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Structural Neuroimaging and Neuropsychologic Signatures of Vertically Acquired HIV

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Abstract

BACKGROUND—Children with vertically acquired human immunodeficiency virus (HIV) exhibit persistent cognitive impairments, yet the corresponding neuroimaging signature of vertical infection remains unclear.

METHODS—Fifty healthy control children and 51 vertically infected children were included in the study. The HIV-infected group consisted of survivors who had not received antiretroviral therapy (ART) at birth. The HIV-infected group averaged 11.4 (2.5) years of age, with a median CD4 count of 683 cells/mm³. Most (71%) of the HIV-infected children were on ART for a median

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of 34 months (range: 33–42) with HIV RNA <40 copies/ml in 89% of the sample. The HIV-uninfected group averaged 10.6 (2.6) years of age. Magnetic resonance imaging was acquired to determine volumes of the caudate, putamen, thalamus, pallidum, hippocampus, nucleus accumbens, total white matter, total gray matter, and cortical gray matter. Correlational analyses examined the degree of shared variance between brain volumes and both cognitive performances and laboratory markers of disease activity (T-cells and plasma viral load).

RESULTS—HIV-infected children exhibited larger volumes of the caudate, nucleus accumbens, total gray matter, and cortical gray matter when compared to the controls. Volumetric differences were predominately evident in children under 12 years of age. HIV-infected children performed worse than controls on most neuropsychological tests, though neither cognitive performances nor laboratory markers corresponded to brain volumes in the HIV-infected children.

CONCLUSIONS—Outcomes of the present study suggest abnormal brain maturation among HIV-infected pediatric survivors. Longitudinal studies of brain integrity and related resilience factors are needed to determine the impact of neuroimaging abnormalities on psychosocial function in pediatric HIV.

Vertical HIV infection remains a substantial public health concern with nearly 2 million children living with HIV infection worldwide.¹ Despite proven interventions to prevent vertical HIV transmission, new cases of pediatric HIV continue to occur while the existing population of HIV-infected children is growing older and reaching adolescence.^{2–4} A major gap exists in our understanding of the neurodevelopmental outcomes in vertically infected individuals. This is particularly true regarding measures of brain integrity, as regions of the world that shoulder the burden of pediatric HIV often do not have access to neuroimaging methods and standardized neuropsychologic measures to support controlled investigations of pediatric brain function. Neuroimaging studies focused on adults with chronic HIV infection generally reveal subcortical brain atrophy and reduced total brain volumes.^{5–10} Fewer neuroimaging studies have focused on children with vertical HIV infection, and the outcomes are not consistent. Cohen et al.¹¹ reported reduced volumes of total gray and total white matter, increased white matter lesions, and reduced white matter microstructural integrity in HIV-infected children when compared to demographically similar controls. Volumes of subcortical gray matter nuclei did not differ between groups and brain volumes did not correlate with cognitive performance in the HIV-infected sample. A different neuroimaging signature was recently reported by Sarma et al.¹² using voxel-based morphometry in a sample of HIV-infected children. Results revealed larger subcortical gray matter volume and smaller white matter volumes in the HIV-infected sample, with no differences between groups in total gray or total white matter volumes. The present study was conducted to further clarify the neuroimaging phenotype of pediatric HIV, using both regional and global indices of structural brain volumes. Neuropsychologic performances were measured as functional correlates of brain integrity. Given the lack of consistent outcomes in previous studies,^{11–12} directional hypotheses were not determined, and therefore two-tailed hypothesis testing was completed.

METHODS

Participants

The present study included 101 Thai children (51 HIV-infected and 50 HIV-uninfected) age 6 to 17 (mean: 11.4 ± 2.5) enrolled in the neuro substudy of the Pediatric Randomized Early vs. Deferred Initiation in Cambodia and Thailand cohort (PREDICT; clinicaltrials.gov identification number NCT00234091)¹³ PREDICT enrolled 300 antiretroviral therapy (ART)-naïve children (<18 years old) between 2006 and 2008. By protocol, eligible HIV-infected children from Thailand (n=180) and Cambodia (n=120) were randomized to early (ART initiation at CD4 15–24%) vs. deferred (ART initiation at CD4 < 15%) treatment for 144 weeks. Children enrolled into PREDICT were ART-naïve, per national treatment guidelines at the time of the study (CD4 % < 15% or AIDS-defining illness), until randomization at a median age of 6.5 years (IQR 3.9 – 8.4).

The neuro substudy of PREDICT¹⁴ began several years after the start of the main PREDICT trial. We included only those children with neuroimaging (structural MRI), neuropsychologic testing, and laboratory assays (T cells, viral load). MRI was not available in Cambodia and therefore only Thai children were enrolled in the neuro substudy. PREDICT¹³ and the neuro substudy¹⁴ were approved by the relevant institutional review boards. Caregivers provided written consent and children 8 years of age and older provided assent to participate in both studies per local ethics requirements.

Most (31/51) of the HIV-infected children included in the present study were enrolled in the early treatment arm of PREDICT. These children were on ART for a median of 34 months (range=33–42 months), with HIV RNA <40 copies/ml in 89% of the children, median log VL=1.6, (IQR = 1.6–1.6, min-max (1.3–3.8)), and median CD4 count of 853 (IQR = 637–942, min-max (470–1443)). First line ART included zidovudine, lamivudine, and nevirapine; children unable to take nevirapine received efavirenz or lopinavir-ritonavir. The remaining 20 HIV-infected children were enrolled in the deferred arm of PREDICT and reported a median log viral load (VL) of 4.1, (interquartile range (IQR) = 2.3–4.7, min-max (1.3–5.4)), and median CD4 count of 352 cells per mm³ (IQR = 255–400, min-max (66–625)).

Exclusion criteria for the HIV-infected group included: (1) previous or current brain infection; (2) neurologic or psychiatric disorder known to affect brain integrity; (3) congenital abnormalities; (4) previous use of immunomodulators within the past month of enrollment; and (5) abnormal lab tests including absolute neutrophil count < 750 cells/mL, hemoglobin < 7.5 g/dL, platelet counts < 50,000 per mL or alanine aminotransferase more than 4 times the upper limit of normal levels. Demographically similar HIV-uninfected children were recruited from siblings of the HIV-infected children and local well-child clinics following the same inclusion/exclusion criteria. The HIV-uninfected control group was comprised of two subgroups including HIV exposed but uninfected children (n=24) and HIV unexposed children (n=26). We previously reported no significant differences in brain imaging indices between these two groups,¹⁵ and therefore we collapsed the two samples into one control group for the present study.

Neuroimaging Acquisition and Analyses

Whole brain structural T1-weighted MRI was performed on GE 1.5 tesla scanners at Chulalongkorn University Hospital in Bangkok and Chiang Mai University Hospital in Chiang Mai, Thailand. The structural imaging used the following protocol: axial plane, 3D SPGR images with a minimum TE at full echo, TR = 11.2ms, slice thickness = 1.0mm; 256x256 imaging matrix. Volumetric analyses were conducted on the structural scans acquired at week 144 for the early treatment arm and approximately 4 weeks after starting treatment for the 15 children enrolled in the deferred arm. Brain volumes were determined from the T1-weighted images following a standardized approach to quantify regional and global anatomical structures. The FSL image processing library was used to run FIRST, a tissue segmentation protocol, which also performs intensity inhomogeneity correction. These images were then processed with FreeSurfer.¹⁶ ENIGMA protocols¹⁷ were used to extract volumetric measures from FreeSurfer outputs and perform visual and statistical quality control assessments. Extra-cerebral tissue was removed from anatomical scans using the brain extraction tool (BET)¹⁸ from the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Regions of interest included the caudate, putamen, pallidum, amygdala, nucleus accumbens, hippocampus, total white matter, total gray matter, and cortical gray matter. Intracranial volume (ICV) was included as a covariate in the statistical analyses.¹⁹

Neuropsychologic Assessment

Participants completed a standardized neuropsychologic battery sensitive to pediatric HIV.¹⁴ The battery was comprised of the following measures: **Intelligence:** Verbal Intelligence Quotient (VIQ) and Performance Intelligence Quotient (PIQ) from the Thai version the Wechsler Intelligence Scale for Children- third edition (WISC-III, ages 6 to 17). **Attention/Short-Term Memory:** Digit Span from the WISC III and Memory for Beads/Sentences (ages 5 to 17) and Memory for Digits/Objects (ages 6–17) from the Stanford Binet. **Working Memory/Executive Function:** Similarities and Arithmetic subtests from the WISC-III and Child Color Trails Test 2 (Color Trails 2, ages 8–17). **Psychomotor:** The Beery Visual Motor Integration scale (Beery VMI; ages 5–17), Symbol Search and Coding from the WISC-III (ages 6–17), Child Color Trails Test 1 (Color Trails 1, ages 8–17), and Purdue Pegboard average pin placements of the dominant and non-dominant hand, ages 6–17. Standardized scores were used for the WISC-III measures and raw scores were used for the other neuropsychologic tests.

Laboratory Variables

Laboratory measures of HIV disease activity and immunologic status were obtained through standard blood assays. Dependent measures included CD4 and CD8 cell count, viral load, and CD4/CD8 ratio. Clinical laboratory procedures were approved by NIAID-DAIDS and passed annual quality assurance programs of the United Kingdom National External Quality Assessment Service and Mahidol University, Bangkok, Thailand. Additional laboratory information is available in the [online repository](#).

Statistical Analysis

Analyses were conducted with STATA 14.1.²⁰ Chi-square or Fisher's exact tests and independent t-tests, as appropriate, were conducted to examine differences between the HIV-infected group and the HIV-uninfected group on age, sex, child educational level, and caregiver's educational level, household income and child living situation. Linear regression models were employed to calculate unadjusted mean differences in regional brain volumes and neuropsychologic test scores between groups. Regional brain volume analyses were adjusted for age, sex and ICV, and income in univariate models. Only household income was included in the adjusted models for VIQ and PIQ since these scores represent demographically standardized scores. A factor analysis was completed to consolidate the individual neuropsychologic tests into separate cohesive domains and the resulting factors were included as the primary neuropsychologic outcomes in the subsequent analyses. This method provides a data-driven approach to limit the number of comparisons and reduce the frequency of chance findings.

RESULTS

Demographic and Clinical Characteristics

The HIV-infected and uninfected children did not differ statistically in age ($p=.15$). However, the HIV-infected children were nearly one year older than the HIV-uninfected children (mean difference -0.7 (95% CI -1.7 to 2.7)), and therefore we included age into the adjusted models as a conservative approach. The HIV-infected and uninfected groups were similar in sex, child school grade, and caregiver's educational levels (Table 1). Twelve (24%) HIV-infected children but no HIV-uninfected children lived in orphanages ($p<0.01$) and a higher proportion of HIV-uninfected children had above average household incomes, while a higher proportion of HIV-infected children had below average income ($p=0.007$). Since all the children in the orphanages had below average household income, we adjusted for income but not living arrangement where appropriate.

Neuroimaging Comparisons between HIV-infected and HIV-uninfected Children

Results of the adjusted models revealed larger brain volumes in HIV-infected children compared to the HIV-uninfected children in the caudate, nucleus accumbens, and total gray matter. A similar trend ($p = .06-.07$) was observed in the putamen, pallidum, and amygdala (Table 2). Secondary analyses revealed that larger brain volumes were most pronounced in children younger than 12 years of age. These younger children had significantly larger volumes of the caudate, pallidum, and amygdala when compared to the HIV-uninfected children younger than 12. By contrast, no differences in brain volumes were observed between groups comprised of children 12 years of age and older.

Neuropsychologic Comparisons between HIV-infected and HIV-uninfected Children

In adjusted analyses, the HIV-infected group performed significantly worse than HIV-uninfected children on Verbal and Performance IQ, Similarities, Arithmetic, Memory for Sentences, Memory for Beads, Memory for Objects, Symbol Search, Coding, and Beery VMI ($p \leq 0.01$; Table 3). The HIV-infected group performed better than the HIV-uninfected

group on the Pegboard test, though the difference was clinically negligible. Performances on Digit Span, Color Trails 1 and Color Trails 2 did not differ by group.

Correlations between Neuropsychologic Performance and Neuroimaging Outcomes

Brain volumes did not correspond to neuropsychologic performances (factors) among the HIV-infected children (see Table 4 for the factor loadings). In the HIV-uninfected group, positive correlations were observed between thalamic volume and both Working Memory/Executive Function ($\rho = 0.392$, $p < .01$) and Attention/Short-Term Memory ($\rho = 0.368$, $p < .01$; Figure 1 and Table 5).

Relationships between Laboratory, Neuropsychologic and Neuroimaging Indices

Neither neuroimaging indices nor neuropsychologic performances covaried with CD4 count or CD4/CD8 ratio. However, HIV-infected children with undetectable viral load had larger volumes of the nucleus accumbens (coefficient 81.1 (95%; CI 17.2 – 145.0)); $p = 0.01$) and thalamus (coefficient 831 (95%; CI 32.4 – 1631.3); $p = 0.04$) than children with detectable viral loads. Neuropsychologic performance did not differ by detectable versus undetectable viral load.

DISCUSSION

The present study helps to clarify the neuroimaging profile of children with vertical HIV infection. Using robust and standardized volumetric methods, we identified larger volumes of subcortical brain regions, cortical gray matter, and total gray matter in HIV-infected children compared to HIV-uninfected controls, with the most pronounced effects evident in younger children. Significant differences in brain volumes remained after controlling for the potential impact of socioeconomic and demographic factors. HIV-infected children also performed worse than controls on most neuropsychologic tests. Cognitive status corresponded to brain volumes in the uninfected but not the HIV-infected children. These results provide novel evidence of brain imaging and neuropsychologic abnormalities among young HIV-infected children with clade CRF01_AE disease, the dominant genetic viral clade in Southeast Asia.²¹

Interpretation of the neuroimaging signature described in the current study must consider the selection of the sample, defined by HIV-infected children who had survived early childhood (mean age of 6 at randomization) without having met clinical criteria at the time to initiate ART. These children represent survivors and it is possible that resilience factors influenced the neuroimaging phenotype described in this sample of children. Unique to this sample, most HIV-children exhibited a high nadir CD4 and were virologically suppressed following ART. Additionally, it is important to note that differences in brain volumes may reflect uncontrolled variance due to developmentally relevant differences in age rather than disease-specific mechanisms. Our adjusted regression models included age as a covariate, yet it is possible that statistical corrections are not sufficient controls for the inherent variability in pediatric brain volumes, particularly in the absence of age-specific morphometric templates.^{22–23} With these caveats noted, our finding of larger brain volumes in HIV-infected children

aligns with previous outcomes reporting deleterious effects of vertical HIV transmission on brain integrity.¹²

HIV infection during fetal development and/or early childhood might disrupt neurodevelopmental processes that ultimately govern or influence brain volume. Under conditions of healthy brain development, the volume of subcortical gray matter increases until early adolescence at which point volumetric decline occurs due to programmed neuronal pruning.^{24–26} Prior work has suggested that larger brain volumes in pediatric populations with various medical conditions reflect abnormalities in the pruning mechanisms.^{27–28} However, selective pruning of the neuronal architecture typically begins at the onset of adolescence (approximately age 12)²⁴ and our secondary analyses revealed that HIV-infected children younger than age 12 exhibited the most pronounced differences in brain volumes compared to HIV-uninfected controls. As such, it is unlikely that abnormal pruning accounts for the larger brain sizes observed in the present study.

Previous studies report larger subcortical gray matter and reduced cortical white matter in pediatric HIV,¹² whereas other studies report no differences in subcortical volumes but more pronounced atrophy of total gray and total white matter in this population.⁶ In the present study, white matter volume did not differ by infection status in either adjusted or unadjusted statistical models. Additional investigations focused on select white matter tracts and MR diffusion metrics examined over a multi-year period would allow a more complete examination of the relationship between HIV and developmental stage. Prior studies using diffusion tensor imaging (DTI) reveal microstructural white matter abnormalities in vertically infected children, including individuals on ART and individuals with slow progressive disease.^{29–31} Additional investigations using DTI and related approaches such as diffusion-based spectral imaging³² will facilitate a more complete understanding of the brain connectome in children with vertically infected HIV.

We observed worse neuropsychologic performance among the HIV-infected children in the context of ART-mediated viral suppression. Preliminary work from other studies suggest that sustained CD4 depletion is not mandatory for the expression of cognitive symptoms in vertically infected children. Hoare et al.²⁹ reported significantly lower Verbal and Performance IQ scores, and worse performance on tests of executive function, visuospatial processing and visual learning and memory among HIV-infected children who were ART naïve with CD4 > 25%. Similarly, Ruel et al.³³ identified worse performance on tests of attention, motor function and intelligence among treatment-naïve HIV-infected Ugandan children with CD4 cell counts > 350 cells/mm³ compared to controls. Higher plasma HIV RNA was associated with poorer performance on numerous cognitive measures and the pattern remained unchanged when analyses were restricted to individuals with WHO clinical stage 1 or 2 disease. These studies indicate that clinical interventions and accommodations may be necessary for vertically infected children independent of past or current immunologic status and treatment history. Several limitations of the current study should be noted. Cerebrospinal fluid levels of immunologic/virologic indices were not available and therefore the analyses of disease burden focused on peripheral measures. Additionally, conclusions regarding the progression of brain injury are limited by the cross-sectional design employed in this study. Prospective studies are needed to model the evolution of

neuropsychologic and neuroimaging abnormalities in HIV-infected children. Outcomes from these additional studies would inform the potential interactions between developmental processes and disruption to brain integrity in both younger and older children.

In summary, we report increased volumes of subcortical and cortical brain regions in children with vertically infected HIV who did not meet clinical criteria to initiate ART until later childhood. HIV-infected children performed worse than HIV-uninfected controls on most neuropsychologic tests, though performances did not correlate with brain volumes. The observation of more pronounced group differences among younger children suggests the involvement of mechanisms other than neuronal pruning. Additional studies are needed to determine whether potential “survivor” characteristics inherent in our sample and related resilience factors influence the neuroimaging signature of pediatric HIV. Finally, longitudinal studies are needed to model the trajectory of brain integrity in the context of sustained viral suppression to determine the functional relevance of residual brain abnormalities in this vulnerable population.

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Figure 1.

Scatter plots with line of best fit for the correlation between thalamic volume and the Working Memory/Executive factor score factor score (1A), thalamic volume and the Attention/Short-Term Memory function factor score (1B) ICV and the Working Memory/Executive factor score, (1C) and ICV and Attention/Short-Term Memory factor score in HIV-uninfected children.

Table 1

Demographic characteristics for HIV-uninfected and HIV-infected children.

	HIV-uninfected	HIV-infected	P
Mean Age (SD)	10.6 (2.60)	11.4 (2.46)	0.15
Sex, N (%)			0.49
Male	20 (40)	17 (33)	
Female	30 (60)	34 (67)	
Child education, N (%)			0.75
Kindergarten	1 (2)	1 (2)	
Elementary	33 (66)	37 (73)	
High school	16 (32)	29 (25)	
Caregiver's education, N (%)			0.64
None	3 (6)	4 (8)	
Elementary	21 (42)	26 (51)	
High school or above	23 (46)	20 (39)	
Unknown	3 (6)	1 (2)	
Living arrangements, N (%)			<0.001
Living with family	50 (100)	39 (76)	
Orphanage	0	12 (24)	
Household income, N (%)			0.007
Above average	9 (18)	1 (2)	
Average	26 (53)	24 (47)	
Below average	14 (29)	25 (49)	
Unknown	0	1 (2)	
Mean (SD) CD4 cell count (cells/mm ³)		683 (308)	
Median (IQR) nadir CD4 cell count		578 (290 – 946)	
Median (IQR) CD8 cell count (cells/mm ³), n = 33		1004 (694–1286)	
Median (IQR) CD4/CD8 ratio (n=33)		0.82 (0.48 – 0.97)	
Median (IQR) HIV-RNA (log10 copies/mL)		1.60 (1.60 – 2.32)	
N (%) on ART for > 6 months		36 (71)	
N (%) with viral load < 40 copies/ml (whole group)		34 (67)	
N (%) with viral load <40 copies/mL (on ART > 6 months)		32/36 (89)	

Percentages are rounded and may not total 100%.

Table 2

Regression models showing mean differences between brain volumes (mm³) in HIV-uninfected and HIV-infected children.

Variable	HIV-uninfected (n=50)		HIV-infected (n=51)		Mean difference (95% CI) between groups		P
	Mean (SD)		Mean (SD)		Unadjusted	Adjusted	
Caudate *	6370.0 (869.73)		6973.3 (984.66)		603.3 (236.2 to 970.4)	579.1 (214.5 to 943.8)	0.002
Putamen	9769.5 (1249.17)		10194.2 (1014.78)		424.7 (-24.2 to 873.6)	396.5 (-11.4 to 804.5)	0.06
Thalamus	14414.5 (1307.37)		14637.0 (1321.76)		222.5 (-297.3 to 742.2)	38.3 (-323.6 to 400.2)	0.83
Pallidum	2602.6 (267.14)		2697.6 (365.02)		95.0 (-31.5 to 221.5)	106.2 (-2.2 to 214.7)	0.06
Hippocampus	7892.1 (830.66)		7974.7 (856.12)		82.6 (-250.5 to 415.7)	5.8 (-230.4 to 242.0)	0.96
Amygdala	2499.7 (255.29)		2592.8 (268.55)		93.1 (-10.4 to 196.5)	81.5 (-5.6 to 168.4)	0.07
Nucleus Accumbens *	676.7 (108.35)		734.8 (108.82)		58.1 (15.2 to 101.0)	52.4 (9.1 to 95.7)	0.02
Total Gray Matter	630116 (55438.5)		646259 (54971.0)		161423 (-5656 to 37942)	13899 (356 to 27443)	0.04
Total White Matter	9260070 (84277.1)		944046 (91007.6)		18038 (-16609 to 52687)	8445 (-9599 to 26489)	0.36
Cortical Gray Matter	477477 (42783)		489975 (44884)		12497 (-4821 to 29816)	11747 (373 to 23121)	0.04

Models are adjusted for age, sex, and ICV.

* Volumes also adjusted for income based on the results of univariate group differences ($p < .01$).

Table 3

Regression models showing mean differences between cognitive measures in HIV-uninfected and HIV-infected children.

Variable	HIV-uninfected	HIV-infected	Mean difference (95% CI) between groups			
	Mean (SD)	Mean (SD)	Unadjusted	P	Adjusted	P
Intelligence						
Verbal	81.4 (11.42)	67.6 (11.32)	-13.9 (-18.3 to -9.4)	<0.001	-12.8 (-17.5 to -8.2)	<0.001
Performance	93.7 (13.87)	84.0 (14.71)	-9.7 (-15.4 to -4.0)	0.001	-8.0 (-13.9 to -2.0)	0.009
Working Memory/Executive						
Similarities	11.8 (5.96)	8.6 (5.73)	-3.2 (-5.4 to -0.9)	0.007	-4.2 (-5.9 to -2.5)	<0.001
Arithmetic	15.4 (2.23)	14.2 (2.89)	-1.2 (-2.4 to 0.01)	0.051	-1.4 (-2.4 to -0.5)	0.005
Color Trails 2	48.2 (18.88)	48.3 (18.08)	0.1 (-7.7 to 7.8)	0.98	0.3 (-6.6 to 7.2)	0.93
Attention/Short-Term Memory						
Sentences	19.4 (4.21)	17.2 (3.67)	-2.2 (-3.7 to -0.6)	0.006	-2.4 (-3.8 to -0.9)	0.001
Beads	25.1 (4.63)	22.4 (5.02)	-2.6 (-4.5 to -0.7)	0.008	-2.8 (-4.5 to -1.1)	0.002
Digit Span	12.7 (3.13)	12.1 (3.66)	-0.6 (-2.0 to 0.7)	0.36	-0.8 (-2.0 to 0.4)	0.19
Objects	7.9 (1.86)	6.9 (1.69)	-1.0 (-1.7 to -0.3)	0.006	-1.1 (-1.7 to -0.4)	0.002
Psychomotor						
Pin placements*	13.6 (2.15)	14.7 (2.28)	1.1 (0.2 to 1.9)	0.02	0.8 (0.1 to 1.5)	0.03
Symbol Search	26.0 (9.64)	22.0 (7.61)	-4.0 (-7.4 to -0.5)	0.03	-4.6 (-7.4 to -1.7)	0.01
Coding	48.8 (14.19)	44.8 (13.11)	-4.0 (-9.3 to 1.4)	0.15	-5.2 (-10.0 to -0.4)	0.03
Beery	23.2 (3.33)	21.6 (4.26)	-1.6 (-3.1 to -0.08)	0.04	-2.0 (-3.2 to -0.8)	0.002
Color Trails 1	28.4 (14.66)	25.4 (10.7)	-3.0 9-8.4 to 2.3)	0.26	-3.4 (-8.0 to 1.2)	0.15

Verbal and Performance IQ scores are adjusted for income; raw cognitive scores are adjusted for age, sex, and income.

* Average of dominant and non-dominant hand

Table 4

Factor loadings for the neuropsychological measures.

Test	Factor Loadings			
	Intelligence	Working Memory/Executive	Attention/Short -Term Memory	Psycho-motor
VIQ	0.6928			
PIQ	0.6928			
Similarities		0.7088		
Arithmetic		0.7294		
Color Trails 2		-0.5877		
Sentences			0.7695	
Beads			0.6767	
Digit Span			0.7575	
Objects			0.6892	
Pin placements				0.6240
Symbol Search				0.7704
Coding				0.8230
Beery				0.6100
Color Trails 1				-0.6603

Table 5

Pearson correlations for volumetric measures and cognitive factors in HIV-uninfected and HIV-infected children.

	HIV status	Intelligence	Working Memory/ Executive	Attention/Short-Term Memory	Psychomotor
Caudate	Negative	0.003	-0.233	-0.339	-0.216
	Positive	0.193	0.046	0.059	-0.121
Putamen	Negative	0.045	-0.130	-0.175	-0.027
	Positive	0.179	-0.092	-0.065	-0.141
Thalamus	Negative	0.163	0.392	0.458	0.174
	Positive	0.200	-0.054	0.026	-0.011
Pallidum	Negative	0.183	-0.054	-0.179	-0.071
	Positive	0.122	-0.026	-0.017	-0.244
Hippocampus	Negative	0.044	0.191	0.149	0.039
	Positive	0.240	-0.019	-0.046	0.025
Amygdala	Negative	-0.005	-0.008	0.145	-0.196
	Positive	0.009	-0.068	0.027	0.007
Nucleus Accumbens	Negative	0.058	-0.121	-0.200	-0.153
	Positive	0.193	-0.088	-0.047	-0.268
Total Gray Matter	Negative	0.018	-0.009	-0.029	-0.202
	Positive	0.267	-0.026	-0.075	-0.073
Total White Matter	Negative	0.051	0.230	0.165	0.023
	Positive	0.234	-0.01	-0.012	0.020
Cortical Gray Matter	Negative	0.081	-0.066	-0.083	-0.212
	Positive	0.218	-0.092	-0.101	-0.116

Coefficients shown in bold are significant at $p < 0.01$.