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Learning and Memory in Children and Adolescents with Perinatal HIV Infection and Perinatal HIV Exposure

Sharon L. Nichols, PhD¹, Miriam C. Chernoff, PhD², Kathleen Malee, PhD³, Patricia A. Sirois, PhD⁴, Paige L. Williams, PhD², Veronica Figueroa, MA¹, Steven P. Woods, PsyD⁵, and for the Memory Substudy of the Pediatric HIV/AIDS Cohort Study

¹University of California, San Diego; La Jolla, California

²Harvard School of Public Health; Boston, Massachusetts

³Northwestern University Feinberg School of Medicine; Chicago, Illinois

⁴Tulane University School of Medicine; New Orleans, Louisiana

⁵University of Houston; Houston, Texas

Abstract

Background—Learning and memory in youth with perinatally acquired HIV (PHIV) are poorly understood despite their importance for academic, healthcare, and daily functioning.

Methods—PHIV (n=173) and perinatally HIV-exposed but uninfected (PHEU, n=85) participants (age 9–19 years) in a substudy of the Pediatric HIV/AIDS Cohort Study completed age-standardized tests of verbal and visual learning and delayed memory. Linear regression models implemented via generalized estimating equations were used to compare memory measures in PHEU participants versus PHIV youth with and without Centers for Disease Control and Prevention (CDC) Class C diagnosis (PHIV-C, n=45; PHIV-non-C, n=128, respectively), adjusting for sociodemographic covariates.

Results—Participants (mean age=14.10 years) were 54% female, 75% Black, and 18% Hispanic. Although unadjusted analyses showed significantly lower visual recognition memory and verbal delayed recall for PHIV-C compared to PHEU participants and lower verbal learning for PHIV-C and non-C groups compared to PHEU, differences persisted only for visual recognition memory after adjusting for sociodemographic covariates. For PHIV youth, current CD4%<25 was associated with poorer verbal learning, and older age at peak viral load was associated with poorer verbal delayed recall and design memory.

Conclusions—Youth with PHIV, particularly those with CDC Class C diagnosis, showed poorer performance on some measures of learning and memory compared to PHEU. Although group differences in verbal memory were largely attributable to sociodemographic characteristics,

Corresponding author: Sharon L. Nichols, Ph.D., University of California, San Diego, 9500 Gilman Drive, Mail Code 0935, La Jolla, California 92093, Phone: 858-822-6700/Fax: 858-822-6707, slnichols@ucsd.edu.

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associations of Class C diagnosis with poorer visual recognition memory and of current CD4% with poorer verbal learning suggest subtle effects of HIV on learning and memory in youth with PHIV.

Keywords

HIV; children; adolescents; learning; memory; perinatal HIV exposure

INTRODUCTION

Decades of research have demonstrated neurocognitive risks of perinatally acquired HIV (PHIV)¹⁻⁴. Results of studies comparing children with PHIV to those perinatally exposed to HIV but uninfected (PHEU) and examining the impact of disease severity largely agree that children with PHIV and history of severe immunosuppression (Centers for Disease Control and Prevention [CDC] Class C [AIDS-defining] diagnosis⁵) are at risk for global neurocognitive impairments despite later immune reconstitution and viral control^{6,7}. Concern persists that youth with well-controlled PHIV remain at risk for subtle neurocognitive abnormalities in specific cognitive domains that could affect academic, functional, and health outcomes, particularly during the transition through adolescence into adulthood.

Learning and memory are cognitive domains known to be at risk in adults with HIV⁸ and youth with behaviorally acquired HIV⁹ in the era of combination antiretroviral therapy¹⁰. The profile of memory deficits in HIV disease is typically characterized by difficulties in efficiently acquiring and retrieving new information in non-structured formats (e.g., free recall vs. recognition); there is no strong evidence of prominent forgetting *per se*. HIV-associated learning and memory deficits in adults have demonstrated associations with poorer functional outcomes such as medication non-adherence and loss of independence in activities of daily living¹¹⁻¹³. However, few studies of memory and learning have been conducted with children and adolescents with PHIV, despite the relevance of these processes to the primary developmental tasks of childhood and adolescence as well as occupational and healthcare outcomes in adulthood. The limited literature on learning and memory in PHIV suggests poorer performance on measures of verbal and visual recall in children with PHIV compared to non-infected youth or normative data¹⁴⁻¹⁸, although some studies have not shown differences¹⁸. Like adults, children may also show a pattern of differentially worse recall than recognition memory, suggesting difficulties in acquiring and retrieving new information¹⁹. One study of children with PHIV, using magnetic resonance spectroscopy, demonstrated relationships between choline concentrations and spatial memory¹⁹. The existing pediatric literature is limited by small sample sizes, lack of studies that include measures of verbal and nonverbal learning and memory, and inadequate consideration of other cognitive functions such as language and processing speed, despite studies indicating PHIV-associated differences in these additional functions²⁰.

Advances in antiretroviral therapy have transformed HIV disease into a chronic, manageable illness, and youth with PHIV are living longer lives. Along with the possibility of adulthood comes the responsibility for assuming productive roles in society while managing a chronic

illness. If present, HIV-associated impairments in learning and memory require educational and life-skills interventions to prepare youth for transition to adulthood. Such impairments may also offer clues to the neuropathogenesis of PHIV.

The present study compared verbal and nonverbal memory and learning in children and adolescents with PHIV to PHEU children. We hypothesized that youth with PHIV and more severe HIV disease would show impaired learning and memory compared to PHEU youth and to population normative standards, and furthermore that impairments would not be completely accounted for by poorer functioning in other cognitive domains.

METHODS

Participants and Study Procedures

Participants for this study were enrolled in a substudy of the Pediatric HIV/AIDS Cohort Study (PHACS) network Adolescent Master Protocol (AMP; the parent study), a prospective cohort study of long-term effects of perinatal HIV infection and its treatments on biomedical and neurobehavioral outcomes in PHIV and PHEU youth (<https://phacsstudy.org>). The parent study's cohorts of 451 PHIV and 227 PHEU participants were enrolled in 2007–2009 at ages 7–15 years. Participants in the substudy were enrolled in 2010–2012 at 8 of the 15 parent study sites in the United States. The substudy was a longitudinal assessment of retrospective and prospective memory and executive functions following perinatal HIV exposure and/or infection. Eligibility criteria included perinatal HIV infection or exposure, age 9 to <19 years, enrollment in the parent study, ability to participate in testing procedures, and fluency in English (some study measures were available only in English). This paper presents analyses of baseline data from the retrospective memory and learning component of the study.

The Institutional Review Boards at each site and at the Harvard School of Public Health approved the parent study and memory substudy. Informed consent for participation was obtained from all participants and from parents or legal guardians of participants younger than 18, according to local Institutional Review Board guidelines. Data collection for the parent study occurred at 6-month (2007–2010) and annual (2010–2014) visits and included a physical exam, medical record review, structured interviews for demographic information, and neurodevelopmental evaluations. The baseline assessment for the memory substudy occurred around the 2.5 or 3 year parent study visit to coincide with collection of other medical, demographic, and neurodevelopmental data.

Measures

Learning and memory—Two subtests of the Wide Range Assessment of Memory and Learning—Second Edition²¹ (WRAML-2), standardized for ages 5–90 years, were administered to assess learning and retrospective memory. The Verbal Learning subtest requires the examinee to listen to a 16-word list read by the examiner three times and recall the words immediately following each presentation (learning trials). Examinees are asked for delayed recall of the list after approximately 15 minutes of intervening nonverbal tasks, immediately followed by yes/no recognition of words from the list embedded in a longer list

of distractor words. Recall of words that were not on the list counts as intrusion errors. For the Design Memory subtest, the examiner sequentially presents five geometric designs to the examinee, who is asked to draw each from memory following a 10-second delay (referred to as immediate visual memory below). Approximately 15 minutes later, to assess delayed visual recognition memory, the examinee is shown 46 geometric shapes and asked to indicate which ones were seen previously. Analyses of both subtests used age-adjusted scaled scores, normed with a mean of 10 and standard deviation of 3.

Covariates—The parent study collected demographic information via structured interviews with primary caregivers. Child information included age, sex, race/ethnicity, and primary language. Caregiver information included relationship to child, household income, and caregiver education. For youth with PHIV, the following historical and current health indicators were included, collected by the parent study via chart abstraction at entry and at the visit closest in time to the memory substudy visit: current HIV-1 RNA viral load; peak viral load and age at peak viral load; current, nadir, and age at nadir CD4+ T-lymphocyte count and percent (CD4%); CDC classification of HIV disease⁵ and age at first CDC Class C classification; diagnosis of encephalopathy and age at diagnosis; and use of antiretroviral treatment.

Other measures of behavioral, cognitive and academic functioning administered as part of the parent study were used as covariates in some analyses to examine whether their inclusion altered the observed relationships of learning and memory with HIV disease and severity. These measures included parent- and child-reported symptoms of depression (Behavior Assessment System for Children--Second Edition²² Depression Scale [T-scores]); Digit Span and Coding subtests (scaled scores) of the Wechsler Intelligence Scale for Children, Fourth Edition²³ or Wechsler Adult Intelligence Scale, Fourth Edition²⁴, to measure auditory attention and processing speed, respectively; the Word Reading subtest (standard score) of the Wechsler Individual Achievement Test, Second Edition, Abbreviated²⁵; and the Clinical Evaluation of Language Fundamentals, Fourth Edition²⁶ Core Language Score (standard score) to measure language functioning. The Digit Span and Coding subtests were administered at the same visit or within two weeks of the memory substudy assessment. The other measures were administered at scheduled parent study visits at 2, 2.5, or 3 years after parent study entry.

Statistical Methods

Univariate and multivariable linear regression models were used to analyze group differences among PHIV youth with prior CDC Class C diagnosis (PHIV-C), PHIV youth without Class C diagnosis (PHIV non-C), and PHEU youth. Multiple regression models were used to control for the following potential confounders: participant sex, age at evaluation, race (black versus non-black), ethnicity (Hispanic versus non-Hispanic), participant's primary language (English versus non-English), caregiver relationship to child (biological parent versus other relationship), annual household income (<\$20,000 versus ≥\$20,000), and whether or not the caregiver was a high school graduate. Generalized estimating equation models were used to compare the three groups with respect to memory outcomes, both unadjusted and adjusting for covariates with $p < 0.15$. Covariates retained in the adjusted

model were selected by first considering those with unadjusted $p < 0.20$ and using a modified stepwise algorithm to reduce to a multivariable model including covariates with $p < 0.15$. Among PHIV youth, generalized estimating equation models were also used to evaluate associations between memory outcomes and markers of disease severity noted previously, after adjusting for base models developed for each outcome using child and family characteristics. Pre-specified pairwise comparisons were tested between measures of immediate and delayed verbal recall and between measures of delayed verbal recall and recognition. Last of all, the influence of other cognitive functions, reading and depression on the observed differences between PHIV-C and PHEU groups was evaluated by refitting models showing significant pairwise comparisons by adding each of the scores from other behavioral and cognitive measures (described above) separately to assess the impact on estimated group differences. A significance level of $p < 0.05$ was used for analyses; correction for multiple comparisons was not performed due to the exploratory nature of the study. Analyses were performed using SAS V9.2.

RESULTS

Participant Characteristics

Participants included youth with PHIV (PHIV-C = 45; PHIV non-C = 128) and PHEU youth ($n = 85$). Table 1 presents the means and/or proportions for demographic and disease-related variables. The participants were 54% female, 75% Black, and 18% Hispanic. Mean ages for each group at entry were 12.9 years (PHEU), 14.5 years (PHIV non-C), and 15.5 years (PHIV-C). Youth with PHIV were significantly older than PHEU, and PHIV-C were significantly older than PHIV non-C. PHEU youth were more likely to live with a biological parent, with a caregiver with HIV, and in homes with lower annual income. More than two thirds of study participants with PHIV entered the memory substudy with suppressed viral load (< 400 copies/mL) and with CD4% ≥ 25 . At study entry, 11 (6.4%) participants with PHIV were not on antiretroviral therapy. Youth with PHIV-C were more likely to have lower current CD4%, lower nadir CD4%, higher peak viral load, and previous diagnosis of encephalopathy. Demographic and disease characteristics of substudy participants were comparable to those of the parent study except that a greater proportion of substudy (75%) than parent study (61%) participants had peak viral load $> 100,000$ copies/mL ($p = 0.03$).

Measures of Learning and Memory: Group Comparisons

Table 2 shows mean subtest scores for the WRAML-2 and comparisons for the three groups. In unadjusted analyses, group means for verbal and visual learning and recognition were generally within the low-average to average range relative to the WRAML-2 normative sample. Delayed visual recognition memory was significantly lower for PHIV-C compared to PHEU youth in both unadjusted (mean difference = -1.14 , $p = 0.04$) and adjusted (mean difference = -1.12 , $p = 0.04$) analyses. Significantly lower verbal learning scores were also observed in unadjusted analyses for PHIV-C and PHIV non-C compared to PHEU and lower verbal delayed recall for PHIV-C compared to PHEU (Table 2); however, these differences did not persist after adjustment for caregiver education and relationship to child. Following adjustment for core model covariates, there were no significant differences in delayed verbal recognition, immediate visual memory, or number of verbal intrusion errors among the

PHIV-C, PHIV non-C, and PHEU youth. The proportion of participants with scores in the clinically impaired range (defined as >2.0 standard deviations below the normative mean) ranged from 0 to 6.7% and did not differ between groups.

Pairwise comparison of verbal immediate versus delayed recall and of verbal delayed recall versus recognition revealed significantly lower immediate than delayed recall for the PHIV non-C group and lower delayed recall than recognition for all three groups. There were no significant interactions between HIV group and performance on the verbal memory tasks.

Associations of learning and memory with disease severity

Certain markers of HIV disease severity were associated with specific aspects of verbal and visual learning and memory among youth with PHIV (Table 3). Lower current CD4% was associated with poorer verbal learning. Higher viral load at study entry was associated with lower delayed visual memory scores. Children who were older at the time of peak viral load achieved lower mean scores on measures of immediate and delayed visual memory and delayed verbal memory.

Adjustment for associations with other cognitive and behavioral measures

Adjusting in separate models for Digit Span and Coding subtest scores and Word Reading standard scores attenuated the contrast between the PHIV-C and PHEU youth so that they were no longer significant. Adjusting for the Core Language Score increased the size of the HIV effects and significance level in the comparison of delayed visual memory scores across groups.

DISCUSSION

The findings from this study indicated that youth with PHIV achieved lower scores on measures of verbal learning (word list acquisition) and delayed visual memory (recognition of designs) than PHEU youth. This pattern was evident in youth with PHIV who had lower current (CD4%) and historical (Class C diagnosis) markers of immune functioning, respectively. Of interest, their lower verbal learning performance was mediated by socioeconomic factors, but their lower performance on the delayed visual memory task persisted in multivariable models that included those socioeconomic factors. In the absence of HIV-associated deficits in immediate visual memory, these data suggest that youth with PHIV are at risk for inefficient encoding and forgetting of visual information. Attenuation of the significant effect for visual memory by adjustment for variables measuring attention, processing speed, and reading suggests cognitive processes that may be involved in the poorer visual memory of youth with PHIV-C.

Similar to prior studies of global cognitive functioning, youth with PHIV generally performed within the low-average to average range on measures of memory and learning^{6,27}, although youth with CDC Class C diagnoses demonstrated poorer performance than youth with PHIV non-C and PHEU. It should be noted that all three groups had the greatest difficulty with immediate recall on the learning trials. For both groups with HIV, this was particularly true on the verbal task, with verbal learning being the only measure on which the PHIV-C group performed below age expectations. Thus, acquisition of verbal

information may present an area of particular risk for this population, consistent with the relatively high rate of learning disabilities reported among youth with PHIV⁷. The analyses demonstrated that influences other than HIV infection may account for much of this risk. A number of factors known to affect memory and language development in children were present in our cohort; for example, poverty is associated with differences in brain functioning^{28,29} and may amplify pre-existing cognitive risks³⁰. The relative contributions of some other risks likely present in our sample, including prenatal exposure to antiretroviral medications and family history of language delay or learning disability, could not be evaluated due to the absence of a control group without perinatal HIV exposure.

The significant association of verbal learning and visual recognition with markers of current disease severity suggests the possibility of an ongoing subtle impact of HIV infection that warrants further study. This is consistent with the literature on HIV in adults demonstrating associations between cognitive functioning and recent clinical history³¹, and with data from PHACS showing associations of cognitive functioning with measures of ongoing inflammation and endothelial dysfunction^{32,33}. These findings indicate that learning and memory should be monitored carefully in children and adolescents with PHIV. Associations of lower memory functioning with Class C diagnosis emphasize the importance of early treatment to prevent significant disease progression³⁴. The lower scores observed with older age at peak viral load seem counterintuitive; it is possible, however, that high viral load earlier in life triggered the initiation of early antiretroviral therapy, which, with adequate adherence, prevented cognitive impairment. Further study is needed to examine this hypothesis.

The implications of learning and memory problems for child and youth development are critical regardless of the origin of the problems. In general, there is concern regarding the cumulative toll of mild cognitive deficits and other mental health and psychosocial risks on long-term functional outcomes as youth with PHIV transition to adulthood and acquire skills required for independent living. Their ability to manage healthcare and medication needs and to maintain viral suppression is important to prevent transmission of HIV to sexual partners and unborn children, thus having clear public health implications as well as affecting longevity and quality of life. It will be important to determine whether difficulties in verbal learning contribute to poorer educational, occupational, and health management outcomes and, if so, to promote appropriate interventions. Acquisition of knowledge and skills is a major life task for youth in general. Identification of learning and memory deficits in youth with PHIV and of the relative contribution of other cognitive processes could guide neurocognitive rehabilitation efforts earlier in the disease process as well as individualized training in healthcare management skills, using techniques drawn from the rich literature in cognitive psychology that have been useful in educational settings³⁵.

The present study had several limitations. Because the instruments used are available only in English, we were unable to evaluate monolingual Spanish-speaking youth. Youth who had significant motor, sensory, or intellectual impairment that precluded participation in testing were excluded. A comparison group of youth without perinatal HIV exposure was not available; however, the comparison group we used was conservative. The normative sample of the WRAML-2 was representative of the entire U.S. population rather than matching the

demographic characteristics of our sample. Participation in the parent study and substudy required substantial time commitments; participants might not be representative of all youth with PHIV. Finally, analyses were performed without correction for multiple comparisons.

In summary, our research suggests that youth with perinatal exposure to HIV, regardless of infection status, are at risk for impairments in learning and memory, but youth with PHIV who have also experienced severe immunocompromise are particularly vulnerable. Although the results suggest that there may be ongoing effects of HIV on learning, further research is needed to understand the findings more fully. In the meantime, clinical evaluation of learning and memory in young people with PHIV may provide medical and educational personnel with important information that can guide treatment and intervention planning.

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Table 1

Demographic and disease characteristics for all groups.

Characteristic		PHEU (N=85)	PHIV Non-C (N=128)	PHIV-C (N=45)	P-value*
Participant age	Mean (SD)	12.86 (2.57)	14.45 (2.72)	15.46 (2.37)	<0.001
Sex	Female	41 (48.2%)	69 (52.9%)	29 (64.4%)	0.21
	Male	44 (51.8%)	59 (46.1%)	16 (35.6%)	
Race	White	18 (21.2%)	28 (21.9%)	8 (17.8%)	0.62
	Black	65 (76.5%)	95 (74.2%)	34 (75.6%)	
	Other	1 (1.2%)	2 (1.6%)	0 (0.0%)	
	Not known/not reported	1 (1.2%)	3 (2.3%)	3 (6.7%)	
Hispanic ethnicity		19 (22.4%)	19 (15.0%)	8 (17.8%)	0.39
Child's primary language not English		10 (11.8%)	7 (5.5%)	3 (6.7%)	0.24
Primary caregiver is biological parent		66 (77.6%)	61 (47.7%)	21 (46.7%)	<0.001
Primary caregiver HIV status	Negative	18 (21.2%)	59 (46.1%)	20 (44.4%)	<0.001
	Positive	62 (72.9%)	50 (39.1%)	17 (37.8%)	
	Unknown	5 (5.9%)	19 (14.8%)	8 (17.8%)	
Caregiver is high school graduate		64 (75.3%)	99 (77.3%)	32 (71.1%)	0.70
Annual household income	\$20,000	56 (65.9%)	50 (39.1%)	20 (44.4%)	0.002
	> \$20,000	29 (34.1%)	73 (57.0%)	23 (51.1%)	
Current CD4%	Mean (SD)	32.79 (11.31)	27.54 (13.12)		0.01
	< 25%	29 (22.7%)	15 (33.3%)	15 (33.3%)	0.16
Current Log10 HIV viral load	25%	99 (77.3%)	30 (66.7%)		
	Mean (SD)	2.29 (1.06)	2.66 (1.44)		0.33
	> 400 copies		32 (25.0%)	16 (35.6%)	0.17
Nadir CD4%	400 copies		96 (75.0%)	29 (64.4%)	
	Mean (SD)		18.81 (8.71)	9.96 (7.90)	<0.001

Characteristic	PHEU (N=85)	PHIV Non-C (N=128)	PHIV-C (N=45)	P-value*
Age (years) at nadir CD4%	15%	85 (66.4%)	14 (31.1%)	< 0.001
	< 15%	43 (33.6%)	31 (68.9%)	
	0–3 years	55 (43.0%)	16 (35.6%)	0.63
	3.1–5 years	15 (11.7%)	7 (15.6%)	
	5.1 years or older	58 (45.3%)	22 (48.9%)	
Peak Log10 HIV viral load	Mean (SD)	5.50 (0.70)	5.76 (0.59)	0.03
	0–100,000 copies	27 (21.1%)	5 (11.1%)	0.14
	> 100,000 copies	101 (78.9%)	40 (88.9%)	
Age at peak HIV RNA viral load	0–3 years	83 (64.8%)	26 (57.8%)	0.40
	3.1–5 years	7 (5.5%)	5 (11.1%)	
	5.1 or older	38 (29.7%)	14 (31.1%)	
Encephalopathy	Mean (SD)	1 (0.8%)	15 (33.3%)	< 0.001
Age at most recent CDC classification		4.31 (4.20)	3.37 (4.57)	0.10
Antiretroviral regimen	HAART + PI	79 (64.8%)	31 (70.5%)	0.85
	HAART no PI	27 (22.1%)	9 (20.5%)	
	Non-HAART ARV	6 (4.9%)	2 (4.5%)	
	Not on ARV	10 (8.2%)	2 (4.5%)	

* P-values by Kruskal-Wallis analysis for continuous covariates and chi-square test for categorical covariates.

PHIV-non-C, perinatally HIV-infected without CDC Class C diagnosis; PHIV-C, perinatally HIV-infected with CDC Class C diagnosis; PHEU, perinatally HIV-exposed, uninfected; SD, standard deviation; CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; PI, protease inhibitor; ARV, antiretroviral

Table 2
Unadjusted and adjusted WRAML-2 subtest scaled scores for all groups and pairwise group comparisons

Outcome	PHEU			PHIV non-C			PHIV-C			Significant Pairwise Differences
	Unadjusted Mean (95% CI)	Adjusted Mean (95% CI)	Unadjusted Mean (95% CI)	Adjusted Mean (95% CI)	Unadjusted Mean (95% CI)	Adjusted Mean (95% CI)	Unadjusted Mean (95% CI)	Adjusted Mean (95% CI)	Adjusted Mean (95% CI)	
Immediate Design Memory	8.81 (8.15, 9.48)	8.51 (7.86, 9.17)	8.84 (8.34, 9.35)	8.87 (8.37, 9.37)	8.31 (7.56, 9.06)	8.35 (7.60, 9.10)				
Design Recognition ¹	9.32 (8.62, 10.02)	9.65 (8.92, 10.39)	8.72 (8.20, 9.24)	9.09 (8.43, 9.76)	8.18 (7.36, 9.00)	8.54 (7.62, 9.46)				PHIV-C<PHEU *
Verbal Learning ²	8.99 (8.41, 9.56)	8.38 (7.76, 9.00)	8.21 (7.74, 8.68)	8.05 (7.55, 8.55)	7.62 (6.92, 8.33)	7.61 (6.93, 8.28)				PHIV-C<PHEU ** PHIV non-C<PHEU **
Verbal Delayed Recall ³	9.29 (8.68, 9.90)	9.22 (8.55, 9.88)	8.88 (8.45, 9.31)	8.93 (8.42, 9.45)	8.24 (7.53, 8.96)	8.41 (7.60, 9.22)				PHIV-C<PHEU **
Verbal Recognition	10.04 (9.36, 10.71)	10.36 (9.71, 11.00)	10.21 (9.75, 10.68)	10.49 (9.99, 11.00)	9.27 (8.37, 10.17)	9.63 (8.68, 10.57)				
Verbal Intrusion Errors, Total (raw scores)	1.85 (1.33, 2.36)	1.55 (1.07, 2.03)	1.66 (1.29, 2.03)	1.43 (1.05, 1.82)	1.42 (0.89, 1.95)	1.09 (0.54, 1.65)				

* p<0.05 for unadjusted and adjusted mean scores

** p<0.05 for unadjusted mean scores only

¹ Adjusted for child's primary language

² Adjusted for age at study entry; caregiver is biological parent; caregiver is high school graduate

³ Adjusted for black race; caregiver is biological parent; caregiver is high school graduate

WRAML-2, Wide Range Assessment of Memory and Learning, Second Edition; PHIV, perinatally HIV-infected; C, Centers for Disease Control and Prevention Class C diagnosis; PHEU, perinatally HIV-exposed, uninfected

Table 3

Significant adjusted associations of retrospective memory outcomes with HIV disease severity in participants with PHIV.

Outcome	Disease severity measure	Covariate/ Level	Adjusted Results*	
			Mean (95% Confidence Interval)/ Estimate (Standard Error)	P- Value
Immediate Design Memory ¹	Age at peak HIV RNA viral load	0–3.0 years	9.06 (8.54, 9.58)	0.04
		3.1 years or older	8.17 (7.49, 8.85)	
Design Recognition ²	Log10 HIV RNA viral load at study entry	(continuous)	–0.38 (0.19)	0.05
	Age at peak HIV RNA viral load	(continuous)	–0.11 (0.05)	0.03
	Age at peak HIV RNA viral load	0–3.0 years	9.07 (8.52, 9.62)	0.003
		3.1 years or older	7.73 (7.04, 8.43)	
Verbal Learning ³	CD4% at study entry	(continuous)	0.04 (0.02)	0.03
	CD4% 25 at study entry	< 25%	7.04 (6.33, 7.76)	0.01
		25%	8.04 (7.55, 8.54)	
Verbal Delayed Recall ⁴	Age at peak HIV RNA viral load	3 years	9.07 (8.50, 9.65)	0.02
		3.1–5 years	9.88 (8.67, 11.09)	
		> 5 years	8.03 (7.20, 8.87)	

* The adjusted mean and 95% CI are provided for each level of categorical covariates, and for continuous covariates the adjusted mean increase (and standard error) in outcome for each 1 unit change in predictor is presented.

¹ Design memory is adjusted for caregiver is biological relation

² Design recognition is not adjusted because no covariates met model-building criteria

³ Verbal learning is adjusted for age at study entry, biological relation to caregiver, and caregiver is high school graduate

⁴ Verbal Delayed recall is adjusted for age at study entry, black race, caregiver is biological relation and caregiver is high school graduate