Published in final edited form as:

AIDS Behav. 2010 December ; 14(6): 1213–1226. doi:10.1007/s10461-010-9684-1.

Neurocognitive Impairment and HIV Risk Factors: A Reciprocal Relationship

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Abstract

Cognitive impairment among populations at risk for HIV poses a significant barrier to managing risk behaviors. The impact of HIV and several cofactors, including substance abuse and mental illness, on cognitive function is discussed in the context of HIV risk behaviors, medication adherence, and risk-reduction interventions. Literature suggests that cognitive impairment is intertwined in a close, reciprocal relationship with both risk behaviors and medication adherence. Not only do increased risk behaviors and suboptimal adherence exacerbate cognitive impairment, but cognitive impairment also reduces the effectiveness of interventions aimed at optimizing medication adherence and reducing risk. In order to be effective, risk-reduction interventions must therefore take into account the impact of cognitive impairment on learning and behavior.

Keywords

Cognitive impairment; Substance abuse; HIV/AIDS; Mental illness; Medications; Antiretroviral therapy; Prevention; Interventions; Methadone; Buprenorphine

Introduction

HIV is a global epidemic, affecting nearly 33 million people in every country [1]. In spite of its diverse reach, several hallmarks of HIV cut across the populations affected, not least among them frequent comorbidity with neurocognitive impairments resulting from both neurological effects of HIV itself and other shared risk factors. Although the widespread use of highly active antiretroviral therapy (HAART) has both ameliorated the severity of the HIV epidemic and reduced the incidence of serious HIV-associated dementia, other neurocognitive impairments

continue to pose a significant barrier to both effective HAART use and the management of HIV.

Neurocognitive impairments can lead to behaviors such as suboptimal medication adherence and increased HIV risk-taking behaviors, both of which can exacerbate HIV symptoms in HIV-infected individuals and increase the risk of becoming infected among HIV-uninfected individuals. In turn, many of the risk factors for HIV infection, such as mental illness or substance abuse, can trigger neurocognitive impairments, and poor medication adherence can lead to HIV-associated neurological dysfunction. In order to effectively reduce the transmission and progression of HIV, it is necessary to understand better the complex, reciprocal relationship between neurocognitive impairment and HIV risk factors.

Methods

PubMed and Google Scholar databases were queried and searches were primarily limited to studies published in the past 10 years; however, a few seminal earlier studies were also included. Search terms characterizing cognitive impairments resulting from HIV infection included “HIV-associated neurocognitive disorders” and “HIV neurological symptoms.” Similarly, search terms used for substance abuse-related impairments included “cognitive impairment,” “substance abuse,” “alcohol,” “methadone,” “buprenorphine,” “opiate substitution,” and “long-term cognitive substance abuse.” To identify HIV risk behaviors, “cognitive impairment” was combined with search terms, including “HIV risk,” “sexual risk behaviors,” “substance abuse treatment adherence,” and “drug- or injection-related risk.” Search terms regarding medication adherence included “cognitive impairment,” “adherence,” “non-adherence,” and “antiretroviral therapy.” Search terms used to find information on interventions were “cognitive-behavior,” “information-motivation-behavior,” “cognitive remediation,” “cognitive remediation schizophrenia,” “HAART,” “antiretroviral therapy,” and “HIV risk intervention.” The reference sections of several recent reviews were also queried [2], [3], [4], and [5].

HIV-Associated Neurocognitive Impairment

HIV-associated neurocognitive disorders (HAND) have been well-characterized, ranging from the severe (HIV-associated dementia) to milder forms (mild neurocognitive disorder and asymptomatic neurocognitive impairment). HAND encompasses cognitive impairment, including slowed processing and deficient memory and attention; motor symptoms, such as a loss of fine motor control; and behavioral changes, such as apathy or lethargy [6]. Based on the most recent classification revisions, diagnosis of HIV-associated dementia or mild neurocognitive impairment entails different degrees of impairment in cognitive performance across two domains (e.g. learning of new information, information processing speed, and/or attention, and different levels of interference in daily functioning [7]). Asymptomatic neurocognitive impairment does not interfere with cognitive functioning, although it is also characterized by impairment in at least two domains of cognitive ability. HAND is not associated with general delirium or clouding of consciousness. Rather, in patients displaying symptoms of HAND, HIV has been found to specifically affect executive functions, episodic memory, information-processing speed, motor skills, attention/working memory, language, and sensoriperception [3].

In a meta-analysis of HIV-related impairments, asymptomatic HIV-infected individuals were found to have the largest deficits in language and verbal functions, while individuals with symptomatic HIV and AIDS were found to have the greatest deficits in motor and executive functioning. As HIV disease progresses, motor functioning, executive skills, and speed of information processing demonstrate the greatest decline [8]. In another study, cognitive

deterioration was found to occur as frequently in subjects with an undetectable viral load as in those with a detectable viral load, although lower CD4 cell counts were associated with cognitive impairment in the long term [9].

Understanding the effects of HIV on the central nervous system is complicated by comorbid conditions that also affect cognitive function. Recent studies, however, have begun to disentangle the independent contribution of HIV infection itself from treatment for opioid dependence. Among HIV-infected and uninfected subjects prescribed methadone, HIV infection, but not addiction severity or comorbid depression, predicted neuropsychological impairment, though the prevalence of mild depressive symptoms and active drug use was extremely high in the sample [10].

The onset of HIV-related neurological symptoms occurs when infected monocytes and CD4 cells transport the virus across the blood–brain barrier within hours or days of initial infection. Although HIV rarely infects neurons, mediators shed by other infected cells, such as proinflammatory cytokines, chemokines, excitotoxins, and proteases, as well as HIV-1 proteins Tat and gp120, induce neuronal apoptosis and lead to documented cerebral atrophy [11]. Although these gross cerebral changes alone have not been positively correlated with HAND, reduced caudate, hippocampal, putamen, and frontal lobe volume, as well as diminished gray matter bordering the basal ganglia and lateral ventricles, have all been correlated with neurocognitive impairments [2].

Several of the neurocognitive deficits seen in patients with HAND have overt consequences for HIV risk behavior. The symptoms of HAND are similar to those seen in diseases that affect frontal-striatal circuit function, suggesting that HAND can disrupt the subcortical structures responsible for impulse control [12], and HIV-related deficits in episodic memory are thought to be highly prevalent, impairing the ability to plan and execute intentions [3].

Effects of Substance Abuse

Although injection drug use (IDU) has declined as an acquisition risk factor for new HIV infections in the United States, an estimated 22% of people living with HIV today were initially infected through IDU [13]. Drug use, even through its behavioral disinhibition, remains a common cofactor associated with HIV infection, and drug users are particularly at risk for underutilization of HIV care compared to other groups [14]. Chronic drug use itself is also strongly correlated with a host of neurocognitive impairments.

Opioids

Individuals with opioid dependence and abuse demonstrate deficits in attention, working memory, episodic memory, and executive function during active use. Moreover, deficits in complex working memory, executive function, and fluid intelligence persist into periods of early abstinence, while executive function impairments showed no signs of declining during abstinence [15]. Other studies have found that, during periods of intoxication, opioid users are impaired in working memory, metamemory, decision-making, attention, concentration, and fine motor function, while subtle long-term deficits have been seen in impulse control and features of executive function [16]. Opioid dependence may also exacerbate HAND by reducing immune system integrity and stimulating viral replication [17]. When opioids were used in conjunction with cocaine, worsening neurocognitive function was observed in HIV-infected individuals [18] to the extent that practitioners have incorporated therapeutic techniques specifically designed to accommodate such impairments in HIV-infected opioid dependent patients [19].

Cocaine and Amphetamines

Like opioid dependence, chronic cocaine use exacerbates HIV replication; evidence also exists that cocaine increases the permeability of the blood–brain barrier to HIV and promotes cellular apoptosis [20]. To a greater extent than opiates, cocaine is associated with lasting changes in brain morphology and neurological function, inducing vasoconstriction and cerebral atrophy and reducing activation of the frontal lobe and basal ganglia [21]. Chronic cocaine users have impaired executive function, new learning, information-processing speed, memory, visuospatial perception, and attention, which may persist into abstinence [2].

Unlike cocaine, methamphetamine is neurotoxic, damaging dopaminergic neurons and depleting both dopamine and norepinephrine in the brain [22]. In a study of the interacting effects of HIV infection and methamphetamine use on the central nervous system, a significant correlation was observed between reduced hippocampal volume and cognitive impairment among HIV-infected methamphetamine users [23]. Both cocaine and methamphetamine use can result in intracerebral hemorrhage and other cerebrovascular syndromes [21].

Although cocaine and methamphetamine act through separate biological pathways, both are psychostimulants with similar and profound effects on the brain (see Table 1). Less data exist on the neuropsychological consequences of methamphetamine use, but some studies suggest that it mirrors the effects of cocaine use. Within 72 h of acute intoxication, methamphetamine use negatively impacted performance on working memory tasks, including short-term memory and attention [24]. Acute cocaine intoxication and methamphetamine intoxication have been found to inhibit impulse control [25,26]. Chronic use of either cocaine or methamphetamine results in impaired explicit memory and attention, and methamphetamine users were found to have greater information-processing deficits than cocaine users [27].

In human methamphetamine users, loss of dopamine axonal proteins consistent with injury to axon terminals of dopaminergic neurons has been observed [22,28]. Several case reports have also described a Parkinsonian-like choreatic syndrome resulting from chronic methamphetamine use [29,30]. Although the underlying hallmark of Parkinson's disease, loss of dopamine cell bodies in the substantia nigra, does not result from long-term amphetamine use, the symptoms are attributed to a reduction in the integrity of dopaminergic neurons [31].

Alcohol

Lifetime alcohol dependence has been found to impair attention, memory, and learning, and as with cocaine use, not all cognitive dysfunction is transient [32]. Although short-term memory and psychomotor skills were recovered after abstinence, impairments in long-term memory were found to persist for up to 7 years into sobriety [33]. In a study comparing HIV-infected and HIV-uninfected subjects with a history of alcohol dependence, significant impairment was seen in the HIV-infected group in the cognitive domains of verbal reasoning, reaction time, and auditory processing, whereas no significant impairments were seen in the HIV-uninfected group. This indicates that alcohol and HIV have synergistic effects on the central nervous system [34]. Alcohol dependence can also lead to persistent brain damage, including cortical and subcortical atrophy and hypometabolism in the frontal and parietal lobes [2].

A number of the neuropsychiatric syndromes resulting from chronic alcohol use are associated with vitamin B deficiency, and vitamin supplementation plays a significant role in treatment. Among these syndromes are Wernicke-Korsakoff, a form of delirium caused by thiamine deficiency, and alcoholic pellagra, characterized by confusion, hallucinations, and ataxia and caused by a deficiency in niacin [35].

Additional Risk Factors

In addition to substance abuse itself, several cognitive risk factors are common to HIV-infected drug users, including opioid substitution therapy, drug-related infections, traumatic brain injury, and mental illness.

Opioid Substitution Therapy

The unique effects of substance abuse on neurocognitive impairment are currently unclear. In part, findings are complicated by the fact that a number of studies have demonstrated that pharmacological treatments for substance use disorders can also lead to neurocognitive deficits. When patients on methadone maintenance were compared to non-heroin-using controls, they performed significantly more poorly on tasks measuring information processing, attention, short-term and delayed visual memory, short- and long-term verbal memory, and problem-solving [32]. When the effect of lifetime heroin use was controlled for by comparing methadone maintenance patients with abstinent heroin users, the methadone maintenance patients demonstrated significantly slower processing speed, visuospatial attention, and cognitive flexibility, and less accuracy in working memory and analogical reasoning tests [36].

Compared to the full mu-opioid agonist methadone, buprenorphine, a partial mu-agonist and kappa-antagonist, has been found to significantly increase simple reaction time and story recall. Both buprenorphine and methadone maintenance patients demonstrate impaired working memory and verbal list learning compared to controls [37]. However, these effects are limited in comparison to the extensive cognitive deficits seen in those actively using heroin or other drugs.

Hepatitis C Coinfection

Hepatitis C viral infection (HCV), a blood-borne virus transmitted primarily through IDU and present in 55–90% of HIV-infected IDUs, may also have neuropsychological manifestations [38]. HCV can replicate in the central nervous system, resulting in cognitive deficits independent of co-occurring substance abuse. In one study, the effects of HCV, methamphetamine use, and HIV infection were found to have additive effects on global cognitive impairment, learning, speed, problem solving, and recall tasks [39]. Moreover, interferon, an immunomodulator used for the treatment of chronic HCV infection, causes cognitive impairment through a variety of direct and indirect mechanisms [38,40].

Traumatic Brain Injury

Few studies have focused on the contribution of brain injury, which is frequently co-morbid with risk factors such as mental illness, to cognitive deficits in HIV-infected populations. The available literature suggests that a history of brain injury contributes to poor neuropsychological performance among HIV-infected individuals, and that a high frequency of head trauma is present among HIV-infected individuals. Individuals with HIV who have experienced head trauma reported a greater number of neuropsychological symptoms and a different pattern of symptomatology [41].

Mental Illness

The disproportionate prevalence of HIV infection among adults with mental illness is well-documented [42]. Substance use and psychiatric disorders are also highly prevalent in HIV-infected individuals, and over 60% will suffer from one or both at some point during infection [40]. Among people with mental illness, alcohol users have been found to engage in riskier sexual behaviors compared to control subjects [43].

The contribution of mental illness to cognitive dysfunction is not limited to those with substance use disorder comorbidity, but the effects of both substance abuse and mental illness itself on HIV risk behaviors make it difficult to specify the impact of cognitive dysfunction caused by mental illness. For instance, a study found that HIV risk behaviors were increased in adolescents with externalizing disorders (e.g. attention deficit hyperactive disorder and conduct disorder) and among mentally ill adolescents with a substance use disorder, even when the contribution of cognitive impairment was excluded [44].

Several studies, however, have suggested that cognitive deficits associated with mental illness may exacerbate HAND or contribute to risk behaviors. Individuals with a family history of mood disorders (e.g. bipolar disorder) demonstrated impaired cognitive control and slowed reaction time to the same extent as HIV-infected individuals, suggesting that the two conditions affect overlapping brain regions [45]. Hippocampal atrophy and resulting impairments in declarative memory have also been reported in individuals with mood disorders, although this atrophy was thought to be reversible [46]. Thought disorders (e.g. schizophrenia) were associated with deficits in information processing, as well as behavioral inhibition, suggesting damage to cortical-striatal-pallidal-thalamic circuitry [47].

Sexual Risk Behaviors

The Centers for Disease Control and Prevention found that sexual transmission was an acquisition risk factor in 88% of new HIV infections, suggesting that managing sexual transmission of HIV is crucial to controlling transmission [48]. A number of studies have analyzed the impact of susceptibility factors for cognitive dysfunction (e.g. substance abuse and mental illness) on sexual risk-taking behaviors (e.g. unprotected sex and multiple partners). In adolescents, major mental disorders increased sexual risk-taking behaviors compared to the general population, while a comorbid substance use disorder further increased the risk [49].

The nature of cognitive impairments caused by HIV and its cofactors suggests that they may play a role in increased risk-taking behavior. Impaired executive function inhibits rational decision-making by preventing the consideration of future outcomes in favor of current rewards and may prevent individuals from making safe sexual choices. Slowed information processing or reaction time may prevent the timely, appropriate consideration of risk variables during decision-making. Dysfunctional impulse control, which can result from the effects of HIV, substance abuse, or mental illness on the frontal-striatal circuit, may prevent individuals from executing safe sexual practices.

One study explored the contribution of implicit cognition, the unconscious retrieval of memories that influence behavior, to sexual risk-taking. Implicit memory was tested using word association tasks where the priming words related to health or sexual behaviors [50]. This memory task predicted the risk of unprotected sex when drug use and other psychosocial factors were excluded.

Findings conflict regarding the contribution of substance abuse-related cognitive impairment on disinhibition compared to factors such as expectancy, the beliefs people hold about the impact that substance abuse should have on sexual behavior. One study, which employed a placebo to control for expectancy, found that alcohol-related sexual disinhibition resulted in part from a reduction in perception of risk [51]. The authors reasoned that this effect could be caused by cognitive dysfunction, in particular an inability to retrieve information about negative consequences from long-term memory. Participants who expressed a stronger belief that alcohol would disinhibit their sexual behaviors, however, were also more likely to engage in unsafe sexual practices, suggesting that the cognitive effects of alcohol and expectancy interact to increase sexual risk behaviors.

A second important distinction must be made between cognitive function and the underlying personality traits that have long been thought to account for excessive risk behaviors, particularly “sensation seeking,” described as an inclination towards both novel experiences and risk-taking in order to achieve those experiences. Two hypotheses have been made regarding the frequent co-occurrence of substance abuse and sexual risk behaviors: (1) that an underlying sensation-seeking personality is responsible for both; and (2) that other features of substance use, for instance, cognitive impairment, can account for increased risk behavior. One study found that sensation seeking could not fully account for the association between substance abuse and sexual risk-taking and indicated that other factors (e.g. cognitive impairment) must underlie the relationship [52].

A more recent study directly compared the influence of executive function and sensation seeking on sexual risk behaviors among polysubstance users with a history of cocaine or cocaine/heroin dependence. Executive function was measured using the Iowa Gambling Task, which assesses decision-making, the delayed non-matching task, which assesses working memory, and the Stroop reaction time task. Greater addiction severity and HIV-infected status were found to correspond with executive dysfunction. Sensation seeking was found to account for risky sexual behavior only among individuals with more intact executive function, suggesting that cognitive impairment independently contributes to risk-taking behavior via decision-making dysfunction [53].

Drug-Related Risk Behaviors

Because of impaired memory, executive function, and cognitive speed that result from both chronic substance use and HIV infection, cognitive impairment may directly influence drug-related risk behaviors (e.g. sharing of needles and paraphernalia). Much of the research on the impact of cognitive function on HIV risk-taking, however, has focused on sexual, not drug-related, behaviors.

One study explored needle-sharing among young Australians to test the validity of the Rational Decision-Making model of risk, which posits that individuals who understand that their behavior puts them at risk of contracting HIV will be motivated to avoid those behaviors. The study found that the model could not account for drug-related risk-taking, describing subjects’ “impediments to rationality.” In short, young people who knew that HIV is transmitted through needle sharing were still inclined to share needles [54]. Although the authors allow for the influence of social factors, biologically impaired executive function and the resulting decision-making dysfunction provides an alternative explanation for this phenomenon.

A more recent study explored the relationship between cognitive functioning, personal knowledge of someone who died of AIDS, and risk behaviors. The authors found that the effect of knowing someone who had died of AIDS was moderated by cognitive function: Among those individuals who knew someone who had died of AIDS, those who demonstrated a lower cognitive function were more like to engage in high-risk injection behaviors (sharing drugs and injection equipment) than those who showed a higher cognitive function. The skills necessary to translate the understanding of HIV risk represented by knowing someone who died of AIDS into a reduction in risk behavior were identified as: (1) recognizing the risk, (2) identifying risk-reduction strategies, (3) weighing consequences, and (4) implementing the least risky option [55]. Impaired information processing might inhibit the first stage of this process, executive dysfunction and slowed information-processing speed the second and third, and lack of impulse control the last. Moreover, disruption of long-term memory formation and retrieval might prevent the representation of risk from being appropriately stored and accessed.

In part, controlling drug-related risk relies on patients’ retention in drug treatment programs (e.g. opioid substitution therapies such as methadone and buprenorphine). Studies of adherence

to methadone treatment found that continuous adherence was closely associated with a reduction in risky injection drug use [56,57]. A recent study found that the degree to which methadone maintenance programs are effective, however, depends on the cognitive status of the individual [58]. In particular, one study found that the majority of patients in a community-based drug treatment program who performed normally on two decision-making tasks, and none of the patients who were impaired at both, were able to abstain from drug use [59]. Interestingly, this finding was reinforced by neuroimaging in a study in which relapse among methamphetamine addicts in treatment was reliably predicted by fMRI activation during decision-making tasks [60].

Medication Adherence

In the HAART era, one primary cause of HIV treatment failure is resistance to antiretroviral medications, an outcome that both has widespread implications for HIV management and is closely linked with suboptimal medication adherence [61]. For instance, one early review found that across several studies, nonadherence to one medication in a triple combination regimen resulted in, not only an increased viral load, but also viral resistance to all three medications [62]. A number of studies have found associations between cognitive factors such as memory impairment and executive dysfunction and medication adherence [4]. Although a comprehensive review of studies characterizing the relationship between cognitive function and adherence [4] has recently been published, several relevant findings will be briefly discussed here.

A study of adherence found that both neurocognitive impairment and the complexity of a medication regimen were predictive of lower adherence rates; cognitively impaired participants prescribed more complex regimens demonstrated the lowest rates of adherence. The cognitive impairments most closely associated with poor adherence were deficits in executive function, memory, and attention [63]. A subsequent study, spurred by the increasing existence of an older HIV-infected patient population, confirmed the impact of cognitive impairment among older adults, a group with better overall medication adherence. The authors acknowledged the possibility of a bidirectional influence, wherein poor adherence may contribute to cognitive dysfunction just as readily as impaired executive function may impede adherence [64].

Several more recent studies have focused on specific impairments that may contribute to poor adherence. Two studies tested cognitive function with a memory task that employed a distracter and a prescribed task to measure prospective memory, the type of memory required to execute a future intention. The tests measured both content recall at the prescribed task and the time at which it was accomplished relative to a target execution time.

When other biological and psychosocial factors were accounted for, non-adherent individuals were found to have significantly poorer prospective memory by contrast to adherent individuals. Moreover, the index of difference was time scale—although the non-adherent individuals remembered to perform the prescribed task, they did so at the wrong time. The authors cite findings from an HIV-associated prospective memory impairment trial, and suggest that non-adherent individuals have cognitive deficits that hinder their ability to adequately monitor time, thereby missing cues to take scheduled medication doses [65,66].

In a study measuring literacy in conjunction with cognitive function among HIV-infected injection drug users, the lowest adherence rates were found in the group with both low literacy and cognitive impairment [67]. Moreover, the compounding effects of low literacy and cognitive impairment are likely to impede the potency of conventional behavioral interventions.

HIV Risk-Reduction Interventions

The impaired new learning, information processing, and memory seen in HIV-infected individuals, substance abusers, and the mentally ill may prevent appropriate acquisition and retention of behavioral content conveyed in traditional risk-reduction programs. Moreover, cognitive impairment has been found to affect other behavioral predictors of intervention effectiveness, such as motivation. A study of drug users with comorbid psychiatric conditions measured motivation to change substance use behaviors and found that lower executive, memory, and intellectual function corresponded closely with lower motivation to change [68].

A second study of alcohol and other substance use disordered individuals found no evidence that executive impairment significantly predicted poorer drinking or substance abuse outcomes, nor were neurocognitive impairments associated with a failure to acquire or maintain the 12-step change strategies presented in treatment. The study did find, however, that change processes were strongly correlated with substance abuse outcome in unimpaired individuals, but weakly for impaired individuals, thus further implicating the role of impaired motivation [69]. A more recent review suggested that cognitive rehabilitation strategies should be incorporated into treatment, particularly in cases of executive dysfunction [70].

Pharmacological Interventions

A number of pharmacological alternatives have been found to assist the recovery of cognitive function or to mitigate impairment in the risk groups discussed. In particular, studies have highlighted the effects of pharmacological treatments on HAND, opiate-related impairment, and impairment resulting from mental illness and its treatments.

Opioid Substitution Therapy—Treatment for drug dependence for HIV-infected individuals not only increases access to care but also facilitates adherence [71] and reduces injection-related risk behaviors. Moreover, data suggest that opioid substitution therapy may mitigate the cognitive decline associated with active opioid use and withdrawal. In particular, although methadone treatment has been found to have adverse effects when compared with abstinent control subjects, it also positively affects cognitive function by reducing opioid use. Methadone maintenance has been found to improve verbal learning and memory, visuospatial memory, and psychomotor speed compared to baseline measures taken during drug use.

As a partial mu-opioid receptor agonist, buprenorphine has also been found to preserve cognitive function to a greater degree than treatment with methadone, a full mu-opioid receptor agonist [37,72]. In one study that used an event-related potential as a physiological measure of cognitive activity among opioid and cocaine users in response to an auditory task, buprenorphine treatment preserved activity following detoxification [73]. Another study focusing on decision-making abilities found that buprenorphine maintenance improved the performance of former opioid users to that of non-opioid using control subjects [74]. The study involved tasks requiring a comparison between long- and short-term gains and losses to select the option with the greatest overall gain. From a subjective standpoint, injectors of buprenorphine preferred it over heroin and methadone as it improved their daily function and allowed them to work [75]. Because of its relatively slow dissociation from mu-opioid receptors, buprenorphine also has a longer duration of action than either heroin or methadone, particularly salient to its ability to suppress withdrawal [76].

Treatment of Mental Illness—By treating psychiatric symptoms and stabilizing mood, the primary effect of medication may be to limit the HIV risk behaviors and non-adherence to HAART associated with mental illness [42]. Still, evidence on the effects of pharmacological treatments for mental illness on cognition is conflicting. Acute side effects of lithium treatment

for mood disorders include reduced psychomotor speed and, to a lesser degree, impaired verbal memory [77]. By contrast, in a recent pilot study limited to HIV-infected individuals with HAND, low-dose lithium was found to improve global neuropsychological function, suggesting it may mitigate HIV-related cognitive impairment [78].

One central concern is the increased risk of cerebrovascular events associated with antipsychotics, which is further increased in both patients taking atypical antipsychotics and those with dementia [79]. Although it is unclear how this finding will bear on HIV-infected populations, the changing demographics of the HIV pandemic—a growing number of new cases among middle-aged and older adults, as well as the aging HIV-infected population as a result of decreased mortality and morbidity—suggest that more research is necessary [64]. Several studies have also reported that patients with thought disorders who are treated with atypical antipsychotics, however, demonstrate a significant recovery of executive function and memory compared to those with untreated mental illness [80]. Clozapine was found to improve attention, verbal fluency, and some measures of executive function. Risperidone improved working memory, executive functioning, and attention, and olanzapine improved verbal fluency, verbal learning and memory, and executive function [81].

Highly Active Antiretroviral Therapy—Findings regarding the impact of HAART on cognitive function have been particularly promising. Studies have found that HAART reduces viral levels in the plasma and cerebrospinal fluid of infected individuals and improves neurocognitive function [82]. Indeed, it has also resulted in a decrease in depressive symptoms that has been demonstrated to affect neurocognitive function [83]. This effect seems to be in part, dependent on differences in the degree to which various HAART regimens penetrate the blood–brain barrier, as measured by a CNS Penetration Effectiveness scoring system. Neuroactive antiretrovirals are defined as those that reduce cerebrospinal fluid HIV-1 RNA levels to an undetectable level [84].

Studies have found zidovudine, stavudine, lamivudine, nevirapine, indinavir, and abacavir to be more efficient at reducing concentrations in the central nervous system than other medications [85]. The degree to which HAART regimens penetrate the central nervous system was found to be predictive of neuropsychological improvement after 12 weeks of treatment [86]. Other studies have also suggested, however, that HAART may have an effect on HIV levels in the cerebrospinal fluid even when it does not cross the blood–brain barrier, perhaps by reducing systemic immune activation [87].

HAART has been found to improve concentration, speed of mental processing, mental flexibility, fine motor function, visuospatial and constructional abilities, and memory in HIV-infected individuals [88]. In a study that tracked patients for up to 5 years following the initiation of HAART, cognitive function continued to improve [89]. In another study of HIV-infected individuals on HAART, improved cognitive function over a 27-month period was associated with a neuroactive HAART regimen—a HAART regimen comprising at least three neuroactive antiretrovirals—but not CD4 count or plasma viral load [9].

While HAART has primarily been credited for reducing the incidence of more severe forms of HAND, some evidence suggests that neuroactive antiretrovirals may be associated with psychiatric symptoms because of increased blood–brain barrier penetration. Adverse effects are reported with the use of efavirenz in a small percentage of patients, including cognitive side effects such as impaired concentration and rarely, neuropsychiatric complications [90].

Behavioral Interventions

Successful behavioral risk-reduction interventions must tailor learning to those likely to be at least minimally cognitively impaired, either by incorporating strategies to remediate

impairment or by incorporating motivation and reinforcing behavioral skills through a focus on applications and improved outcomes.

Cognitive Remediation—Several therapeutic approaches have been identified as effective at remediating the effects of cognitive impairment on risk behaviors and adherence through compensatory techniques and cognitive enhancement. For schizophrenics, cognitive adaptation training, which employs environmental supports such as checklists, alarms, and organization to cue adaptive behaviors and adherence, increased adherence to oral antipsychotic medications as measured during the 6 months after training [91]. One neuroimaging study showed altered brain activation in schizophrenic subjects following the therapy: While schizophrenics were initially found to have lower-than-normal left inferior frontal cortex activation during verbal memory tasks, after 15 weeks of cognitive training, activation was comparable to that of control subjects [92].

Among former drug users, the extent of cognitive recovery was found to increase through cognitive remediation focusing on memory training and the development of problem-solving strategies. Memory training focuses on improving attention and strategies such as visual imagery and peg-words, while problem-solving sessions focus on strategies such as goal identification, brainstorming, and approach flexibility based on success rate [93].

Cognitive-Behavior Model—One study employed cognitive remediation techniques as part of a group-based harm-reduction intervention with HIV-uninfected methadone maintenance patients to facilitate acquisition of knowledge and skills. These techniques included presenting information multimodally, providing frequent review, minimizing distraction and fatigue, providing immediate feedback from assessments, including real-world examples and at-home exercises, and employing a memory book to enhance retention and organize material. Compared to those receiving standard care, this group was more likely to remain abstinent from cocaine and to report fewer high-risk sexual practices [94]. Similar results were seen among HIV-infected methadone maintenance patients receiving a harm-reduction intervention, who were less likely than a control treatment group to use illicit opioids and more likely to be adherent to medication during treatment, and had lower addiction severity scores and a lower likelihood of engaging in high-risk behaviors at follow up [95].

The harm-reduction intervention was informed by the Information-Motivation-Behavior (IMB) model of HIV-risk reduction, which holds that effective interventions should include information relevant to HIV transmission, motivation to practice risk-reduction behavior, and behavioral skills, including specific behaviors such as needle cleaning and condom application [96]. As would be predicted by the impact of motivation on behavior change in cognitively impaired subjects described above, interventions based on the IMB model have been found to be effective in reducing HIV risk behaviors among cognitive impairment risk groups.

In a study of adults receiving outpatient psychiatric care, patients receiving HIV-risk-reduction interventions based on the IMB model had significantly improved sexual risk behaviors compared to those receiving standard care, including stronger condom use intentions, fewer new sexually transmitted infections, fewer casual sex partners, and less unprotected sex [97].

There are conflicting findings regarding the efficacy of cognitive-behavioral interventions at reducing risk behavior and increasing psychosocial adjustment. A study of sexual risk behaviors among men who have sex with men found that cognitive-behavioral therapy in conjunction with case management increased serosorting practices compared to wait-list control and decreased risk acts significantly at five, 10, 15, and 20 months [98]. A study involving a diverse sample not limited to gay men, however, found no cognitive-behavioral intervention-related changes [99].

Integration—Evidence suggests that interventions informed by cognitive limitations are more effective for at-risk groups. Such interventions are only feasible, however, if they can be incorporated into other treatment programs. One approach relies on the observation that cognitive strategies for increasing adherence closely parallel risk-reduction skills. A 2008 review suggested that an effective approach to cognitive-behavioral therapy is an integrated method that simultaneously addresses adherence and risk-reduction in order to manage factors that correlate with both behaviors [100].

In a more recent study, women at a range of different community treatment sites, including both outpatient psychosocial treatment and methadone maintenance programs, were given a series of “Safer Sex Skills Building” (SSB) sessions [101]. SSB sessions involved many of the principles of cognitive-behavioral interventions, utilizing role-playing, problem-solving, and peer feedback and support, among other strategies. Outcomes were compared to those of subjects enrolled in a control condition, who received a single didactic HIV education session, and although the number of unprotected sexual encounters was reduced in both groups at 3 months, at 6 months, reductions in risky behavior were sustained only in the SSB condition.

A parallel study compared the traditional approach to an intervention based on the Information, Motivation and Behavioral Skills (IMB) model and delivered to men at a series of community sites [102]. Again, by 6 months, only the participants receiving the IMB intervention demonstrated a sustained reduction in unprotected sex. Both studies incorporated role-plays and substantially more specific HIV risk information than standard HIV counseling, an explicit approach that may be particularly effective among cognitively impaired populations. Although severely cognitively impaired subjects were excluded from both studies, the outcomes speak to the feasibility of incorporating cognitive-behavioral therapies into standard treatment programs, and to the long-term efficacy of such approaches by contrast to traditional interventions.

Conclusions and Future Directions

Understanding the close, bidirectional relationship between cognitive impairment and HIV risk factors is crucial to effectively reducing HIV risk. Although a number of studies have explored the impact of cognitive dysfunction on sexual risk behaviors, the corresponding impact on drug-related risk behaviors must be more thoroughly investigated. Further studies employing measures of cognitive impairment specific to dysfunction caused by HIV infection, substance abuse, and mental illness should be pursued. For instance, the time-based prospective memory impairments linked to poor adherence [65] should be studied in relation to HIV risk behaviors.

Prior studies suggest that interventions incorporating cognitive remediation strategies, diverse presentation of information, and a focus on practical applications (e.g. motivation and role-play) are the most successful at reducing risk among cognitively impaired populations. A clearer picture of the populations that benefit most from cognitive-behavioral or pharmacological approaches, however, should be developed, and further studies examining the specific impact of utilizing cognitive remediation strategies in HIV-specific interventions should be conducted. As suggested [100], the efficacy of integrated interventions designed to manage both medication adherence and HIV risk behavior should be investigated, and future studies should focus on the feasibility of incorporating cognitive-behavioral and cognitive remediation strategies into existing treatment programs. Ultimately, better understanding and addressing cognitive impairment could significantly enhance HIV prevention and care.

Acknowledgments

The authors would like to thank the National Institute on Drug Abuse for career development awards for Drs. Springer (K23 DA019381), Copenhaver (K23 DA17015), and Altice (K24 DA017072), and the Yale College Fellowship for Research in Health Studies for Pria Anand.

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Table 1

Factors that contribute to cognitive impairment

	General	Pathognomonic	Attention	Memory	Learning/verbal	Frustration	Academic
HIV	Cognitive impairment is seen in 10–30% of asymptomatic, 44% of symptomatic, and 55–86% of AIDS patients Speed of information-processing damaged, particularly in symptomatic patients	HIV generates multinucleated giant cells from which the disease is replicated and expressed in the brain	Deficits in executive function seen, particularly in AIDS patients	Symptomatic HIV patients have impaired working memory, particularly retrieval	Language dysfunction is the most commonly observed deficit among asymptomatic PLWH Symptomatic HIV patients show impaired verbal fluency	HIV damage to frontal-striatal circuitry results in impaired impulse control	Problem-solving deficits result from localization of HIV to frontal-striatal circuits
Cocaine and amphetamines	Decrease information-processing speed	Induce vasoconstriction and cerebral atrophy Cocaine alters basal ganglia, orbitofrontal cortex, and cingulate gyrus Methamphetamine is toxic to dopaminergic neurons Cocaine increases the permeability of the blood–brain barrier to HIV; also acts as an immunosuppressant Together, methamphetamine and HIV infection may reduce hippocampal volume	Impair executive function	Impair explicit memory, e.g. word and picture recall	Impair new learning		
Opioids	Psychomotor speed impaired in polysubstance users	Induces hypoperfusion in the frontal and temporal lobes	Impaired in polysubstance users	Working memory impaired in polysubstance users			Problem-solving ability impaired in polysubstance users
Alcohol	Impaired information-processing speed	Damages neurotransmitter systems such as acetylcholine, norepinephrine,	Impaired in chronic alcohol users				Abstract reasoning, non-verbal intelligence, and concept-formation are impaired, even after periods of abstinence

	General	Pathognomonic	Attention	Memory	Learning/verbal	Frustration	Academic
Opioid substitution		glutamate, and GABA					
		Cortical atrophy, reduced subcortical volume, white matter abnormalities					
		Hypometabolism in frontal and parietal lobes					
		Increases permeability of the blood-brain barrier to HIV					
			Methadone results in deficient attention	Methadone improves visuospatial memory	Compared to drug use, methadone improves verbal learning and memory		Methadone impairs analogical reasoning
			Buprenorphine improves decision-making abilities of former opioid users to that of non-opioid using control subjects	Methadone lowers working memory accuracy, as does buprenorphine	Compared to abstinence, buprenorphine and methadone both impair verbal list recall; verbal memory is more impaired in methadone than buprenorphine patients		
Hepatitis C	Reduces speed of processing and has an additive effect on global cognition			Impairs recall	Impairs new learning		Impairs problem solving
Mental illness	Antipsychotics may reduce speed of information processing		Schizophrenia results in impaired executive function	Impaired working memory in thought disorders such as schizophrenia	Impaired verbal learning as related to social cues in schizophrenics	A family history of mood disorders results in diminished cognitive control in HIV patients	
	Low-dose lithium may mitigate HIV-related global cognitive impairment		Patients taking atypical antipsychotics demonstrate a significant recovery of executive function compared to those with untreated mental illness				
	Thought disorders such as schizophrenia reduce information-processing speed						

The impact of HIV infection, pharmacology, and mental illness on various domains of cognitive function. Cognitive domains are defined based on categories identified by the Neuropsychological Impairment Scale