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Original Article

HIV-Related Cognitive Impairment of Orphans in Myanmar With Vertically Transmitted HIV Taking Antiretroviral Therapy

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ABSTRACT

OBJECTIVE: We determined the effect of perinatally acquired HIV on neurocognition in Myanmar children treated with antiretroviral therapy by comparison to demographically matched seronegative children. **BACKGROUND:** Myanmar has one of the highest HIV-1 prevalence rates in Southeast Asia. Studies from other resource-poor countries have shown that HIV-infected children differ in socioeconomic, nutritional and caregiver status compared to normal controls. Some vertically infected orphans in Myanmar reside separately from HIV-uninfected children in separate orphanages, thus the demographic variables of interest are naturally controlled. This study provides a unique evaluation of the neurocognitive effects of HIV in children, with control over key demographic variables. We hypothesized that HIV-infected orphans would perform significantly worse on cognitive indices compared with HIV-negative orphans. **DESIGN/METHODS:** A battery of cognitive tests sensitive to HIV-associated impairments in children was administered to 28 perinatally acquired HIV-positive children and 31 HIV-negative children from two orphanages in Myanmar; 21 children from each cohort underwent testing at baseline and again after 12 months. **RESULTS:** Baseline comparison of the two groups indicated that the HIV-infected children performed poorly across all tests, with significant group differences in executive function, visuospatial reasoning, fine motor dexterity, and visual motor integration. On subsequent testing, both cohorts of children showed improvements across multiple domains, with no significant effect of age at treatment initiation. **CONCLUSIONS:** Our results demonstrate a strong effect of HIV infection on specific neurocognitive deficits in vertically infected children. Understanding viral and host determinants and timing and choice of antiretroviral therapy on cognition will be critical to preventing cognitive impairment of children with HIV.

Keywords: HIV, neurocognitive, children, social confounders

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Introduction

Worldwide there are approximately 35 million people living with HIV, including 3.2 million children younger than age 15 years. Each year, an estimated 240,000 children are diagnosed with HIV, the overwhelming majority from vertical transmission.[1] Outside of sub-Saharan Africa, Asia has the highest number of individuals living with HIV at approximately 5.0 million.[2]

The negative impact of HIV infection on neurocognitive function is well-established for both adults and children.[3-6] Neurocognitive outcomes in vertically acquired HIV before the advent of antiretroviral medications were quite poor. Deficits ranged from static to progressive encephalopathy with variable severity. Since the initiation of combination antiretroviral therapy (cART), children have experienced

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dramatically improved morbidity, mortality, and neurocognitive outcomes, but children with HIV infection still lag behind uninfected peers.[7] Subtle, but quantifiable deficits in language, processing speed, executive function, motor function and working memory, and behavioral disturbances remain in children with HIV relative to uninfected children.[8]

The reason for this gap is still unclear. HIV infection itself may irreparably alter brain development in the setting of vertically acquired infection.[9,10] cART may cause neurotoxic effects on the developing brain,[11] although studies otherwise suggest benefit from these medications.[12,13] Further, the socioeconomic status of children with HIV, particularly in developing countries, influences cognitive outcomes.[9] Most studies of HIV-infected children in both resource-rich and resource-poor settings report results compared with normative data from the standardization of the instrument, rather than a matched control group, which can exaggerate cognitive deficits. Existing studies of pediatric HIV and neurocognitive function are limited by inadequate control populations for comparison.[14-16] Although many studies have characterized the pattern of deficits among adults with HIV and children living with HIV, relatively few have controlled for socioeconomic confounders. Our study uniquely controlled for differences in environment and biases in interpretation that limit previous studies.

We compared children in two orphanages in Myanmar. Neurocognition was assessed in children with vertically acquired HIV compared with HIV-negative children with identical nutrition, caregiver status, education, and access to services. In doing so, we could control for important stressors that are likely to confound neurocognitive outcomes, such as illness, loss of caregivers, obligations to care for family, malnutrition, and limited access to education because of economic constraints. Moreover, to eliminate the effect of insufficient HIV treatment, the children in the present study were supervised when taking their daily medications and adherence to their treatment was nearly 100%.

Methods

Study design

This was a cross-sectional study of school-aged children from 6 to 16 years of age, with a longitudinal component for a subset of the cohort. This study was approved by Myanmar Ministry of Health according to set protocols and guidelines for human studies in Myanmar as well as by the Institutional Review Boards at Washington University and the University of Missouri, St. Louis.

Setting

Children were recruited from two large orphanages in Yangon, Myanmar: one orphanage for HIV-infected children and the other orphanage for HIV-negative children. Each orphanage holds more than 150 children. The orphanages are well-staffed and run by nongovernmental organizations. All children speak Myanmar as the primary and current language, go to school, and receive formal education. All the HIV-infected children are on cART according to national guidelines, which are adopted from World Health Organization guidelines.[17] cART is provided by the National AIDS Program, international and local nongovernmental organizations in Myanmar using the national protocol "Guidelines for the clinical management of HIV infection in children." Most HIV-infected children in the orphanages we studied were on the same cART regimen, with at least one central nervous system–penetrating agent, according to the national protocol. Compliance is effectively 100%.

Participants and study size

The study population included 28 HIV-infected and 31 HIV-negative children. Twenty-one of the children from each group were tested twice, at 1-year intervals. The participants were selected by orphanage staff to have a similar distribution of age, sex, and education level. We excluded children with known neurodevelopmental disorders or other chronic medical conditions unrelated to the complications of HIV, but that might affect cognition. Additionally, children were excluded if they had an acute illness; coinfection with hepatitis C, tuberculosis, or other opportunistic infections; were not on cART; were unable to understand the assent process because of severe cognitive impairment; or if they were malnourished.

Consent was obtained from the caretakers and each child provided consent. All testing data were deidentified before analysis.

Variables

We collected demographic data including age, education level, current CD4 count, and treatment duration.

A battery of cognitive tests (Supplementary Table 1) sensitive to deficits associated with HIV in children was administered to all subjects. The battery comprised tests that captured performance on (1) executive function, (2) visuospatial skills, (3) attention span, (4) learning and memory, (5) visual motor integration, (6) and fine motor dexterity and speed. This battery provides breadth of coverage to adequately define the neuropsychological signature associated with HIV. As such, our selection of tests for the battery balances both HIV specificity and overall breadth to ensure adequate coverage across domains. These tests have been used in other pediatric studies of HIV[8] and were selected based on ease of cultural application and feasibility of translation, test administration, and scoring. All measures were translated into the Myanmar language and back translated to English to ensure accuracy. Additionally, letters on the Trails A test were replaced with corresponding Burmese symbols, and semantic category words on the verbal learning task were replaced with culturally relevant terms (see test descriptions in the following section).

Data sources/measurement

Demographic information, current CD4 counts, and treatment duration were obtained from each child's medical chart. Educational level was provided by orphanage staff.

All tests were administered according to standard procedures by trained pediatricians fluent in the Myanmar language. The dependent variables included time to completion for Trail Making and Pegs, and total correct for Digit Span, design fluency, and Object Assembly. Verbal learning was tested with the Hopkins Verbal Learning Test–Revised.[18] The test consists of a word list presented to the participant on three successive learning trials. These words were carefully chosen to make sure that the children in the testing age groups would be familiar with them and to ensure cultural relevance (e.g., we replaced gemstones with fruits and vegetables). Participants were required to recall as many words as possible on each learning trial and then again after a 20-minute delay. A recognition trial was administered after the delay, but the primary dependent variable included total recall across the learning trials. Visual motor learning was examined with Visual Motor Integration (Beery VMI)[19] and fine motor dexterity with the Grooved Pegboard.[20] The total time for test administration is approximately 50 minutes. The test administration was sequenced to avoid fluency confounds during verbal recall on the memory test.

Statistical methods

Preliminary group analyses were conducted using independent means *t* tests for age and education variables to assess the need to include these as covariates in subsequent analyses. Both the HIV-positive

and HIV-negative groups had similar levels of education and did not differ in terms of age (Table 1); therefore, no covariates were used in the analysis.

Independent means *t* tests were used to compare group differences on the –neuropsychological measures. Additionally, Z-scores were computed for the HIV-infected group using the means and standard deviations from the HIV-negative group in the Z score equation. These scores are reported only to provide a comparison of the meaning of the differences between the HIV-infected and HIV-negative groups and were not used in any analyses. A hierarchical linear regression analysis was performed to determine the unique contribution of age of treatment initiation on cognitive performance (using raw scores), beyond the variance accounted for by age. Finally, Pearson's correlations controlling for age were used to assess the relationship between cognitive performance, time since treatment initiation, age at treatment initiation and current CD4 count.

A subset of the participants were tested on five of the neuropsychological measures a year prior, and we conducted repeated measures *t* tests in the HIV-infected and HIV-negative groups to assess change in cognitive performance after the 1-year interval.

Results

Demographic and clinical characteristics: there were no differences between groups in terms of age or education (Table 1).

Neurocognitive measures

The HIV-infected group performed worse than the HIV-negative group on all neuropsychological measures, with significant differences on six of the 13 measures assessed (Table 2). Significant group differences were seen for Trails A ($t = 3.11$ $P = 0.003$), motor speed ($t = 3.04$ $P = 0.004$), design fluency ($t = 3.15$ $P = 0.003$), visual motor integration ($t = 3.89$ $P < 0.001$), grooved pegboard ($t = 2.78$ $P = 0.009$), and block design ($t = 3.75$ $P < 0.001$). These differences all remained significant after correction for multiple comparisons (false discovery rate, Benjamini and Hochberg, 1987). The largest effect size was noted for the Beery VMI and block design, with more moderate effects for Trails A, motor speed, design fluency, pegboard, and digits backwards.

Correlation analysis did not reveal a relationship between cognitive performance and current CD4 counts or time since cART treatment was initiated. However, there were several cognitive measures that significantly correlated with age at treatment initiation. To explore these results further, we conducted a linear regression analyses in the HIV-infected group to determine the degree to which age at treatment initiation contributed to improvements in cognitive performance above and beyond the expected contribution of age. A hierarchical linear regression was used, with age entered into the first step of the model and age of treatment initiation entered into the second step. Scores on the cognitive measures were entered as dependent variables. Age accounted for a significant degree of variance in all of the measures, as expected. However, there was no unique effect of age at treatment initiation on cognitive performance for any of the measures after correction for multiple comparisons (Table 3).

Age and current CD4 count were inversely associated, such that older children tended to have lower CD4 counts than the younger children. However, there was no association between age and time since treatment initiation.

Longitudinal performance

We also compared performance among both HIV-infected children and controls who were tested at 1-year intervals (Table 4). Both groups of children showed improvements in scores across multiple domains, with the HIV-infected children showing a more consistent improvement within the group, as can be seen in the correlation in scores between year 1 and year 2. The HIV-negative children showed significant improvements in Hopkins Verbal Learning Task (HVLT) delay Trails A and fluency measures, whereas the HIV-infected children improved in all areas, except for HVLT learning.

TABLE 1.
Demographics of Subjects and Controls

Demographic Characteristics			
	HIV-negative (n = 31)	HIV-positive (n = 28)	*P* Value
Age (years)			
Mean	10.7	10.6	0.96
SD	3.17	3.36	
Gender			
M	16	12	0.09
F	15	16	
Education (years)			
Mean	3.87	2.85	0.176
SD	3.01	2.62	
CD4 cell count			
Mean		827	
IQR		545-1063	
Years on cART			
Mean		4	
SD		2.08	

Abbreviations:
cART = Combination antiretroviral therapy
F = Female
IQR = Interquartile range
M = Male
SD = Standard deviation
Significant *P* values were calculated using independent means tests for age and education and a chi-square test for gender.

Discussion

Our results demonstrate significantly poorer performance among HIV-infected children in the domains of visual-motor skills, executive function, fine motor speed, and dexterity. The largest effect sizes were noted for the Beery VMI and block design. Object assembly, HVLT learning and delay, digit span, verbal fluency, and symbol search were the tests in which differences between the HIV-infected and HIV-negative children did not reach statistical significance. These tests represent global intelligence, attention, and memory, with the exception of object assembly, which is a test of visual-spatial skills and executive function.

When we compared the performance of those children who were tested in consecutive years, results show that both HIV-infected children and HIV-negative children improved in multiple domains. This improvement is expected both due to age-dependent cognitive development and increased familiarity with the testing process and potential practice effects. The HIV-infected children show within-subject

TABLE 2.
Comparison of Scores on Neuropsychological Measures Between Groups

Neurocognitive Performance					
N	HIV Status		Z score	Significance, *P*	Effect size, d
	HIV-negative	HIV-positive			
	31.00	**28.00**			
Verbal Memory: HVLT Delay					
Mean	11.61	10.46	−1.61	0.069	0.60
SD	0.72	3.14			
HVLT Learning					
Mean	23.13	20.92	−0.29	0.287	0.29
SD	7.72	7.34			
Verbal fluency					
Mean	10.77	9.29	−0.31	0.218	0.33
SD	4.70	4.34			
Attention: Visual scanning					
Mean	53.29	54.72	−0.04	0.869	0.04
SD	40.48	23.40			
Digit span					
Mean	14.87	12.82	−0.43	0.113	0.42
SD	4.81	4.95			
Psychomotor: Grooved pegboard					
Mean	81.23	104.00	−1.33	0.009*	0.79
SD	17.16	40.25			
Trails A					
Mean	72.23	114.54	−s1.06	0.003*	0.92
SD	40.02	52.02			
Symbol search					
Mean	20.03	17.26	−0.31	0.204	0.34
SD	8.82	7.37			
Motor speed					
Mean	77.22	103.32	−0.83	0.004*	0.84
SD	31.56	30.37			
Visuospatial: Object assembly					
Mean	18.76	15.18	−0.50	0.078	0.47
SD	7.19	8.03			
Block design					
Mean	13.48	6.14	−0.84	<0.001*	0.98
SD	8.71	6.21			
Beery VMI					
Mean	16.58	11.46	−1.03	<0.001*	1.01
SD	4.97	5.12			
Executive function: Design fluency					
Mean	22.61	15.29	−0.77	0.003*	0.82
SD	9.48	8.41			

Abbreviations:
Beery VMI = Beery Visual Motor Integration
HVLT = Hopkins Verbal Learning Task
SD = Standard deviation
Mean scores for each of the measures are reported as raw outcome scores. Z scores were calculated for the HIV-positive group by subtracting the mean score of the HIV-negative group from the mean score of the HIV-positive group and dividing by the SD of the HIV-negative group.
* Denotes Significant group difference.

significant gains in more domains than the controls. This may represent differing trajectories in the cognitive development of HIV-infected and unaffected children, whereby HIV-infected children are gradually catching up to their HIV-negative peers. Alternatively, the performance by the HIV-negative children was significantly better than the HIV-infected children at the first time point and, as such, the smaller magnitude of improvement seen in the control group may be the result of a ceiling effect.

Altogether, our results confirm the findings of numerous studies of HIV-infected children in American, European, African, and Asian cohorts, showing that there are significant differences in neurocognitive performance compared with HIV-negative children, most prominently in the areas of visual motor learning and executive function.[21,22] In our cohort, we noted more pronounced improvement encompassing more domains of neurocognitive function among the HIV-infected children than among controls. The significance is not clear, but may suggest that with adequate resources, appropriate learning and nurturing environment, and antiretroviral therapy, HIV-infected children may be able to narrow the gap between themselves and their HIV-negative peers. These results suggest that aggressive social interventions to provide optimal nutrition, education, and adherence to HIV medications could lead to health outcomes similar to seronegative children. Further, our results shed

TABLE 3.
Step-wise Linear Regression for Effect of Age and Age at cART Treatment Initiation on Cognition in HIV-positive Children

	r^2	*P* Value
Verbal fluency		
Age	0.569	0.002*
Age begin treatment	0	0.981
Attention: Visual scanning		
Age	0.21	0.021*
Age begin treatment	0.008	0.641
Digit span		
Age	0.498	0.001*
Age begin treatment	0.021	0.3
Psychomotor: Grooved pegboard		
Age	0.269	0.205
Age begin treatment	0.015	0.471
Trails A		
Age	0.619	0.028
Age begin treatment	0.038	0.145
Symbol search		
Age	0.737	<0.001*
Age begin treatment	0.013	0.28
Visuospatial: Object assembly		
Age	0.463	0.021
Age begin treatment	0.005	0.621
Beery VMI		
Age	0.619	<0.001*
Age begin treatment	0.066	0.031
Executive function: Design fluency		
Age	0.497	0.026
Age begin treatment	0.017	0.364

Abbreviations:
Beery VMI = Beery Visual Motor Integration
cART = Combination antiretroviral therapy
Sig. = Significance
r^2 indicates the percent of variance in the scores accounted for by age and age at start of treatment. Age is expected to account for a large degree of variance in the test scores. Age at treatment initiation does not account for a large percentage of variability in the performance, after taking age into account.
* Significant after FDR correction for multiple comparisons.

light on why some studies have not shown significant differences in the cognitive performance of HIV-positive and HIV-unaffected children, because the age and timing of testing or use of a less comprehensive battery of tests may influence the results.

It is worth noting that age and current CD4 count were inversely associated, such that older children tended to have lower CD4 counts than the younger children. Changes in World Health Organization treatment guidelines may explain this finding. In the past, guidelines suggested initiation when CD4 counts dropped below 200 cells/mL. More recently, guidelines changed to recommend treatment initiation when CD4 counts drop below 350 cells/mL, or in cases of symptomatic disease.[16] As such, it is possible that the older children in this sample initiated treatment when they had lower CD4 counts, limiting CD4 recovery to the same extent as the younger children who were treated earlier. The magnitude of this potential effect is unclear, and likely small, in this study, as duration of therapy did not show statistically significant association with performance. We also did not see an effect of age at treatment initiation on neurocognitive performance. Although some studies[23] have found better cognitive outcomes with earlier initiation of cART, other studies have not found such a relationship.[24] The Prospective Evaluation of Diabetic Ischemic Heart Disease by Computed Tomography trial[8] suggests that higher CD4 count at initiation did not improve developmental outcomes after 1 year. Because most of the children in our trial were started on cART after the age of 1 year, they may have missed the proposed window for seeing an effect of earlier treatment initiation. The effect of age at treatment initiation warrants further study in larger cohorts of children.

Beyond the small sample size, a limitation of our study is the lack of detailed medical historical data, including specific information about past HIV-related complications, World Health Organization staging, CD4 nadir, and lack of uniform age of initiation of cART among the HIV-infected children. Any unknown history of HIV-related complications or later initiation of cART would most likely have led to an underestimate of the magnitude of effects of our findings. We do not have a way to account for parental intelligence or socioeconomic status between the two cohorts, which may confound attribution of differences in cognitive testing performance to HIV status. An ideal comparison group would be nonseroconverting children of HIV-positive mothers, as this would control for parental intelligence and socioeconomic status. Additionally, the cohorts were not directly matched on a one-to-one basis. Although the demographic differences between them are not statistically significant, a nonrandom selection of subjects from each orphanage could have biased the results of our study in either direction.

Finally, the testing instruments were translated from English to Burmese and then back-translated, with culturally appropriate substitutions of word categories on verbal learning tasks, for example. These substitutions have not been validated for children in Myanmar. Myanmar has multiple linguistic groups, and as such, children likely have varying exposure to the Burmese language depending on the language(s) spoken in their home and surrounding community. Although the literature is limited on this topic, adaptation of cognitive testing in Vietnam[25] and India[26] has

TABLE 4.
Comparison of Year 1 and Year 2 Neuropsychological Scores for HIV-positive and HIV-negative Children

	Mean Difference	Significance	Correlation	Significance
HIV-negative				
HVLT learning	0.46	0.83	−0.02	0.95
HVLT delay	−3.71	0.00	0.13	0.58
Digit span	−0.24	0.84	0.21	0.36
Trails A	33.13	0.01	0.39	0.15
Fluency	−2.24	0.06	0.03	0.90
HIV-positive				
HVLT learning	−1.58	0.33	0.46	0.05
HVLT delay	−4.63	0.00	0.05	0.83
Digit span	−1.63	0.01	0.81	<0.001
Trails A	26.94	0.00	0.82	<0.001
Fluency	−1.32	0.06	0.63	0.00

Abbreviation:
Sig. = Significance
Mean difference shows the group change in raw scores for each of the measures from year 1 to year 2 followed by the significance of that change in scores. The correlation shows the degree of consistency in performance from year 1 to year 2 in each of the groups followed by the significance of that correlation in performance from year 1 to year 2. In general, the individuals in the HIV-positive group had more consistent performance from year 1 to year 2 and improved their performance from year 1 to year 2.

been described, and certainly further neurocognitive research in Myanmar would benefit from the strategies used by these studies. Generalizability of our study and similar studies will likely depend on use of standardized tools that can be adapted appropriately to diverse cultural settings. It is important to recognize that the neurocognitive and developmental data from children in orphanages may not be generalizable to the larger population that typically benefits from greater parental nurturing.

Conclusions

Although this is a small cohort, our study uniquely controlled for many of the socioeconomic factors that confound other studies of children with HIV. Caregiver status, nutritional status, family income, educational access, and social stigma can all impact neurocognitive development, but these factors are controlled by studying children in two orphanages that are similarly funded with identical educational curricula and services. Another advantage of our study is the high compliance with cART in the orphanage setting, where caregivers administer and observe the taking of daily medications by HIV-infected children.

Future studies are required to more comprehensively study viral and host factors that affect neurocognitive development among HIV-infected children. Receptor tropism studies in adult populations suggest preferential interaction with CXCR4 receptors may correlate with greater neurocognitive dysfunction.[22] HIV subtype and tat protein genotype are similarly thought to influence neuropathogenicity.[27] Conventional measures of recent CD4 counts and viral load have not been shown to correlate closely with neurocognition in patients with well-controlled HIV, but viral levels in peripheral blood monocytes may represent a more sensitive biomarker for monitoring treatment.[28] Our cohort is uniquely suited to evaluating neurocognitive function and various biologic determinants in pediatric HIV over time in a well-controlled setting. Ideally, by examining HIV and cognition more closely, therapeutic interventions can be modified to more effectively serve populations affected by HIV.[29]

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Conflicts of Interest: None.

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SUPPLEMENTARY TABLE 1.
List of Neuropsychological Tests Utilized in this Study, with the Principle Cognitive Domain Tested and the Measured Outcome

Summary of Neuropsychological Measures		
	Outcome Measure	Cognitive Domain Tested
Visual scanning	Time to completion in seconds	Attention
Digit span	Number correct	Attention span
Design fluency	Number completed	Executive function
Motor speed	Time to completion in seconds	Motor
Grooved pegboard	Time to completion in seconds	Psychomotor speed
Trails A	Time to completion in seconds	Psychomotor speed
Symbol search	Number correct	Psychomotor speed
Fluency	Number completed	Verbal fluency
HVLT learning	Number of items repeated correctly	Verbal memory
HVLT delay	Number of items recalled	Verbal memory
Beery VMI	Number completed	Visual-motor integration
Block design	Number correct	Visuospatial
Object assembly	Number correct	Visuospatial