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The aggregate effects of multiple comorbid risk factors on cognition among HIV-infected individuals

Sapna M. Patel[1], **April Thames**[1], **Natalie Arbid**[2], **Stella Panos**[1], **Steven Castellon**[1,2], and **Charles H. Hinkin**[1,2]

[1]University of California, Los Angeles, Psychiatry and Biobehavioral Sciences

[2]VA Greater Los Angeles Healthcare System

Abstract

This study developed and then cross-validated a novel weighting algorithm based on multiple comorbid risk factors (stimulant use, vascular disease, hepatitis C, HIV disease severity, cognitive reserve) to predict cognitive functioning among 366 HIV+ adults. The resultant "risk severity score" was used to differentially weight, as a function of age, the impact and magnitude of multiple risk factors on cognition. Among older adults (> 50 years) the risk severity index was differentially predictive of learning/memory and verbal fluency, whereas among younger adults it was linked to working memory and executive function. Cognitive reserve was found to be the most robust predictor of neurocognition.

Despite advances in combination antiretroviral therapy (cART), cognitive impairment persists among individuals with HIV infection (Becker et al., 2011; Heaton et al., 2010). Many factors contribute to the development and severity of cognitive dysfunction including potentially irreversible brain injury that developed before patients were started on highly effective antiviral therapy as well as incomplete blood-brain-barrier penetrance leading to inadequate suppression of the adverse effects of HIV on central nervous system function (see Review - Heaton et al., 2011). In addition, there is a high prevalence of comorbid conditions that continue to plague individuals with HIV (Weiss, Osorio, Ryan, Marcus, & Fishbein, 2010). Approximately 15–30% of HIV+ individuals are infected with the hepatitis C virus (HCV) (Sherman, Rouster, Chung & Rajicic, 2002) and 40% are substance users (Bing et al., 2001). Additionally, with the advent of antiretroviral therapy, more individuals are living over the age of 50, which makes them more vulnerable to long-term toxicity from HIV treatment and age-related illnesses (e.g., vascular disease).

Although it has been difficult to disentangle comorbid conditions that are associated with HIV and its treatment from those that are independent of HIV, various comorbid factors have been demonstrated to place HIV positive individuals at greater risk for cognitive as well as functional declines. Furthermore, recent research has demonstrated that HIV+ individuals with low cognitive reserve have an increased vulnerability to syndromic HIV-associated neurocognitive disorders (HAND), which is characterized by both cognitive and functional difficulties (Morgan et al., 2012).

Correspondence concerning this paper should be addressed to Sapna M. Patel, University of California, Los Angeles, Psychiatry and Biobehavioral Sciences, 760 Westwood Plaza, C8-746, Los Angeles, CA 90095. Phone: 310-478-3711, ext: 49565. smpatel@mednet.ucla.edu.

Cognitive Reserve

Although low cognitive reserve has not been generally viewed as a “risk factor”, there is evidence to suggest that cognitive reserve capacity (usually indexed by estimated premorbid intelligence and/or educational attainment) may be a good indicator of which HIV infected individuals will display neurobehavioral abnormalities (Basso & Bornstein, 2000). Researchers have theorized that individuals may not begin to exhibit overt signs of neurobehavioral dysfunction until after a certain threshold of brain damage has been sustained; therefore, individuals with high cognitive reserve may have a higher threshold for neuropsychological dysfunction and more cognitive resilience to continuous cerebral insults (Satz, 1993). Satz et al. (1993) found that the predicted prevalence of cognitive dysfunction was 38% in HIV individuals with no more than 12 years of education while, in the other education-serostatus groups, the prevalence was less than 17%. One study estimated cognitive reserve based on education, occupation and premorbid intelligence and demonstrated similar findings. On measures of attention, memory, executive functioning and visuospatial ability, asymptomatic HIV individuals with low reserve displayed more cognitive deficits than asymptomatic seropositive individuals with high reserve, and seronegative individuals with low or high reserve (Stern, Silva, Chaisson, & Evans, 1996). In a recent study by our lab (Thames, Foley, Panos, Singer, & Hinkin, 2011), individuals with high levels of reserve who were matched on overt neurocognitive status evidenced greater striatal atrophy compared to individuals with lower levels of reserve. This suggests that individuals with high levels of cognitive reserve may be able to shoulder greater levels of neuropathology before neurobehavioral manifestations occur.

HIV Disease Severity

Immunological markers (e.g., CD4 count) provide clinical information about the severity of HIV disease. Low CD4 count has been linked to neurological complications in the pre-HAART era (Childs et al., 1999). More specifically, individuals with a CD4 count below 200 cells/mm^3 are considered highly vulnerable to such complications (e.g., CNS opportunistic infections; Chiesi et al., 1996). In the era of cART, a low current CD4 count among patients on pharmacotherapy is less frequently encountered. However, studies have demonstrated that the historical lowest CD4 count (or nadir CD4) remains a strong predictor of neurocognitive impairment (Valcour et al., 2006; Heaton et al., 2011; Tate et al., 2011; Ellis et al., 2011) and is related to a current diagnosis of HIV-associated neurocognitive dysfunction (HAND; Valcour, Paul, Neuhaus, & Shikuma, 2011).

Hepatitis C Virus (HCV)

Cognitive dysfunction (particularly within the domains of attention/working memory and psychomotor speed) has been demonstrated in HCV-infected individuals (independent of severity of liver disease, e.g. cirrhosis). Given the overlap in pattern of neurocognitive dysfunction and neurophysiologic abnormality common to both HIV and HCV it has been suggested that there may be additive (Letendre et al., 2005; Lu, Robinson, & Zhang, 2009; Hilsabeck, Perry, & Hassanein, 2002; Morgello et al., 2005; Perry et al., 2005) and synergistic (Laskus et al., 2004) effects of co-infection on cognition. It has been also been demonstrated that co-infected individuals have higher rates of AIDS, lower CD4 counts and higher plasma viral load compared to HIV mono-infected individuals (Greub et al., 2000). Several groups have demonstrated that co-infected individuals are more likely to exhibit neurocognitive impairment than individuals infected with HIV or HCV alone (Letendre et al., 2005; Letendre et al., 2007; Martin et al., 2004; Hilsabeck, Castellon, & Hinkin, 2005; Hinkin, Castellon, Levine, Barclay, & Singer, 2008), though others have failed to replicate these findings (Ryan, Morgello, Isaacs, Naseer, & Gerits, 2004; Perry et al., 2005).

Substance Use

History of substance use is extremely common among the HIV infected populace, with 40–74% of HIV-infected individuals reporting past or current substance use disorders (Gonzalez, Barinas, & O'Cleirigh, 2011). It has been suggested that HIV individuals who abuse psychostimulants (i.e., cocaine and methamphetamine) are at greater risk for poor medication adherence, which places them at greater risk for adverse clinical outcomes (Arnsten et al., 2002; Hinkin et al., 2004; Hinkin et al., 2007; Tucker et al., 2004). While the independent neuropsychological effects of HIV and methamphetamine use have been well documented, less is known about the combination of these factors. Several studies have shown that methamphetamine use aggravates HIV associated cognitive declines (Rippeth et al., 2004; Carey et al., 2006). Mixed results have been found with regards to the impact of cocaine use on HIV associated cognitive disorders, with some (Meade, Lowen, MacLean, Key, & Lukas, 2011; Durvasula et al., 2000) but not all (Chang et al., 2008) finding that cocaine use potentiates the adverse CNS effects of HIV infection. Recency of last use appears to be the strongest predictor of whether additive cognitive deficits emerge.

Vascular Risk

HIV infected individuals demonstrate a higher prevalence of vascular risk factors (i.e., myocardial infarction, coronary heart disease, atherosclerosis, hypertension, diabetes and obesity) compared to seronegative individuals (Adeyemi, 2007; Hsue et al., 2004; Lebech et al., 2007; Magalhaes, Greenberg, Hansen, & Glick, 2007; Tipping, de Villers, Wainwright, Candy, & Bryer, 2007; Triant, Lee, Hadigan, & Grinspoon, 2007). Numerous studies have demonstrated that cART is associated with an increased risk of atherosclerosis and vascular events (Carr et al., 1999; Holmberg et al., 2002; Stein et al., 2001). Previous research has suggested that vascular risks such as high total cholesterol, diabetes, myocardial infarction, and congestive heart failure are associated with neuropsychological impairments in HIV-positive individuals, particularly in the areas of processing speed, learning/memory and executive functioning (Foley et al., 2010; Wright et al., 2010). Furthermore, markers of atherosclerosis [e.g., common carotid artery intima-media thickness (IMT), coronary artery calcium (CAC)] have also been linked to cognitive dysfunction (Bots, Dijk, Oren, & Grobbee, 2002; Greenland, Smith, & Grundy, 2001; Mangili et al., 2006). Becker et al. (2009) demonstrated that IMT and estimated glomerular filtration rate (GFR; a marker of vascular disease) were associated with slowing of psychomotor speed. Additionally, coronary artery calcium was marginally associated with memory function. Wright et al. (2010) also found that HIV-positive individuals with preexisting cardiovascular disease had a 6.2 fold higher likelihood of evidencing neurocognitive impairment relative to those without vascular risk factors.

Aging & HIV

Whether advancing age accelerates HIV associated cognitive decline remains unclear. This is a question of critical importance since increasing proportions (approximately 50%) of HIV+ individuals are age 50 or over. With the reduced morbidity and mortality that has accompanied the advent and standard implementation of cART, more individuals 50 and older are living with HIV (Valcour et al., 2006). Much of the literature has demonstrated that normal aging confers its own risk for the development of medical illnesses including diabetes, coronary angioplasty, and myocardial infarction. Hence, there is reason to suspect that older adults may be particularly vulnerable to neurocognitive impairment due to normal age related immunosenescence and the adverse effects of age-linked medical co-morbidities.

While a host of prior studies have targeted a subset of the above discussed risk factors, few studies have attempted to simultaneously model the impact of multiple risk factors. Justice

& colleagues (2012) combined a number of factors (e.g., HIV biomarkers and age) into an index that predicted mortality rates. Similarly, Cysique et al. (2010) created a noncognitive-based algorithm that utilized age, current CD4 cell count, past central nervous system (CNS) HIV-related diseases, and current treatment duration in order to identify HIV+ individuals at risk of HIV-associated neurocognitive impairment. However, the current study advances the aforementioned studies in that it includes multiple comorbid conditions that have demonstrated to impact cognition, and that have not been examined by the aforementioned studies. Given the ubiquity of multiple comorbid risks among the HIV-infected population, there is a clear need to continue to find novel ways to study the relative impact of these risk factors, both individually and in aggregate, on cognition. There are several advantages to examining a combination of comorbidities as opposed to examining them separately. Foremost, it allows for examination of the relative contribution of each comorbid factor and provides us an understanding of the complex interplay of such factors on cognition. Furthermore, it increases the predictive power of the relationship between multiple comorbidities and cognition.

The objective of this study was to develop and validate a weighting algorithm (to be described below) to model the relative impact of multiple comorbid risk factors on neurocognition in order to ascertain: (1) whether certain risk factors are associated with differential cognitive deterioration and (2) whether these risk factors, individually and in aggregate, exert similar effects in younger versus older HIV+ adults.

Methods

Participants

Participants consisted of 366 HIV+ individuals recruited through advertisements posted at university-affiliated infectious disease clinics, as well as through community agencies in the Los Angeles area that specialize in providing services to HIV-infected individuals. All individuals were prescribed a highly active antiretroviral therapy (HAART) regimen. Exclusionary criteria included diagnosis of psychotic spectrum disorder, CNS opportunistic infections, traumatic brain injury with loss of consciousness in excess of 30 min, and seizure disorders. These exclusion criteria were selected because they are not typically thought to be associated with either HIV infection or its treatment.

Measures

Neuropsychological assessment—Participants were administered one of two similar fixed widely-used neuropsychological test batteries (Battery A or Battery B) to yield summary scores for the domains of attention/working memory, information processing speed, verbal fluency, learning and memory, executive functioning and motor functioning (Ettenhofer et al., 2009) (see Table 1 for a list of specific cognitive tests and normative data used). Raw test scores were converted to demographically-corrected T scores (with a mean of 50 and a standard deviation of 10) using published normative data. Domain T scores were calculated by using the mean T score for all the individual tests comprising the given domain. A global cognitive T score was also created by summing the individual test T scores and dividing by the number of administered tests. See Heaton et al. (1995) for a detailed description of this approach.

Risk factors—Below we discuss our approach to the assessment and categorization of various risk factors thought to place individuals “at risk” for the development of neurocognitive dysfunction.

Cognitive reserve—Although studies have examined cognitive reserve through various measurements (e.g., occupational attainment), a combination of word reading and educational attainment appears to be the most robust and widely used method in recent studies (Foley et al., 2012; Brickman et al., 2011; Rentz et al., 2010). Therefore, cognitive reserve scores were based on word-reading ability as measured by the American National Adult Reading Test (AMNART - a measure of premorbid intelligence), and years of education attained. This measure combines an index of *quantity* of education (years attained) along with an index thought to reflect *quality* of education (ability to pronounce orthographically irregular words that do not follow the usual grapheme –to-phoneme rules of pronunciation); therefore, it is able to capture two key components that contribute to cognitive reserve. The distribution of years of education for the entire sample (i.e., range = 5–20 years, $M = 13$, and $SD = 2.25$) closely mirrors studies that have used HIV populations with similar demographics (Dawes et al., 2008; Heaton et al., 1995). The following formula was utilized to convert years of education to standard scores: (*[subject raw score – sample mean]/standard deviation x 15 + 100*). This created a scale that was consistent with the AMNART scale. AMNART scores were not standardized within sample, but derived from the general population normative data. AMNART standardized scores and the standardized years of education were averaged to create a cognitive reserve score. For the purposes of statistical analyses, a median split was utilized to dichotomize scores into high and low cognitive reserve. Individuals with low cognitive reserve were considered to be more susceptible to cognitive dysfunction.

HIV Disease Severity—Self-reported biomarkers (e.g., nadir cd4+ and recent cd4+) were used to characterize HIV disease severity. Individuals were considered ‘at risk’ for cognitive difficulties if they had one (***either*** nadir or recent CD4+ to be < 200) or both (nadir ***and*** recent cd4+ of < 200).

Vascular—Individuals were classified as having vascular risk based on self-report of one or more of the following conditions: hypertension, diabetes, myocardial infarction, congestive heart failure, or stroke.

Hepatitis C—Individuals with Hepatitis C (based on self-report) were considered to be ‘at risk’ for cognitive difficulties.

Stimulant Use—Patients with current use (i.e., in the past month) and/or patients meeting criteria for abuse or dependence of methamphetamine and/or cocaine (based on SCID, and a modified version of SCID assessing substance use, self-report, or urine analysis) were characterized as being ‘at risk’ for cognitive dysfunction.

Analyses

Analytic procedures were as follows: (a) Younger (< 50 years old, $n = 296$) and older (> 50 years old, $n = 70$) HIV+ individuals were compared on demographic and risk factor variables; (b) In order to examine the aggregate impact of multiple risk factors on neuropsychological performance, study risk factors (i.e., cognitive reserve, HIV disease severity, vascular, hepatitis C and stimulant use) were weighted based on the results of linear regression conducted using all of the risk factors as predictors of global cognitive functioning. Subsequently, each of the risk factors were multiplied by the unstandardized beta weights and then combined to create a ‘risk severity score’; (c) Cross-validation analyses were employed (using random split half samples) in order to validate the beta weights derived from the above analyses; (d) Linear regressions were conducted utilizing the ‘risk severity score’ and functioning within each of the cognitive domains (information processing speed, learning and memory, attention and working memory, executive

functioning, verbal fluency and motor functioning) in order to determine whether risk severity differentially predicts performance within individual cognitive domains and whether the severity of the risks exert similar effects in younger versus older HIV+ adults; (e) Linear regressions were conducted utilizing individual risk factors and functioning within each of the cognitive domains in order to examine the relationship between specific risk factors and specific neurocognitive domains among younger and older individuals. To control for Type I error associated with the number of analyses employed, the false discovery rate (FDR) was used (Benjamini & Hochberg, 2000).

Results

(a) Demographic and risk factor variables

As shown in Table 2, younger (< 50 years) and older (> 50 years) groups were not significantly different in terms of gender, race/ethnicity, and education. Additionally, there were no significant differences between the two groups with regards to cognitive reserve score, hepatitis C status, stimulant use, and mean weighted risk (risk severity score). However, individuals in the younger group demonstrated greater disease severity (nadir CD4 < 200, higher percentage of AIDS diagnosis) compared to the older group. The older group had more individuals with vascular risks compared to the younger group (Table 2 about here).

(b) Weightings of risk factors

Results of linear regression conducted using all of the risk factors in the prediction of global cognitive functioning (T score) demonstrated that cognitive reserve exerted the greatest predictive association ($B = -5.06$), followed by disease severity ($B = -1.38$), hepatitis C ($B = 1.11$), stimulant use ($B = -0.38$), and vascular risks ($B = -0.32$). All relationships were in the expected direction.

(c) Cross-validation of weights

The above weighting system was further validated using a split-half technique in which a linear regression was conducted using all of the risk factors as predictors of global cognitive functioning on a random sample of cases (approximately 50% of the entire group), which produced virtually identical weightings (See Table 3) (Table 3 about here).

(d) Risk severity score and neuropsychological performance

As anticipated given the manner in which it was calculated, for both younger and older HIV + individuals the weighted risk severity score was significantly predictive of neurocognitive functioning across virtually all domains. More specifically, among younger adults the weighted risk severity score significantly predicted performances on information processing speed, $F(1, 295) = 14.48$, $p < .001$, learning and memory, $F(1, 295) = 35.40$, $p < .001$, attention and working memory, $F(1, 295) = 45.66$, $p < .001$, executive functioning, $F(1, 295) = 49.73$, $p < .001$, verbal fluency, $F(1, 295) = 19.99$, $p < .001$, and motor functioning, $F(1, 295) = 14.98$, $p < .001$, tasks. In older adults, the weighted risk severity score significantly predicted performances on learning and memory, $F(1, 69) = 11.41$, $p = .001$], verbal fluency, $F(1, 69) = 19.92$, $p < .001$, executive functioning, $F(1, 69) = 4.52$, $p = .04$], and motor functioning, $F(1, 69) = 4.30$, $p = .04$, tasks (See Table 4) (Table 4 about here). Interaction effects between age and risk severity were not found for information processing speed, learning and memory, attention and working memory, executive functioning and motor functioning. However, there was a significant interaction effect of age and risk severity on verbal fluency, $t(365) = -3.53$, $p < .01$, such that older adults with greater risk severity performed worse than the other age/risk severity groups on verbal fluency tasks.

Interestingly, an examination of the effect sizes suggests that there may be a differential impact of risk severity on cognitive functioning amongst the older vs. younger individuals. The effect sizes were larger for younger compared to older individuals in the domains of attention and working memory (R^2 = .13 versus .04) and executive functioning (R^2 = .15 versus .06). In contrast, the effect sizes were larger for older individuals relative to the younger participants in the domains of learning and memory (R^2 = .14 versus .11) and verbal fluency (R^2 = .23 versus .06). Both younger and older individuals were comparable in terms of effect sizes in the domains of information processing speed and motor functioning.

(e) Individual risk factors and neuropsychological performance

As detailed in the following section, an examination of individual risk factors revealed a differential impact of each risk on the various cognitive domains (See Table 5) (Table 5 about here).

Information Processing Speed—Among younger individuals, cognitive reserve significantly predicted information processing speed to a greater extent than did the other risk factors (B = −0.18, $t(250)$ = −2.91, p = .004). Vascular risk was also predictive of information processing speed (B = −0.15, $t(250)$ = −2.48, p = .01). For the older individuals, no risk factors were predictive of information processing speed. However, the beta weights for stimulant use, disease severity, cognitive reserve and hepatitis C were, for the most part, larger than that seen among the younger subjects. This suggests that these factors may predict information processing speed in older adults to a greater degree than in younger adults and that the absence of statistical significance was attributable to insufficient power rather than a lack of association.

Learning and Memory—For younger individuals, cognitive reserve significantly predicted learning and memory, exerting a greater impact than the other risk factors (B = −0.33, $t(250)$ = −5.52, p < .001). For older individuals, no risk factor was significantly associated with learning and memory; however, the beta weights for hepatitis C and vascular risks were larger than that seen among the younger subjects.

Attention and Working Memory—Among younger individuals, cognitive reserve was the only factor that significantly predicted attention and working memory (B = −0.35, $t(250)$ = −5.85, p < .001). Similarly, among older subjects cognitive reserve was the only factor that significantly predicted attention and working memory (B = −.39, $t(41)$ = −2.56, p = .02); however, the beta weights for vascular risk suggests that it predicts attention and working memory to a greater degree in older adults than younger adults. Additionally, the beta weight for stimulant use demonstrated a positive impact of stimulants on attention and working memory.

Executive Functioning—In younger individuals, cognitive reserve was the only factor that significantly predicted executive functioning (B = −.36, $t(250)$ = −6.11, p < .001). In older individuals, no risk factors significantly predicted executive functioning. However, the beta weight for cognitive reserve is suggestive of a relationship between cognitive reserve and executive functioning.

Verbal Fluency—For both younger and older individuals, cognitive reserve was the only factor that significantly predicted verbal fluency, with the older adults being impacted to a greater degree (B = −.49, $t(41)$ = −3.37, p = .002). Furthermore, examination of the beta weight for vascular risk suggests that it predicts verbal fluency to a greater degree in older adults compared to younger adults.

Motor Functioning—Cognitive reserve in younger individuals significantly predicted motor functioning ($B = -.20$, $t(250) = -3.14$, $p = .002$). Although no risk factors predicted motor functioning in older adults, the beta weight for cognitive reserve and disease severity suggested a relationship between these factors and motor functioning.

Discussion

The present study sought to examine the independent and aggregate effects of various comorbid risk factors on cognitive functioning among younger and older HIV-infected individuals. Although studies have examined such risk factors in isolation, to our knowledge, the present study is the first to create and validate an algorithm to differentially weight the impact and magnitude of multiple risk factors on cognition.

In order to examine the aggregate impact of risk factors, findings from an initial analysis of risk factors and global cognition were utilized to create a 'risk severity score'. Results were consistent with expectations such that risk severity predicted differential neurocognitive functioning across a number of domains for both younger and older adults. Specifically, we found that individuals with higher risk severity scores demonstrated greater cognitive impairment than individuals with lower risk scores. Furthermore, despite comparable risk severity scores among both younger and older groups, a high risk severity in younger adults had more predictive power in determining functioning in the domains of attention/working memory and executive functioning while a high risk severity in older adults had more predictive power in determining functioning in the domains of learning/memory and verbal fluency. Therefore, this differential manifestation of risk severity on cognitive functioning may be dependent on the age of the individual. Although we would expect older adults to be impacted by the study risk factors to a greater degree than younger adults across *all* cognitive domains, this was not found to be the case. This could reflect the fact that older HIV+ adults typically produce greater dispersion or intra-individual variability in cognitive performance (Morgan et al., 2011).

Such variability could also be a function of the types of risk factors included or endorsed by the younger and older adults. For example, a unique feature of this study is that low cognitive reserve was shown to be a risk factor for neurocognitive compromise. The differential impact of risk may also be attributed to younger adults having a significantly higher degree of disease severity than the older adults (i.e., higher proportion of AIDS and lower nadir CD4) producing a more frontal-subcortical neurocognitive profile. Additionally, the nature of deficits associated with the risk index that strongly loaded for younger adults (e.g., information processing speed and executive functioning) are findings that have been characteristically seen in HIV and indicative of subcortical involvement. However, among the older cohort, a differing pattern of loadings emerged (e.g., learning/memory and verbal fluency) in terms of the impact of the risk index. While verbal fluency clearly involves subcortical and cortical regions alike, the fact that among older adults, learning/memory (rather than more subcortical functions) was strongly implicated with the risk index may suggest the possibility of a different presentation with increasing age.

There may be some cohort effects contributing to the type of cognitive impairments observed between younger and older HIV+ participants (i.e., differences in HIV transmission route, greater risk taking behavior in younger adults) that may increase the likelihood of poor medication adherence, particularly among the younger individuals; thereby amplifying the impact of advanced disease severity among the younger sample. Interestingly, despite a similar length of HIV infection among the younger and older adults (8.8 years and 9.1 years, respectively), the younger cohort demonstrated greater disease

severity, which can possibly be attributed to poor medication adherence, lending further support to possible differences among the cohorts.

Examination of the impact of individual risk factors on cognitive domains revealed several unexpected findings. Interestingly, cognitive reserve appeared to be the most important and influential predictor of performance in the attention/working memory and the verbal fluency domains for both younger and older adults. Cognitive reserve predicted additional areas of performance in information processing speed, executive functioning, and motor functioning in younger adults. These results are consistent with previous findings from our group that utilized a different dataset (Foley et al., 2012) that have demonstrated the protective role of cognitive reserve in terms of neurocognitive dysfunction. Low cognitive reserve has not been generally viewed as a risk factor because it does not independently *cause* cognitive problems, though it does mediate the overt expression of cognitive dysfunction. Nevertheless, low cognitive reserve has demonstrated to increase susceptibility to the adverse effects of other types of neurological insults, including HIV-associated neurological problems.

Surprisingly, the other risk factors that were studied were not found to impact neurocognitive functioning to the same degree. Vascular risk was found to be predictive of information processing speed for the younger adults. Such findings are consistent with other studies that have demonstrated similar deficits among HIV+ adults (Sacktor et al., 2007; Becker et al., 2009). A previous study by our group examining the impact of vascular risk factors and age on cognitive functioning demonstrated an association between vascular risk and slowed processing speed even after controlling for age (Foley et al., 2010). Surprisingly, despite a greater rate of vascular risks among the older adults, this was not found to be predictive of neurocognitive dysfunction in this particular dataset. While we were able to identify isolated risk factors and neurocognitive associations, these were not as robust as was the relationship between cognitive reserve and neurocognition. The lack of significance between the high and low cognitive reserve groups in terms of the number and types of risk factors present, further supports this relationship.

Although the focus of the current manuscript was to examine differential risk factors between older and younger HIV+ individuals, we recognize that advanced age is considered to also be a risk factor to cognitive impairment. Therefore, we conducted ancillary analyses where age was included in the model as a predictor of global cognitive functioning. We found that age was not significantly predictive of cognition, and that cognitive reserve continued to account for most of the variance in cognitive functioning. This provides rather strikingly support for the role of cognitive reserve and underscores how low levels of reserve can place HIV+ individuals at risk for cognitive impairments.

An important limitation to the current study concerns the unequal sample sizes of the two groups, with a significantly underpowered older HIV group. This explains our failure to detect a statistically significant relationship between risk and certain cognitive domains despite effect sizes that were similar to that seen among the younger subjects (e.g., cognitive reserve and processing speed). Furthermore, although the age of our older HIV group was consistent with other HIV aging studies, it is still young compared to most non-HIV aging research. Therefore, we may not be observing the full effect of age. If the mean age of the older group was increased, there may have been an even greater distinction in the cognitive profiles of younger and older adults.

Another limitation concerns the self-reported nature of most variables (i.e., vascular, hepatitis C, stimulant use, and disease severity). Although previous studies have demonstrated associations between these risk factors and cognition, our inability to

document such a relationship for many of the risk factors suggests that the utilization of self-reported variables (which is often considered to be less reliable) may have contributed to the lack of findings. This may especially be problematic in terms of reporting specifics of disease severity (e.g., CD4 count). However, previous studies have demonstrated a strong agreement between self-reported diagnoses and medical records (Azar et al., 2005; Simpson et al., 2004; Bush et al., 1989). Even after controlling for advanced age and cognitive impairment, Simpson et al (2004) observed continued agreement between self-reported conditions and medical records among cancer, stroke, myocardial infarction, and Parkinson's disease. While there is little reason to suspect this relationship would not hold for the HIV infected population, the findings reflect possible unreliability of the measures to detect expected associations; and therefore a significant limitation.

We were also constrained by the nature and extent of the data collection aspect of the present study. Hence, we lacked access to data, such as cholesterol level, which may have also shown to be predictors of neurocognitive dysfunction. Similarly, the prevalence of other substances (e.g., alcohol use/abuse/dependence) within our data was lower than that found in the general HIV population, and therefore, was not included as a possible risk factor despite the fact that such substances have been shown to impact cognition.

Furthermore, in order to reduce the number of predictors, we decided to not include psychiatric comorbidities. We recognize that HIV individuals demonstrate higher rates of depression than the general population; however, several studies have demonstrated inconsistent findings in terms of its impact on cognition (Shimizu et al., 2011), with many studies demonstrating no effect of depression on cognition (Thames et al., 2011; Cysique et al., 2007; Millikin et al., 2003; von Giesen et al., 2001; Mason et al., 1998; Goggin et al., 1997; Grant et al., 1993; Mapou et al., 1993; Hinkin et al., 1992).

Despite these limitations, the findings of this study are promising. Future studies should consider employing medically-confirmed (e.g., via lab reports, current or previous medical records) as opposed to self-reported risk factors. Furthermore, studies would benefit by expanding on the breadth of each risk factor (e.g., including substances other than stimulants), as well as adding psychiatric comorbidities. Future studies should also consider utilizing a risk weighting algorithm as was done in the present study to model the relative impact of risk factors on cognitive functioning and such an approach will provide a better, more accurate picture of the complex interplay of multiple risk factors and cognition over time, and give us a greater understanding as to how aging alters the impact of these risk factors among HIV+ individuals. Cognitive reserve appears to play a very influential role in cognitive functioning and has often been overlooked in many HIV studies examining the relationship between risk and cognition. Given that low cognitive reserve as a "risk factor" is a relatively new focus in HIV research, it is an area that warrants further examination. Furthermore, assuming that greater risk severity results in greater cognitive declines, we would expect there to also be functional declines (i.e., problems with medication management) (Thames et al., 2011). Therefore, it would be interesting for future studies to examine whether risk severity moderates the relationship between cognition and functional measures, especially among older adults.

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References

Adeyemi O. Cardiovascular risk and risk management in HIV-infected patients. Topics in HIV Medicine. 2007; 15:159–162. [PubMed: 18073451]

Arnsten JH, Demas PA, Grant RW, Gourevitch MN, Farzadegan H, Howard AA, Schoenbaum EE. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. Journal of General Internal Medicine. 2002; 17:377–381. [PubMed: 12047736]

Azar AR, Murrell SA, Mast BT. Race and vascular depression risk in community-dwelling older adults. American Journal of Geriatric Psychiatry. 2005; 13:329–332. [PubMed: 15845760]

Basso MR, Bornstein RA. Estimated premorbid intelligence mediates neurobehavioral change in individuals infected with HIV across 12 months. Journal of Clinical and Experimental Neuropsychology. 2000; 22:208–218. [PubMed: 10779835]

Becker JT, Kingsley L, Mullen J, Cohen B, Martin E, Miller EN, Visscher BR. Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men. Neurology. 2009; 73:1292–1299. [PubMed: 19841381]

Becker BW, Thames AD, Woo W, Castellon SA, Hinkin CH. Longitudinal change in cognitive function and medication adherence in HIV-infected adults. AIDS and Behavior. 2011; 15:1888–1894. [PubMed: 21437726]

Benjamini Y, Hochberg Y. The adaptive control of the false discovery rate in multiple comparison problems. Journal of Education and Behavioral Statistics. 2000; 25:60–83.

Bing EG, Burnam MA, Longshore D, Fleishman JA, Sherbourne CD, London AS, Shapiro M. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Archives of General Psychiatry. 2001; 58:721–728. [PubMed: 11483137]

Bots ML, Dijk JM, Oren A, Grobbee DE. Carotid intima-media thickness, arterial stiffness and risk of cardiovascular disease: Current evidence. Journal of Hypertension. 2002; 20:2317–2325. [PubMed: 12473847]

Brickman AM, Siedlecki KL, Muraskin J, Manly JJ, Luchsinger JA, Yeung LK, Stern Y. White matter hyperintensities and cognition: Testing the reserve hypothesis. Neurobiology of Aging. 2011; 32:1588–1598. [PubMed: 19926168]

Bush TL, Miller SR, Golden AL, Hale WE. Self-report and medical record report agreement of selected medical conditions in the elderly. American Journal of Public Health. 1989; 79:1554–1556. [PubMed: 2817172]

Carey CL, Woods SP, Rippeth JD, Gonzalez R, Heaton RK, Grant I. Additive deleterious effects of methamphetamine dependence and immunosuppression on neuropsychological functioning in HIV infection. AIDS & Behavior. 2006; 10:185–190. [PubMed: 16477511]

Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: A cohort study. Lancet. 1999; 353:2093–2099. [PubMed: 10382692]

Chang L, Wang GJ, Volkow ND, Ernst T, Telang F, Logan J, Fowler JS. Decreased brain dopamine transporters are related to cognitive deficits in HIV patients with or without cocaine abuse. Neuroimage. 2008; 42:869–878. [PubMed: 18579413]

Chiesi A, Vella S, Dally LG, Pedersen C, Danner S, Johnson AM, Antunes F. Epidemiology of AIDS dementia complex in Europe: AIDS in Europe Study Group. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology. 1996; 11:39–44. [PubMed: 8528731]

Childs EA, Lyles RH, Selnes OA, Chen B, Miller EN, Cohen BA, McArthur JC. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology. 1999; 52:607–613. [PubMed: 10025796]

Cysique LA, Deutsch R, Atkinson JH, Young C, Marcotte TD, Dawson L. Incident major depression does not affect neuropsychological functioning in HIV-infected men. Journal of International Neuropsychological Society. 2007; 13:1–11.

Cysique LA, Murray JM, Dunbar M, Jeyakumar V, Brew BJ. A screening algorithm for HIV-associated neurocognitive disorders. HIV Medicine. 2010; 11:642–649. [PubMed: 20456505]

Delis, D.; Kramer, J.; Kaplan, E.; Ober, B. California Verbal Learning Test. San Antonio, TX: The Psychological Corporation; 1987.

Delis, D.; Kaplan, E.; Kramer, J.; Ober, B. California Verbal Learning Test-II. San Antonio, TX: The Psychological Corporation; 2000.

Dawes S, Suarez P, Casey CY, Cherner M, Marcotte TD, Letendre S, Heaton RK. Variable patterns of neuropsychological performance in HIV-1 infection. Journal of Clinical and Experimental Neuropsychology. 2008; 30:613–626. [PubMed: 18608689]

Durvasula RS, Myers HF, Satz P, Miller EN, Morgenstern H, Richardson MA, Forney D. HIV-1, cocaine, and neuropsychological performance in African American med. Journal of the Neuropsychological Society. 2000; 6:322–335.

Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, Grant I. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS. 2011; 25:1747–1751. [PubMed: 21750419]

Ettenhofer ML, Hinkin CH, Castellon SA, Durvasula R, Ullman J, Lam M, et al. Aging, neurocognition, and medication adherence in HIV infection. American Journal of Geriatric Psychiatry. 2009; 17:281–290. [PubMed: 19307857]

Foley J, Ettenhofer M, Wright MJ, Siddiqi I, Choi M, Thames AD. Neurocognitive functioning in HIV-1 infection: Effects of cerebrovascular risk factors and age. Clinical Neuropsychologist. 2010; 24:265–285. [PubMed: 20162495]

Foley JM, Ettenhofer ML, Kim MS, Behdin N, Castellon SA, Hinkin CH. Cognitive reserve as a protective factor in older HIV-positive patients at risk for cognitive decline. Applied Neuropsychology. 2012; 19:16–25. [PubMed: 22385375]

Goggin KJ, Kisook S, Heaton RK, Atkinson JH, Marshall S, McCutchan JA. Neuropsychological performance in HIV-infected men with major depression. Journal of the International Neuropsychological Society. 1997; 3:457–464. [PubMed: 9322405]

Gonzalez A, Barinas J, O'Cleirigh C. Substance use: Impact on adherence and HIV medical treatment. Current HIV/AIDS Report. 2011; 8:223–234.

Grant I, Olsen RA, Atkinson JH, Heaton RK, Nelson J, McCutchan JA. Depressed mood does not explain neuropsychological deficits in HIV-infected persons. Neuropsychology. 1993; 7:53–61.

Greenland P, Smith SC Jr, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: Role of traditional risk factors and noninvasive cardiovascular tests. Circulation. 2001; 104:1863–1867. [PubMed: 11591627]

Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, Telenti A. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: The Swiss HIV Cohort Study. Lancet. 2000; 356:1800–1805. [PubMed: 11117912]

Heaton, R.; Grant, I.; Matthews, C. Comprehensive norms for an expanded Halstead-Reitan battery: demographic corrections, research findings, and clinical implications. Odessa, FL: Psychological Assessment Resources; 1991.

Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, Abramson I. The HNRC 500—neuropsychology of HIV infection at different disease stages. Journal of the International Neuropsychological Society. 1995; 1:231–251. [PubMed: 9375218]

Heaton RK, Clifford DB, Franklin DR, Woods SP, Ake C, Vaida F, Grant I. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010; 75:2087–2096. [PubMed: 21135382]

Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, LeBlanc S, Grant I. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: Differences in rates, nature, and predictors. Journal of Neurovirology. 2011; 17:3–16. [PubMed: 21174240]

Hilsabeck RC, Perry W, Hassanein TI. Neuropsychological impairment in patients with chronic hepatitis C. Hepatology. 2002; 35:440–446. [PubMed: 11826421]

Hilsabeck RC, Castellon SA, Hinkin CH. Neuropsychological aspects of coinfection with HIV and hepatitis C virus. Clinical Infectious Diseases. 2005; 41:S38–S44. [PubMed: 16265612]

Hinkin CH, van Gorp WG, Satz P, Weisman JD, Thommes J, Buckingham S. Depressed mood and its relationship to neuropsychological test performance in HIV-1 seropositive individuals. Journal of Clinical and Experimental Neuropsychology. 1992; 14:289–297. [PubMed: 1572950]

Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, Stefaniak M. Medication adherence in HIV-infected adults: Effect of patient age, cognitive status, and substance abuse. AIDS. 2004; 18:S19–S25. [PubMed: 15075494]

Hinkin CH, Barclay TR, Castellon SA, Levine AJ, Durvasula RS, Marion SD, Longshore D. Drug use and medication adherence among HIV-1 infected individuals. AIDS & Behavior. 2007; 11:185–194. [PubMed: 16897351]

Hinkin CH, Castellon SA, Levine AJ, Barclay TR, Singer EJ. Neurocognition in individuals co-infected with HIV and hepatitis C. Journal of Addictive Diseases. 2008; 27:11–17. [PubMed: 18681187]

Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, Janssen RS. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet. 2002; 360:1747–1748. [PubMed: 12480430]

Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, Waters DD. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. Circulation. 2004; 109:1603–1608. [PubMed: 15023877]

Justice AC, Modur S, Tate JP, Althoff KN, Jacobson LP, Gebo K, Gange S. Predictive accuracy of the Veterans Aging Cohort Study (VACS) index for mortality with HIV infection: A North American cross cohort analysis. Journal of Acquired Immune Deficiency Syndromes. 2013; 62:149–163. [PubMed: 23187941]

Kongs, SK.; Thompson, LL.; Iverson, GL.; Heaton, RK. Wisconsin Card Sorting Test – 64 Card, Computerized Version. Odessa, FL: Psychological Assessment Resources; 2000.

Laskus T, Radkowski M, Jablonska J, Kibler K, Wilkinson J, Adair D, Rakela J. Human immunodeficiency virus facilitates infection/replication of hepatitis C virus in native human macrophages. Blood. 2004; 103:3854–3859. [PubMed: 14739225]

Lebech AM, Wiinberg N, Kristoffersen US, Hesse B, Petersen CL, Gerstoft J, Kjaer A. Carotid intima-media thickness in HIV patients treated with antiretroviral therapy. Clinical Physiology and Functional Imaging. 2007; 27:173–179. [PubMed: 17445068]

Letendre SL, Cherner M, Ellis RJ, Marquie-Beck J, Gragg B, Marcotte T, Grant I. The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance: Biological correlates of disease. AIDS. 2005; 19:S72–S78. [PubMed: 16251831]

Letendre S, Paulino AD, Rockenstein E, Adame A, Crews L, Cherner M, Masliah E. Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. Journal of Infectious Diseases. 2007; 196:361–370. [PubMed: 17597450]

Lu Y, Robinson M, Zhang FJ. Human immunodeficiency virus and hepatitis C virus co-infection: Epidemiology, natural history and the situation in China. Chinese Medical Journal. 2009; 122:93–97. [PubMed: 19187624]

Magalhaes MG, Greenberg B, Hansen H, Glick M. Comorbidities in older patients with HIV: A retrospective study. Journal of the American Dental Association. 2007; 138:1468–1475. [PubMed: 17974644]

Mangili A, Gerrior J, Tang AM, O'Leary DH, Polak JK, Schaefer EJ, Wanke CA. Risk of cardiovascular disease in a cohort of HIV-infected adults: A study using carotid intima-media thickness and coronary artery calcium score. Clinical Infectious Diseases. 2006; 43:1482–1489. [PubMed: 17083026]

Mapou RL, Law WA, Martin A, Kampen D, Salazar AM, Rundell JR. Neuropsychological performance, mood, and complaints of cognitive and motor difficulties in individuals infected with the human immunodeficiency virus. Journal of Neuropsychiatry and Clinical Neurosciences. 1993; 5:86–93. [PubMed: 8428141]

Martin EM, Novak RM, Fendrich M, Vassileva J, Gonzalez R, Grbesic S, Sworowski L. Stroop performance in drug users classified by HIV and hepatitis C virus serostatus. Journal of the International Neuropsychological Society. 2004; 10:298–300. [PubMed: 15012850]

Mason KI, Campbell A, Hawkins P, Madhere S, Johnson K, Takushi-Chinen R. Neuropsychological functioning in HIV-positive African-American women with a history of drug use. Journal of the National Medical Association. 1998; 90:665–674. [PubMed: 9828581]

Meade CS, Lowen SB, MacLean RR, Key MD, Lukas SE. fMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence. Psychiatry Research. 2011; 192:167–175. [PubMed: 21546221]

Millikin CP, Rourke SB, Halman MH, Power C. Fatigue in HIV/AIDS is associated with depression and subjective neurocognitive complaints but not neuropsychological functioning. Journal of Clinical and Experimental Neuropsychology. 2003; 25:201–215. [PubMed: 12754678]

Morgan EE, Woods SP, Delano-Wood L, Bondi MW, Grant I. HIV Neurobehavioral Research Program (HNRP) Group. Intraindividual variability in HIV infection: Evidence for greater neurocognitive dispersion in older HIV seropositive adults. Neuropsychology. 2011; 25:645–654. [PubMed: 21574712]

Morgan EE, Woods SP, Smith C, Weber E, Scott JC, Grant I. HIV Neurobehavioral Research Program (HNRP) Group. Lower cognitive reserve among individuals with syndromic HIV-associated neurocognitive disorders (HAND). AIDS and Behavior. 2012; 16:2279–2285. [PubMed: 22677976]

Morgello S, Estanislao L, Ryan E, Gerits P, Simpson D, Verma S, Sharp V. Effects of hepatic function and hepatitis C virus on the nervous system assessment of advanced-stage HIV-infected individuals. AIDS. 2005; 19:S116–S122. [PubMed: 16251806]

Perry W, Carlson MD, Barakat F, Hilsabeck RC, Schiehser DM, Matthews C, Hassanein TI. Neuropsychological test performance in patients co-infected with hepatitis C virus and HIV. AIDS. 2005; 19:S79–S84. [PubMed: 16251832]

Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, Johnson KA. Cognition, reserve, and amyloid deposition in normal aging. Annals of Neurology. 2010; 67:353–364. [PubMed: 20373347]

Rippeth JD, Heaton RK, Carey CL, Marcotte TD, Moore DJ, Gonzalez R, Grant I. Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. Journal of the International Neuropsychological Society. 2004; 10:1–14. [PubMed: 14751002]

Ryan EL, Morgello S, Isaacs K, Naseer M, Gerits P. Neuropsychiatric impact of hepatitis C on advanced HIV. Neurology. 2004; 62:957–962. [PubMed: 15037699]

Sacktor N, Skolasky R, Selnes OA, Watters M, Poff P, Shiramizu B, Valcour V. Neuropsychological test profile differences between young and old human immunodeficiency virus-positive individuals. Journal of Neurovirology. 2007; 13:203–209. [PubMed: 17613710]

Satz P. Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. Neuropsychology. 1993; 7:273–295.

Satz P, Morgenstern H, Miller EN, Selnes OA, McArthur JC, Cohen BA, Visscher B. Low education as a possible risk factor for cognitive abnormalities in HIV-1: Findings from the multicenter AIDS Cohort Study (MACS). Journal of Acquired Immune Deficiency Syndromes. 1993; 6:503–511. [PubMed: 8483113]

Selnes OA, Jacobson L, Machado AM, Becker JT, Wesch J, Miller EN, McArthur JC. Normative data for a brief neuropsychological screening battery. Multicenter AIDS Cohort Study. Perceptual Motor Skills. 1991; 73:539–550.

Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: A cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clinical Infectious Diseases. 2002; 34:831–837. [PubMed: 11833007]

Shimizu SM, Chow DC, Valcour V, Masaki K, Nakamoto B, Kallianpur KJ, Shikuma C. The impact of depressive symptoms on neuropsychological performance tests in HIV-infected individuals: A study of the Hawaii Aging with HIV Cohort. World Journal of AIDS. 2011; 1:139–145. [PubMed: 23061029]

Simpson CF, Boyd CM, Carlson MC, Griswold ME, Guralnik JM, Fried LP. Agreement between self-report of disease diagnoses and medical record validation in disabled older women: Factors that modify agreement. Journal of the American Geriatrics Society. 2004; 52:123–127. [PubMed: 14687326]

Smith, A. Symbol Digit Modalities Test (SDMT) Manual (revised). Los Angeles, CA: Western Psychological Association; 1982.

Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, Sosman JM. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. Circulation. 2001; 104:257–262. [PubMed: 11457741]

Stern RA, Silva SG, Chaisson N, Evans DL. Influence of cognitive reserve on neuropsychological functioning in asymptomatic human immunodefiency virus-1 infection. Archives of Neurology. 1996; 53:148–153. [PubMed: 8639064]

Stuss DT, Stethem LL, Pelchat G. Three tests of attention and rapid information processing: an extension. Clinical Neuropsychologist. 1988; 2:246–250.

Tate DF, Delong A, McCaffrey DE, Kertesz K, Paul RH, Conley J, Hogan JW. Recent clinical history and cognitive dysfunction for attention and executive function among human immunodeficiency virus-infected patients. Archives of Clinical Neuropsychology. 2011; 26:614–623. [PubMed: 21873325]

Thames AD, Foley JM, Panos SE, Singer EJ, Hinkin CH. Cognitive reserve masks the neurobehavioral expression of HIV neurological disorder in older adults. Neurobehavioral HIV Medicine. 2011; 3:87–93.

Thames AD, Kim MS, Becker BW, Foley JM, Hines LJ, Singer EJ, Hinkin CH. Medication and finance management among HIV-infected adults: The impact of age and cognition. Journal of Clinical and Experimental Neuropsychology. 2011; 33:200–209. [PubMed: 20694873]

Tipping B, de Villiers L, Wainwright H, Candy S, Bryer A. Stroke in patients with human immunodeficiency virus infection. Journal of Neurology, Neurosurgery, and Psychiatry. 2007; 78:1320–1324.

Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. Journal of Clinical Endocrinology and Metabolism. 2007; 92:2506–2512. [PubMed: 17456578]

Tucker JS, Orlando M, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Psychosocial mediators of antiretroviral nonadherence in HIV-positive adults with substance use and mental health problems. Health Psychology. 2004; 23:363–370. [PubMed: 15264972]

Valcour V, Yee P, Williams AE, Shiramizu B, Watters M, Selnes O, Sacktor N. Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection: The Hawaii Aging with HIV Cohort. Journal of Neurovirology. 2006; 12:387–391. [PubMed: 17065131]

Valcour V, Paul R, Neuhaus J, Shikuma C. The effects of age and HIV on neuropsychological performance. Journal of the International Neuropsychological Society. 2011; 17:190–195. [PubMed: 21144102]

von Giesen HJ, Baecker R, Hefter H, Arendt G. Depression does not influence basal ganglia-mediated psychomotor speed in HIV-1 infection. Journal of Neuropsychiatry & Clinical Neurosciences. 2001; 13:88–94. [PubMed: 11207334]

Wechsler, D. Wechsler Adult Intelligence Scale. 3rd ed.. San Antonio, TX: Psychological Corporation; 1997.

Weiss JJ, Osorio G, Ryan E, Marcus SM, Fishbein DA. Prevalence and patient awareness of medical comorbidities in an urban AIDS clinic. AIDS Patient Care and STDs. 2010; 24:39–48. [PubMed: 20095901]

Wetzel, L.; Boll, T. Short Category Test, booklet format. Los Angeles, CA: Western Psychological Services; 1987.

Wright EJ, Grund B, Robertson K, Brew BJ, Roediger M, Bain MP, Price RW. Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. Neurology. 2010; 75:864–873. [PubMed: 20702792]

Table 1

Neuropsychological Tests by Domain

Domain/Test	Battery	Normative Source
Speed of Information Processing		
Trail making test Part A	A, B	Heaton et al., 1991
Symbol digit modalities test	A	Smith A., 1982
Digit symbol coding	B	Wechsler, D., 1997
Learning and Memory		
CVLT trials 1–5	A	Delis et al., 1987
CVLT-II trials 1–5	B	Delis et al., 2000
CVLT short delay free recall	A	Delis et al., 1987
CVLT-II short delay free recall	B	Delis et al., 2000
CVLT long delay free recall	A	Delis et al., 1987
CVLT-II long delay free recall	B	Delis et al., 2000
Verbal Fluency		
COWAT letter fluency	A, B	Selnes et al., 1991
COWAT category fluency	A, B	Selnes et al., 1991
Attention and Working Memory		
Paced auditory serial addition test	A, B	Stuss et al., 1988
Executive Functioning		
Trail making test Part B	A, B	Heaton et al., 1991
Stroop color-word test – interference	A, B	Selnes et al., 1991
Short category test	A	Wetzel & Boll, 1987
Wisconsin card sorting test – 64 card version	B	Kongs et al., 2000
Motor Functioning		
Grooved pegboard dominant hand	A, B	Heaton et al., 1991
Grooved pegboard nondominant hand	A, B	Heaton et al., 1991

Note: CVLT - California Verbal Learning Test; CVLT-II – California Verbal Learning Test – Second Edition; COWAT – Controlled Oral Word Association Test

Table 2

Demographic Characteristics of Younger and Older Individuals

	Age Group		
	Young (< 50 years) *n* = 296	**Old (> 50 years) *n* = 70**	***p***
Age	40.44 (range 18–49)	53.49 (range 50–69)	<.01
Education	12.97 (2.236)	13.44 (2.268)	
AMNART	103.72 (9.70)	105.07 (11.19)	
Ethnicity (%)			
Caucasian	15.2	20.0	
African American	66.9	64.3	
Hispanic	12.2	10.0	
Asian	2.0	1.4	
Other	3.7	4.3	
Sex (%)			
Male	81.1	80.0	
Female	18.9	20.0	
Risk factors			
Cognitive reserve (% low)	50.5	47.1	
Cognitive reserve (mean)	103.72 (9.702)	105.07 (11.193)	
High HIV disease severity (%)	62.6	50.0	<.10
Nadir CD4 (median IQR)	154 (32–266)	203 (51–393)	<.05
Recent CD4 (median IQR)	350 (207–557)	464 (293–645)	
Undetectable viral load (%)	35.7	47.6	
AIDS diagnosis (%)	68.0	50.0	<.05
Vascular (%)	25.3	42.6	<.01
Hepatitis C (%)	15.7	17.9	
Current stimulant use, abuse and/or dependence (%)	30.0	29.8	
Weighted risk (mean)	3.35 (2.55)	2.94 (2.70)	

Table 3

Split-half Regression Results for Global Cognition and Risk Factors

	Split-half 1	95% Confidence Interval		Split-half 2	95% Confidence Interval	
	B	**Lower**	**Upper**	***B***	**Lower**	**Upper**
Cognitive Reserve	−4.58	−6.44	−2.72	−4.41	−6.19	−2.64
Stimulants	−0.26	−2.29	1.78	−0.68	−2.64	1.28
Disease Severity	−1.96	−3.89	−.04	−0.56	−2.39	1.27
Hepatitis C	0.996	−1.46	3.46	1.64	−0.80	4.08
Vascular	−0.81	−2.83	1.20	−0.49	−2.48	1.51

Table 4

Regression Results for Cognitive Domains and Risk Severity Score – by Age Groups

	Young (< 50 years)				Old (> 50 years)			
	F	***R*²**	***B***	***p***	***F***	***R*²**	***B***	***p***
Information Processing Speed	14.48	.05	−.22	<.001	3.46	.05	−.22	.07
Learning and Memory	35.40	.11	−.33	<.001	11.41	.14	−.38	.001
Attention & Working Memory	45.66	.13	−.37	<.001	2.89	.04	−.20	.09
Executive Functioning	49.73	.15	−.38	<.001	4.52	.06	−.25	.04
Verbal Fluency	19.99	.06	−.25	<.001	19.92	.23	−.48	<.001
Motor Functioning	14.98	.05	−.22	<.001	4.30	.05	−.24	.04

Table 5

Regression Results for Individual Risk Factors and Cognitive Domains – by Age Groups

	Young (< 50 years)		Old (> 50 years)	
	B	***p***	***B***	***p***
Information Processing Speed				
Cognitive Reserve	−0.18	.004	−0.16	.34
Stimulants	0.10	.09	−0.17	.30
Disease Severity	−0.08	.21	−0.18	.25
Hepatitis C	0.08	.18	−0.12	.46
Vascular	−0.15	.01	0.08	.65
Learning and Memory				
Cognitive Reserve	−0.33	<.001	−0.19	.25
Stimulants	−0.04	.50	0.02	.90
Disease Severity	−0.09	.12	−0.30	.06
Hepatitis C	0.10	.09	−0.12	.44
Vascular	0.11	.06	0.19	.24
Attention and Working Memory				
Cognitive Reserve	−0.352	<.001	−0.39	.02
Stimulants	−0.046	.44	0.26	.11
Disease Severity	−0.058	.34	0.13	.40
Hepatitis C	0.045	.46	−0.09	.54
Vascular	0.020	.74	−0.17	.27
Executive Functioning				
Cognitive Reserve	−0.36	<.001	−0.22	.21
Stimulants	−0.01	.87	0.03	.87
Disease Severity	−0.09	.14	−0.02	.90
Hepatitis C	0.09	.15	0.002	.99
Vascular	−0.08	.17	0.04	.79
Verbal Fluency				
Cognitive Reserve	−0.27	<.001	−0.49	.002
Stimulants	−0.004	.95	0.06	.69
Disease Severity	−0.02	.77	0.01	.97
Hepatitis C	−0.004	.94	0.08	.60
Vascular	0.05	.42	−0.19	.19
Motor Functioning				
Cognitive Reserve	−0.20	.002	−0.15	.38
Stimulants	−0.03	.68	−0.07	.69
Disease Severity	−0.02	.73	−0.13	.42
Hepatitis C	−0.01	.86	−0.10	.56
Vascular	−0.10	.13	−0.09	.60