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Impact of Perinatally Acquired HIV Disease Upon Longitudinal Changes in Memory and Executive Functioning

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Abstract

Background—Little is known regarding effects of perinatally-acquired HIV infection (PHIV) on longitudinal change in memory and executive functioning (EF) during adolescence, despite the importance of these skills for independence in adulthood.

Methods—PHIV (n=144) and perinatally HIV-exposed uninfected youth (PHEU, n=79), ages 12–17, completed standardized tests of memory and EF at baseline and two years later. Changes from baseline for each memory and EF outcome were compared between PHEU and PHIV youth with (PHIV/C, n=39) and without (PHIV/non-C, n=105) history of CDC Class C (AIDS-defining) diagnoses. Among PHIV youth, associations of baseline and past disease severity with memory and EF performance at follow-up were evaluated using adjusted linear regression models.

Results—Participants were primarily black (79%); 16% were Hispanic; 55% were female. Mean memory and EF scores at follow-up generally fell in the low-average to average range. Pairwise comparison of adjusted mean change from baseline to follow-up revealed significantly greater change for PHIV/non-C compared to PHEU youth in only one verbal recognition task, with a

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difference in mean changes for PHIV/non-C versus PHEU of −0.99 (95%CI: −1.80, −0.19; p=0.02). Among youth with PHIV, better immunologic status at baseline was positively associated with follow-up measures of verbal recall and recognition and cognitive inhibition/flexibility. Past AIDS-defining diagnoses and higher peak viral load were associated with lower performance across multiple EF tasks at follow-up.

Conclusions—Youth with PHIV demonstrated stable memory and EF during a two-year period of adolescence, allowing cautious optimism regarding long-term outcomes.

Keywords

perinatal HIV infection; adolescents; memory; executive functioning; longitudinal

INTRODUCTION

The development of higher-order cognitive functions, including retrospective memory and executive functioning (EF), among youth with perinatally acquired human immunodeficiency virus infection (PHIV) is of significant concern due to their influence on academic learning, medication adherence and successful transition to adulthood.[1–3] Memory and EF are known areas of vulnerability among adults with HIV infection yet their integrity and development in youth with PHIV are not fully understood.[4–6] PHIV may affect children's neural networks early and during sensitive periods of development, with potential for ongoing or intermittent damage, particularly in the absence of viral suppression.[7] Global and selective cognitive risks associated with PHIV and its medical treatments may be amplified by children's concomitant exposure to psychosocial and environmental stressors often present among families living with PHIV, including poverty, violence, and stigma. [8–12]

Inconsistencies in the engagement of higher-order skills are often observed during the adolescent period and are related to hormonal and physical changes, substantial structural changes in the brain, and variability in genetics and in affective and social contexts.[13–16] As the brain matures, with increasing myelination and synaptic pruning in prefrontal regions and activation in parietal and motor regions and subcortical structures, executive networks consolidate and become more refined, and behavior becomes more modulated.[17–20] This developmental process may be delayed or altered in the context of PHIV, with variable effects related to timing and/or severity of HIV disease and efficacy of medical treatment with combination antiretroviral therapy (ART). Furthermore, variable penetrance of the blood-brain barrier by ART may allow a reservoir of latent HIV to persist in the brain, increasing risk for cognitive deficits even with peripheral viral suppression.[21–25]

Recent neuroimaging studies of youth with PHIV revealed associations among historical markers of HIV disease severity, combination antiretroviral therapy and alterations in overall and regional white matter microstructure, functional connectivity, and/or subcortical deformation. These, in turn, have been associated with risk for deficits in memory, EF, attention or information processing. Atypical neuroimaging results have been observed among those who remain immunologically stable during childhood as well as those with more significant HIV related disease, including encephalopathy.[26–31]

Results of cross-sectional studies comparing memory and EF among children with PHIV with children with HIV exposure who are uninfected (PHEU) and children without HIV exposure have been mixed, depending in part upon measures used to evaluate memory and EF, health status of PHIV participants, sample sizes, and comparison groups.[32–34] A systematic review highlighted greater impairment among PHIV children compared to HIV unexposed and uninfected children in working memory, executive function and processing speed.[35] Memory and EF appear to vary among youth based on individual histories of disease severity and viral suppression, yet other factors, including socio-demographic characteristics, are also implicated.[36–37] Associations of Centers for Disease Control and Prevention (CDC)[38] Class C (AIDS-defining) diagnosis with poorer visual recognition memory among youth with PHIV have been observed, as well as associations between current immunologic status and poorer verbal learning.[39] Youth with Class C diagnoses also performed more poorly on some EF measures compared to PHEU youth and demonstrated poorer performance relative to youth with PHIV without class C diagnoses, particularly on timed measures of cognitive flexibility and inhibitory interference and control.[40]

While it appears clear that children and adolescents with PHIV are at risk for divergent development of higher-order cognitive functioning, little is known about the stability of their functioning as they age into adulthood. Few studies have addressed longitudinal changes in higher-order cognitive functioning in youth with PHIV and their relationship with disease severity and viral suppression in the era of effective ART. Early identification of persistent or newly developing problems would provide guidance regarding ART efficacy and offer opportunities for interventions to alter long-term cognitive outcomes and their impact on skills for successful adulthood. The purpose of this investigation was to examine associations of HIV infection and socio-demographic factors with change or stability of memory and EF outcomes during two years of follow-up among PHIV youth and a comparison group of PHEU youth; among PHIV youth, we evaluated the role of HIV disease characteristics in stability of such outcomes.

METHODS

Participants

Participants for this study were enrolled in the Memory and Executive Functioning Substudy (Memory/EF) of the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS).[41] Participants in the Memory/EF substudy, including PHIV and PHEU youth, were enrolled between 2010 and 2012 at 8 of the 15 AMP sites in the United States.[40] This paper presents analyses of change in memory and EF from baseline to follow-up two years later (herein referred to as “follow-up”). Eligibility criteria included enrollment in AMP, age 9 to <19 years at Memory/EF enrollment, ability to participate in testing procedures, and fluency in English (because some study measures were available only in English). PHIV youth were enrolled regardless of immune status or adherence history.

The Institutional Review Boards (IRBs) at each site and at the Harvard University T. H. Chan School of Public Health approved PHACS AMP and Memory/EF. Informed consent and assent were obtained from all participants and parents or legal guardians of participants younger than 18, according to local IRB guidelines. Data collection for AMP occurred at 6-

month (2007–2010) and annual (2010–2014) visits and included a physical exam, medical record review, structured interviews to obtain demographic and psychosocial information, and neurodevelopmental evaluations. The baseline assessment for the Memory/EF substudy was timed to coincide with collection of medical, demographic, and neurodevelopmental data in AMP. The follow-up evaluation occurred two years (±3 months) after baseline.

Measures

Retrospective memory and EF were evaluated using standardized measures with nationally representative normative samples for the age range of study participants and with established reliability and validity.[42–44] Invalid data were excluded from analysis based on data reviews by study psychologists. Details about the measures are presented below and in Supplemental Table 1.

Memory—Two subtests of the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2) were administered to assess learning and retrospective memory.[42] The Verbal Learning subtest, a measure of verbal memory, is a list-learning task that measures immediate and delayed recall, delayed recognition, and intrusion errors. The Design Memory subtest, measuring visual memory, requires examinees to draw geometric designs from memory and assesses delayed recall (10 sec.) and delayed recognition (10–15 mins.). The analyses included age-referenced scaled scores (Mean = 10; standard deviation [SD] = 3) and error scores.

Executive Function—Four subtests of the Delis-Kaplan Executive Function System (D-KEFS) were administered: Verbal Fluency, Design Fluency, Color-Word Interference (CWI), and Twenty Questions.[43] These tasks assess verbal and nonverbal fluency, cognitive flexibility, inhibitory control, problem-solving, and concept formation. Alternate versions of the D-KEFS Verbal Fluency and Twenty Questions subtests were used at follow-up to reduce likelihood of practice effects. The analysis included age-referenced scaled scores for the four subtests (Mean = 10, SD = 3) and error scores for all but Twenty Questions. For all D-KEFS subtests, higher scaled scores reflected better performance. For all measures of task errors, higher scaled scores indicated fewer errors.

Covariates and Potential Confounding Variables

Demographic information was obtained through parent and youth interviews conducted within AMP. Child information included age at study entry, sex, race/ethnicity, and primary language. Caregiver information included biological relationship to child, household income, and education. For youth with PHIV, historical and current health indicators were collected via chart abstraction and laboratory tests. The following variables were collected at entry into AMP and at the AMP visit closest in time to Memory/EF visits: current, nadir, and age at nadir CD4+ T-lymphocyte count and percent (CD4%); current HIV RNA viral load (VL), peak VL, and age at peak VL; CDC classification of HIV disease and age at first Class C classification; diagnosis of encephalopathy and age at diagnosis; and ART regimen.

Statistical Analysis

Three groups were defined: perinatally HIV-exposed, uninfected (PHEU); perinatally HIV-infected, no Class C diagnosis (PHIV/non-C); and perinatally HIV-infected with Class C diagnosis (PHIV/C). Only participants who completed both entry and follow-up Memory/EF evaluations were included in the analysis. Child and caregiver characteristics for the three groups were compared, using a Chi-Square test for categorical measures and Kruskal-Wallis test for continuous measures. The primary outcomes (memory and EF mean scores at baseline and follow-up) were summarized, and the proportions of the sample with scaled scores more than two SDs below the mean at each of the two time points were computed.

Our analysis included three different components: (1) comparison of changes in memory and EF across HIV status cohorts, 2) for PHIV, evaluation of baseline HIV disease measures as predictors of follow-up memory and EF, and (3) evaluation of changes in HIV disease severity measures as predictors of follow-up memory and EF. More specifically, changes from baseline (follow-up value minus baseline value) for each memory and EF outcome were computed and compared among the HIV-status cohorts, both unadjusted and adjusted for covariates. Adjusted linear models included HIV cohort and all potential confounders with unadjusted $p < 0.20$, with backward steps requiring $p < 0.15$ for inclusion in the final multivariable models. Generalized estimating equations (GEE) and robust error variances were used in all regression analyses. Least squares means and pairwise contrasts between cohorts were estimated along with their 95% confidence intervals.

For analyses of the associations of markers of baseline HIV disease severity and changes in HIV disease severity with follow-up memory and EF outcomes, unadjusted GEE linear regression models were used to estimate the association of child/caregiver characteristics and HIV disease severity measures with each memory and EF outcome. Based on these results, a core multivariable model was built for each memory and EF outcome, initially including all personal and family covariates with $p < 0.20$ in the univariable models and retaining only those with $p < 0.15$ in the core multivariable model. To each core model, we added each HIV disease severity marker (or change in HIV disease severity) and performed an adjusted regression analysis. Observations with missing values on any covariate were excluded from the analysis. Results with p-values < 0.05 were considered statistically significant. Given the exploratory nature of these analyses, no corrections were made for multiple comparisons, and observed findings warrant confirmation in future studies. Analyses were based on Memory/EF data submitted as of April 2015 and relevant AMP data submitted as of January 2015. SAS v9.2 or v9.4 (SAS Institute, Cary, NC) were used for all analyses.

RESULTS

Participant Characteristics

Table 1 presents relevant demographic and HIV-related characteristics of the study sample at follow-up (N = 223; PHEU = 79, PHIV/non-C = 105, PHIV/C = 39). The majority of youth were black (78%); 16% were Hispanic, and 55% were female. Youth with PHIV were significantly older than PHEU at follow-up (PHIV/non-C= 16.5 years, PHIV/C=17.2 years,

PHEU=14.9 years). Compared to the PHIV groups, PHEU youth were more likely to live in homes with a biological parent, a caregiver with HIV, and lower annual household income.

Compared with PHIV/non-C youth, those with PHIV/C diagnoses were significantly younger at the time of their most severe CDC staging and more likely to have nadir CD4% <15% and an encephalopathy diagnosis prior to or at entry (Table 2). Other disease severity markers among youth with PHIV did not differ at entry or follow-up and did not change significantly from baseline to follow-up. Approximately 75% entered the substudy with suppressed VL (< 400 copies/mL) and with CD4% ≥ 25%; there were no significant changes at follow-up. There were no differences in ARV regimens between PHV/C and PHIV/non-C at entry or follow-up.

Thirty-five (14%) of the original 258 study participants were unable to complete follow-up evaluations due to relocation (n = 14), unwillingness to participate (n = 13), severe debilitation or death (n = 5), or inability to contact (n = 3). Compared to participants with baseline but no follow-up data, those who were included in the longitudinal analysis were younger ($p = 0.04$), more often black ($p < 0.05$), and living with an HIV-uninfected caregiver ($p < 0.001$); fewer of their caregivers had unknown HIV status ($p < 0.001$).

Memory

Comparisons by HIV status and prior AIDS diagnosis—In unadjusted analyses, group means on the WRAML2 memory subtests were generally in the low-average to average range at both time points relative to the U.S. general population (Supplemental Table 2). Comparisons among the three cohorts revealed minimal, nonsignificant changes from baseline to follow-up in most memory measures (Supplemental Figure 1). Only a single pairwise comparison of adjusted mean change from baseline to follow-up in the Verbal Recognition task revealed significantly greater change; PHIV/non-C participants declined from baseline to follow-up by 0.79 points on average, whereas the PHEU group improved by 0.21 points (respective difference in mean changes for PHIV/non-C versus PHEU = −0.99; 95%CI: −1.80, −0.19; $p = 0.02$). No other significant differences in change in memory functioning across the three groups were observed.

Prospective associations with HIV disease markers—Among the two groups with PHIV, performance on follow-up measures of retrospective memory was associated with markers of HIV disease, adjusted for significant sociodemographic factors (Table 3). Participants with CD4% ≥ 25% at baseline achieved higher scores at follow-up than those with baseline CD4% <25% on tasks assessing Verbal Learning Delay Recall and Verbal Recognition, yet improvement in CD4% from baseline to follow-up was associated with poorer Verbal Learning scores at follow-up. Higher HIV VL at baseline was associated with lower performance on Verbal Recognition at follow-up. Participants in the PHIV/C group who were diagnosed before age 3 had lower Design Memory scores at follow-up than those diagnosed at older ages and those in the PHIV/non-C group.

Executive Function

Comparisons by HIV status and prior AIDS diagnosis—In unadjusted analyses at baseline and follow-up, group mean scores were generally in the low-average to average range among youth with PHIV/non-C and PHEU youth and in the borderline to low-average range among youth with PHIV/C (Supplemental Table 2). There were no significant group differences in change scores for PHIV and PHEU youth (Supplemental Figure 2); however, all three groups showed significant improvement from baseline to follow-up on the Verbal Category Switching Accuracy and CWI Inhibition tasks and fewer errors on both CWI Inhibition and CWI Inhibition/Switching. Participants performed more poorly on Verbal Category Fluency and Verbal Category Switching at follow-up.

Prospective associations with HIV disease markers—Among the two groups with PHIV, historical markers of HIV disease severity were associated with specific aspects of EF at follow-up, after adjusting for significant sociodemographic factors (Table 4). Youth with CDC Class C diagnoses at baseline and those with PHIV/C before age 3 achieved lower scores at follow-up on measures of Verbal Category Switching, Verbal Category Switching Accuracy, Design Fluency, and CWI Primary Combined. Youth with encephalopathy diagnoses similarly achieved lower scores on Verbal Category Switching, Verbal Category Switching Accuracy, and CWI Primary Combined. At follow-up, peak VL > 100,000 copies/mL was associated with lower scaled scores on CWI Inhibition/Switching, and more frequent errors on CWI Inhibition and CWI Inhibition/Switching.

Youth with nadir CD4% after age 5 performed more poorly at follow-up on CWI Inhibition, CWI Inhibition/Switching, and Twenty Questions; peak VL after age 5 was also associated with lower CWI Inhibition/Switching scores. Peak VL between ages 3 and 5 was associated with poorer performance on Verbal Letter Fluency.

Additional HIV disease markers evaluated during the two-year study interval were significantly associated with performance on EF tasks at follow-up. CD4% > 25% at baseline was associated with higher CWI Inhibition/Switching scores and fewer Design Fluency set loss errors. Higher CD4% at follow-up compared to baseline was associated with better performance on the CWI Primary Combined measure while higher VL at follow-up compared to baseline was associated with lower CWI Primary Combined scores and more frequent errors (lower scores) on CWI Inhibition at follow-up. Suppressed VL at baseline (VL < 400 copies/mL) was also associated with a greater number of CWI Inhibition errors, contrary to expectations.

Prevalence of Impairment in Memory and EF

Impairment, defined as performance > 2.0 SDs below the population mean (scaled scores ≤ 4, 2nd percentile), was observed more frequently than expected among study participants compared to the general population (Supplemental Table 3). The proportion of participants with scores in the impaired range at baseline or follow-up varied across measures and ranged from 0–29%. With rare exceptions, prevalence of impairment was generally <6 % for WRAML2 memory subtests and D-KEFS Design Fluency subtests. Impaired performance

was observed more frequently than expected for D-KEFS Verbal Category Fluency (0–29 %), Verbal Category Switching (5–14 %), and CWI tasks (2–23 %).

DISCUSSION

The development and integrity of memory and executive functions among youth with PHIV warrant careful consideration given their influence on learning and potential role in risk behaviors, adult health care management, and activities of daily living.[2] Our results are similar to other studies of youth with PHIV and PHEU youth in that they reveal generally low-average to average functioning across multiple memory and EF tasks, with increased risk observed among youth with histories of CDC Class C diagnoses.[37, 39–40] The results are encouraging in that they reveal no significant group differences or declines in performance among youth with PHIV and PHEU during two years of follow-up. The noted slight improvement in multiple EF and memory tasks could be a result of age-appropriate development, non-specific support services and/or to familiarity with test activities; the longitudinal reliability of each measure may be implicated as well. There was a very modest diminution among youth with PHIV/non-C compared to PHEU youth in only one task, a measure of verbal recognition memory, despite participants' potential risks for medication nonadherence and immune compromise during adolescence. Adequate immune health, which was observed among the majority of participants with PHIV, is likely protective and was positively associated with performance at follow-up, particularly on verbal memory tasks and several EF tasks.

Our results support the UNAIDS goals of early HIV diagnosis and early initiation of ART to prevent severe HIV-related complications and associated impact on higher-order cognitive functioning. In this study, youth with histories of severe HIV disease, as indicated by classification of CDC Class C diagnoses (including encephalopathy), achieved lower, clinically relevant scores on a number of memory and EF tasks. In addition, rates of impairment in EF tasks related to cognitive inhibition and interference control were higher at baseline and follow-up than rates observed in the US general population, particularly among those with PHIV/C. This pattern of impairment among those with PHIV/C has been observed in studies of global cognitive function and other cognitive domains among children with PHIV [45] and may be related to the early impact of HIV and its treatments on neural circuits supporting EF and early or intermittent inflammation of the central nervous system.

Deficits or impairment in specific memory or EF tasks, if present and especially if persistent, may have implications for youth with PHIV during transition to adulthood, when they are expected to simultaneously avoid risk, manage multiple demands, understand information in varied formats, and organize and communicate complex information regarding their HIV status, medication adherence, side effects, and other health needs. Youth with PHIV and memory or EF difficulties may require extensive preparation, practice, and collaboration as they assume responsibility for such tasks in adulthood, particularly if they are at greater sociodemographic risk. At the same time, the absence of significant impairment in memory and some EF tasks as well as relative memory and EF stability among many youth with PHIV in our study suggests the possibility of successful self-management of health care and

other adult responsibilities if other complications are avoided and adequate partnership and preparation for transition are provided.

Assumption of responsibilities for independent adulthood is challenging for most young people, with incremental change occurring across a number of years. If risk is apparent, our results may guide youth affected by HIV, including PHEU youth, their families and clinicians to identify strategies and implement interventions to support memory and EF prior to and during youth transition to adulthood. Educational or targeted training programs that recognize relative strengths and address specific weaknesses in memory or EF may be beneficial, especially among youth with global cognitive deficits.[46–48] Strategy-based interventions that have clear links to functional outcomes of interest may be appropriate for youth with PHIV who are assuming specific and critical adult responsibilities, such as health care self-management.[49] Cognitive behavioral therapy to address motivational factors, stress, and mental health may also have direct and indirect effects on new learning and development of adaptive skills, regardless of the presence or absence of memory and/or EF difficulties, particularly in light of increased risk for mood disorders and anxiety among adolescents and young adults with perinatal HIV exposure.[50–51] Further study is needed to delineate the efficacy and ecological validity of available approaches.

Our work is not without limitations. Participants who were lost to follow-up may have been at higher risk for memory and EF difficulties or more significant changes in physical health over time than those who remained enrolled. We did not enroll youth who were not fluent in English or those with significant impairment that precluded participation in testing procedures, limiting the generalizability of findings; we also were unable to include an HIV-unexposed comparison group. The two year interval between memory and EF evaluations and use of published alternative forms for two EF subtests, particularly the D-KEFS verbal fluency measure, likely minimized potential practice effects; however, differences in the alternative test norms may account in part for observed scaled score decline in several conditions. It is also possible that our measures of memory and EF were not sufficiently sensitive to subtle or non-linear memory or EF development or regression during the developmental period of adolescence.

Despite limitations, this study is one of the first to describe stability in memory and EF among youth with PHIV during adolescence, when risks to adherence, physical and mental health and behavioral functioning sometimes accelerate. Although HIV is among the diseases with dynamic effects upon the brain and cognitive development throughout life, our results, which warrant confirmation in future studies, allow cautious optimism regarding the cognitive developmental trajectory of children and adolescents with PHIV and their potential readiness to assume age-appropriate responsibilities as they become young adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

The following institutions, clinical site investigators and staff participated in conducting PHACS AMP; sites participating in the Memory Study and the site PI are marked with an asterisk. In alphabetical order: **Ann & Robert H. Lurie Children's Hospital of Chicago***: Ram Yogev, Margaret Ann Sanders, Kathleen Malee*, Scott Hunter; **Baylor College of Medicine***: William Shearer, Mary Paul, Norma Cooper, Lynnette Harris*; **Bronx Lebanon Hospital Center:** Murli Purswani, Mahboobullah Baig, Anna Cintron; **Children's Diagnostic & Treatment Center***: Ana Puga, Sandra Navarro, Patricia Garvie*, James Blood; **Children's Hospital, Boston*:** Sandra Burchett, Nancy Karthas, Betsy Kammerer*; **Jacobi Medical Center***: Andrew Wiznia, Marlene Burey, Molly Nozyce*; **Rutgers - New Jersey Medical School:** Arry Dieudonne, Linda Bettica, Susan Adubato; **St. Christopher's Hospital for Children:** Janet Chen, Maria Garcia Bulkley, Latreaca Ivey, Mitzie Grant; **St. Jude Children's Research Hospital***: Katherine Knapp, Kim Allison, Megan Wilkins*; **San Juan Hospital/Department of Pediatrics:** Midnela Acevedo-Flores, Heida Rios, Vivian Olivera; **Tulane University Health Sciences Center***: Margarita Silio, Medea Jones, Patricia Sirois*; **University of California, San Diego***: Stephen Spector, Kim Norris, Sharon Nichols*; **University of Colorado Denver Health Sciences Center**: Elizabeth McFarland, Alisa Katai, Jennifer Dunn, Suzanne Paul; **University of Miami:** Gwendolyn Scott, Patricia Bryan, Elizabeth Willen.

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Table 1

Personal and Family Characteristics of 223 Perinatally HIV-Infected and Perinatally HIV-Exposed Uninfected Participants of the PHACS Memory and Executive Functioning Study

		Study Group			
Characteristic	**Total (N=223)**	**PHEU (n=79)**	**PHIV/ non-C (n=105)**	**PHIV/C (n=39)**	**P-Value**
Male sex	101 (45%)	39 (49%)	49 (47%)	13 (33%)	0.24
Age at entry, years, mean (SD)	14.0 (2.8)	12.8 (2.6)	14.4 (2.8)	15.2 (2.3)	<0.001
Age at follow-up, years, mean (SD)	16.1 (2.8)	14.9 (2.6)	16.5 (2.8)	17.2 (2.3)	<0.001
Race					0.46
White	43 (19%)	15 (19%)	22 (21%)	6 (15%)	
Black	173 (78%)	62 (79%)	81 (77%)	30 (77%)	
Other/Unknown	7 (3.1%)	2 (2.5%)	2 (1.9%)	3 (7.7%)	
Hispanic ethnicity	36 (16%)	16 (20%)	13 (13%)	7 (18%)	0.35
Child's primary language is English	207 (93%)	70 (89%)	101 (96%)	36 (92%)	0.14
Primary caregiver is biological parent	123 (55%)	60 (76%)	45 (43%)	18 (46%)	<0.001
Primary caregiver is high school graduate	172 (77%)	60 (76%)	84 (80%)	28 (72%)	0.55
Annual household income > $20,000	108 (48%)	26 (33%)	63 (60%)	19 (49%)	<.001
Caregiver HIV status					
HIV-uninfected	94 (42%)	18 (23%)	58 (55%)	18 (46%)	<.001
HIV-infected	110 (49%)	56 (71%)	40 (38%)	14 (36%)	
HIV status unknown	19 (8.5%)	5 (6.3%)	7 (6.7%)	7 (18%)	
Caregiver Race					
White	68 (32%)	21 (28%)	36 (35%)	11 (31%)	0.17
Black	136 (64%)	52 (69%)	64 (62%)	20 (57%)	
Other/Unknown	9 (4.2%)	2 (2.7%)	3 (2.9%)	4 (11%)	
Missing	10	4	2	4	

Note. P-value by Chi-Square Test for categorical measures and by Kruskal-Wallis Test for continuous measures. PHEU: perinatally HIV-exposed, uninfected; PHIV/non-C: perinatally acquired HIV, without CDC Class C diagnosis; PHIV/C: perinatally acquired HIV, with CDC Class C diagnosis.

Table 2

Measures of HIV Disease Severity and Antiretroviral Regimens for 144 Perinatally HIV-Infected Participants of the PHACS Memory and Executive Functioning Study

Characteristic	Total (N=144)	Study group PHIV/non-C (N=105)	Study group PHIV/C (N=39)	P-Value
HIV disease history, n (%)				
Nadir CD4% < 15%	58 (40%)	33 (31%)	25 (64%)	<.001
Age at nadir CD4%, years				0.66
0 – 3	59 (41%)	43 (41%)	16 (41%)	
> 3 to 5	20 (14%)	13 (12%)	7 (18%)	
> 5	65 (45%)	49 (47%)	16 (41%)	
Log peak HIV VL, median (IQR)	5.73 (5.34, 5.88)	5.73 (5.20, 5.88)	5.84 (5.43, 5.89)	0.17
Peak HIV VL > 100,000 copies/mL	121 (84%)	85 (81%)	36 (92%)	0.10
Age at peak viral load, years				0.45
0 – 3	97 (67%)	73 (70%)	24 (62%)	
> 3 to 5	12 (8%)	7 (7%)	5 (13%)	
> 5	35 (24%)	25 (24%)	10 (26%)	
Prior encephalopathy	15 (10%)	1 (1%)	14 (36%)	<.001
Age at first CDC Class C diagnosis prior to entry				0.025
0 – 3	83 (58%)	55 (52%)	28 (72%)	
> 3 to 5	18 (13%)	12 (11%)	6 (15%)	
> 5	43 (30%)	38 (36%)	5 (13%)	
HIV disease severity at study entry				
CD4 count (cells/mm^3), median (IQR)	655 (489, 882)	660 (495, 884)	620 (450, 861)	0.48
CD4 percent ≥ 25%, n (%)	112 (78%)	82 (78%)	30 (77%)	0.88
Log HIV-1 RNA VL, median (IQR)	1.68 (1.67, 2.57)	1.68 (1.68, 2.48)	1.68 (1.60, 2.96)	0.99
Unsuppressed VL (>400 copies/mL, n (%)	36 (25%)	25 (24%)	11 (28%)	0.59
HIV disease severity at follow-up, median (IQR)				
CD4 count (cells/mm^3)	639 (461, 880)	660 (487, 868)	573 (368, 885)	0.31
CD4 percent	35 (27, 41)	36 (29, 41)	31.4 (22, 40)	0.15
Log HIV-1 RNA VL	1.60 (1.30, 2.69)	1.60 (1.30, 2.50)	1.60 (1.30, 3.15)	0.16
Changes in HIV disease severity (follow-up – entry), median (IQR)				
CD4 count (cells/mm^3)	−34 (−164, 83)	−30 (−162, 73)	−78 (−193, 83)	0.38
CD4 percent	0.9 (−3.1, 3.2)	1.0 (−3.0, 3.1)	0.0 (−4.0, 3.2)	0.52
Log HIV-1 RNA VL	0.00 (−0.38, 0.19)	−0.08 (−0.38, 0.00)	0.00 (−0.38, 0.68)	0.12
Antiretroviral (ARV) Regimens				
ARV regimen at entry				0.86

Characteristic	Total (N=144)	Study group PHIV/non-C (N=105)	PHIV/C (N=39)	P-Value
HAART with PI	96 (67%)	69 (66%)	27 (69%)	
HAART without PI	32 (22%)	23 (22%)	9 (23%)	
Non-HAART ARV	7 (4.9%)	6 (5.7%)	1 (2.6%)	
Not on ARV	9 (6.3%)	7 (6.7%)	2 (5.1%)	
ARV regimen at follow-up				0.35
HAART with PI	66 (52%)	48 (53%)	18 (51%)	
HAART without PI	44 (35%)	31 (34%)	13 (37%)	
Non-HAART ARV	6 (4.8%)	4 (4.4%)	2 (5.7%)	
Not on ARV	10 (7.9%)	8 (8.8%)	2 (5.7%)	
ARV regimen change in 4 months before study entry	15 (10%)	11 (11%)	4 (10%)	0.97

Note. P-value by Chi-Square Test for categorical measures and by Kruskal-Wallis test for continuous measures. The following characteristics were unavailable or not reported for some participants: follow-up CD4 count and CD4% (n=5), follow-up VL (n=4), change in CD4 count and CD4% (n=5), change in VL (n=4). PHEU: perinatally HIV-exposed, uninfected; PHIV/non-C: perinatally acquired HIV, without CDC Class C diagnosis; PHIV/C: perinatally acquired HIV, with CDC Class C diagnosis; VL: viral load; IQR=interquartile range; ARV=antiretroviral; HAART=highly active antiretroviral treatment (at least 3 drugs from at least 2 drug classes); PI=protease inhibitor.

Table 3

Adjusted Means and Adjusted Mean Changes in Follow-up Measures of Retrospective Memory (WRAML2) for Specific HIV Disease Severity Measures* in Youth with PHIV

		Adjusted Results	
Disease Severity Measure	**Covariate/Level**	**Mean (95% CI) or Estimate (SE)**	**P-Value**
Verbal Learning [1,2,3]			
Positive Change in CD4%	(continuous)	−0.08 (0.03)	0.01
Verbal Delay Recall [1,2,4]			
CD4% ≥ 25% at entry	≥ 25%	9.45 (8.94,9.96)	0.05
	< 25%	8.60 (7.80,9.40)	
Verbal Recognition [2,5]			
CD4% ≥ 25% at entry	≥ 25%	9.94 (9.45, 10.44)	0.001
	< 25%	8.45 (7.65, 9.24)	
Log HIV RNA VL at entry	(continuous)	−0.50 (0.21)	0.02
Design Memory [2,6]			
Age at CDC Class C	0 – 3 years	7.63 (6.71, 8.56)	0.01
	> 3 years	9.83 (8.06, 11.60)	
	PHIV/non-C status	9.14 (8.60, 9.69)	

Note. *Table includes only those HIV disease severity measures with significant differences in adjusted means (categorical covariates) or significant regression coefficients (continuous measures). The adjusted mean and 95% CI are provided for each level of categorical covariates. For continuous covariates, the adjusted mean change (and standard error) in outcome for each one-unit change in predictor is presented. Adjusted models included the following covariates: 1-Black race; 2-age at Memory/EF entry; 3-annual household income > $20,000; 4-male sex; 5-caregiver is high school graduate; 6-caregiver is biological parent. PHIV/non-C: perinatally acquired HIV, without CDC Class C diagnosis; VL: viral load.

Table 4

Adjusted Means and Adjusted Mean Changes in Follow-up Measures of Executive Function (D-KEFS) for Specific HIV Disease Severity Measures in Youth with PHIV *

		Adjusted Results	
Disease Severity Measure	**Covariate/Level**	**Mean (95% CI) or Estimate (SE)**	**P-Value**
Verbal Letter Fluency[7]			
Age at peak HIV VL, years	0 – 3	8.33 (7.66, 9.00)	0.04
	> 3 – 5	6.90 (5.59, 8.21)	
	> 5	8.77 (7.59, 9.96)	
Verbal Category Switching [2,7]			
CDC Class C	PHIV/C	6.31 (5.32, 7.31)	0.05
	PHIV/non-C	7.39 (6.61, 8.16)	
Age at CDC Class C, years	0 – 3	5.85 (4.76, 6.93)	0.01
	> 3	8.00 (6.19, 9.82)	
	PHIV/non-C	7.41 (6.63, 8.19)	
Encephalopathy diagnosis	Encephalopathy	5.25 (3.91, 6.59)	0.003
	No encephalopathy	7.33 (6.63, 8.02)	
Verbal Category Switching Accuracy [2,4]			
CDC Class C	PHIV/C	9.19 (8.75, 9.63)	0.04
	PHIV/non-C	9.78 (9.43, 10.13)	
Age at CDC Class C, years	0 – 3	8.94 (8.49, 9.38)	0.01
	> 3	10.08 (8.98, 11.18)	
	PHIV/non-C	9.78 (9.43, 10.12)	
Encephalopathy diagnosis	Encephalopathy	8.73 (8.13, 9.34)	0.004
	No encephalopathy	9.74 (9.43, 10.04)	
Design Fluency Composite [3,6]			
CDC Class C	PHIV/C	7.97 (7.27, 8.67)	0.01
	PHIV/non-C	9.05 (8.60, 9.50)	
Age at CDC Class C, years	0 – 3	7.93 (7.14, 8.73)	0.04
	> 3	8.09 (6.63, 9.54)	
	PHIV/non-C	9.05 (8.60, 9.50)	
Design Fluency Set Loss Errors[1]			
CD4% ≥ 25% at entry	≥ 25%	12.39 (12.04, 12.74)	0.05
	< 25%	11.24 (10.15, 12.32)	
Color-Word Interference (CWI)Primary Combined [1,2,3,5,7]			
CDC Class C	PHIV/C	7.33 (6.22, 8.44)	0.02

		Adjusted Results	
Disease Severity Measure	**Covariate/Level**	**Mean (95% CI) or Estimate (SE)**	**P-Value**
	PHIV/non-C	8.61 (7.93, 9.29)	
Age at CDC Class C, years)	0 – 3	6.97 (5.84, 8.10)	0.02
	> 3	8.48 (6.37, 10.58)	
	PHIV/non-C	8.63 (7.95, 9.31)	
Encephalopathy diagnosis	Encephalopathy	6.31 (4.82, 7.79)	0.003
	No encephalopathy	8.50 (7.86, 9.15)	
Positive Change in CD4%	(continuous)	0.05 (0.02)	0.02
Change in log HIV-1 RNA VL	(continuous)	−0.67 (0.26)	0.01
Color-Word Interference (CWI) Inhibition [1,2]			
Age at nadir CD4% (years)	0 – 3	8.87 (7.98, 9.77)	0.01
	> 3 – 5	10.38 (9.19, 11.57	
	> 5	8.02 (7.05, 9.00))	
Color-Word Interference (CWI) Inhibition/Switching [1,8]			
CD4% ≥ 25% at entry	≥ 25%	10.03 (9.30, 10.76)	0.05
	< 25%	8.68 (7.26, 10.10)	
Age at nadir CD4%, years	0 – 3	10.05 (9.06, 11.04)	0.03
	> 3 – 5	11.18 (9.98, 12.38)	
	> 5	9.50 (8.49, 10.51)	
Change in log HIV-1 RNA VL	(continuous)	−0.54 (0.26)	0.04
Peak HIV VL > 100,000 copies/mL	> 100,000	9.51 (8.89, 10.12)	0.01
	0 – 100,000	10.99 (10.00, 11.98)	
Age at HIV peak VL, years	0 – 3	10.23 (9.30, 11.15)	0.04
	> 3 – 5	11.33 (9.87, 12.79)	
	> 5	9.11 (7.93, 10.29)	
Color-Word Interference (CWI) Inhibition Total Errors [8]			
Log HIV-1 RNA VL at entry	≤ 400	10.13 (9.04, 11.21)	0.04
	> 400	11.26 (10.11, 12.42)	
Peak HIV VL > 100,000 copies/mL	> 100,000	10.02 (9.00, 11.04)	< 0.001
	0 – 100,000	11.87 (10.82, 12.93)	
Change in log HIV-1 RNA VL	(continuous)	−0.76 (0.31)	0.01
Color-Word Interference (CWI) Inhibition/Switching Total Errors [1,2]			
Peak HIV VL > 100,000 copies/mL	> 100,000	9.53 (8.95, 10.11)	0.01
	0 – 100,000	10.89 (10.03, 11.75)	
20 Questions Weighted Achievement [1,3]			
Age at nadir CD4%, years	0 – 3	9.72 (9.20, 10.23)	0.01

		Adjusted Results	
Disease Severity Measure	**Covariate/Level**	**Mean (95% CI) or Estimate (SE)**	**P-Value**
	> 3 – 5	10.29 (9.38, 11.21)	
	> 5	8.64 (7.85, 9.43)	

Note. *Table includes only those HIV disease severity measures with significant differences in adjusted means (categorical covariates) or significant regression coefficients (continuous measures). The adjusted mean and 95% CI are provided for each level of categorical covariates; for continuous covariates, the adjusted mean change (and standard error) in outcome for each one-unit change in predictor is presented. Adjusted models included the following covariates: 1-Black race, 2-age at entry, 3-annual household income > $20,000, 4-male sex, 5-caregiver is high school graduate, 6-caregiver is biological parent, 7-Hispanic ethnicity, and 8-primary language of child is English. PHIV/non-C: perinatally acquired HIV, without CDC Class C diagnosis; PHIV/C: perinatally acquired HIV, with CDC Class C diagnosis; VL: viral load.