and without HIV over an 8-year period observing their cognitive functioning and found that compared to the adults without HIV, those with HIV demonstrated significant neuropsychological deficits in speed of processing and fine psychomotor speed. These deficits were more severe in those with AIDS. Other studies also show that increased HIV severity, as measured by a CD4+ lymphocyte count under 200 cells/ μ l (i.e., AIDS) or CD4+ lymphocyte count nadir (i.e., lowest ever CD4+ lymphocyte count) and higher viral load, is predictive of poorer cognitive functioning (Heaton et al.; Valcour et al., 2006).

These neuropsychological deficits are objectively detected by standardized neuropsychological measures (i.e., Trails A & B, Wisconsin Card Sorting Test) and can occur in several cognitive domains including executive functioning and problem solving, language, psychomotor ability, speed of processing, attention, and memory (Hardy & Vance, 2009). Yet, metacognition (i.e., the ability to monitor and think about one's own thinking) may also be compromised in about one-third of those with HIV. Such metacognitive deficits mean that some patients with HIV may not be able to accurately recall and report on their cognitive health (Vance, Farr, & Struzick, 2008).

The purpose of this article is to provide nurses, nurse practitioners, and nurse researchers information on the cognitive issues pertaining to those living and aging with HIV. As such, the potential causes of such neuropsychological deficits are discussed within the framework of neuroplasticity and cognitive reserve. Recommendations for cognitive protection and rehabilitation and mitigation are provided, including such approaches as HAART, treatment of co-morbidities known to impact cognitive functioning, psychostimulants, and cognitive remediation therapies such as speed of processing training. Finally, implications for nursing practice and research are posited.

Cognitive Aging with HIV

HIV is often considered to accelerate the aging process (Kirk & Goetz, 2009). The primary mechanisms of this accelerated aging are microbial translocation (i.e., leaky gut syndrome) and systemic inflammation (Vance, Bayless et al., 2011). These mechanisms in turn lead to neuroinflammation. Although HIV does not directly kill neurons, it does produce neuroinflammation and enter glial cells (i.e., macrophages and microglia) which support neuronal health (right side of Figure 1). As macrophages and microglia die, they secrete inflammatory molecules such as quinolic acid and cytokines that promote oxidative stress that further promotes neuroinflammation and results in neuronal death (Fields, 2009). Unfortunately, even with HAART's ability to reduce viral load in the plasma which enables the immune system to function more normally, such neuroinflammation persists (Harezlak et al., 2011). Using magnetic resonance imaging (MRI), Thompson and colleagues (2005) compared 26 adults with HIV on HAART to 14 adults without HIV. They found evidence of such continued neuroinflammation as exhibited by cortical thinning in the prefrontal cortices in the adults with HIV compared to those without HIV.

Another sign of accelerated aging in HIV is the early onset of comorbid conditions such as hypertension, hypercholesterolemia, heart disease, renal and hepatic diseases, and diabetes. In fact, HAART has been implicated in causing or exacerbating many of these co-morbidities (Malaspina et al., 2011; Vance, Mugavero, Willig, Raper, & Saag, 2011). These co-morbidities also can promote neuroinflammation and negatively impact brain health resulting in poorer cognitive functioning (Vance, Larsen, Eagerton, & Wright, 2011). For

example, Bruehl and colleagues (2009) compared 41 middle-age adults with type 2 diabetes to 47 demographically matched adults without diabetes and found that those with diabetes performed poorer as a group on cognitive measures and had a decreased volume in the prefrontal cortex (the area of the brain responsible for executive functioning and reasoning) and the hippocampi (the area of the brain responsible for memory consolidation). In addition, poorer glycemic control was significantly related to decreased volume of the prefrontal cortex. Studies on the relationship between cognition and other co-morbidities (i.e., heart disease, hypertension) demonstrate similar findings (Vance, Larsen et al., 2011).

Neuroplasticity and Cognitive Reserve

These neurological insults in adults with HIV caused by accelerated aging, neuroinflammation, and co-morbidities can demote positive neuroplasticity and reduce cognitive reserve, making people more vulnerable to poorer cognitive and everyday functioning. To understand the processes of neuroplasticity on cognitive reserve, two classic studies elucidate this interaction. One is the enriched environmental paradigm and the other is the London Taxi Driver Study.

Enriched Environmental Paradigm

The enriched environmental paradigm has been used extensively by neuroscientists to understand the neurological impact the environment exerts on the brain; and as such, it clearly demonstrates the effects of positive and negative neuroplasticity on cognitive reserve (Diamond, 1993; Kobayashi, Ohashi, & Ando, 2002). Neuroplasticity allows the neurons (i.e., nerve cells) in the brain to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment. Although there are numerous variations of this paradigm, the basic component consists of placing animals, typically rats from the same colony so they are genetically similar, into one of three environments: enriched, standard, or impoverished. In the enriched environment, rats are placed in a large cage together and are provided the opportunity to interact freely with each other. In addition, various toys are placed in the cage so these rats have something to explore and use in play. These toys are exchanged with new ones periodically so the rats are always exposed to novel stimuli. In the standard environment, rats are placed three to a cage and are also provided the opportunity to interact freely with each other. Otherwise, they have no toys and items to explore. Finally, in the impoverished environment, rats are placed in isolation and have no toys.

Once the rats are exposed to these environments for a set time period, the rats are euthanized to examine their brain morphology. It has been found consistently that rats placed in the enriched environment possessed larger brains, more neurotrophic growth factors, and more dendritic branching between neurons compared to the rats placed in the other two environments. Similarly, when compared to the rats in the impoverished environment, the same pattern of findings is observed for the rats placed in the standard environment. Thus, the enriched environmental paradigm elucidates the role that environmental complexity and mental stimulation play on brain morphology.

In subsequent studies, it has been clearly shown that these environmentally-derived changes in brain morphology are related to better cognitive functioning (e.g., problem solving, memory) in rats, as measured by maze performance tasks. Rats placed in the enriched environment not only developed bigger and healthier brains compared to those in the standard and impoverished environments, they also were able to find their way through such mazes at a faster rate. Furthermore, regardless of the age of the rats or duration placed in these environments (i.e., a few weeks to a few months), the results remain the same (Vance, Webb, et al., 2008).

From the enriched environmental paradigm, the effects of positive and negative neuroplasticity on cognitive reserve are clearly demonstrated. Rats placed in the enriched environment experienced positive neuroplastic changes that increase brain size and health (i.e., cognitive reserve), which in turn improved cognitive function. Similarly, rats placed in the impoverished environment experienced negative neuroplastic changes that decreased brain size and health, which in turn reduce cognitive function. Although it would be unethical to conduct this same type of study in humans, several studies have examined positive and negative neuroplasticity in people.

London Taxi Driver Study

Capitalizing on a naturalistic phenomenon paralleling the enriched environmental paradigm, the London Taxi Driver Study is a seminal work in neurology that compared MRI scans between London taxi drivers and London bus drivers (Maguire, Woollett, & Spiers, 2006). Similar to the enriched environment, as part of their training to earn their license, London taxi drivers must study 2 to 4 years to familiarize themselves with the 25,000 city streets and points of interest as well as how to connect and negotiate through them. Similar to the standard environment, London bus drivers do not have a rigorous training like the taxi drivers. They drive a repetitive, less complex, route through the London streets. In comparison to the bus drivers, MRI scans revealed that the taxi drivers possessed larger mid-posterior hippocampi. In fact, the size of this brain region was significantly proportional to the years of taxi driving. More years driving was reflective of larger mid-posterior hippocampi. This study and others (e.g., Boyke Driemeyer, Gaser, Büchel, & May, 2009) highlight the roles learning and environment exert on neuroplasticity and cognitive reserve.

Enriched Versus Impoverished Environment with HIV

For many infected with HIV, like in the enriched environmental paradigm, they too may be living in impoverished conditions that may promote negative neuroplasticity which can lead to poorer cognitive reserve. Basso and Bornstein (2000) found that over a 1-year period those adults with HIV with higher premorbid intelligence experienced fewer cognitive declines. This suggests having more cognitive reserve, as exhibited by intelligence, can insulate adults from HIV-related neurological insults.

Further, certain lifestyle factors are reflective of an impoverished environment. First, approximately 45% of adults with HIV are unemployed (Rabkin, McElhiney, Ferrando, van Gorp, & Lin, 2004). Employment can be mentally stimulating and promote positive neuroplasticity; likewise, staying home with nothing to do is tantamount to the impoverished environment and can promote negative neuroplasticity (Vance, 2010). Second, and related to employment, many adults with HIV lack economic resources; such resources can be of value in traveling, taking classes, and seeking entertainment that is mentally stimulating and promotes positive neuroplasticity and cognitive reserve (Vance).

Third, HIV-related stigma is common in adults and may lead to withdrawal and social isolation. As a result, the lack of social stimulation may lead to negative neuroplasticity (Vance, 2010). And finally, substance abuse is quite common in adults with HIV with recognized drug abuse and alcohol abuse affecting approximately 27% and 13%, respectively (Vance, Mugavero et al., 2011). Not only does substance abuse negatively impact cognition directly (Vance, Eagerton, Harnish, McKie-Bell, & Fazeli, 2011), but engaging in such substance abuse can lead to self-isolation and result in poorer engagement in vocational and social situations which are mentally stimulating.

Clearly, many with HIV may be living in impoverished environments that promote negative neuroplasticity; however, it is worth noting that nearly half of those with HIV do not have

any observed cognitive problems (Heaton et al., 2010). Although the literature is not clear on this, perhaps those who are faring well cognitively may be the ones who are still working, staying actively engaged socially, and promoting their own positive neuroplasticity (Vance, 2010). As such, this suggests possible areas to protect and possibly augment cognitive reserve in all adults with HIV.

Recommendations for Cognitive Protection and Rehabilitation

Nurses and nurse practitioners need practical advice on how to promote and protect the cognitive reserve of their patients with HIV. Figure 2 highlights such evidence-based approaches known to promote cognitive reserve and cognition. These include HAART, treatment of co-morbidities, treatment of mood problems, psychostimulants, lifestyle factors, and cognitive remediation therapy.

HAART

HAART is likely the most important approach for protecting against and treating cognitive problems in HIV. As discussed, HIV crosses the blood brain barrier and produces neuroinflammation and infects glial cells which in turn damages or destroys neurons (right side of Figure 1). By reducing the amount of HIV in the body, and especially the brain, HAART protects cognitive reserve and allows the brain the opportunity to repair and function normally. In a review of 23 studies on HAART and cognition, Al-Khinid, Zakzanis, and van Gorp (2011) concluded that HAART was moderately effective in improving several cognitive domains (i.e., attention, motor function, and executive function) in adults with HIV. Furthermore, increases in CD4+ lymphocyte count were significantly correlated to improvement in cognitive functioning. This significant correlation highlights the close connection between brain health and immune health. Epitomizing this connection, Parsons, Braaten, Hall, and Robertson (2006) examined the relationship between immune function and cognitive function in 59 adults with HIV over a 6-month period. These adults were either HAART-naïve or had to change their HAART regimen because their current regimen failed to suppress their plasma viral load; in both circumstances, participants were about to receive an HAART regimen novel to their current treatment. In comparison to those adults who failed to reach viral suppression, researchers found those who did reach adequate viral suppression improved significantly on neuropsychological measures of speed of processing. Likewise, those adults who failed to reach viral suppression reported more cognitive problems. Similar studies confirm the efficacy of successful treatment with HAART on improving cognition in this clinical population (e.g., Koopmans, Ellis, Best, & Letendre, 2009).

Although HIV is able to cross the blood brain barrier, not all HAART medications are equally effective in doing so; this means that the medications may not be sufficiently present in the brain and as a result, HIV may continue to be destructive to the nervous system despite its beneficial effect on reconstituting the immune system. Therefore, selecting HAART medications with better penetration of the blood brain barrier remains an essential component of treating cognitive problems (Koopmans et al., 2009). Based on a schema developed by Letendre and colleagues (2008) and Antinori and colleagues (2011), the left side of Figure 1 displays the blood brain barrier potential of different HAART medications. Although the class of HAART medications (e.g., Nucleoside Reverse Transcriptase Inhibitors) does not make a difference in such blood brain barrier penetration efficacy, the individual medications with each HAART class possess unique penetration properties. Thus, if patients are experiencing cognitive problems, considering blood brain barrier penetration in one's HAART regimen represents a viable solution for protecting cognitive reserve and ameliorating neurological functioning.

Despite the efficacy of HAART to protect neurological functioning in adults with HIV, there are certain drawbacks that must be considered when balancing the use of HAART to improve both immunological and neurological functioning. First, efavirenz has been associated with an increased risk for cognitive problems (Ciccarelli et al., 2011). Although it is effective in reducing viral replication, it appears to be neurotoxic and may negatively impact brain metabolism and mitochondria. Other HAART medications are being examined for similar iatrogenic effects (Koopmans et al., 2009; Schweinsburg et al., 2005).

Second, HAART can produce metabolic abnormalities such as hypertension, hypercholesterolemia, heart disease, and diabetes. These co-morbidities, in addition to HIV itself, are known to reduce cognitive reserve and lead to cognitive problems. Thus, management of these HAART-related co-morbidities is essential in protecting neurological functioning (Vance, Larsen et al., 2011). Finally, once someone is prescribed HAART, an adherence rate of 95% or greater is highly recommended to avoid viral resistance to these medications (Howard et al., 2002). However, for someone with cognitive problems, forgetting to take medications is common; this can lead to poorer viral suppression which in turn can increase viral load in the plasma and brain, which ultimately leads to reduced cognitive reserve and poorer cognition (Becker, Thames, Woo, Castellon, & Hinkin, 2011). Thus, when a patient is prescribed HAART and experiences memory or other cognitive problems that can interfere with medication adherence, mnemonics and other strategies (i.e., spaced-retrieval method, method of loci) must be considered (Vance, Webb et al., 2008).

Treatment of Co-morbidities

As mentioned, HAART can promote metabolic syndromes in adults with HIV, leading to a high prevalence across the lifespan for hypertension (~33%), hypercholesterolemia (~38%), heart disease (~4%), and diabetes (~9%). These metabolic syndromes rise sharply with advanced age (Vance, Mugavero et al., 2011). In addition, other co-morbidities are commonly associated with HIV such as hepatitis C (25%), alcohol abuse (13%), and substance abuse (23%) (Vance, Mugavero et al.). Generally, that which is good for the body is good for the brain; likewise, that which is bad for the body is bad for the brain. Thus, it has been well documented that those individuals experiencing these co-morbidities, even without HIV, suffer from poorer cognitive functioning compared to those without such medical conditions (Vance, Larsen et al., 2011).

As a means to abate the neurological sequelae of HIV with such co-morbidities, treatment of such co-morbidities is also recommended to promote cognitive health. Minimizing the negative neurological and cognitive impact of such co-morbidities through medications and lifestyle changes (i.e., diet, exercise) are needed to protect against cognitive reserve depletion (Vance, Eagerton et al., 2011). In treating one or more co-morbidities in adults with HIV, nurse practitioners must be aware of balancing such treatment with the number of medications needed to do so. Polypharmacy, as well as the potential for adverse side effects, can also impair cognitive functioning especially in medically vulnerable adults including adults with HIV as well as in older adults who typically possess less adipose tissue and poorer hepatic and renal functioning (Malaspina et al., 2011). In addition, certain medications such as anticholinergics, benzodiazepines, and opiates can adversely impact cognitive functioning (Julien, 1998; Vance, Larsen et al., 2011). Therefore, patients should be monitored closely for possible polypharmacy issues. Likewise, patients should be encouraged to use non-pharmacological, lifestyle modifications to address and treat co-morbidities in order to reduce the impact of such medical conditions on cognition.

Treatment of Mood Problems

A diagnosis of HIV produces severe mood problems such as anxiety and depression, which in more severe cases can result in suicidal ideation. For example, of 207 women with HIV living in New York City, 27% and 42% reported considering suicide within the first week and first month after being diagnosed, respectively (Cooperman & Simoni, 2005). Yet, the prevalence of anxiety and depression in those with HIV remain at high levels after the initial diagnosis. Using medical chart extraction of 1,478 adults with HIV, Vance, Mugavero, and colleagues (2011) found that across each decade of life (e.g., 18–29, 30–39, etc.) the prevalence of anxiety (~20%) and depression (~40%) was quite high. The prevalence of such mood problems is significant considering that such problems can negatively affect cognition even in the general population without HIV (Vance, Larsen et al., 2011). Such mood problems can increase cytokines and other stress hormones that can increase neuroinflammation that negatively impacts positive neuroplasticity, cognitive reserve, and cognition (Sartori Vance, Slater, & Crowe, in press).

In a sample of 107 adults with HIV, Thames and colleagues (2011) found those with higher levels of depression reported more cognitive problems than those with lower levels. Similarly, in a sample of 98 adults with HIV, Fazeli and colleagues (2011) found that higher levels of mood disturbance were significantly related to poorer cognitive performance on measures of reasoning, speed of processing, and psychomotor speed and visuomotor coordination. With the interaction between mood problems and cognition, treatment for anxiety and depression (e.g., counseling, selective serotonin reuptake inhibitors) has been suggested as a means to improve cognition. In a sample of 75 adults with HIV experiencing depression, Claypoole and colleagues (1998) found that after these adults were treated with antidepressants over a 12-week period, self-reported cognitive problems abated and improvements in objective measures of cognitive performance were observed. Thus, treatment of mood problems appears to be a practical approach to bolstering cognitive ability in adults with HIV.

Psychostimulants

Two psychostimulants have been found to improve cognition in adults with HIV — methylphenidate (i.e., Ritalin) and modafinil (i.e., Provigil). Traditionally, both have been used safely to treat attention deficit/hyperactivity disorder and improve the ability to focus in patients. Neither agent is currently FDA approved to treat HIV-related cognitive disorders. Methylphenidate may also be effective in treating fatigue (Mar Fan et al., 2008) and hypercholesterolemia (Charach, Kaysar, Grosskopf, Rainovich, & Weintraub, 2009) in some patients. This added effect is particularly advantageous since nearly 50% (Leserman, Barroso, Pence, Salahuddin, & Harmon, 2008) and 38% (Vance, Mugavero et al., 2011) of adults with HIV experience fatigue and hypercholesterolemia, respectively.

Several studies show that adults with HIV may be vulnerable to dopaminergic dysfunction. For example, in a sample of 22 adults with HIV (five participants were HIV-seronegative, but at risk for HIV infection while 11 were HIV-seropositive without neurological disease; six had HIV-related neurological disease), Berger and colleagues (Berger, Kumar, Kumar, Fernandez, & Levin, 1994) found low levels of dopamine and homovanillic acid, a dopamine metabolite, in the cerebrospinal fluid. Additional studies indicate that over or under production of dopamine impairs memory (Williams & Goldman-Rakie, 1995). Such dopamine dysfunction in adults with HIV may be another cause of cognitive problems. Methylphenidate is a dopamine agonist (Frenette et al., 2012) and modafinil may block the dopamine transporter while the dopamine D1 receptor may contribute to its effects on cognitive and motivation enhancement (Young & Geyer, 2010). This dopamine relationship

may explain why both agents are both effective in improving cognitive functioning in adults with HIV.

Although studies have shown methylphenidate can improve cognitive functioning in healthy adults (Tomasí et al., 2011) and in those with multiple sclerosis (Harel, Appleboim, Lavie, & Achiron, 2009), no large clinical trials have been conducted to investigate the efficacy of this medication on improving cognition in adults with HIV. In eight methadone patients with HIV, van Dyck and colleagues (1997) used sustained release methylphenidate in a double-blind crossover, placebo controlled study. Forming a composite score of cognition based on a variety of neuropsychological measures, results revealed that methylphenidate did improve cognitive functioning. Later, in 16 adults with HIV, Hinkin and colleagues (2001) used methylphenidate (once daily 30 mg dose) in a single-blind crossover, placebo controlled study and found those adults with HIV who had greater depression severity and cognitive slowing at baseline experienced better cognitive functioning, as measured by dual task time and computerized neuropsychological measures, as a result of the methylphenidate. Unfortunately, compared to placebo, methylphenidate did not appear to be effective in those who did not exhibit any cognitive slowing at baseline. Since these participants did not have any cognitive impairment in the beginning, they may not have had any dopamine dysfunction for which the methylphenidate could compensate. Furthermore, in this study, given that mood problems can exacerbate cognitive problems, Hinkin and colleagues examined whether methylphenidate was effective in abating depression severity. Although these researchers concluded that methylphenidate is effective in improving cognition in adults with HIV experiencing cognitive problems, it does not appear effective in ameliorating depression severity.

Modafinil has also shown similar effects to methylphenidate in treating fatigue and cognitive problems. In 103 adults with HIV, McElhiney, Rabkin, van Gorp, and Rabkin (2010) used modafinil in a placebo controlled study over a 4-week period. Those participants randomized to the modafinil group improved on a neuropsychological measure of global cognition compared to those randomized to the placebo control group. Furthermore, participants in the modafinil group reported fewer cognitive problems. This study is particularly salient because the sample was very heterogeneous (i.e., 20% with hepatitis C, 29% taking antidepressants, 51% with a substance use history, 40% with a DSM-IV depression diagnosis) and representative of the general HIV population (Vance, Mugavero et al., 2011).

Lifestyle Factors

Lifestyle modifications can be used to abate the effect that co-morbidities exert on cognitive functioning. Likewise, in the general population, several studies have demonstrated the benefits of physical activity and exercise, stress reduction, intellectual exercise, social engagement, proper sleep hygiene, and substance use reduction have on cognitive reserve and cognitive functioning (Vance, Eagerton et al., 2011). For example, methamphetamine cessation improves motor and speed of processing functioning after one year (Iudicello et al., 2010). Many of these lifestyle modifications protect and promote cognitive reserve and cognitive functioning, increasing brain-derived neurotrophic growth factors, as well as reducing neuroinflammation and oxidative stress (Atkins et al., 2010; Foster, Rosenblatt, Kuljiš, 2011; Malaspina et al., 2011).

Although a change in one lifestyle modification may be effective in supporting cognitive reserve and cognitive functioning, several lifestyle modifications may act synergistically to better abate neurological sequelae and improve cognition. Thus, integrating various lifestyle modifications has the potential to improve cognitive functioning. Vance, Eagerton, and

colleagues (2011) developed an individualized behavioral modification strategy to improve cognitive functioning called “Cognitive Prescriptions.”

Cognitive Prescriptions are designed to simultaneously modify behaviors in certain categories (i.e., physical exercise, intellectual exercise, sleep hygiene) with specific target goals in each category along with health education and tips on why and how to achieve these goals. For example, for physical exercise, during the motivational interviewing session the adults may indicate that he or she used to enjoy walking and gardening. Thus, targeted goals for physical exercise includes – “Go for a 30-minute walk 3 times a week” and “Spend 30-minutes on your flower garden twice a week.” Then, the adults would monitor their progress in achieving these goals. Such a non-pharmacological, non-invasive approach to improve cognition can improve both mental and physical health, and promote self-efficacy in adults with HIV.

Cognitive Remediation Therapy

Global cognition and specific cognitive domains (i.e., reasoning, memory, and speed of processing) were improved in several clinical populations (e.g., geriatric) using cognitive remediation therapies. These therapies typically use computer programs in a gaming platform to improve cognitive functioning but can also consist of pencil-and-paper exercise, videotape exercises, and even specially-designed theatre classes (Vance, Graham, Fazeli, Heaton, & Moneyham, 2012; Vance Webb et al., 2008).

Since such training is effective in non-HIV infected community-dwelling older adults, it may also benefit those with HIV. In a recent two-group pre-post experimental design, Vance, Fazeli, Ross, Wadley, and Ball (in press) randomized middle-aged and older adults with HIV ($M_{age} = 51.6$; range = 40.7 – 70.6) to either a speed of processing training group ($n = 22$) where they engaged in the protocol over a 4 to 6 week period or to a no-contact control group ($n = 24$). Those adults in the speed of processing training group engaged in approximately 10 hours of computer exercises that were specially designed to maximize their ability to attend to visual stimuli presented at increasingly faster rates at or near participants’ perceptual threshold. To stretch and improve this cognitive ability, the exercises varied by complexity by changing colors and presentation speeds of the stimuli accordingly. As observed in similar studies, compared to the no-contact control group those in the speed of processing training group improved on the Useful Field of View Test; this speed of processing improvement transferred to better functioning on a laboratory measure of everyday functioning (i.e., Timed Instrumental Activities of Daily Living Test). The improvement in the Useful Field of View Test is particularly important because performance on this measure is predictive of driving safety and at-fault crashes (Vance, 2009). In fact, in a study of 68 adults with HIV, Marcotte and colleague (1999) found that nearly 50% of their sample had Useful Field of View impairments. Such impairments were also predictive of accidents in a driving simulator. Thus, improvement in the Useful Field of View Test due to speed of processing training may be effective in improving driving safety in adults with HIV. Speed of processing training and other cognitive remediation therapies represent an affordable and non-invasive strategy for protecting and improving cognition in adults with HIV.

Implications for Nursing Research

There are several research vectors that are being investigated to restore cognition and improve cognitive reserve in adults with HIV. Although these strategies cannot be recommended for implementation into clinical practice yet, such vectors may eventually be considered within the scope of standard of care once enough evidence is collected to

validate their use. Such vectors include treatment of neuroinflammation, administering neurotropic medications, and advancements in HAART delivery.

Neuroinflammation

Whereas neuroinflammation can cause cognitive problems, methods for reducing such neuroinflammation may facilitate cognitive health and cognitive reserve (Malaspina et al., 2011). One way to reduce neuroinflammation is through polyphenols and other antioxidants. For example, Rrapo and colleagues (2009) used green tea, a powerful polyphenol, to reduce astrogliosis in HIV-1 Tat transgenic mice. This approach should be studied in adults with HIV. Likewise, the second generation tetracycline antibiotic derivative, minocycline, is also an antioxidant that is able to cross the blood brain barrier which allows this medication to be delivered where it is needed in order to abate such neuroinflammation. In fact, a study (ACTG5235) is currently in progress to determine whether minocycline can be used to treat HIV-associated neurocognitive disorder (Lindl, Marks, Kolson, & Jordan-Scuitto, 2010). Similarly, the monamine oxidase type B inhibitor, selegiline, is a neurotropic antioxidant that can be delivered safely via transdermal administration and has been considered as a possible treatment for HIV-associated cognitive decline (Lindl et al.). Finally, regular non-steroidal anti-inflammatory medications may have similar neuroprotective and anti-neuroinflammatory properties in adults with HIV (Eggert et al., 2010; McCombe et al., 2009). Although these are exciting vectors of research, their effectiveness in clinical practice have not been established.

Neurotrophic Medications

Neurotrophic medications such as insulin-like growth factor 1, memantine, and lithium are also being considered as potential vectors for treatment. Preliminary studies in HIV, stroke, Alzheimer's disease, and diabetes suggest that intranasal delivery of insulin-like growth factor 1 can improve short- and long-term memory as well as mood and odor detection. With this delivery method, no iatrogenic effects have been observed.

In HIV mice models and Alzheimer's disease, memantine, a glutamate-*N*-methyl-D-aspartate antagonist, has been shown to abate glutamate excitotoxicity. Such excitotoxicity is tantamount to overworking the neuron until it is damaged or dies. In 140 adults with HIV administered memantine over a 16-week period, magnetic resonance spectroscopy revealed that it may be neuroprotective as exhibited by a significant increase in the N-acetyl aspartate to creatine ratio in frontal white matter and the parietal cortex (Schifitto et al., 2007).

In a 12-week pilot study, Letendre and colleagues (2006) investigated the use of lithium in ameliorating cognitive problems in eight adults with HIV and found that all participants experienced improvements in cognition. Although lithium is not recommended for everyone due to potential side effects (e.g., nausea, diarrhea, dry mouth) and lithium toxicity, this vector of research represents a viable treatment.

As discussed earlier, it is vital that HAART penetrate the blood brain barrier in order to reduce the amount of virus in the brain and thus provide the needed protection to glial cells and neurons. Unfortunately, not all HAART medications are effective in crossing the blood brain barrier. To address the CNS penetration problem, Duo and colleagues (2009) are developing nanoparticle delivery of HAART. Targeted delivery of antiretroviral drugs to CD4⁺ T lymphocyte cells and macrophages as well as delivery to the brain and other organ systems could ensure that drugs reach latent reservoirs, allowing delivery of the medication to where it is needed (Mamo et al., 2010; Vyas, Shah, & Amiji, 2006).

Conclusion

Cognition can be overlooked within a medical visit unless there are frank impairments. Thus, assessing cognition or inquiring about one's cognitive functioning can be easily neglected by medical professionals when more salient patient problems dominate the clinic visit. Yet, adults with HIV, especially those who are older, are more vulnerable for developing cognitive declines that may progress to mild cognitive impairment or dementia (Hardy & Vance, 2009). Such change in cognition is important as it impacts everyday functioning such as remembering clinic appointments and adhering to medication schedules, which in turn can negatively impact clinical outcomes. If such cognitive problems are presented, nurses have evidence-based options to treat their patients (e.g., psychostimulants). Meanwhile, nurse researchers have a variety of vectors (e.g., reducing neuroinflammation) to explore to promote positive neuroplasticity and thus increase cognitive reserve.

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]
- Antinori, A.; Lorenzini, P.; Giancola, ML.; Picchi, G.; Baldini, F.; Monno, L.; Tozzi, V. Antiretroviral CNS penetration-effectiveness (CPE) 2010 ranking predicts CSF viral suppression only in patients with undetectable HIV-1 RNA in plasma (poster n°430); 17th Conference on Retroviruses and Opportunistic Infections; San Francisco, CA. 2011.
- 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):793–802.10.1080/09540120903482994 [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):345–355.10.1023/B:AIBE.0000044081.42034.54 [PubMed: 15475681]
- 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):208–218.10.1076/1380-3395 [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; 15(8):1888–1894.10.1007/s10461-011-9924-z [PubMed: 21437726]
- 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]
- Boyke J, Driemeyer J, Gaser C, Büchel C, May A. Training-induced brain structure changes in the elderly. *Journal of Neuroscience*. 2008; 28:7031–7035.10.1523/JNEUROSCI.0742-08.2008 [PubMed: 18614670]
- 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; 1280:186–194.10.1016/j.brainres.2009.05.032 [PubMed: 19463794]
- Centers for Disease Control and Prevention. HIV/AIDS surveillance report. Centers for Disease Control and Prevention; Atlanta, GA: 2008.
- 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):848–851.10.1177/0091270009336736 [PubMed: 19553406]
- Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, Balbonero E, Bracciale L, Silveri MC. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology*. 2011; 76(16):1403–1409.10.1212/WNL.0b013e31821670fb [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):74–84.10.1207/s15324826an0502_3 [PubMed: 16318457]
- Cooperman NA, Simoni JA. Suicidal ideation and attempted suicide among women living with HIV/AIDS. *Journal of Behavioral Medicine*. 2005; 28:149–156. doi:10/1007/s10865-005-3664-3. [PubMed: 15957570]
- Diamond MC. An optimistic view of the aging brain. *Generations*. 1993; 17(1):31–33.
- 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):661–669.10.4049/jimmunol.0900274
- 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):746–756.10.4049/jimmunol.0902962
- Fazeli PL, Marceaux JC, Vance DE, Slater L, Long CA. Predictors of cognition in adults with HIV: Implications for nursing practice and research. *Journal of Neuroscience Nursing*. 2011; 43(1):36–50.10.1097/JNN.0b013e3182029790 [PubMed: 21338043]
- Fields, RD. *The other brain*. New York, NY: Simon & Schuster; 2009.
- 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):1–15.10.3389/fneur.2011.00028 [PubMed: 21331281]
- Frenette AJ, Kanji S, Rees L, Williamson DR, Perreault MM, Turgeon AF, Bernard F, Fergusson DA. Efficacy and safety of dopamine agonists in traumatic brain injury: A systematic review of randomized controlled trials. *Journal of Neurotrauma*. 2012; 29(1):1–18.10.1089/neu.2011.1812 [PubMed: 21846248]
- Hardy D, Vance D. The neuropsychology of HIV/AIDS in older adults. *Neuropsychology Review*. 2009; 19(2):263–272.10.1007/s11065-009-9087-0 [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):38–40.10.1016/j.jns.2008.08.025
- 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):625–633.10.1097/QAD.0b013e31823427da7 [PubMed: 21297425]
- 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; 75:2087–2096.10.1212/WNL.0b013e318200d727
- 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):248–254.10.1176/appi.neuropsych.13.2.248
- 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; 16:2175–2182.10.1097/00002030-200211080-00010 [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):704–718.10.1080/13803390903512637 [PubMed: 20198527]
- 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 compilation of success. *Journal of the American Geriatrics Society*. 2009; 57(11):2129–2138.10.1111/j.1532-5415.2009.02494.x [PubMed: 19793157]
- Kobayashi S, Ohashi Y, Ando S. Effects of enriched environments with different durations and starting times on learning capacity during aging in rats assessed by a refined procedure of the Hebb-Williams maze task. *Journal of Neuroscience Research*. 2002; 70(3):340–346.10.1002/jnr.10442 [PubMed: 12391594]

- 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.
- 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):220–229.10.1007/s13365-011-0030-9 [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; 20:1258–1265.10.1080/09540120801919410 [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):65–70.10.1001/archneurol.2007.31 [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-Scuitto KL. HIV-associated neurocognitive disorder: Pathogenesis and therapeutic opportunities. *Journal of Neuroimmune Pharmacology*. 2010; 5:294–309.10.1007/s11481-010-9205-z [PubMed: 20396973]
- Maguire EA, Woollett K, Spiers HJ. London taxi drivers and bus drivers: A structural MRI and neuropsychological analysis. *Hippocampus*. 2006; 16(12):1091–1101.10.1002/hipo.20233 [PubMed: 17024677]
- 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; 17:110–119.10.1007/s13365-010-0008-z [PubMed: 21165783]
- Mamo T, Moseman EA, Kolishetti N, Salvador-Morales C, Shi J, Kuritzkes DR, Farokhzad OC. Emerging nanotechnology approaches for HIV/AIDS treatment and prevention. *Nanomedicine*. 2010; 5(2):269–285.10.2217/nnm.10.1 [PubMed: 20148638]
- 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):577–583.10.1007/s00520-007-0341-9 [PubMed: 17972110]
- Marcotte TD, Heaton RK, Wolfson T, Taylor MJ, Alhassoon O, Arfaa K, the HNRC Group. The impact of HIV-related neuropsychological dysfunction on driving behavior. *Journal of the International Neuropsychological Society*. 1999; 5:579–592.10.1017/S1355617799577011 [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):835–841.10.1212/01.wnl.0000343854.80344.69 [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):474–480.10.1080/13803390903201769 [PubMed: 19937504]
- Parsons TD, Braaten AJ, Hall CD, Robertson KR. Better quality of life with neuropsychological improvement on HAART. *Health and Quality of Life Outcomes*. 2006; 4:11.10.1186/1477-7525-4-11 [PubMed: 16504114]
- Rabkin JG, McElhiney M, Ferrando SJ, van Gorp W, Lin SH. Predictors of employment of men with HIV/AIDS: A longitudinal study. *Psychosomatic Medicine*. 2004; 66:72–78. [PubMed: 14747640]
- Rrapo 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]
- Sartori AC, Vance DE, Slater LZ, Crowe M. The impact of inflammation on cognitive function in older adults: Implications for health care practice and research. *Journal of Neuroscience Nursing*. (in press).

- Schifitto G, Navia BA, Yiannoutsos CT, Marra CM, Chang L, Ernst T, HIV MRS Consortium. 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; 11:356–364.10.1080/13550280591002342 [PubMed: 16206458]
- 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; 24:1243–1250.10.1097/QAD.0b013e3283354a7b [PubMed: 19996937]
- 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):224–243.10.1080/13854046.2010.539577
- 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):15647–15652.10.1073/pnas.0502548102
- 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; 54:3101–3110.10.1016/j.neuroimage.2010.10.060 [PubMed: 21029780]
- 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):387–391.10.1080/13550280600915339 [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. Speed of processing in older adults: A cognitive overview for nursing. *Journal of Neuroscience Nursing*. 2009; 41(6):290–297.10.1097/JNN.0b013e3181b6beda [PubMed: 19998680]
- Vance DE. Implications of positive and negative neuroplasticity on cognition in HIV. *Medical Science Monitor*. 2010; 16(4):HY3–5. [PubMed: 20357724]
- Vance DE, Bayless H, Kempf MC, Keltner NL, Fazeli PL. Aging, HIV, and wellness: Augmenting the components of successful aging. *Aging Health*. 2011; 7(3):435–446.10.2217/AHE.11.28
- 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):22–29.10.3928/00989134-20101202-03 [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):36–41.10.3928/00989134-20080101-11 [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]. 10.1097/JNN.0b013e31823ae48b
- 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):215–224.10.1097/JNN.0b013e3182212a04 [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):17–25.10.1016/j.jana.2010.04.003 [PubMed: 20471864]

- 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):241–249.10.1097/01376517-200808000-00008 [PubMed: 18727340]
- Vyas TK, Shah L, Amiji MM. Nanoparticulate drug carriers for delivery of HIV/AIDS therapy to viral reservoir sites. *Expert Opinions in Drug Delivery*. 2006; 3(5):613–628.10.1517/17425247.3.5.613
- Williams CG, Goldman-Rakic PS. Modulation of memory fields by dopamine D₁ receptors in the prefrontal cortex. *Nature*. 1995; 376:572–575. [PubMed: 7637804]
- Young JW, Geyer MA. Action of modafinil--increased motivation via the dopamine transporter inhibition and D1 receptors? *Biological Psychiatry*. 2010; 67:784–787.10.1016/j.biopsych.2009.12.015 [PubMed: 20132929]

Figure 1.

The impact of HIV on the brain and HAART penetration of the blood brain barrier. Note. HAART = Highly Active Antiretroviral Therapy.

Figure 2.

Causes of accelerated cognitive aging with HIV. Note. HAART = Highly Active Antiretroviral Therapy.