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Impact of human immunodeficiency virus on neurocognition and risky behaviors in young adults

Laurie M. Baker[1], **Robert H. Paul**[1], **Jodi Heaps**[1], **Elizabeth Westerhaus**[2], **Jee Yoon Chang**[2], **Samuel Williams**[2], **Matthew R. Brier**[2], **Katie Plax**[3], and **Beau M. Ances**[2,4]

[1]Department of Psychology, University of Missouri- Saint Louis, One University Blvd, Stadler 326, St.Louis, MO 62121

[2]Department of Neurology,Washington University in Saint Louis, Campus Box 8111, 660 S. Euclid, St. Louis, MO 63110

[3]Department of Pediatrics, Washington University in Saint Louis, One Childrens Place, St. Louis, MO 63110

[4]Department of Radiology, Washington University in Saint Louis, 510 S Kingshighway Blvd, St Louis, MO 63110

Abstract

Previous studies have identified cognitive impairments due to human immunodeficiency virus (HIV) in adults. However, few studies have examined the impact of HIV on cognition in young adults (18-24 years old). Yet, this group is one of the largest populations of individuals with new HIV infection. Young adulthood is also an important developmental window as the brain has not fully matured and individuals are prone to engage in risky behavior. The purpose of the present study was to examine the impact of HIV on neurocognition and risky behaviors. We hypothesized that HIV+ young adults (n=23) would exhibit greater cognitive impairment and risky behaviors compared to seronegative controls (n=21). In addition, we predicted that self-reported risky behavior as assessed by the Risk Assessment Battery (RAB) would covary with cognitive performances. Results revealed poorer executive function in HIV+ young adults compared to seronegative controls. HIV+ young adults also exhibited significantly greater risk scores on the RAB ($p < 0.01$) compared to HIV- young adults. However, there were no relationships between risky behavior and cognitive performance. Overall, our results suggest that HIV is associated with poorer cognition and increased risky behaviors in young adults.

Keywords

HIV; Cognition; Risky Behavior; Neuropsychology; Executive Function

Correponding Author: Beau Ances, MD, PhD, Washington Unversity in Saint Louis School of Medicine, Department of Neurology, 660 South Euclid Avenue, Campus Box 8111, St. Louis, MO 63110, Phone: 314-747-8423; ancesb@neuro.wustl.edu.

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1. Introduction

HIV is associated with neuropsychological impairments known collectively as HIV-associated neurocognitive disorders (HAND). Individuals with HAND often have difficulties in learning and recall, psychomotor/processing speed, and executive function (reviewed in Hardy and Hinkin 2002; Reger et al. 2002), which may reflect abnormalities in fronto-striatal-thalamo-cortical brain circuits (Jernigan et al. 1993; Stout et al. 1998). Observed neurocognitive deficits have been associated with viral and host factors including CD4 nadir, viral load (VL), and psychiatric illness (Ellis et al, 1997; McArthur et al, 1997; Robertson et al. 1999; Childs et al. 1999; Cartellon, et al. 1998; Valcour et al. 2006; Ellis et al. 2011).

According to the Center for Disease Control (CDC), adolescents and young adults experience the highest risk for HIV infection of any age group, accounting for 39% of new infections (CDC, 2011), and represent a unique, yet diverse population requiring specialized medical and psychosocial HIV care. Research has revealed that horizontally infected (transmission via drugs or sexual behavior) young adults are prone to medication non-adherence, high-risk sexual behavior, psychosocial stressors, and comorbid psychiatric disorders, which may further exacerbate cognitive dysfunction (Nichols et al. 2013). However, most previous studies of HAND have focused on either HIV+ adults (> 25 years old) or perinatally infected children. Until recently, little research has been devoted to examining the neurocognitive profile of HIV+ young adults (age 18-24).

Results of a previous study revealed that perinatally infected HIV+ individuals between ages 13 and 25 performed significantly more poorly on tests of attention and processing speed than age matched HIV- controls (Nagarajan et al. 2012). More recently, Nichols and colleagues demonstrated a high prevalence of HAND within a relatively large sample of horizontally infected HIV+ young adults between the ages of 18 and 24 naïve to treatment. In particular, the young adults were impaired on tests of executive function, motor function and verbal memory. However, these individuals had less impairment on tests of global intellectual functioning as well as attention and working memory compared to findings from prior studies of perinatally infected young adults in the same age group. Results of this study also revealed a significant association between neuropsychological performance and measures of HIV disease severity (CD4 cell count, viral load). A limitation of this study was that HIV- controls were not included (Nichols et al. 2013). No study to date has examined cognition in HIV+ young adults between the ages of 18-24 on cART in comparison to a group of seronegative individuals.

Further understanding of the relationship between neurocognition and engagement in risky behaviors is important in HIV+ individuals between the ages of 18-24 especially given that young adulthood is a period of significant brain development. Synaptic pruning and myelination occur into the early twenties, suggesting that young adults often lack optimal speed of processing (Steinberg 2007) and efficient decision making capabilities (Blakemore and Choudhury 2006). This may lead these individuals to make choices based on current rewards without considering long-term consequences (reviewed in Bechara, 2003). Adolescence and young adulthood are developmental periods characterized by acquisition of

essential life skills and increased experimentation and risk taking. As such, acquisition of HIV during young adulthood could potentially lead to significant brain dysfunction and an associated increase in risky behavior.

The present study examined the impact of HIV serostatus on cognition and risky behaviors in young adults (18-24 years old). We examined neuropsychological performance in three cognitive domains, including; executive function, psychomotor/processing speed, and memory between HIV+ (n=23) and HIV- (n=21) young adults. Furthermore, we examined risky behaviors using the Risk Assessment Battery (RAB; Metzger et al., 2001). We hypothesized that HIV+ young adults would exhibit greater cognitive deficits and risky behaviors than HIV- controls. We also hypothesized that individuals self-reporting greater engagement in risky behavior would perform more poorly on neuropsychological tests.

2. Methods

2.1 Participants

Table 1 provides a summary of demographic information for the 23 HIV+ and 21 HIV- young adults (18-24 years old) who participated in this study. Participants were from similar socioeconomic backgrounds. Participants were recruited from the Washington University School of Medicine (WUSM) Infectious Disease Clinic, the WUSM AIDS Clinical Trial Unit (ACTU), and the Supporting Positive Opportunities with Teens (SPOT). Exclusionary criteria for all participants included: history of claustrophobia, loss of consciousness > 30 minutes, seizures, developmental delays, contradictions for magnetic resonance imaging (MRI) scanning (metal implants in head, pacemakers, claustrophobia, etc.), any schizophrenic diagnosis or other psychiatric conditions associated with cognitive dysfunction, a Beck Depression Inventory-II (BDI-II) score > 29, fewer than 8 years of education, and inability to provide written informed consent. All participants provided signed informed consent. This study was approved by the Washington University Institutional Review Board.

HIV+ individuals were infected for ≥3 months. Plasma HIV RNA levels were available for all HIV+ participants. Most HIV+ young adults were on a stable cART regimen (15/23) with 15 (65%) having undetectable plasma HIV VL. The remaining 8 HIV+ participants had detectable plasma HIV VL (mean log HIV VL= 2.9). See Table 2. All participants received a neuromedical examination by a neurologist.

2.2. Neuropsychological Evaluation

The assessment battery included neurocognitive measures with previously demonstrated sensitivity to HAND (Antinori et al. 2007). Standardized scores were computed using published normative standards, with adjustments for age and, where available, ethnicity, education, and/or gender (Gladsjo et al. 1999; De Santi et al. 2008; Norman et al. 2011; Ruff & Parker 1993; Wechsler 1997; Woods et al. 2005). All normative scores are represented as z-scores.

The battery assessed four cognitive domains:

1. Psychomotor/Processing Speed: Trail Making Test A (TMT-A; Reitan & Davison 1974); Grooved Pegboard Test dominant and nondominant hand (Klove 1963), and Digit-Symbol Coding (Wechsler 1997).
2. Executive Functioning: Trail Making Test B (TMT-B; Reitan & Davison 1974); Verbal fluency (FAS words; Borkowski et al. 1967); WAIS-III Letter-Number Sequencing (LNS; Wechsler, 1997); Verb Fluency (Piatt et al. 1999)
3. Memory: Hopkins Verbal Learning Test – Revised (HVLT-R), immediate recall on trials 1–3; HVLT-R delayed recall (Benedict et al. 1998; Brandt and Benedict)

2.3 Depression and Risky Behavior

Participants completed questionnaires regarding depression (Beck Depression Inventory II; BDI-II; Beck 1996) and engagement in risky behaviors (RAB; Metzger et al., 2001). See Table 1. The BDI-II is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV; 1994). Items each correspond to a symptom of depression and the items are summed to generate a single total score. Total score of 0-13 is considered minimal range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe (Beck 1996).

The RAB is a self-administered questionnaire designed for substance-abusing populations to assess HIV risk behavior in the past 6 months (Metzger et al., 2001). It is comprised of two subscales: total sex risk (18 items, e.g., sexual orientation, number of sex partners; frequency of unprotected intercourse) and total drug risk (22 items, e.g., number of people with whom they shared needles). Total sex and drug risk subscales are summed for calculating total risk score (range 0–40). In the present study, we used a modified RAB and scoring cutoffs were used based on the original RAB. However, we added lifetime questions and utilized the higher score of the two time periods (6 months and lifetime) to calculate our results (i.e. if a subject had injected drugs 2 times in the past six months but 4 or more in their lifetime we used the 4-or-more response to calculate the total drug RAB score). Alcohol and marijuana use scores were also derived from the RAB questionnaire. Scores were calculated on a scale of 0-3 (0=never; 1=a few times each month; 2= a few times each week; 3= everyday) based on use in the last month.

2.4 Statistical analysis

Differences in age, sex, education, ethnicity, alcohol use, marijuana use, and BDI-II scores were examined between the HIV+ and HIV- controls using independent sample t-tests and chi-squared analyses. Cognitive performance between groups was measured utilizing multivariate analysis of variance (MANOVA). HIV serostatus served as the independent variable and standardized z scores in each separate cognitive domain served as the dependent variables in each analysis. Univariate analysis of variance (ANOVA) was used to examine the difference in total RAB scores between groups. Partial correlational analyses were computed between RAB scores and performance on each cognitive test, controlling for demographic and psychosocial variables. Lastly, Pearson's correlational analyses were

computed to determine the relationship between viral factors and RAB score. Bonferroni correction was used to adjust for multiple comparisons.

3. Results

Subject characteristics are included in Table 1. The MANOVA models examining the impact of serostatus on neurocognitive performance revealed significant differences between groups, with HIV+ young adults exhibiting greater executive dysfunction (Wilks' $\lambda = .54$, $F(4, 39) = 8.21$ $p < .001$) than seronegative controls. Specifically, HIV+ individuals performed worse on the verb fluency task ($p < .001$) after Bonferroni correction compared to HIV- individuals. Results did not reveal significant differences in any other cognitive domain. See Table 3 (p-values were calculated based on the F and df of the ANOVA). Furthermore, there were no significant correlations between laboratory measures (e.g. CD4, CD4 nadir, or VL) and neuropsychological performance in the HIV+ group.

Independent sample t-tests and chi-squared analyses revealed significant differences in age, gender, and ethnicity between the HIV+ and HIV- groups; therefore these variables were utilized as covariates in the analyses. ANCOVA revealed that HIV+ young adults reported higher total RAB scores than HIV- young adults ($F(1,39)= 17.29$, $p < .01$). HIV+ young adults also had significantly higher scores on the sex risk component of the RAB ($F(1,39)=17.18$, $p < .01$). No differences were identified in the total drug score of the RAB between HIV+ and HIV- young adults, as only two HIV+ participants reported any prior intravenous (IV) drug use. There were no significant correlations between RAB scores and cognitive function (See Table 4). Furthermore, correlation analyses did not reveal any significant relationships between laboratory measures and RAB score in the HIV+ group.

4. Discussion

The present study utilized neuropsychological assessment and a self-report risk questionnaire to examine the impact of HIV serostatus on cognition and risky behavior in young adults between the ages of 18 and 24. We also aimed to determine the relationship between engagement in risky behavior and cognition among young adults. Our results revealed that HIV+ young adults performed significantly worse than HIV- controls on a measure of executive function. In our study sample viral factors did not influence neuropsychological performance. Consistent with our hypothesis, results also showed that HIV+ young adults reported engagement in more risky behaviors than HIV- controls, a finding that is not surprising given the method by which this sample was infected. Viral factors did not influence RAB scores in this cohort. Lastly, increased risky behavior was not associated with cognitive dysfunction in this cohort.

To our knowledge only one previous study has examined cognitive performance in HIV+ horizontally infected young adults aged 18-24 (Nichols et al. 2013). Specifically, Nichols and colleagues demonstrated impairment in executive function, motor function, and verbal memory in horizontally infected individuals between the ages of 18-24 (Nichols et al. 2013). Similar to the findings from Nichols et al. 2013, results of the present study revealed impairment in executive function. However, our results did not indicate motor dysfunction or verbal memory impairment in HIV+ individuals compared to HIV- controls. Lastly,

previous research demonstrated an inverse relationship between current CD4 and global cognitive functioning (Nichols et al. 2013), however, these relationships were not evident in our cohort. Differences in the results may be due to the fact that the majority of individuals in the present study were on cART while individuals in the previous study of horizontally infected young adults (Nichols et al. 2013) were cART naïve.

In the present study impairment was observed in the executive function domain on one test. Executive functions include complex problem solving abilities, self- directed independent behaviors, and set shifting functions (Mega and Cummings 1994). Executive functions are often assessed by measures of abstraction, problem solving, and reasoning. Intact executive functions are most notably dependent on the frontal cortex (i.e., dorsolateral prefrontal cortex), posterior parietal cortex, and the basal ganglia (Stuss & Levine 2002). In young adulthood, the brain is still undergoing significant development, particularly in the frontal lobe. Although the brain has reached its full adult size by about 5 to 10 years of age (Giedd et al., 1996; Reiss et al. 1996), more subtle developments occur over a longer period of time (Jernigan et al., 1991; Reiss et al., 1996; Giedd et al., 1999; Sowell et al., 2001). A prior MRI study revealed significant decreases in gray matter density in individuals between 23 and 30 years old compared to individuals between 12 and 16, suggesting that increased myelination and synaptic pruning occurs between these periods (Sowell et al., 2001). Functional neuroimaging also supports the concept of continued prefrontal development during this time period, as young adults tend to show different patterns of activation on tasks that recruit the dorsolateral prefrontal cortex (Bunge et al. 2002; Casey et al. 2000; Kwon et al. 2002). Therefore, our finding that behaviorally infected HIV+ young adults exhibit significant executive dysfunction indicates an increased need for evaluation of cognitive functioning and studies of mechanisms underlying observed impairments. Future studies should incorporate structural and functional neuroimaging to examine these mechanisms. This research could potentially lead to the development of interventions to lessen the impact of HIV on executive function in horizontally infected young adults and may be necessary to prevent negative functional outcomes, such as medication non-adherence.

Specific deficits were observed on the verb fluency task within the executive function domain in HIV+ young adults. HIV-associated verb fluency deficits reflect executive dysfunction of search and retrieval from lexico-semantic memory stores, perhaps indicative of frontostriatal dysfunction (Woods et al. 2004). Previous research has shown that HIV+ individuals aged 18-66 generate significantly fewer verbs relative to HIV- individuals on the verb fluency task (Woods et al. 2005). Consistent with the findings from our study, the results of a prior meta-analysis revealed that HIV infection is associated with significant deficits in verb fluency (Iudicello et al., 2008). Furthermore, Woods and colleagues demonstrated that HIV-associated verb fluency deficits and executive impairment in general is associated with elevated S100beta, indicative of astrocyte activation (Woods et al. 2010). These results support the role of frontal lobe involvement in HIV and indicate a probable neurobiological dissociation in verb generation. Thus, we expected our young adult population to show similar, or more severe, HIV-related deficits on tests of verb fluency as previously observed in adults, due to the ongoing development of the frontal system (Bunge et al. 2002; Casey et al. 2000; Kwon et al. 2002).

Verb (action) generation deficits may also have a negative impact on everyday functioning. Specifically, verb fluency is strongly related to executive dysfunction and sensitive to declines in instrumental activities of daily living (Heaton et al. 2010, Woods et al. 2006). It has been hypothesized that verb fluency impairment reflects inefficiencies in engaging motor representations during action retrieval, which may disrupt the generation and organization of action-based programs required for effective engagement activities of daily living (Woods et al. 2009). These findings suggest that verb fluency may provide ecological validity in the identification of HAND.

It is well documented that young adults are more likely than adults to engage in risky behavior. For example, young adults are more likely than adults to drive recklessly, to drive while intoxicated, to use varied illicit substances, and engage in unprotected sex (Arnett 1999). Given that the majority of HIV+ young adults become infected with the virus due to engagement in risky behaviors, there has been particular interest in the examination of these behaviors. Results of the present study indicate that HIV+ young adults report more engagement in risky behavior than HIV- controls. Furthermore, risky behavior was not significantly associated with viral factors, indicating that HIV+ young adults engage in greater amounts of risky behavior than HIV- young adults regardless of current CD4, CD4 nadir, and current VL. Therefore, understanding the mechanisms behind these risky behaviors is essential in order to provide appropriate interventions.

Conclusions regarding the relationship between HIV serostatus, cognitive function, and engagement in risky behavior should be tempered by several limitations of the current study. The assessment of risky behavior was measured utilizing a retrospective, self-report questionnaire. However, the internal consistency of the RAB is strong, with reliabilities of 0.42-0.82 and test retest reliabilities of 0.69-0.88 (Metzger et al. 2001). Another potential limitation to this study was the restricted sample size. While our sample was well matched, a larger sample size is warranted to improve reliability. It is possible that a larger sample size would provide us with the ability to detect significant relationships between HIV serostatus and dysfunction in the other cognitive domains and between risky behavior and cognitive function. Lastly, studies have revealed a relationship between neuropsychological performance, VL, and CD4 nadir. However, no relationships were observed between viral factors and neuropsychological performance in the present study. This may be due to the fact that the young adults in our cohort had relatively high CD4 nadir and an undetectable VL. Future studies examining the relationships between viral factors and neuropsychological performance in a broader, longitudinally followed sample of HIV+ young adults are warranted to provide a more comprehensive model of the cognitive profile in this age group.

Taken together, our findings demonstrate that HIV+ young adults between the ages of 18-24 have poorer performance on a test of executive function than HIV- young adults. Additionally, young adults with HIV reported greater engagement in risky behavior, yet there was no relationship between neurocognitive and risky behavior scores. Further research investigating the contribution of other host factors, such as, genetics, psychological disorders, trauma, substance use, may be useful to clarify the mechanisms underlying neurocognitive impairments and risky behavior in HIV+ young adults.

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Table 1

Subject Characteristics

	HIV+ (n=23)	HIV- (n=21)	p value
Mean Age (SD)	22.30 (1.55)	20.29 (2.1)	<.01**
Mean Education (SD)	13.04 (1.19)	13.42 (1.78)	0.39
Sex (% Male)	76%	33%	<.01**
Ethnicity (C/AA/A)	2/21/0	7/12/2	<.05*
Beck Depression Inventory–II Score	12.22 (11.70)	6.85 (8.64)	0.30
Total Risk Assessment Battery Score	5.96 (2.51)	3.24 (2.61)	<.01**
Total Sex Risk Assessment Battery Score	5.91(2.54)	3.24 (2.61)	<.01**
Total Drug Risk Assessment Battery Score	.04 (.21)	0 (0)	0.35
Marijuana Use	.91 (1.16)	.33 (.66)	.05
Alcohol Use	1.04 (.82)	.76 (.70)	.23

[a] Education based on mean number of years completed

[b] C= Caucasian, AA= African American, A= Asian

* Statistically significant p < .05

** Statistically significant p < .01

Table 2

Clinical HIV Characteristics

	Count (%)
Time Since HIV diagnosis, months	
<6	0 (0)
6-11	2 (9)
12-23	6 (26)
>24	15(65)
Current CD4 count, cells/mm3 (n=22)	
Mean (SD)	562.41 (265.04)
Min/Max	93/1137
Range	1044
Current CD4 count, cells/mm3 (n=22)	
< 200	3 (14)
200-349	1(4)
350-499	5 (23)
> 500	13 (59)
Unknown	1
CD4 nadir count, cells/mm3 (n=20)	
Mean (SD)	316.3 (171.5)
Min/Max	22/660
Range	638
CD4 nadir count, cells/mm3 (n=20)	
< 200	4 (20)
200-349	8 (40)
350-499	5 (25)
> 500	3 (15)
Unknown	3
Viral Load (HIV-1, RNA copies/mL, plasma (n=23)	
< 400	18 (78)
400-10,000	3 (13)
10,001-100,000	2 (9)
Unknown	0

Table 3

Neuropsychological Performance

	HIV+(n=23) Mean (SD)	% ≥ 1σ below mean	% ≥ 2σ below mean	HIV- (n=21) Mean (SD)	% ≥ 1σ below mean	% ≥ 2σ below mean	p-value	ηp2
Executive Functioning								
FAS	–.29 (.93)	26.1%	8.7%	–.22 (.94)	19.1%	4.8%	0.79	.00
Trail Making Test B	–.06 (1.30)	21.7%	13.0%	–.31 (1.41)	23.8%	14.3%	0.54	.01
Letter Number Sequencing	–.66 (1.00)	26.1%	17.4%	–.31 (1.05)	28.6%	14.3%	0.26	.03
Verb Fluency	–.99 (.87)	52.3%	8.7%	.70 (1.3)	4.8%	4.8%	<.001*	.35
Psychomotor/Processing Speed								
Grooved Pegboard- D	–.99 (.84)	56.5%	17.4%	–.31 (.98)	28.6%	9.5%	<.05	.13
Grooved Pegboard- ND	–.53 (.96)	43.5%	8.7%	–.55 (.87)	9.5%	0%	0.93	.00
Digit Symbol	–.21 (.81)	17.4%	8.7%	.16 (1.29)	23.8%	0%	0.24	.03
Trail Making Test A	–.21 (1.39)	21.7%	17.4%	.01 (1.41)	23.8%	9.5%	0.60	.01
Memory								
HVLT-R Immediate Recall	–1.02 (.92)	52.2%	17.4%	–1.06 (.89)	61.9%	9.5%	0.90	.00
HVLT-R Delayed Recall	–.88 (.97)	52.1%	9.0%	–1.06 (1.16)	71.4%	4.8%	0.59	.01

p-values extracted from ANOVA

HVLT-R- Hopkins Verbal Learning Test- Revised; Grooved Pegboard D=Grooved Pegboard Dominant; Grooved Pegboard-ND= Grooved Pegboard Nondominant

*Statistically significant at Bonferroni corrected threshold (p =.01)

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Table 4
Correlations between RAB and Neuropsychological Performance

	RAB Total Score	RAB Sex Score	RAB Drug Score
Executive Functioning			
FAS	.15	.14	.18
Trail Making Test B	.06	–.06	.09
Letter Number Sequencing	–.20	–.21	.12
Verb Fluency	–.35	–.35	.02
Psychomotor/Processing Speed			
Grooved Pegboard- D	–.17	–.18	.07
Grooved Pegboard-ND	.04	–.03	.08
Digit Symbol	–.38	–.38	.00
Trail Making Test A	–.32	–.32	.19
Memory			
HVLT-R Immediate Recall	–.05	–.05	.03
HVLT-R Delayed Recall	.00	.00	.02

RAB- Risky Assesment Battery; HVLT-R- Hopkins Verbal Learning Test- Revised; Grooved Pegboard D=Grooved Pegboard Dominant; Grooved Pegboard-ND= Grooved Pegboard Nondominant

*Statistically Significant ($p < .05$)