Real-World Impact of HIV-Associated Neurocognitive Impairment

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An estimated 1.1 million individuals in the USA live with HIV infection (CDC, 2010), with over 34 million individuals infected worldwide (UNAIDS, 2012). In the early days of the HIV epidemic, infection was typically associated with a rapidly deteriorating immunovirologic course and high rates of mortality. Advances in the clinical management of HIV disease over the past two decades, however, have significantly reduced morbidity and mortality rates associated with infection. In particular, the wide-spread use of combination antiretroviral therapy (cART) beginning in 1996 has lead to more effective viral suppression and improved immune functioning, fewer opportunistic infections, and better health-related quality of life

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(HRQoL; CDC, 2010). Nevertheless, the cART era has introduced new clinical and scientific challenges to maximizing health and other real-world outcomes in persons living with HIV, which is now perceived as a chronic, manageable illness. Younger and middle-aged HIV-infected individuals are faced with the challenges of developing and maintaining independence in everyday functioning (e.g., employment) while managing a chronic disease. Improved survival rates have also increased the prevalence of older adults infected with HIV (CDC, 2010), who may be more likely to experience chronic immune activation, longer exposure to cART, and an increased burden of non-HIV associated medical conditions (e.g., cardiovascular diseases; High et al., 2012), all of which may adversely impact real-world outcomes. Although real-world functioning is complex and multidetermined, one factor that may play an important role in a variety of different everyday activities is neurocognitive impairment, which remains highly prevalent among persons living with HIV in the cART era (Heaton et al., 2010). This chapter reviews the literature regarding the effects of HIV-associated neurocognitive impairment on real-world functions, including activities of daily living, medication adherence, employment, automobile driving, HIV transmission risk behaviors, and HRQoL.

HIV and the Central Nervous System

HIV crosses the blood–brain barrier early in the course of infection via a "Trojan Horse" mechanism (i.e., inside infected monocytes or cluster of differentiation 4 [CD4+] lymphocytes), and causes injury to both immunological and neurological systems (Gonzalez-Scarano & Martin-Garcia, 2005). Although HIV does not typically infect neurons, it exerts adverse effects on the central nervous system (CNS) through both direct viral mechanisms (e.g., multinucleated giant cells, a hallmark of HIV encephalitis) and secondary processes (e.g., cytokines, chemokines) that are associated with synaptodendritic neural injury (Hult, Chana, Masliah, & Everall, 2008; Kaul, Garden, & Lipton, 2001). Approximately 50 % of HIV-infected persons evidence neuropathology, which in the cART era is diverse and can include HIV encephalitis, gliosis, and vasculopathy (Everall et al., 2009). HIV-associated structural and metabolic abnormalities are observed throughout the brain, though they are primarily found in the striatum, frontal cortex, medial temporal lobe, and broadly throughout the cerebral white matter (Ellis, Calero, & Stockin, 2009).

HIV-associated neurocognitive disorders (HAND) are observed in up to 50 % of HIV-infected adults (Heaton et al., 2010) and are thought to primarily arise from neural injury to frontostriatal networks (Archibald et al., 2004; Castelo, Sherman, Courtney, Melrose, & Stern, 2006). Although the prevalence of HIV-associated dementia (and CNS opportunistic infections) has dropped dramatically with cART (Grant et al., 2005), the prevalence of milder forms of HAND is largely unchanged and may have even increased among persons with less severe HIV disease (Heaton et al., 2011). HAND is observable even in the asymptomatic phase of infection (Heaton et al., 2011) and is most likely to emerge in persons with histories of severe immunosuppression (Ellis et al., 2011). Other notable risk factors for HAND in the cART era include older age (e.g., Valcour, Shikuma, Watters, & Sacktor, 2004), alcohol (e.g., Sassoon, Rosenbloom, Fama, Sullivan, & Pfefferbaum, 2012) and substance (e.g., methamphetamine; Rabkin, McElhiney, Ferrando, van Gorp, & Lin, 2004) use, and a host of non-HIV-associated medical comorbidities, such as vascular disease (e.g., Becker et al., 2009), metabolic syndrome (e.g., McCutchan et al., 2012), and coinfection with hepatitis C (e.g., Hinkin, Castellon, Levine, Barclay, & Singer, 2008). The profile of HAND is characterized primarily by mild-to-moderate impairment in the domains of executive functions (e.g., cognitive flexibility, novel problem solving, and inhibition), episodic learning and memory, attention/working memory, and psychomotor speed and coordination (Heaton et al., 2010). HIV is also a risk factor for neurobehavioral symptoms of frontal systems dysfunction, including impulsivity (Marquine et al., 2014) and apathy (e.g., Kamat, Woods, Marcotte, Ellis, & Grant, 2012).

HIV-associated neurocognitive impairment and related declines in real-world functioning are fundamental elements of the diagnosis of HAND. As outlined by the Frascati criteria (Antinori et al., 2007), there are three primary subtypes of HAND. A diagnosis of *HIV-associated Asymptomatic Neurocognitive Impairment (ANI)* requires at least mild global neuropsychological impairment (i.e., performance > 1 SD below a normative mean in at least two cognitive domains) that is related to HIV infection, but does not ostensively affect real-world functioning. Although there is some controversy regarding the prevalence and syndromic nature of Asymptomatic Neurocognitive Impairment (Blackstone et al., 2012), the diagnosis is thought to comprise approximately 50 % of the cases of HAND (Grant et al., 2005). Diagnoses of *HIV-associated Mild Neurocognitive Disorder a*nd *HIV-Associated Dementia,* on the other hand, require the presence of notable functional declines in multiple domains that may be attributable to global cognitive impairment. The severity of both the neurocognitive and functional problems required for a diagnosis of Mild Neurocognitive Disorder are less than those of Dementia, which is present in only 2–5 % of persons infected with HIV.

A Model of Real-World Outcomes in HIV

Twenty years of clinical research demonstrates that HIV-associated neurocognitive impairment increases risk of adverse real-world outcomes independent of important cofactors, such as depression (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009). From a historical prospective, the first empirical study to report a case of HIV-associated dementia, which by definition involves severe functional problems related to cognitive abilities, was Navia and colleagues in 1986. In 1989, McArthur et al. reported the first data directly linking neurocognitive complaints and vocational functioning among HIV+ individuals, which revealed no significant relationship. On the other hand, Heaton and colleagues (1994) published the first study

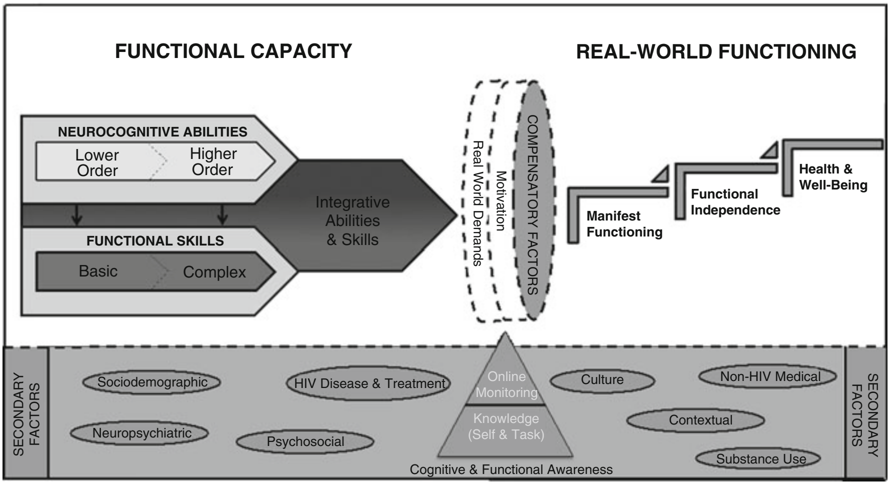

Fig. 10.1 Conceptual model depicting the role of HIV-associated neurocognitive deficits in real-world outcomes, which is influenced by the match between the specific profile of deficits and the particular demands of the real-world function, motivation, awareness of cognitive and functional deficits, biopsychosocial cofactors, and the availability, effectiveness, and use of compensatory strategies

showing that HIV associated neurocognitive impairment was a risk factor for unemployment and poorer vocational functioning. Since these studies, neurocognitive declines in HIV infection have been associated with an array of poorer functional outcomes, including problems with basic and instrumental activities of daily living (BADLs and IADLs; Heaton et al., 2010), poor cART adherence (Hinkin et al., 2004), risky automobile driving (Marcotte et al., 2004), vocational difficulties (Heaton et al., 2004), lower health-related quality of life (e.g., Tozzi et al., 2003), and HIV transmission risk behaviors (e.g., Martin et al., 2007). Figure 10.1 represents our efforts in integrating multidisciplinary approaches to everyday functioning from neuropsychology (e.g., Marcotte & Grant, 2010; Morgan & Heaton 2009), occupational therapy (Baum & Katz, 2010), and HRQoL (Wilson & Cleary, 1995) to better understand how real-world outcomes may be associated with neurocognitive functioning in a chronically ill population such as persons living with HIV. The model is based on the premise that the association between functional and neuropsychological deficits and real-world outcomes depends on multiple factors, including the match between the specific profile of deficits and the particular demands of the real-world function, motivation, awareness of cognitive and functional deficits, the availability, effectiveness, and use of compensatory strategies, and the presence and influence of a host of biological, psychological, and social cofactors. The model is also highly dynamic (i.e., changes in one area may impact other areas of functioning) and reciprocal, such that real-world declines may also feedback to adversely influence neurocognitive functions, which in turn may exacerbate disability

(Ettenhofer, Foley, Castellon, & Hinkin, 2010). A case example illustrating the elements of this model is provided at the end of the chapter.

Real-World Functioning

A primary distinction is made between related but separable aspects of health outcomes: "functional capacity" and "real-world functioning" (Brunswik, 1949; Christiansen & Baum, 1991; Goldstein, 1996). In this model, real-world functioning refers to what the person can actually do, which is one's "manifest" status. Manifest real-world functioning is typically measured by self-report and/or objective behavioral indicators of what one *actually does* in everyday life (e.g., medication adherence). At the first level is *Manifest Functioning*, describing an individual's success in accomplishing various real-world activities in daily life; for example, adhering to a complex medication regimen or maintaining gainful employment. Failures at this first step of the model can compromise *Functional Independence*, which refers to one's level of autonomy in their activities of daily living, with varying levels of "dependence" ranging from requiring occasional assistance from others to frank disability and assisted living placement. The *Health and Well-being* endpoint of the model is one's perceived health (e.g., perceptions of experienced symptoms and functional status) and HRQoL, which includes mental, physical, and social aspects (Wilson & Cleary, 1995).

Functional Capacity

Functional Capacity represents the cognitive abilities and functional skills that are typically measured in laboratory settings that assess what an individual *can do*, or is capable of completing in everyday life. Traditional clinical neuropsychological tests of list learning and trail-making are examples of relevant cognitive abilities, whereas tests of medication management and bill paying are examples of functional skills. Cognitive abilities may be further separated into lower-order (e.g., simple attention) and higher-order (e.g., information processing speed, working memory, episodic memory) functions. Similarly, functional skills may be classified as basic (e.g., opening a pill bottle) and complex (e.g., planning a dosing schedule). Cognitive abilities are thought to influence functional skills, which are generally learned competencies; for example, medication management skills may be largely dependent on learning and executive functions (e.g., Patton et al., 2012). The two constructs (i.e., cognitive abilities and functional skills) are nonetheless independently predictive of real-world functioning in HIV. For instance, Heaton et al. (2004) found that summary scores from a large standard clinical neuropsychological battery and a novel battery of functional tasks (e.g., bill paying and checkbook balancing as measured by performance in the laboratory) were concurrent, unique predictors of declines in instrumental activities of daily living in a large HIV-infected cohort.

Integrative Abilities and Skills

An emerging body of literature in HIV (and other clinical conditions) now shows that "integrative" cognitive and functional constructs are unique predictors of real-world outcomes (e.g., Woods et al., 2009). Here we define *Integrative Abilities and Skills* as complex functions that bridge higher-level cognitive abilities (e.g., memory) and functional skills (e.g., medication management) with real-world outcomes (e.g., medication adherence). An example is prospective memory, which describes one's ability to successfully execute a delayed intention and is a strong predictor of real-world outcomes in HIV independent of traditionally measured neurocognitive abilities, such as retrospective memory (e.g., Woods et al., 2008). Although prospective memory comprises familiar neuropsychological ability areas, most notably retrospective memory and executive functions, it nevertheless represents a unique constellation of these abilities in service of a specific cognitive goal (i.e., "remembering to remember") and is dissociable from them in terms of its cognitive architecture (Gupta, Woods, Weber, Dawson, Grant, & The HIV Neurobehavioral Research Center (HNRC) Group, 2010) and neurobiological underpinnings (Woods et al., 2006). In other words, these integrative, translational constructs "work with" established cognitive and functional skills in an applied setting (see also Moscovitch, 1992), and thus may be considered macro-level functions for which the whole is greater than the sum of their parts. Other examples of integrative constructs potentially relevant to real-world outcomes in HIV include multitasking, decision-making, health literacy, and social cognition**.** Thus, these ability areas are essential to understanding the link between laboratory abilities and real-world outcomes because they capture one's ability to use cognitive and functional skills in the context of day-to-day life.

Cofactors Affecting Functional Capacity and Real-World Functioning

Of course, the path from cognitive and functional capacity to real-world functioning outcomes is replete with a complex series of twists and turns. Indeed, the two constructs are separable, such that deficits in functional capacity alone, although a formidable risk factor, are neither necessary nor sufficient for poor real-world outcomes. It is also important to consider the match between *demands* of a real-world activity (e.g., its overall complexity and cognitive and functional requirements) and an individual's *profile* of neuropsychological strengths and weaknesses. Another critical cofactor is the use of compensatory strategies, which can dampen the influence of neurocognitive and functional deficits on real-world functioning by capitalizing on relatively intact processes (e.g., basic attention), for example by using internal (e.g., chunking) and/or external (e.g., cueing reminders) strategies to enhance overall performance (Twamley, Jeste, & Bellack, 2003). For example, an individual with mild prospective memory deficits may be able to properly adhere to their medication regimen with timely reminders from a significant other.

Effective deployment of compensatory strategies, however, may depend in part on one's motivation and the accuracy of one's perception and assessment of his/her cognitive, functional, and real-world abilities and performance (i.e., self-awareness). With regard to motivation, it can be viewed in terms of apathy/self-initiation, as well as both internal and external representations regarding the importance of the real-world task. As concerns the latter, we separate *Cognitive and Functional Awareness* into: (1) knowledge, which refers to a general understanding of one's own cognitive and functional abilities/disabilities, as well as knowledge of their performance (and experience with) the real-world outcome; and (2) online awareness, which represents the ability to monitor and apply one's knowledge about his/her abilities/disabilities appropriately during task performance (Toglia & Kirk, 2000). Finally, there is a variety of secondary factors that can influence both real-world functioning outcomes independent and/or in concert with functional capacity. Most notable among these secondary factors in the HIV literature are: (1) sociodemographics (e.g., age, education, socioeconomics); (2) HIV disease severity (e.g., a history of severe immune compromise) and treatment (e.g., type and complexity of cART regimen); (3) neuropsychiatric (e.g., mood, apathy); (4) substance use (e.g., alcohol, methamphetamine); (5) non-HIV medical (e.g., hepatitis C coinfection, cardiovascular disease, frailty); (6) psychosocial (e.g., coping, self-efficacy, social support); (7) cultural; and (8) contextual (e.g., health care infrastructure) factors.

A Case Example

To illustrate some of the points in this conceptual model, consider the case of a 62-year-old HIV-infected man with 14 years of education, who is referred for neuropsychological evaluation based on his complaints of everyday memory problems. This gentleman has been living with HIV infection for 25 years, and although he has received a diagnosis of AIDS based on a history of severe immune suppression and opportunistic infections, his HIV disease has been well-controlled since beginning cART in the late 1990s. He is currently prescribed cART, his viral load is undetectable in blood, and his current immune health is good. Aside from HIV disease, he has type II diabetes mellitus and hypertension, which are also well-controlled with daily medications. There was no indication of significant current mood or substance use comorbidity, but he does have a lifetime history of alcohol and cocaine dependence. Within the last 3 years, he has noticed increasing forgetfulness in important daily tasks, such as leaving the stove burner on, forgetting laundry in the washer for days, and inability to maintain his social role functioning (e.g., running errands for ill relatives). As such, he reported he now only orders take-out meals, sends his laundry out for cleaning, and has become socially isolated. He has worked as a secretary for an accounting firm for 30 years and is able to carry out his work responsibilities adequately. Additionally, he has been adherent to his medications, which he attributes to his use of a pillbox and a reminder alarm on his cell phone. On assessment, he evidenced mild executive dysfunction (i.e., cognitive inflexibility) and low average performances on both verbal and visual memory, but was generally above average with respect to working memory, information processing speed, language, and motor skills. Functionally, he performed within normal limits on medication management and a vocational-based assessment, but demonstrated impairment on a laboratory test of everyday multitasking.

With respect to the guiding conceptual model (Fig. 10.1), this older HIV-infected gentleman is in tact with regard to his basic neurocognitive (e.g., attention) and functional (e.g., grooming, bathing) abilities. However, he shows deficits in higher-order neurocognitive abilities, namely executive dysfunction, as well as multitasking, which is a critical integrative ability. These deficits are adversely affecting his actual (i.e., "manifest") everyday functioning in the area of household management and social role functioning. Given the remote nature of his substance use history and the absence of severe neuropsychiatric and medical comorbidities, we can more confidently attribute his IADL problems to his neurocognitive deficits. Given his awareness of his cognitive difficulties and success using compensatory strategies to manage his medications, it would be recommended that he extend his deployment of external strategies (e.g., calendars, alarms) to circumvent his executive deficits in order to improve his IADL functioning (e.g., home cooked meals, increased social interaction), and ultimately, increase his quality of life.

Real-World Outcomes in HIV Disease

With this guiding conceptual model in mind, below we review the literature regarding the role of neurocognitive impairment in selected real-world outcomes (i.e., ADLs, cART adherence, automobile driving, employment, risk, and HRQoL) in persons living with HIV during the cART era. We focus our review on the real-world outcomes for which there was a reasonable body of literature at the time of writing, although it should be noted that HIV-associated neurocognitive impairment is also associated with other important outcomes not reviewed here, including mortality (Sevigny et al. 2007a, 2007b), cognitive complaints (e.g., van Gorp, Baerwald, Ferrando, McElhiney, & Rabkin, 1999) and psychosocial functioning (e.g., Mustanski et al., 2007). Figure 10.2 provides a graphical display of the strength of the associations between key neurocognitive domains and all of the individual real-world outcomes examined in this review.

Activities of Daily Living (ADLs)

In the cART era, HIV-associated functional declines are most commonly observed on complex or "instrumental" activities of daily living (i.e., one-third of HIV+ persons demonstrate, such as cooking or financial management). One fifth of HIV+ persons show declines on Basic ADLs, such as grooming or dressing (Crysta, Fleishman, Hays, Shapiro, & Bozzette, 2000). Across the literature, ADL declines are associated with advanced HIV disease severity, lower socioeconomic status, older age, mood and substance use disorders, and larger non-HIV-associated comorbidity burden (e.g., Malaspina et al., 2011; Morgan, Iudicello et al., 2012). However, there appears to be a dissociation in which Instrumental-ADLs are more commonly related to deficits in higher-order neurocognition (e.g., executive dysfunction), whereas Basic ADLs are more commonly linked to physical

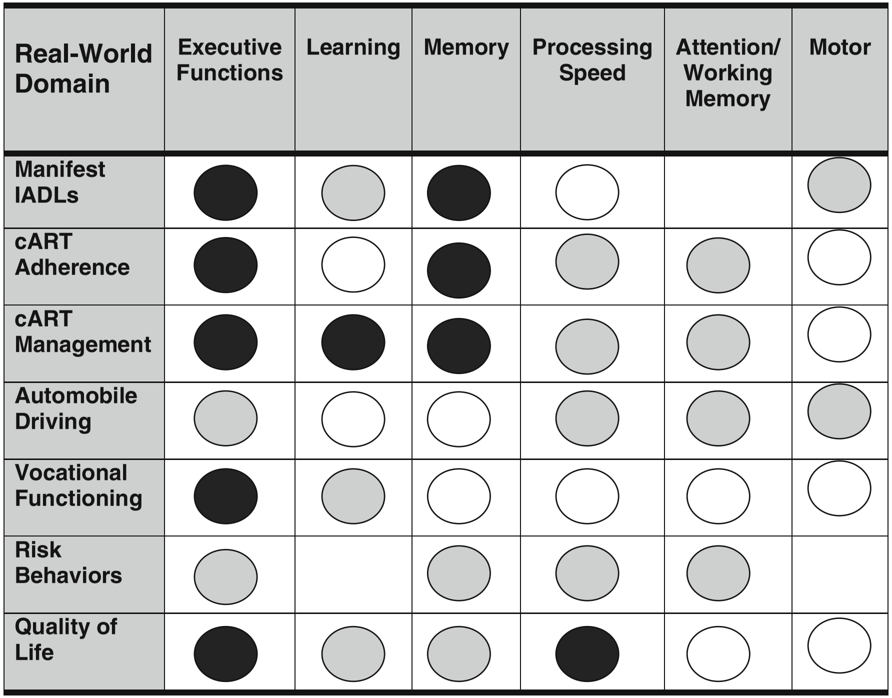

Fig. 10.2 A visual representation of the relative strength of the associations between specific neurocognitive ability areas and real-world functioning outcomes in persons living with HIV during the cART era. Darker shading indicates stronger, more reliable associations evident across the literature, while empty cells indicate that too few studies have evaluated the relationship to base a judgment. *cART* combination antiretroviral therapies. *IADL* instrumental activities of daily living

HIV-associated symptoms in individuals with more advanced disease (Blackstone, Iudicello et al., 2013; Crystal, Fleishman, Hays, Shapiro, & Bozzette, 2000). Given that Basic ADL decline does not appear to be a primary outcome of HIV-associated neurocognitive disorders, this review focuses on HIV-related IADL functioning, which is typically measured via performance-based everyday functioning tasks (i.e., "capacity") or self-report of actual (i.e., "manifest") functioning.

IADL Capacity

Given the complex and oftentimes fluid cognitive demands implicit in many instrumental everyday tasks (e.g., household and fiscal management), it is not surprising that HIV-associated global neurocognitive impairment is consistently and strongly related to deficits in performance-based IADL tasks, i.e., "IADL capacity" (Gandhi et al., 2011; Heaton et al., 2004; Thames et al., 2011, 2012). At the domain level, executive functions (including tests of abstract thinking, set-shifting, and inhibition) and working memory were two of the most consistent cognitive domains linked to IADL-based skills in the laboratory among persons living with HIV (e.g., Heaton et al., 2004; Thames et al., 2011). Learning and verbal fluency have also been associated with performance failures on a comprehensive functional battery that included measures of telephone communication and financial management (Heaton et al., 2004). Taken together, these studies demonstrate the important roles that HIV-associated neurocognitive impairment, and especially higher order cognitive deficits, play in IADL capacity as measured in the laboratory.

In the "real world," instrumental everyday functioning tasks rarely occur in isolation, and instead draw upon simultaneous task performance skills, or multitasking abilities. Multitasking represents the ability to complete a subgoal while maintaining a main goal in mind and draws upon interrelated neural (i.e., frontostriatal) and cognitive systems (i.e., executive functions such as planning as well as retrospective and prospective memory; Burgess, Veitch, de Lacy Costello, & Shallice, 2000) that are particularly vulnerable to dysfunction following HIV infection. In the context of our proposed model (Fig. 10.1), multitasking may represent an "integrative" ability that combines critical aspects of both cognitive and functional capacities. Recently, Scott et al. (2011) developed a novel performance-based IADL skills assessment to objectively measure such everyday multitasking abilities in HIV infection. In this largely unstructured test, individuals must attempt four everyday tasks (i.e., medication management, telephone communication, cooking, and financial management), and, in order to obtain the most optimal score, some of the tasks must be completed simultaneously. HIV+ individuals performed more poorly than HIV− comparison subjects across several aspects of the multitasking test, including fewer overall points scored, fewer simultaneous tasks attempted, and increased omission errors. Importantly, multitasking performance was associated with impairments in executive functions (i.e., abstract thinking, set-shifting, and inhibition), episodic memory, working memory, and psychomotor speed (Scott et al., 2011). Further exploration of the mechanisms driving such complex, "real-world" abilities (e.g., multitasking) may be especially valuable in elucidating the cognitive skills necessary for successful everyday functioning abilities in HIV.

Manifest IADLs

"Manifest" IADL functioning indicates those tasks on which the patient identifies him or herself as actually completing in daily life. These are in contrast to IADL "capacities," which denote those abilities that an individual is capable of carrying out in the laboratory (i.e., has the capacity to complete in a structured environment). Although IADL "capacity" is necessary, it is not sufficient for successful "manifest" IADL functioning. That is, an individual may have the basic cognitive capabilities to complete a given task (e.g., financial management), but when placed in context of complex real-world demands (e.g., balancing a payment while talking on the phone), s/he may not successfully execute the task in real time. Of interest here are these significant "manifest" IADL declines that are commonly reported following HIV infection (Blackstone et al., 2012). Convergent with the IADL capacity literature, global neurocognitive impairment is reliably associated with difficulties in manifest IADLs (Benedict, Mezhir, Walsh, & Hewitt, 2000; Gandhi et al., 2011; Heaton et al., 2004; Morgan, Iudicello et al., 2012). Among the many neurocognitive domains examined in this literature, executive dysfunction is the most robust predictor of manifest IADL declines. The most consistent executive subdomains implicated in IADL declines included deficits in cognitive flexibility, problem-solving, abstraction, planning, and verbal fluency (Benedict et al., 2000; Cattie, Doyle, Weber, Grant, & Woods, 2012; Iudicello, Woods, Cattie, Doyle, & Grant, 2012, 2013; Woods et al., 2006; Woods, Morgan, Dawson, Cobb Scott, & Grant, 2006). Following executive dysfunction, deficits in delayed episodic memory were the next most consistent cognitive factor associated with HIV-associated deficits in reported IADLs. Both complex and structured visual and verbal delayed memory significantly predicted manifest IADL functioning across several studies (Benedict et al., 2000; Woods et al., 2006, 2008). Yet it remains unclear whether deficits at a specific stage of memory processing (i.e., encoding, consolidation, and retrieval) may be differentially impacting this relationship; however, in a recent study, Fazeli et al. (2014) found that shallow encoding and forgetting were associated with IADL declines in older, but not younger HIV-infected adults. Future studies are warranted in order to continue to better delineate these memory-based component relationships with an eye toward potential intervention points (Woods et al., 2005). Fine-motor skills showed mixed results in predicting manifest IADLs in HIV, with one study reporting a positive relationship (Woods et al., 2006), but another reporting a no significant relationship (Benedict et al., 2000). Similarly, no significant findings were reported in one study examining speed of information processing (Benedict et al., 2000). Surprisingly, no studies to date have prospectively examined the mechanisms of attention and working memory on manifest IADL declines, which represents an important future direction given that these are domains that are affected by HIV infection (e.g., Bartok et al., 1997) and, as mentioned earlier, are associated with IADL capacity skills.

Medication Management and Adherence

As noted earlier, cART has dramatically changed the landscape of HIV infection (e.g., (Gifford & Groessl, 2002). However, in order to effectively manage the immunovirological aspects of HIV, relatively strict adherence to sometimes complex, cumbersome, and habitual cART regimens is required (e.g., Bangsberg et al., 2006). Current rates of cART adherence vary widely, and nonadherence remains a problem in up to 50 % of the population (e.g., Hinkin et al., 2002). A recent study examining adherence behaviors among HIV+ individuals identified several groups of "adherence behavior patterns," which ranged from a subset of individuals (10 % of cohort) who had very poor adherence across the entire study period (i.e., mean adherence 24 %) to individuals who demonstrated good adherence only on weekdays but not weekends (12 % of cohort), and those who showed consistently good adherence (Levine et al., 2005). Suboptimal adherence (i.e., below 90–95 %) is associated with viral rebound, evolution of drug-resistant strains of the virus, more rapid progression to AIDS, and death (Arnsten et al., 2001; Bartlett, 2002; Bangsberg et al., 2000, 2001); thus, there is a continued need to characterize and identify those factors that may be contributing to differential patterns of suboptimal adherence. In fact, a number of variables have been shown to adversely influence adherence to cART regimens including active substance use (e.g., methamphetamine; Hinkin et al., 2004), comorbid psychiatric conditions (e.g., bipolar disorder; Moore et al., 2012), increased regimen complexity (e.g., Hinkin et al., 2002), poorer health literacy (e.g., Waldrop-Valverde, Jones, Gould, Kumar, & Ownby, 2010), younger age (e.g., Barclay et al., 2007), and lower socioeconomic status (e.g., Falagas, Zarkadoulia, Pliatsika, & Panos, 2008).

Drawing upon the Wilson and Park (2008) model, successful cART adherence may be modulated by medication-induced side effects (e.g., nausea), beliefs regarding cART efficacy (e.g., "I don't feel sick so why should I take cART?"), environmental complexities (e.g., HIV-related disabilities and cofactors may lead to a less structured daily schedule), and neurocognitive impairment. As articulated in the Wilson and Park (2008) model, the cognitive aspects of cART management and adherence include comprehending instructions associated with each medication or task (i.e., attention and working memory), integrating information across different items into a plan for each day (i.e., working memory, executive functions), remembering the plan (i.e., retrospective memory), and remembering to execute the plan (i.e., prospective memory). Taken together, there are a number of cognitive mechanisms that may subserve successful cART management and adherence, the supporting literature for which is reviewed below for medication management capacity and manifest medication adherence.

Medication Management Capacity

Medication management refers to an individual's real-time abilities to manipulate, understand, calculate, and dispense their medication regimen. Management skills may be dissociated from adherence behaviors in that successful management is a necessary but not sufficient component for actual adherence; for instance, one may have the capacity to correctly calculate and dose a medication regimen, but still not take the medication as prescribed. In the context of HIV infection, although complexity of antiretroviral regimens has been reduced with single medication combination formulas (e.g., triple-drug combinations formulated into one pill), persistent difficulties in medication management are still observed. For instance, in a recent study, Patton and Colleagues (2012) reported that 19 % of their HIV+ sample was impaired on a performance-based task of medication management abilities. Of note, medication management errors were associated with poor cART adherence only among HIV+ individuals with current immunosuppression (i.e., CD4 count <200) in this study (Patton et al., 2012). In terms of neurocognition, global neuropsychological impairment is consistently related to poorer performance-based management skills among HIV+ individuals (Gandhi et al., 2011; Heaton et al., 2004; Patton et al., 2012; Thames et al., 2011, 2012). Specifically, medication management skills in HIV are most consistently associated with an array of executive functions, including inhibition (Patton et al., 2012; Thames et al., 2011, 2012), planning (Waldrop-Verde et al., 2010), abstract thinking (Patton et al., 2012; Thames et al., 2011, 2012), and set-shifting (Patton et al., 2012; Thames et al., 2011, 2012; Waldrop-Valverde et al., 2010). Additionally, both verbal and visual learning and memory are strongly associated with medication management abilities, including complex list learning as well as more structured learning tasks (e.g., story and figure memory; Albert et al., 1999; Patton et al., 2012; Thames et al., 2011, 2012). Though less consistently, sustained attention, working memory, verbal fluency, and speed of information processing have also all been at least modestly related to medication management skills (Patton et al., 2012; Thames et al., 2011). Considering the strength of the executive functions domain reviewed above, one possibility is that it is the executive aspects (e.g., verbal fluency requires executively laden generation and switching abilities) of these other cognitive abilities may be driving their associations with medication management. Although one may conceptualize pill-dispensing as requiring some physical coordination (e.g., opening pill bottles, allocating pills to a pillbox compartment), fine-motor skills demonstrated the weakest association with medication management performance. In the one study that did find an association (Albert et al., 1999), performance on grooved pegboard was only associated with the pill dispensing component (not medication calculations) of the medication management task, suggesting that the match between the motor abilities and functional skills assessed may show some specificity.

Manifest Medication Adherence

Medication adherence encompasses the actual skill of applying medication management capacities in order to take medications as prescribed in real-world settings. Consistent with the literature on medication management in HIV, cART adherence is reliably and uniquely associated with neurocognitive abilities (Barclay et al., 2007; Ettenhofer et al., 2009, 2010; Hinkin et al., 2002, 2004; Wagner, 2002). In fact, HIV+ individuals with global neurocognitive impairment appear to be at a 2.5-fold increased risk for cART nonadherence compared to HIV+ individuals without impairment (Hinkin et al., 2004). Given that cART adherence findings differ slightly depending on how adherence was assessed (i.e., self-reported versus objectively monitored adherence; Liu et al., 2001; Wagner & Miller, 2004), we chose to highlight the literature examining the role of neurocognition on only objectively measured adherence (i.e., the current "gold standard" behavioral measures of adherence, including medication event monitoring systems; see also Lovejoy & Suhr, 2009).

With regard to specific cognitive domains, deficits in executive functions such as accurately completing complex, speeded set-shifting tasks, demonstrated the strongest relationship with adherence among HIV+ individuals (Barclay et al., 2007; Ettenhofer et al., 2009, 2010; Hinkin et al., 2002, 2004; Solomon & Halkitis, 2008; Wagner, 2002). Additionally, better problem-solving and abstract thinking, as well as set-shifting and verbal fluency skills appear to be related to greater medication adherence, although how each of these domains may contribute to aspects of adherence are still unknown (Barclay et al., 2007; Ettenhofer et al., 2009; Hinkin et al., 2002, 2004; Woods et al., 2009). In contrast to medication management skills, which demonstrated consistent relationships with both learning and memory, only complex delayed verbal memory, but not learning, showed a consistent relationship with successful ART medication adherence (Barclay et al., 2007; Hinkin et al., 2002, 2004; Wagner, 2002; Woods et al., 2009). This differential pattern of learning versus memory in the prediction of medication management and adherence may reflect the implicit learning skills that are needed when managing a new ART regimen that may be less relevant when remembering to accurately take medications in daily life. Of note, one study examined the nature of such memory-based impairments on cART adherence and found that although HIV+ individuals with both good (i.e., ≥90 %) and poor (i.e., <90 %) adherence demonstrated comparably worse verbal encoding abilities compared to HIV− participants, those seropositive individuals with poor adherence displayed significantly worse retrieval abilities than the HIV+ individuals with good adherence. Therefore, this study suggests that it may in fact be HIV-associated retrieval deficits that are driving nonadherence behaviors, rather than encoding or consolidation abilities (Wright et al., 2011). In addition, complex working memory and speeded information processing (Ettenhofer et al., 2009, 2010; Hinkin et al., 2002, 2004; Solomon & Halkitis, 2008; Woods et al., 2009) were also related to better cART adherence, albeit less consistently or strongly across the literature relative to executive functions and delayed memory. Lastly, fine motor skills and learning abilities demonstrated the most inconsistent and generally weakest findings when examined across studies of ART adherence. For example, Ettenhofer and colleagues (2009, 2010) published the only studies that found a relationship between ART adherence and grooved pegboard performance, but not verbal learning, whereas Woods et al. (2009) illustrated a relationship between adherence and learning, but not motor skills.

One novel area of cognitive functioning that may be particularly germane to health care management skills and ART adherence in HIV+ is prospective memory (i.e., "remembering to remember"). Given that one of the necessary cognitive components of successful adherence is remembering to take one's medication at a designated time, the role for prospective memory in adherence is particularly face-valid and ecologically relevant. For instance, prospective memory is associated with self-reported cART management skills independent of other important factors known to predict medication management (e.g., mood, psychosocial variables, deficits on traditional neurocognitive batteries), and is associated with implementation of ART adherence strategies (Woods et al., 2008). Importantly, global prospective memory abilities demonstrate medium effect sizes with cART adherence (i.e., Contardo, Black, Beauvais, Dieckhaus, & Rosen, 2009; Woods et al., 2009), and appear to be particularly driven by deficits in time-based prospective memory (i.e., remembering to complete a future intention at a particular time), which have been shown to confer a sixfold increase in the risk of cART nonadherence (Woods et al., 2009), particularly in the context of longer delays between the encoding and execution of the intention (Poquette et al., 2013). Counterintuitively, increased frequency of memory-based adherence strategy use is associated with worse event-based prospective memory and poorer actual cART adherence (Blackstone, Woods et al., 2013); taken in the context of what is known regarding prospective memory abilities and adherence in HIV, this finding may indicate that HIV-associated prospective memory deficits impact adherence strategy implementation resulting in poorer actual adherence. Given that prospective memory is conceptualized to encompass aspects of both executive functions (e.g., planning, working memory) and retrospective memory (e.g., remembering previous intention) and that both medication management and adherence are strongly related to executive and memory functions in HIV+ individuals, prospective memory may provide a highly specific and sensitive target for remediation in the context of ART adherence interventions.

Automobile Driving

The ability to drive an automobile is a complex, multifaceted everyday task that is often a primary factor in maintaining functional independence across the lifespan (e.g., Marottoli et al., 2000). Diminished driving ability can be attributed to a variety of state- (e.g., affective distress) and trait-based (e.g., aggressiveness) personal characteristics (e.g., Beck, Daughters, & Ali, 2013) as well as medical conditions (e.g., osteoporosis; Ackerman, Vance, Wadley, & Ball, 2010). Although basic driving is typically a largely automated behavior for experienced drivers (Norman & Shallice, 1986), many aspects of driving require active, complex engagement of both lower- and higher-order cognitive functions. At face value, drivers must be able to visually scan, perceive, and attend to numerous areas of the environment, make rapid decisions, and plan and follow prescribed sequential motor procedures (Marcotte et al., 1999). Prior evidence shows that safe driving requires the contribution of various attention, executive, spatial, and psychomotor functions (e.g., Marcotte et al., 1999). In healthy adults, driving is thought to involve a variety of neural regions, particularly the parietal, occipital, and prefrontal cortices. Extending the neuroimaging findings, neurocognitive impairment is a significant predictor of driving ability across both healthy (e.g., normal aging, Goode et al., 1998) and clinical populations (e.g., multiple sclerosis; Schultheis, Garay, & DeLuca, 2001).

The research literature estimates that approximately 20 % of individuals with HIV exhibit unsafe driving (Marcotte et al., 2004), with rates of reported accidents higher than those of seronegative counterparts (Marcotte et al., 2006). Although only a handful of studies have examined the impact of HAND on driving, research has consistently shown that global neurocognitive impairment confers a significant risk for diminished driving skills, performance, and safety (e.g., Marcotte et al., 1999, 2004), even when considered alongside other relevant predictors of these outcomes (i.e., demographic characteristics, HIV disease severity, driving history). Numerous measurement strategies and predictor variables have been employed in elucidating the effect of HAND on driving, but the research clearly demonstrates that both neuropsychological testing as well as computer-based driving simulators independently predict real-world driving ability (e.g., on-road driving evaluations, reported number of accidents; e.g., Marcotte et al., 2004, 2006). Consistent with HIV's predilection for disrupting frontostriatal circuitry, the strongest neurocognitive impact on driving across the literature is found in the domain of executive functions, including tests reliant on visual concept formation, novel problem solving, inhibition, complex sequencing, set shifting and speeded word generation abilities. The precise aspects of executive (and supporting) functions driving this relationship remains to be determined, as most prior studies used domain-level summary scores of executive functions defined broadly. For instance, the vast majority of the measures used require performance of executively demanding tasks in the context of speeded visual processing, thus raising the questions of which component(s) of these measures may in fact be impacting the relationship between cognition and driving: executive load, speeded abilities, and/or modality specificity. Future research might determine whether the strategic load of neurocognitive tasks are more influential on driving ability, regardless of sensory modality (i.e., verbal executive tasks), or if the visual component of these tests is uniquely predictive of driving. Furthermore, the multifaceted nature of "executive functions" begs the analysis of other processes often lumped under this umbrella term that are affected in HIV, including multitasking (Scott et al., 2011), visual planning (e.g., Cattie et al., 2012), and decision-making (e.g., Iudicello et al., 2012).

Despite the high prevalence of visually mediated tasks represented in executive functions literature on driving ability in HIV (e.g., Marcotte et al., 1999), there is a dearth of data on more traditional aspects of basic (e.g., detection, recognition, and orientation) and complex (e.g., mental rotation, map navigation, novel route learning) spatial cognition. Two studies observed associations between a speeded test of visual problem-solving (i.e., Block Design) and basic driving simulation (i.e., Foley et al., 2013; Marcotte et al., 1999). Therefore it is plausible that other aspects of spatial cognition are important in automobile driving abilities and safety, especially given the degree to which it is necessary for one to quickly and accurately process and manipulate visual information en route to his destination. Although HAND typically spares brain regions required for basic visual processing (e.g., occipital cortex; cf. Thompson et al., 2005), impairment in higher-order visual abilities have been observed (e.g., mental rotation; Weber et al., 2010), likely due to white matter damage on tracts connecting the frontal lobes to other visual processing centers (e.g., parietal lobes; Schweinsburg et al., 2012).

Other neurocognitive domains that have been minimally dissected within the HIV driving literature include attention and working memory, which like executive functions are broad and multifaceted constructs. For instance, the primary clinical model of attention specifies a hierarchy of attentional processes that each require greater levels of strategic cognitive resources in order to be effectively carried out (i.e., focused, sustained, selective, alternating, and divided attention; Sohlberg & Mateer, 1989). These different aspects of attention may each have related, but separable roles in automobile driving skills and safety. For example, divided, but not selective, visual attention as measured by the Useful Field of View was associated with higher self-reported traffic accidents (Marcotte et al., 2006), but not with on-road driving evaluations (Marcotte et al., 2004) in HIV. Within working memory, the Paced Auditory Serial Addition Test (PASAT) emerged as a relevant predictor of driving across a few studies (e.g., Marcotte et al., 2006), but this measure of auditory working memory also has strong processing speed demands (Gonzalez et al., 2006) so it is difficult to differentiate whether processing speed or working memory may be driving this relationship. Similarly, many of the “executive” tasks reviewed above are multifactorial and include strong attentional and working memory components, but the specific mechanisms underlying the observed effects on driving ability remain uncertain and await future studies guided by strong cognitive theory and current knowledge regarding the profile of HAND. For instance, in the context of Baddeley’s (2003) model of working memory, HIV-associated neurocognitive deficits in working memory are related to difficulties in the central executive system, which is responsible for higher-level processing such as planning, monitoring, and control of cognitive operations (e.g., Law et al., 1994; Woods et al., 2010), rather than the basic sensory slave components (i.e., visuospatial sketchpad; Hinkin et al., 2002). Considered in the context of the executive findings reviewed above, one might hypothesize that HIV-associated deficits in the central executive, but not the slave systems, are important in driving outcomes, which require the prioritization and coordination of cognitive resources to intake, integrate, and make rapid decisions from incoming sensory stimuli.

Across the HIV driving literature, findings were also mixed in regard to several neurocognitive domains that, at face value, one would expect to be highly relevant to driving ability, including information processing speed, fine-motor speed and coordination, and episodic memory. Perhaps most surprisingly, information processing speed evidenced statistically significant relationships in only two out of five studies in which it was examined, which included laboratory-based driving simulator reaction time (Marcotte et al., 1999) and self-reported accidents (Marcotte et al., 2006). Findings regarding the impact of deficits in fine-motor speed and coordination on driving in HIV were similarly mixed across studies and modalities (e.g., Marcotte et al., 1999, 2004). Lastly, most research showed that learning and memory were not associated with driving ability, with the exception of a single study showing that list learning delayed recall predicted self-reported number of accidents

(Marcotte et al., 2006). One aspect of memory that may be worthy of examining in future studies of automobile driving in HIV is procedural learning and memory, aspects of which may be affected in HIV (Gonzalez et al., 2010) and clearly map on to the overlearned, habitual physical and mental aspects of driving.

As has been observed in other real-world functioning domains (e.g., IADLs), a variety of demographic (e.g., age), neuropsychiatric (e.g., substance use), and medical (e.g., hepatitis C coinfection) comorbidities may further increase the risk of poor automobile driving outcomes in HIV. Notable among these factors is older age, which is of particular relevance with the increasing prevalence of HIV-infected older adults who are increased risk of poorer immunovirologic (High et al., 2012), neurocognitive (e.g., Valcour et al., 2004), and real-world outcomes (e.g., Morgan, Iudicello et al., 2012). The impact of HAND on driving behavior may be exacerbated by the normal aging process, which itself is associated with declines in driving ability (e.g., Lee, Cameron, & Lee, 2003). To this end, Foley and Colleagues (2013) recently demonstrated that older HIV-infected adults displayed greater difficulty than their younger HIV-infected counterparts on a driving simulation with relatively few distractors (e.g., pedestrians to avoid). Older HIV-infected adults with HAND evidenced particular difficulty with regard to route finding efficiency and overall completion time, both of which are heavily reliant on information processing speed and visual planning. This may represent the new onset of age-related parenchymal damage and/or the additive effect of aging and its comorbidities (e.g., cerebrovascular disease) on white matter pathways already implicated in HAND. Future studies might examine the role of diminished cognitive control, or intraindividual variability, which may identify fluctuations in attention abilities, and is prevalent in older HIV-infected individuals (e.g., Morgan, Iudicello et al., 2012), and predictive of driving simulator performance in substance users (Morgan et al., 2013).

Vocational Functioning

Approximately two-thirds of individuals with HIV infection are unemployed, which is six times the unemployment estimates for seronegatives in the USA (CDC, 2010). Across various clinical populations, neurocognition is often cited as an independent predictor of employment status and vocational abilities (e.g., McGurk & Meltzer, 2000; Weber et al., 2012), above and beyond noncognitive predictors (e.g., depression). However, a meta-analysis of the literature on cognition and employment across clinical populations yielded generally small-to-medium effect sizes, suggesting that the magnitude of the association between cognition and employment is modest (Kalechstein, Newton, & Van Gorp, 2003). Indeed, in the HIV literature, the relationship between neurocognition and employment is strikingly less robust than that for other aspects of everyday functioning reviewed in this chapter; more specifically, only three of the five studies published on this topic in HIV showed a significant relationship between global neurocognitive impairment and vocational functioning (e.g., Chernoff, Martin, Schrock, & Huy, 2010; Heaton et al., 2004; Morgan, Iudicello et al., 2012; Rivera-Mindt et al., 2003). The strength of the relationship between neurocognition and vocational ability is generally consistent across measures of functional capacity (e.g., measurement of work-related abilities) and manifest (i.e., actual real life performance) vocational functioning (e.g., work status).

Nevertheless, the literature reveals an element of domain specificity to the relationship between neurocognitive deficits and vocational functioning in HIV. Consistent with other aforementioned functional domains, executive dysfunction appears to be highly relevant to vocational success across the HIV literature, with all studies that examined this domain reporting statistically significant associations (i.e., Cattie et al., 2012; Chernoff et al., 2010; Heaton et al., 2004; Rabkin et al., 2004; van Gorp et al., 1999, 2007; Woods et al., 2011). According to this literature, the specific executive subcomponents involved include both speeded and non-speeded aspects of executive functions, such as inhibition, perseverative thinking, visual planning (e.g., rule monitoring), verbal fluency, complex sequencing, concept formation, and logical analysis. It appears that such higher-order executive functions play a critical role in governing the implementation and efficiency of lower-order abilities necessary for gainful employment. The consistency of these findings suggests that it may be prudent to examine other aspects of executive functions (e.g., multitasking) as well as other cognitive and neurobehavioral constructs associated with prefrontal functions (e.g., apathy, Kamat et al., 2012) in relation to vocational outcomes.

Beyond executive functions, learning abilities predict vocational outcomes in two-thirds of the studies that examined their relationship (Chernoff et al. 2010; Heaton et al., 2004; Rueda et al. 2011; van Gorp et al., 1999, 2007; Woods et al., 2011). Of note, studies that revealed significant effects were those that used a demanding supraspan word list-learning test (i.e., California Verbal Learning Test), whereas studies that also examined story and/or figure learning were less reliably predictive of employment. In contrast to other domains of everyday functioning in HIV (e.g., medication adherence), delayed episodic memory was largely unrelated to vocational functioning (e.g., Heaton et al., 2004). At first glance, this lack of significant associations was surprising because one would assume that the retention and recollection of events and information would play an important role in many aspects of work. Interpreted in the context of the strong executive findings for employment and the mixed encoding/retrieval profile of HAND (e.g., Gongvatana, Woods, Taylor, Vigil, & Grant, 2007), one might reason that the strategic organization, acquisition, and retrieval of information are the critical elements for day-to-day vocational functioning in HIV. Indeed, one prior study shows a significant relationship between employment and HIV-associated deficits in prospective memory (Woods et al., 2011), a specific form of episodic memory that requires considerable that requires considerable strategic encoding, monitoring, and retrieval demands and relies heavily on intact executive functions (e.g., McDaniel & Einstein, 2000). A similar argument may be made for findings within the attention domain, such that the only study to find a significant relationship (Heaton et al., 2004) used a domain comprising tests primarily related to strategically demanding working memory abilities rather than more basic aspects of attention. Finally, mostly small and nonsignificant relationships were found for the domains of information processing speed, fine-motor skills, and spatial cognition with vocational functioning.

Although there did not appear to be clear differences in the existing literature regarding the differential impact of cognition on vocational capacity versus manifest employment status, researchers will likely benefit from continued to examination of these questions as the job market and required skills continue to evolve. For example, instruments used to assess vocational capacity (e.g., COMPASS; Valpar International Corporation, 1992) were created and validated prior to the increased reliance on computer-based technology in the workplace. In the modern era, perhaps novel methods of assessing vocational capacity are necessary to capture the intricacies of technologically driven job skills, which may have unique neurocognitive demands. In fact, it is reasonable to assume that the vocational impact different neurocognitive deficits will vary across type and level of job function (e.g., motor skills for manual laborers versus executive functions for corporate executives). Finally, with increasingly encouraging primary health outcomes in HIV during the cART era, many individuals who have been previously unemployed or on disability may consider returning to the workforce. As illustrated in the seminal study by van Gorp et al. (2007), neurocognitive and neuropsychiatric functioning may be particularly relevant moderators of successful return to work in HIV.

Health-Related Quality of Life (HRQoL)

As individuals with HIV infection are living longer in the cART era, there has been increasing interest in identifying the risk and protective factors for health-related quality of life (HRQoL), which is notably reduced in HIV. HRQoL is a multifaceted construct that describes the various ways by which an individual's health impacts his/her perceived level of daily functioning and biopsychosocial well-being (Coons, Rao, Keininger, & Hays, 2000; Hays et al., 2000). One influential conceptual model of HRQoL proposed by Wilson and Cleary (1995) posits a linear relationship whereby physiological/biological factors (e.g., viral load, CD4 counts) influence the expression of symptoms (e.g., opportunistic infections, HAND) that impact everyday functioning (e.g., non-adherence, disability), resulting in altered general health perceptions, and lower overall quality of life. This theoretical framework has been influential in understanding the associations between HRQoL and various health outcome domains and identifying risk factors (e.g., neurocognitive impairment) to target for interventions aimed at improving HRQoL in affected individuals. A considerable body of research conducted during the cART era has demonstrated lower HRQoL in HIV-infected individuals despite effective cART (e.g., Tozzi et al., 2004) and particularly in those with more advanced disease (i.e., symptomatic HIV infection or AIDS; Hays et al., 2000). More specifically, lower HRQoL has been linked to higher HIV viral loads, a greater number of disease-related symptoms (e.g., headaches, nausea/vomiting; Hays et al., 2000), lower CD4 counts (Hays et al., 2000; Jia, Uphold, Wu, Chen, & Duncan, 2005), and ARV failure (Parsons et al., 2006). Other notable risk factors for poorer HRQoL in HIV include demographic factors (e.g., older age, lower education; Hays et al., 2000; Morgan, Iudicello et al., 2012), comorbid medical (Rodriguez-Penney et al., 2013), psychiatric (e.g., depression; Morgan, Iudicello et al., 2012; Sherbourne et al., 2000; Trépanier et al. 2005), and substance use disorders (e.g., alcohol dependence; Rosenbloom et al., 2007), psychosocial issues, interpersonal characteristics (e.g., social support; Emlet, Fredriksen-Goldsen, & Kim, 2013), and unemployment (Hays et al., 2000). Importantly, the magnitude of association between these aforementioned underlying risk factors of poorer HRQoL may differ to some degree depending on the specific domain of HRQoL assessed (e.g., physical functioning versus emotional well being). For example, an increased number of HIV-associated symptoms and a greater comorbid medical burden have been more closely associated with poorer physical HRQoL, whereas factors such as social support and psychological distress are more closely tied to emotional well-being (e.g., Emlet et al., 2013; Hays et al., 2000; Rodriguez-Penney et al., 2013).

HIV-associated neurocognitive impairment is also a strong, independent risk factor for lower overall HRQoL (e.g., Tozzi et al., 2003, 2004). With regard to specific aspects of HRQoL, HAND has been linked to lower physical functioning, emotional well-being, social functioning, and general health perceptions (Morgan, Iudicello et al., 2012; Tozzi et al., 2003, 2004), even when considered alongside other well-established predictors of HRQoL, such as emotional distress, substance use disorders, and HIV disease severity. At the domain level, the most consistent neurocognitive associations are observed for executive functions (i.e., inhibition, sequencing, and mental flexibility) and complex information processing speed, both of which predict the physical and mental aspects of HRQoL (Doyle, Weber, Atkinson, Grant, & Woods, 2012; Osowiecki et al., 2000; Parsons et al., 2006; Schifitto et al., 2001; Tozzi et al., 2003, 2004). Evidence for the role of fine-motor functioning and episodic memory is spottier across this literature; however, the aforementioned prominence of executive dysfunction in HRQoL raises the possibility that a more detailed examination of the specific cognitive (e.g., executive) components of learning and memory (e.g., executive or organizational strategies such as semantic clustering) may be warranted. For example, Doyle et al. (2012) recently reported that PM was a significant predictor of poorer mental and physical HRQoL in younger HIV-infected adults, even when accounting for depression, substance dependence, and immunosuppression.

Risk Behaviors

Approximately 50,000 adults are infected with HIV annually in the USA, with incidence rates highest among men who have sex with men, injection drug users, and ethnic and racial minorities (Prejean et al., 2011). HIV-seropositive individuals are most likely to transmit the virus to others during the acute and early stage of infection (e.g., Pao et al., 2005), due to high viral loads and delayed awareness of their serostatus. Even beyond this initial period of infection, curbing HIV transmission risk behaviors is an essential aspect of everyday functioning that is not only important to prevent new infections, but also to enhance HIV health outcomes by preventing superinfection and the transmission of treatment resistant viral strains among seropositives (Ross et al., 2007). Risk factors that precipitated an individual's initial infection with HIV (e.g., unsafe sex and drug use practices) often persist after infection and diagnosis; in fact, it is estimated that one-third of HIV-infected adults continue unsafe transmission practices after they test positive for the virus (see Kalichman, 2000). Public health HIV prevention efforts have largely relied upon psychoeducation approaches regarding safer sex and drug use practices and psychosocial interventions (e.g., motivational interviewing) to reduce HIV transmission risk (e.g., Garfein, Metzner, Cuevas, Bousman, & Patterson, 2010). As observed in the broader social psychological literature (i.e., intention-behavior relations; Sheeran, 2002), the intention to engage in safe practices does not readily translate into actual behaviors. Numerous psychological avenues have been explored to determine potential individually based mediators and moderators of increased transmission risk behaviors, including mood disorders (e.g., depression), personality traits (e.g., narcissism; Martin, Benotsch, Perschbacher Lance, and Green 2013), and substance use (e.g., Kalichman et al., 2000). Moreover, social programs like clean needle exchanges and condom distribution have made strides in alleviating such problems due to lack of access to materials required for healthier behaviors.

Although psychosocial interventions used to reduce HIV transmission risk behaviors among infected individuals often contain skills (e.g., decision-making and problem-solving; e.g., Kalichman, Rompa, & Cage, 2005) that rely heavily on intact cognitive functioning, research examining the relationship between neurocognitive impairment and risk behavior has been limited. It is reasonable to hypothesize that higher-order neurocognitive abilities such as episodic memory and executive functions (e.g., inhibition and planning) might play an important role in effectively acquiring, processing, and deploying HIV risk prevention knowledge, skills, and behaviors. For example, impulsivity in sexual behavior may preempt controlled cognitive processes that would be responsible for choosing to use a condom. As such, relative to other areas of everyday functioning in HIV infection, greater scientific inquiry has been made at the level of discrete cognitive abilities (cf. global neurocognitive impairment). At the basic skills level, Malow and colleagues (2012) demonstrated that slowed information processing speed was associated with poorer behaviorally assessed condom use skills, suggesting difficulties with carrying out the actions required of safe sexual practices. With regard to higher-level manifest risk behaviors, Martin et al. (2007) showed a moderately strong relationship between self-reported engagement in sexual risk behaviors and time-based PM, but not with event-based PM, working memory, or retrospective memory, in a mixed cohort of HIV-infected substance users (see also Weinborn et al., 2013). This finding suggests that the ability to remember to perform important aspects of health maintenance behavior is more sensitive to dysfunction of strategically demanding cognitive abilities (e.g., monitoring).

Several studies have indicated that the relationship between neurocognition and risk behaviors is highly complex, perhaps by way of its interaction with other important psychosocial factors. For instance, a study by Gonzalez et al. (2005) reported that higher levels of sensation-seeking were associated with engagement in risky behaviors only among HIV-infected persons with intact decision-making. Similarly, Wardle, Gonzalez, Bechara, & Martin-Thormeyer (2010) found that intact decision-making abilities strengthened the relationship between psychological distress and risk behaviors. This relationship has also been demonstrated in the inverse, such that greater spontaneous safe sex-related associations were related to condom use among men with better working memory ability (Grenard, Ames, & Stacy, 2013). These studies suggest that neurocognitive impairment may disrupt the pathways that would typically link important psychological predictors to engagement in risk behaviors, or at a more basic level, between behavior intention and behavior action.

HIV-Associated Everyday Functioning Across Cultures

Assessment of HIV disease-related disability across cultures is essential, as HIV infection is a worldwide epidemic with some of the highest rates of infection in resource-limited settings outside of the USA. Although research has begun to delineate the neurocognitive consequences of HIV infection across countries, the functional and behavioral impact of HAND is less clear. Rates of neurocognitive impairment appear to differ somewhat depending on the country of interest; for example, HIV+ individuals in China demonstrated similar rates and profiles of impairment to those in the USA (i.e., mild-to-moderate impairments across about 40 % of the cohort; Cysique et al., 2007; Heaton et al., 2008), whereas studies in sub-Saharan Africa illustrate a higher prevalence of the most impaired classifications of HAND (i.e., HIV-associated dementia identified in up to 30 % of African cohorts versus <10 % in US-based studies; Heaton et al., 2011; Joska, Fincham, Stein, Paul, & Seedat, 2010; Wong et al., 2007). Given the differential trajectory and impact of HIV infection by the country (e.g., in China, the HIV epidemic was first introduced in rural areas associated with blood product collection whereas in India, the first reported cases of HIV infection were in female sex workers; Heaton et al., 2008; John, Babu, Jayakumari, & Simoes, 1987), such differences in the expression of HAND may be anticipated. Additionally, there may be differential influences to consider when examining real-world functioning versus neurocognition across cultures. For example, the sociocultural context in which HIV infection occurs may differ by country thereby impacting stigma of disease, access to healthcare resources and ART treatment, value of employment, or expression of distress (e.g., Atkinson, McCurdy, Williams, Mbwambo, & Kilonzo, 2011; Jin et al., 2006), to name a few, all of which may have important effects on functional outcomes for HIV+ individuals.

In the past decades, there have been concerted efforts to create appropriate normative data in order to account for cultural and racial differences on neurocognitive functioning which may be applied to individuals with HIV (e.g., Heaton et al., 2004; Norman et al., 2011), yet relatively fewer studies have examined HIV-associated everyday functioning outcomes across cultures both within and outside of the USA. Within the USA, Rivera-Mindt et al. (2003) created a Spanish version of a performance-based functional battery and found that individuals with

HIV-associated neurocognitive impairment performed worse than neurocognitively intact individuals therefore supporting the construct validity of the battery and implicating the role of global neurocognition on everyday functioning for Spanish-speaking HIV+ individuals in the USA. Additionally, in China, HIV+ individuals evidenced greater cognitive complaints, IADL dependence (most commonly in finances, shopping, housekeeping, and cooking), and higher rates of unemployment than seronegative controls, and these functional difficulties were also associated with poorer global neuropsychological performance (Cysique et al., 2007; Heaton et al., 2008). On the other hand, in contrast to some studies in the USA, reported antiretroviral adherence levels are relatively high across countries internationally (i.e., 62 and 57 % reported adherence rates over 95 % in Africa and Brazil, respectively; Pinheiro, De-Carvalho-Leite, Drachler, & Silveira, 2002; Potchoo et al., 2010). Although neurocognition was not examined in these studies, the authors noted that memory complaints, lower adherence self-efficacy, greater perception of negative affective and physical concerns, regimen complexity, and lower educational attainment were all significant predictors of nonadherence (Lawler et al., 2011; Pinheiro et al., 2002; Potchoo et al., 2010). Lastly, again though not examined in the context of neurocognition, poorer HRQoL is consistently reported among HIV+ individuals in India, and is associated with lower current CD4, female gender, marital status, lower educational attainment and income (Nirmal, Divya, Dorairaj, & Venkateswaran, 2008; Subramanian, Gupte, Dorairaj, Periannan, & Mathai, 2009; Wig et al., 2006). Taken together, these studies begin to delineate the important impact of HIV infection on everyday functioning across cultures, yet the role of neurocognition on these outcomes is less well understood, but represents an important future direction for neuroAIDS investigators worldwide.

Summary and Future Directions

Although the health status of persons living with HIV infection has improved dramatically over the past 15 years, HIV is still associated with a variety of adverse real-world outcomes. HIV-associated declines in real-world functioning are multifactorial, but the considerable body of literature reviewed in this chapter suggests that neurocognitive impairment is a unique risk factor for dependence in ADLs, cART non-adherence, unemployment, automobile driving accidents, lower HRQoL, and engagement in HIV transmission risk behaviors. Executive dysfunction, primarily operationalized by measures of cognitive flexibility and novel problem solving, emerged as the most robust neurocognitive risk factor for nearly all of the real-world outcomes reviewed. Delayed episodic memory, and to a slightly lesser extent, learning/acquisition were also strong predictors of real-world outcomes, most notably for IADL declines and cART adherence. Somewhat surprising was the relatively weaker ecological relevance of deficits in information processing speed and motor skills, although this may be due to the reduced prevalence of impairments in these ability areas in the cART era (Heaton et al., 2011). Also striking was the lack of hypothesis-driven research examining the domains of attention and spatial cognition, both of which might play a role in certain real-world outcomes, such as automobile driving. Moreover, the vast majority of this literature has utilized standard indices from well-validated clinical tasks (e.g., learning trials total score), which sets the stage for future hypothesis-driven work to examine the underlying component processes of these associations (e.g., semantic clustering indices). Future studies might also examine other so-called "integrative" constructs, paying particular attention to the conceptual match between the demands of the real-world task and the cognitive and functional capacities under study (e.g., social cognition as a predictor of social and emotional HRQoL).

In-depth examination of the role of neurocognition per functional outcome is critical given the variability observed across type and severity of cognitive impairment in this relationship. The real-world outcomes most strongly (and broadly) related to neurocognitive functioning were IADLs, cART adherence, medication management, and HRQoL, whereas the relationships with automobile driving, risk behaviors, and employment, while clearly present, were nevertheless more variable across neurocognitive domains. A relevant next step for the field might be to examine more specific manifest ADL domains affected in HIV (e.g., cooking, cleaning, shopping) rather than global ADL functioning, which may be differentially impacted by (or impervious to) HIV-associated neurocognitive impairment. NeuroAIDS researchers might also consider expanding the range of real-world outcomes to include other ecologically relevant aspects of the daily lives of persons infected with HIV (e.g., psychosocial functioning). For example, the everyday functioning independence of individuals living with HIV infection is increasingly dependent on navigation of the Internet to engage medical (e.g., pharmacy and health information), household (e.g., shopping and banking), and even psychosocial (e.g., social networking) resources. As such, the development of web-based capacity (e.g., Internet navigation skills) and manifest (e.g., electronic health record utilization) functioning may be increasingly relevant to health outcomes (Goverover & DeLuca et al., 2015). It will also be important to examine cofactors that may modulate the observed relationships between neurocognitive functioning and real-world outcomes in HIV, as we know little about the influence of motivation, awareness, actual real-world demands, and compensatory strategies (see Fig. 10.1).

Considering the prevalence and real-world impact of HAND, the development, validation, and clinical deployment of effective cognitive, behavioral, and pharmacological treatments to improve cognitive health outcomes is a clear priority (Weber, Blackstone, & Woods, 2013). To date, pharmacological (including cART and non-ART approaches) have shown limited effectiveness on HAND (Al-Khindi, Zakzanis, & van Gorp, 2011) and none to our knowledge have examined the trickle down effects of cognitively targeted therapies on real-world outcomes. Only three studies have been published to date on cognitive rehabilitation in HIV (see Weber, Blackstone, & Woods, 2013), all of which have used a restorative approach. Only one study has examined the benefits of cognitive rehabilitation on functional outcomes in HIV. In 2012, Vance et al. reported that a 10-h restorative processing speed intervention was associated with modest improvements in two functional skills tasks (i.e., timed IADLs and Useful Field of View) in a small HIV-infected cohort, but its impact on manifest real-world outcomes remains to be determined. Given the consistency of executive dysfunction and episodic memory as predictors of functional skills and real-world outcomes across the HIV literature, targeting these ability areas for restoration and/or compensatory rehabilitation may be particularly beneficial. For example, the use of cueing paradigms (e.g., alarms) may improve self- and environmental-monitoring of safe driving behaviors (e.g., checking for appropriate speed) and assist in breaking periods of inattention or distracted driving. Additionally, qualitatively, themes such as having a "stable base" (e.g., home and community resources) and "finding and maintaining balance" (e.g., adjusting daily routines according to physical and cognitive symptoms), have been identified as important aspects of successful daily functioning among HIV+ individuals (Bedell, 2000). Therefore, in order to successfully address the functional difficulties observed, it may be important to not only address those neurocognitive factors that may be contributing to declines, but also the important psychosocial domains and comorbidities that may contribute to the global picture of functioning in HIV infection. Viewed in the context of our guiding conceptual model, improving HIV-associated neurocognitive and functional impairment may subsequently improve real-world functioning, which may in turn enhance general health perceptions and overall quality of life.

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