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Neurocognitive Functioning in Antiretroviral Therapy–Naïve Youth With Behaviorally Acquired Human Immunodeficiency Virus

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A B S T R A C T

Purpose: Youth living with human immunodeficiency virus (HIV) account for over one third of new HIV infections and are at high risk of adverse psychosocial, everyday living, and health outcomes. Human immunodeficiency virus–associated neurocognitive disorders (HAND) are known to affect health outcomes of HIV-infected adults even in the era of combination antiretroviral therapy. Thus, the current study aimed to characterize the prevalence and clinical correlates of HAND in youth living with HIV. Here, we report baseline neurocognitive data for behaviorally HIV-infected youth enrolled in a prospective study evaluating strategies of antiretroviral treatment initiation and use.
Methods: A total of 220 participants, age 18–24 years, who were naive to treatment (except for prevention of mother-to-child HIV transmission; n = 3), completed a comprehensive neurocognitive, substance use, and behavioral health assessment battery.
Results: Sixty-seven percent of youth met criteria for HAND (96.4% were asymptomatic and 3.5% were syndromic); deficits in episodic memory and fine-motor skills emerged as the most commonly affected ability areas. Multivariable models showed that lower CD4 count, longer time since HIV diagnosis, and high-risk alcohol use were uniquely associated with neurocognitive deficits.
Conclusions: Over two thirds of youth with behaviorally acquired HIV evidence neurocognitive deficits, which have modest associations with more advanced HIV disease as well as other factors. Research is needed to determine the impact of such neuropsychiatric morbidity on mental health and HIV disease treatment outcomes (e.g., nonadherence) and transition to independent living responsibilities in HIV-infected youth, as well as its long-term trajectory and possible responsiveness to cognitive rehabilitation and pharmacotherapy.

IMPLICATIONS AND CONTRIBUTION

Youth with behaviorally acquired human immunodeficiency virus demonstrate high rates of cognitive impairment. Impairment in certain domains is related to human immunodeficiency virus disease severity and to alcohol use. This impairment could have implications for functional and behavioral outcomes, and raises concerns about subtle central nervous system changes early in infection.

Adolescents and young adults experience the highest risk for human immunodeficiency virus (HIV) infection of any age group, accounting for 39% of new infections [1]. This population also presents unique clinical and public health challenges because of higher rates of poor medication adherence [2] and sexual and

[1] Dr. Garvie's role on the project was initiated while on faculty at St. Jude Children's Research Hospital. At the time of manuscript submission, Dr. Garvie's continued participation was as a contracted consultant.

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substance risk behaviors [3]. Interventions and changes in treatment recommendations for behaviorally infected youth living with HIV (YLWH), such as initiation of combination antiretroviral therapy (cART) at the time of diagnosis, have been implemented in the absence of knowledge regarding their neurocognitive functioning. Cognitive and functional impairments, whether HIV-related or due to other risk factors, may have implications for intervention development and long-term disease and treatment monitoring specifically tailored for adolescents.

The potential public relevance of neurocognitive impairment among YLWH is supported by over 2 decades of clinical research in adults [4] and children with perinatally acquired HIV (pHIV) or HIV acquired through blood products used to treat hemophilia [5,6]. Approximately 30%–50% of HIV-infected adults demonstrate HIV-associated neurocognitive disorders (HAND); in fact, the prevalence of mild-to-moderate neurocognitive deficits has increased in the cART era among persons with less advanced HIV disease [7]. Consistent with its preferential effects on the fronto-striato-thalamo-cortical systems, HIV infection is marked by deficits in executive functions (e.g., planning), memory, and psychomotor speed, with relative sparing of basic language and visuoconstruction skills [4]. Human immunodeficiency virus–associated neurocognitive disorders (HAND) have been linked to a variety of clinical factors, including alcohol and substance abuse [8,9], lower nadir CD4 counts [10], and lower cognitive reserve [11]. Human immunodeficiency virus–associated neurocognitive impairment increases risk of dependence in activities of daily living (ADL), including cART nonadherence [12]. Children and youth with pHIV show a different neurocognitive profile, with impairments in language and global functioning in addition to those seen in adults [6]. Those with HIV acquired postnatally through hemophilia treatment showed declines over time in nonverbal skills, memory, language, and academics that correlated with immunological changes [5].

The authors are unaware of any large-scale neurocognitive studies of adolescents and emerging adults with behaviorally acquired HIV to date. One study of behaviorally infected YLWH that included measures of cognition [13] found impairments in word knowledge and delayed development of abstract reasoning. The potential implications of cognitive impairments in YLWH differ from those in adults, which emphasizes the need for studies targeting this age group. Adolescence and young adulthood are developmental periods characterized by acquisition of skills essential for successful transition to independent adulthood occurring simultaneously with increased experimentation and risk taking. Both of these occur in the context of ongoing brain development, including frontostriatal systems vulnerable to HIV [14]. Furthermore, youth may differ from adults in their profile of substance use and psychiatric and other comorbidities. Here, we report cross-sectional data regarding neurocognitive functioning in treatment naive youth with behaviorally acquired HIV and exploratory analyses of its relationship to HIV disease severity, demographics, substance use, and psychiatric comorbidity.

Methods

Participants

Youth aged 18–24 years with behaviorally acquired HIV infection were enrolled from among clinical patients observed at 15 Adolescent Medicine Trials Network for HIV/Acquired Immunodeficiency Disease (AIDS) Interventions and 12 International Maternal Pediatric Adolescent AIDS Clinical Trials sites across the United States and Puerto Rico into a prospective cohort study evaluating neurocognitive functioning in participants with different illness severity and indications for treatment. At the time this study was initiated, the United States Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents* (*Guidelines*) recommended starting cART in patients whose CD4-positive T-cells were <350 or HIV RNA >100,000 copies/mL plasma, in the absence of clinical or psychosocial contraindications. Participants enrolled into four groups: two groups not yet meeting *Guidelines*, half of whom were randomized to initiate early ART within a treatment strategy study; and two groups who met *Guidelines* and either started treatment or did not because of patient preference or provider concerns about adherence. For the present analysis of baseline neurocognitive functioning, all groups were combined and CD4-positive count was treated as a continuous variable. All participants were treatment naive except for <6 months ART to prevent mother-to-child HIV transmission ($n = 3$). Self-reported English or Spanish fluency was required. Exclusion criteria included prior ART experience other than preventing mother-to-child HIV transmission, current pregnancy, active substance use or dependence judged likely to interfere with study requirements, psychosis, or significant non–HIV-related cognitive or motor impairment (e.g., cerebral palsy, severe traumatic brain injury; milder comorbidities including learning disabilities and attention-deficit/hyperactivity disorder were allowed). The study was approved by the institutional review board at all participating institutions; participants provided written informed consent in accordance with local institutional review board requirements.

Study evaluations

Neurocognitive functioning. The assessment battery included neurocognitive measures with previously demonstrated sensitivity to HAND in adults [15]. Domains included memory (Hopkins Verbal Learning Test–Revised [16,17]; Brief Visuospatial Memory Test–Revised [17,18]), motor skills (grooved pegboard [19], timed gait [20]), attention (Wechsler Adult Intelligence Scale–III [WAIS-III] [21], digit span, and letter/number sequencing), and executive functions (verbal fluency [19], Stroop interference [17,22], and trail making test [23,24]). Measures of general cognitive functioning (WAIS-III [21]), reading ability (Wide Range Achievement Test–4 [25]), everyday functioning (activities of daily living (ADL) [26], and Behavior Rating Inventory of Executive Function–Adult [27]) were included to describe the cohort and/or serve as covariates. Standard scores were computed using published normative standards, with adjustments for age and, where available, race, Hispanic ethnicity, education, and/or gender [17]. Scores within domains were converted to *z*-scores and averaged for analytic clarity and to reduce the number of regression analyses performed. In addition, neurocognitive performance was summarized using an approach developed in the adult HAND literature [15,28], which weights the presence and severity of neurocognitive impairment [29]. Deficit scores, computed using T-score conversions and ranging from 0 (T-scores > 39) to 5 (T-scores < 20; higher deficit scores reflect greater impairment), were averaged to derive a global deficit score (GDS). A GDS cut point of ≥.5 was used to classify individuals with global

neurocognitive impairment [29]. Individuals with GDS $\geq$ .5 in two or more domains were classified with HAND (syndromic HAND if they reported a decline in two or more ADL areas relative to best-ever functioning, and otherwise asymptomatic neurocognitive impairment (ANI), i.e., neurocognitive impairment on testing but no reported impact on daily functioning.)

Psychiatric functioning and substance use. Participants completed questionnaires regarding depression (Beck Depression Inventory–II [BDI-II] [30]), general distress (Behavioral Symptom Inventory [BSI] [31]), and frequency of using 10 different substances over 3 months before the study visit, and presence of substance-related issues (e.g., missing work) used to calculate a risk index (Alcohol, Smoking and Substance Involvement Screening Test [32]). Participants were asked whether they used potentially psychoactive substances (PPS) (street drugs or medications) and whether they had used them on the day of testing.

Demographics and psychosocial history

Participants were asked about birth sex, race, ethnicity, primary language, sexual orientation, employment, school enrollment status, past 30-day income, educational attainment, educational risk (history of special education or repeating a grade), and living situation.

Medical record abstraction

Comorbid current and past conditions were rated according to potential impact on current cognition as none, mild (e.g., headache, adjustment disorder), moderate (e.g., chronic migraines, major depressive disorder), or severe (e.g., seizure disorder, skull fracture), following published guidelines [15]. The CD4 T-cell counts and plasma HIV-1 RNA viral load (VL) values within 4 weeks preceding the visit, Centers for Disease Control and Prevention (CDC) classification [33], and date of first positive HIV test were abstracted.

Statistical methods

Chi-square tests were used to compare percentages of impaired study participants with expected population percentages ($\geq$1σ or $\geq$2σ below the mean). Regression models were fit to memory, motor, attention, and executive function domain scores, general cognitive functioning (WAIS-III) score, mean *z*-score, and HAND diagnosis, along with a set of demographic and clinical characteristic covariates. Models were developed using a stepwise approach. Each predictor was first tested for association with each outcome in a single regression model. Covariates with critical alpha values at $p \leq .10$ were included in a stepwise selection procedure; covariates at $p \leq .05$ in the stepwise models were included in the final models. Measures related to HIV disease (CD4 count, $\log_{10}$ VL, and years since first positive HIV test) were included in all multivariable models. Other covariates included age; BDI-II score; BSI score; gender; race/ethnicity; education level; language spoken at home; past 30-day income; educational risk; confounding comorbidity; PPS; and substance use risk for tobacco, alcohol, cannabis, and "other drug." Linear regression was used for all outcome measures except HAND, which was modeled using logistic regression. Final regression models were evaluated for influential outliers, colinearity, and normality and homoscedasticity of residuals. Validity of the logistic regression models was assessed using Hosmer-Lemeshow tests. Analyses were completed using SAS, version 9.2 (Cary, NC).

Results

Population characteristics

A total of 220 study participants enrolled between April 2008 and July 2010 (numbers vary by outcome owing to missing or invalid data). Participants had a mean age of 20.9 years and were predominantly male (80.4%) and African-American (67.6%) or Hispanic (21.5%), self-identified as homosexual or bisexual (72.6%), and were high school educated or beyond (73%), with 41.1% currently in school (Table 1). Approximately 22.4% reported repeating a grade and 22.4% had received special education; group membership overlapped but was not identical. Fewer than half (41.6%) were employed and 48.4% reported living with a family member.

Clinical HIV characteristics

Approximately half of the sample had been diagnosed with HIV for <1 year (Table 2). Youth with CD4-positive counts $\geq$350 accounted for 57% of the sample, with only 6% <200. Almost 90% were in CDC category A; all but 1.4% had VL >400 copies owing to selection criteria for the associated treatment strategy study.

Psychiatric characteristics

Most (73.4%) had BDI-II scores in the minimal or mild range (Table 3); 53% exceeded the BSI clinical cutoff (T-score $\geq$ 63). Reported daily use frequencies were 20.4% for cannabis, 33.6% for tobacco, and 2.8% for alcohol; 23.9% reported weekly alcohol use. Other substances were less common (<10%). Comorbid conditions considered likely to have moderate or serious effects on neurocognition were diagnosed in 39% of participants. Currently using potentially psychoactive medications or substances was reported by 5.5% of participants; 2.8% reported taking them on the day of testing.

Neurocognitive and everyday functioning

Impaired neurocognitive functioning was defined as either $\geq$1 or $\geq$2 standard deviations (SDs) from published means in the direction indicating poorer performance. The percentage identified as impaired using a 2 SD definition exceeded the number expected in a normative sample (2.3%) for most tests, with memory and most motor domain measures indicating impairment rates >15% (Table 4). Whereas mean GDS was .9, 69.4% had scores in the impaired range. More than 13% of Behavior Rating Inventory of Executive Function–Adult index scores also were elevated. However, only 3.67% of study participants indicated ADL declines. Regarding HAND, 62.9% of subjects had ANI and 2.4% showed syndromic HAND.

Association of HIV disease indicators with neurocognitive summary measures

Table 5 shows results for final adjusted regression models for association with HIV disease measures (CD4 count, $\log_{10}$ VL, and time since HIV diagnosis). Lower CD4 counts were associated with poorer performance in executive functions and higher

Table 1
Demographic characteristics of sample (N = 219)

	Mean (standard deviation) or count (%)
Age, years	20.9 (1.8)
Age range, years	18–24
Sex, % men	176 (80.4%)
Transgender	9 (4.1%)
Ethnicity	
African-American	148 (67.6%)
Hispanic	47 (21.5%)
Non-Hispanic white	14 (6.4%)
Other ethnicity	10 (4.5%)
Language at home	
English	208 (95.0%)
Spanish	9 (4.1%)
Other	2 (.9%)
Sexual preference	
Straight (heterosexual)	53 (24.2%)
Gay/lesbian (homosexual)	136 (62.1%)
Bisexual	23 (10.5%)
Not sure/refused to answer	7 (3.2%)
Educational status	
Currently attending school/general education development diploma program	90 (41.1%)
Level of education[a]	
Less than high school graduate	59 (26.9%)
High school graduate	66 (30.1%)
Some education after high school	80 (36.5%)
College graduate or above	14 (6.4%)
Repeated a grade	49 (22.4%)
Special class/special education	49 (22.4%)
Currently employed	
Full-time	51 (23.3%)
Part-time	40 (18.3%)
Not employed	127 (58.0%)
Omitted	1 (.5%)
Living situation	
Independent	75 (34.2%)
With family member	106 (48.4%)
With non-family member	28 (12.8%)
Other	10 (4.6%)
Estimated monthly income, dollars	
<50	86 (39.3%)
51–499	63 (28.8%)
500–999	27 (12.3%)
1,000–2,999	37 (16.9%)
>3,000	1 (.5%)
Unknown or refused to answer	5 (2.3%)

[a] "High school graduate" includes participants who earned a general education development diploma.

Table 2
Clinical human immunodeficiency virus characteristics (N = 219)

	Count (%)
Time since HIV diagnosis, months	
<4	49 (22.4)
4–11	63 (28.8)
12–26	51 (23.3)
≥27	56 (25.6)
Current CD4 count, cells/mm^3	
Mean (standard deviation)	441.6 (216.3)
Median (interquartile range)	397.5 (247.0)
Range	16–1,167
Current CD4 count, cells/mm^3	
<200	13 (5.9)
200–349	82 (37.4)
350–499	55 (25.1)
≥500	69 (31.5)
Current CD4 percentage	
<15	28 (12.8)
15–24	92 (42.0)
>24	99 (45.2)
Centers for Disease Control clinical classification	
Category A	192 (87.7)
Category B	25 (11.4)
Category C	2 (.9)
Viral load, (HIV-1 RNA copies/mL, plasma)	
<400	3 (1.4)
400–10,000	86 (39.3)
10,001–100,000	110 (50.2)
100,001–500,000	18 (8.2)
>500,000	2 (.9)

HIV = human immunodeficiency virus.

likelihood of HAND, whereas longer time since HIV diagnosis was significantly associated with lower WAIS-III intelligence quotient ($p < .05$). Viral load was not significantly associated with any neurocognitive outcomes ($p > .10$).

Association of covariates with neurocognitive measures

The following measures had significant associations with neurocognitive outcomes and were used as covariates in the regression models. Meeting criteria for HAND was associated with lower education level ($p < .01$) and higher risk level for alcohol involvement ($p < .05$). Lower global functioning scores were associated with lower education level ($p < .01$), black race ($p < .05$), educational risk ($p < .05$), diagnoses with potential moderate or severe effects ($p < .05$), and PPS ($p < .01$). Lower attention domain scores were associated with educational risk ($p < .01$), lower education level ($p < .05$), and PPS ($p < .05$). Lower motor domain scores were associated with female gender ($p < .05$), lower education level ($p < .05$), PPS ($p < .05$), and diagnoses with potential moderate or severe effects ($p < .01$). Lower executive domain scores were associated with BSI scores indicating greater distress ($p < .01$). Lower memory domain scores were associated with lower education level ($p < .001$) and income ($p < .05$), higher risk level for alcohol involvement ($p < .05$), and PPS ($p < .05$). Lower mean *z*-score was associated with black race ($p < .001$), lower education level ($p < .001$), educational risk ($p < .05$), and PPS ($p < .01$). Age; BDI-II; language spoken at home; and cannabis, tobacco, or other drug involvement were not significant covariates for any neurocognitive measures.

Discussion

In the current climate of "test and treat" emphasizing early treatment initiation [34], this study represents a unique opportunity to describe neurocognitive functioning in a cohort of youth with behaviorally acquired HIV and a range of disease severity before initiation of cART. Study participants differed from those included in previous adult studies in their status as still developing individuals, and from perinatally infected youth in the timing and recentness of the HIV infection. Cohort demographics, predominantly minority and male, are representative of a group at high risk for acquiring HIV. The comprehensive assessment of psychiatric, substance use, and psychoeducational characteristics enabled us to examine the contribution of both HIV disease parameters and other risk factors to neurocognitive functioning.

Our findings show a strikingly high rate of impairment in some cognitive domains in youth with behaviorally acquired HIV.

Table 3
Psychiatric characteristics

	N	Mean (standard deviation) or count (%)
Beck Depression Inventory, 2nd ed., mean score	218	13.9 (10.5)
Category, %		
Minimal (<13)		124 (56.9%)
Mild (14–19)		36 (16.5%)
Moderate (20–28)		36 (16.5%)
Severe (>28)		22 (10.1%)
Brief Symptom Inventory	218	
Global Severity Index		63.5 (11.6)
Percentage exceeding clinical cutoff[a]		116 (53.2%)
Frequency of alcohol use (past 3 months)	218	
0		46 (21.1%)
1 or 2 times		82 (37.6%)
Monthly		27 (12.4%)
Weekly		55 (25.2%)
Daily		8 (3.7%)
Alcohol risk (past 3 months)[b]	218	
None		46 (21.1%)
Low		102 (46.8%)
Moderate		62 (28.4%)
High		8 (3.7%)
Frequency of cannabis use (past 3 months)[b]	218	
0		109 (50.0%)
1 or 2 times		38 (17.4%)
Monthly		7 (3.2%)
Weekly		21 (9.6%)
Daily		43 (19.7%)
Cannabis risk (past 3 months)[b]	218	
None		109 (50.0%)
Low		13 (6.0%)
Moderate		83 (38.1%)
High		13 (6.0%)
Frequency of tobacco use[b]	218	
0		90 (41.3%)
1 or 2 times		24 (11.0%)
Monthly		17 (7.8%)
Weekly		18 (8.3%)
Daily		69 (31.7%)
Tobacco risk (past 3 months)[b]	218	
None		90 (41.3%)
Low		6 (2.8%)
Moderate		102 (46.8%)
High		20 (9.2%)
Comorbid or contributing condition(s)	218	
None		114 (52.3%)
Mild		19 (8.7%)
Moderate		75 (34.4%)
Serious		10 (4.6%)
Taking potentially psychoactive medications or substances	217	12 (5.5%)
Potentially psychoactive substances on day of testing	217	6 (2.8%)

[a] A T score of 63 was used as the clinical cutoff, per author recommendations.
[b] From the Alcohol, Smoking and Substance Involvement Screening Test. Substances assessed included tobacco, cannabis, alcohol, cocaine, amphetamines, inhalants, sedatives, hallucinogens, opiates, and other.

The number and degree of impairments resulted in most (~65%) participants classified with HAND; however, few participants reported declines in daily functioning consistent with syndromic deficits, instead meeting criteria for ANI. As in the adult HIV literature, youth show high rates of impairment on tests of learning and memory, particularly verbal; the pattern of scores suggests difficulty with acquisition of information rather than rapid forgetting [35]. Similar to adults, our youth had greater than expected rates of impairment on most tests of executive functions [28]. In contrast to recent adult findings showing a decrease in motor impairments in the era of cART [7], 16%–26% of youth had significant difficulty with tests of fine or gross motor functioning. Although impairments in learning and memory, executive functions, and motor functioning are consistent with some studies of children and adolescents with pHIV [6], youth with behaviorally acquired HIV showed less impairment on tests of global intellectual functioning as well as attention and working memory. Thus, youth who acquire HIV during adolescence show a unique profile of neurocognitive functioning.

The psychiatric, demographic and diagnostic profile of the study participants, discussed below, describes a cohort that faces substantial obstacles to optimal neurocognitive outcomes and daily functioning in addition to HIV infection. Nonetheless, multivariate analyses accounting for the influence of other risks show an association of cognitive functioning with measures of HIV disease severity. In contrast to the adult literature, impairment in memory and motor functions was not associated with disease severity in our cohort after accounting for other risk factors. However, HAND diagnosis, which represents impairment across domains, and lower executive function performance were significantly associated with lower current CD4 count, and lower global functioning was significantly associated with time since HIV diagnosis. Studies on adult and perinatal HIV infection have shown the greatest risk for neurocognitive impairment in the context of previous AIDS-defining diagnoses or CD4 nadirs <200 [10,36]. The association of current CD4 count with HAND in our cohort of youth with very low prevalence of past severe HIV disease (CDC class C < 1%) is concerning because recent literature suggests subtle central nervous system effects early in HIV infection [37]. However, the lack of a control group with no HIV infection limits conclusions regarding the relationship of neurocognitive impairments to HIV. Further research is warranted to address the possibility that adolescents with behaviorally acquired HIV may be at heightened risk for impairments resulting from early subclinical neuroimmune events while otherwise relatively healthy. Neuroimaging and investigation of inflammatory and other biomarkers may clarify the underlying mechanisms of neurocognitive impairments in YLWH.

Multivariate modeling identified psychiatric, demographic, and historical characteristics of the study cohort that contribute significantly to neurocognitive outcomes and should be considered in future neurocognitive research involving YLWH. Demographic data indicate that most participants were in racial or ethnic minority groups and had low income, which suggests the possibility of reduced educational and enrichment opportunities and poorer nutrition, and which might reduce cognitive reserve and increase risk of HAND in adulthood [11]. The significant association with race may reflect these factors, and also may have been influenced by the unavailability of norms adjusted for ethnicity for a subset of study measures. More than one fifth of participants reported repeating a grade or receiving special education services, and more than one third had comorbid conditions rated as having moderate or serious potential risk for neurocognitive outcomes. The cohort profile of average intellectual abilities and significant impairment in learning and memory, along with school difficulty, suggests that preexisting learning disabilities may account at least in part for observed impairments; in fact, educational risk was significantly associated with the attention domain and summary *z*-score in addition to global functioning. Replication of our finding and further

Table 4
Neurocognitive and everyday functioning

	N	Mean (standard deviation)	Count (%) impaired[a]		*p* value[b]
Neurocognitive functioning[c]			≥1σ Below mean	≥2σ Below mean	
Global functioning					
WAIS-III full-scale intelligence quotient estimate	218	−.35 (.76)	43 (19.73%)	2 (.92%)	.173
Reading skill					
WRAT-4[b] single word reading	215	−.74 (.91)	74 (34.42%)	15 (6.98%)	<.0001
Memory domain					
HVLT-R[a–c] total learning	218	−1.45 (1.10)	135 (61.93%)	71 (32.57%)	<.0001
HVLT-R delayed recall	217	−1.43 (1.27)	120 (55.30%)	86 (39.63%)	<.0001
BVMT-R[a–c] total learning	214	−1.07 (1.32)	106 (49.53%)	54 (25.23%)	<.0001
BVMT-R delayed recall	214	−.78 (1.35)	96 (44.86%)	39 (18.22%)	<.0001
Attention domain					
WAIS-III digit span	218	−.29 (.87)	36 (16.52%)	1 (.46%)	.070
WAIS-III letter/number sequencing	217	−.36 (.83)	31 (14.28%)	4 (1.84%)	.654
Executive domain					
Verbal fluency[b]—letter	214	−.47 (1.01)	60 (28.04%)	15 (7.01%)	<.0001
Verbal fluency—animals	214	−.25 (1.02)	49 (22.90%)	8 (3.74%)	.160
Stroop[a–c] interference	214	.09 (.86)	17 (7.94%)	0	.061
Trail making test[b] Part B	216	−.51 (1.49)	64 (29.63%)	33 (15.28%)	<.0001
Motor domain					
WAIS-III digit symbol	218	−.60 (.80)	49 (22.48%)	2 (.92%)	.173
Grooved pegboard[a,b] (dominant)	211	−1.01 (1.24)	95 (43.60%)	38 (18.01%)	<.0001
Grooved pegboard (nondominant)	210	−1.34 (1.42)	110 (52.38%)	54 (25.71%)	<.0001
Timed gait[b]	209	−.24 (2.02)	70 (33.49%)	34 (16.27%)	<.0001
Global deficit score[a]	216	.9 (.7)	150 (69.44%)		<.0001
Everyday functioning[a]					
Behavior Rating Inventory of executive function[a]					
Metacognition index	213	.45 (1.13)	42 (19.7%)		<.0001
Behavior regulation index	213	.30 (1.08)	38 (17.8%)		<.0001
Global executive composite	213	.19 (1.01)	29 (13.6%)		<.0001
Activities of daily living areas declined	218	.20 (.70)	31 (3.67%)		
HIV-associated neurological disease (N = 215)					
Normal			75 (34.9%)		<.0001
HIV-associated neurocognitive disorder (HAND)					
Asymptomatic neurocognitive impairment			135 (62.8%)		
Syndromic			5 (2.3%)		

Scores were corrected according to published norms by age (all tests except activities of daily living), gender,[a] education,[b] and race/ethnicity.[c]
BVMT-R = Brief Visuospatial Memory Test—Revised; HAND = HIV-associated neurocognitive disorders; HIV = human immunodeficiency virus; HVLT-R = Hopkins Verbal Learning Test—Revised; WAIS-III = Wechsler Adult Intelligence Scale—III; WRAT-4 = Wide Range Achievement Test-4.

[a] Impairment levels were defined as follows. For all neurocognitive functioning measures, impairment was defined as either 1 or 2 standard deviations below the mean as indicated by column headings. Global deficit scores of ≥.5 were defined as impaired. Behavior Rating Inventory of Executive Function scores of ≥1.5 standard deviations were defined as impaired. Activities of Daily Living were defined as impaired if there were two or more areas of decline.

[b] *p* values shown are for <2σ and reflect comparison with expected percentages. All *p* values for <1σ were significant ($p < .01$) except for WAIS-III full-scale intelligence quotient estimate ($p = .131$), WAIS-III digit span ($p = .828$), and WAIS-III letter/number sequencing ($p = .480$).

[c] All neurocognitive measures are reported as *z*-scores.

research regarding learning risks in this population are warranted.

Psychiatric and substance use measures indicated significant emotional and behavioral issues for many study participants. More than one fourth of participants endorsed current moderate to severe depression, and >50% exceeded the criterion indicating potential clinically significant mental health issues (BSI). One fifth of participants reported using cannabis daily, and one fourth reported daily or weekly alcohol use. Each of these characteristics was significantly associated with at least one neurocognitive domain outcome in multivariate modeling, with the exception of depression and cannabis use, which nevertheless suggest treatment needs for YLWH represented in our cohort. The contribution of alcohol use to HAND diagnosis is particularly concerning given previous findings showing interactive neurocognitive effects of comorbid alcoholism and HIV infection [8] and brain changes after initiation of heavy drinking during adolescence [38].

The impairments seen in this study have potential implications for treatment of youth with behaviorally acquired HIV, regardless of their origin. Relationships with study covariates suggest that some of the observed impairments may result at least in part from modifiable factors such as alcohol use/abuse, psychiatric distress, and educational disadvantage. These factors also represent treatment targets in their own right owing to their influence on mental health and quality of life. The memory and learning impairments require replication and further study regarding their origin, impact on medication management, and other functional outcomes and appropriate interventions. Youth with HIV are in the unique position of being in a life stage characterized primarily by acquisition and practicing of new skills critical for successful transition to adulthood. In adults with HIV, cognitive impairment has been found to affect a wide range of critical skills that are newly being acquired by youth, from driving to medication adherence; furthermore, a reciprocal interaction has been described between cognitive impairment and adherence [39]. Equally worrisome is the potential impact of impairments on sexual risk behaviors [40] through decreased ability to exert self-control, evaluate consequences, or learn alternate coping skills. Further study of the relationship of cognitive functioning to functional outcomes and risk behaviors in youth with behaviorally acquired HIV is needed.

Table 5
Final regression models for association of human immunodeficiency virus disease measures with neurocognitive outcomes

Outcome Variable	CD4 count[a]				Log_{10} viral load				Years since first positive HIV Test[b]			
	Regression effect/odds ratio[c]	Lower 95% CI	Upper 95% CI	*p* value	Regression effect/odds ratio[c]	Lower 95% CI	Upper 95% CI	*p* value	Regression effect/odds ratio[c]	Lower 95% CI	Upper 95% CI	*p* value
Global functioning	.339	−.076	.755	.109	.801	−.616	2.218	.266	−.644	−1.252	−.037	.038
Attention scale	.002	−.045	.049	.927	−.046	−.205	.114	.574	−.038	−.108	.031	.278
Motor scale	.020	−.037	.078	.482	−.004	−.204	.196	.966	−.031	−.122	.060	.504
Executive scale	.063	.015	.110	.010	.141	−.022	.304	.089	−.059	−.128	.010	.096
Memory scale	.040	−.023	.103	.209	.046	−.166	.259	.668	−.029	−.121	.062	.527
Mean *z*-score	.029	−.011	.070	.150	.056	−.083	.194	.428	−.036	−.096	.024	.244
HIV-associated neurocognitive disorders	.820	.708	.950	.008	.701	.430	1.145	.156	.988	.792	1.231	.912

CI, confidence interval; HIV, human immunodeficiency virus.
[a] Model for CD4 count shows change per 100-cell increase.
[b] Models for duration of HIV show change per 1-year increase in duration.
[c] Models adjusted for race/ethnicity, education level, gender, income, concomitant medications that might affect performance, alcohol use severity index, Brief Symptom Inventory, diagnoses potentially affecting performance, and education risk (special classes/repeated year). See Results for further details.

The combination of premorbid cognitive impairments and socioeconomic and educational risks in this cohort raises the possibility of low cognitive reserve, which has been associated with risk for HAND and functional decline in adults with HIV [41]. It is unknown how preexisting impairment might interact with HIV and ART over time after infection and treatment initiation during adolescence; for example, cognitive impairments might interact with accelerated aging hypothesized to characterize HIV [42] to produce greater risk of cognitive and functional decline, or impaired youth might be predisposed to ART-related cognitive or psychiatric toxicities. For these reasons, long-term monitoring of neurocognitive functioning in youth with HIV and inclusion of neurocognitive measures in treatment studies may be warranted.

This study has several limitations. Because this was a study of ART treatment strategies, a cohort without HIV was not included. Although cohort demographics match the population most at risk for new HIV infection (predominantly minority, male, and gay-identified), most study participants were youth who committed to being enrolled in the study for 3 years, and thus might not be representative of all YLWH. Youth with a range of disease severity enrolled; however, the distribution of CD4 counts was determined by desired group sizes and may differ from an unselected population. Although we used an analytic plan designed to reduce the number of comparisons performed, the number of analyses still may result in inflated Type I error. Individual neurocognitive functions may have associations with HIV disease severity or covariates not reflected by the domain summary approach taken in this report. The global functioning measure has since been updated, and results may differ from those that would be obtained using the new version. Measures of substance use and ADL were obtained by self-report and may underestimate these issues; in addition, the ADL measure was not developed for an adolescent population and may be less sensitive to decline in youth.

This cohort of youth age 18–24 years with behaviorally acquired HIV shows a strikingly high rate of impairment in some neurocognitive domains with the potential to affect adherence as well as other functional outcomes. Furthermore, the youth show high rates of psychiatric symptoms, substance use, and histories of educational and other risks. Among markers of HIV disease severity considered here, modest associations of CD4 count and time since HIV diagnosis with neurocognitive outcomes were seen. The significant neurocognitive impairment observed in our cohort highlights the need for evaluation of cognitive functioning in YLWH, studies of mechanisms underlying observed impairments, and development of interventions to lessen the impact on functional outcomes.

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