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Discordance of Cognitive and Academic Achievement Outcomes in Youth with Perinatal HIV Exposure

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Abstract

Background—To evaluate achievement in youth with perinatally acquired HIV (PHIV) compared to HIV-exposed uninfected peers (HEU), and to examine differential effects of HIV on cognition-achievement concordance.

Methods—Cognition and achievement were assessed using standardized measures. IQ-derived predicted achievement scores were subtracted from observed achievement scores to calculate discrepancy values. Linear regression models were used to compare achievement discrepancies between PHIV and HEU, adjusting for demographic covariates.

Results—Participants: 295 PHIV and 167 HEU youth; 71% black, 48% male, mean age 13.1 and 11.3 years, respectively. PHIV youth were relatively healthy (mean CD4%, 32%; viral load ≤400 copies/mL, 72%). PHIV and HEU youth had cognitive and achievement scores significantly below population norm means ($p<0.001$), but did not differ in cognition (mean FSIQ=86.7 vs. 89.4, respectively). In unadjusted models, HEU outperformed PHIV youth on Total Achievement (TA; mean=89.2 vs. 86.0, $p=0.04$) and Numerical Operations (NO; mean=88.8 vs. 82.9, $p<0.001$); no differences remained after adjustment. Mean observed-predicted achievement discrepancies reflected "underachievement". History of encephalopathy predicted poorer achievement ($p=0.039$) and greater underachievement, even after adjustment. PHIV showed greater underachievement than HEU for NO ($p<0.001$) and TA ($p=0.03$), but these differences did not persist in adjusted models.

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Conclusions—Both PHIV and HEU youth demonstrated lower achievement than normative samples, and underachieved relative to predicted achievement scores. Observed-predicted achievement discrepancies were associated with prior encephalopathy, older age and other non-HIV factors. PHIV youth with prior encephalopathy had significantly lower achievement and greater underachievement compared to PHIV without encephalopathy and HEU youth, even in adjusted models.

Keywords

Cognition; academic achievement; perinatally acquired HIV; HIV-exposed uninfected; discordance

Youth with perinatally acquired HIV (PHIV) are now living well into adolescence and young adulthood. Cognitive deficits associated with HIV disease were identified in the pre-HAART (highly active antiretroviral therapy) era, including progressive decline, developmental plateauing or static progression in cognitive skill attainment.[1,2] Since HAART, the impact of HIV on neurocognitive development has been considerably less grave. Reports of central nervous system encephalopathy have declined significantly,[3–5] and long-term effects on cognition generally demonstrate mild to no cognitive impairment,[6–9] with Low Average to Average functioning.[6–8,10,11] Nonetheless, some PHIV youth continue to demonstrate global cognitive deficits, especially those with an early Centers for Disease Control (CDC) Class[12] C event,[8,10,13] while others without such an event exhibit subtle impairments.[1–2,4,9,11] Consequently, HIV may be associated with subtle, specific cognitive deficit(s)[14] that global cognitive tests may lack the sensitivity to detect.[6]

Reports on academic achievement in PHIV youth are limited.[8,9,14–17] Thus, it remains unclear how well PHIV youth are achieving academically compared to same age peers, HIV-exposed uninfected (HEU) peers, and their own cognitive potential. Early reports suggested 56–67% of PHIV youth demonstrated normal academic achievement and no other apparent cognitive deficits.[14–15] In a small sample of pre-adolescents with HIV (n=25), achievement was commensurate with Intelligence Quotient (IQ), whereby both IQ and achievement trended in the Low Average to Average range over 10 years, contrary to the predicted decline in academic achievement over time.[16–17] Other studies reported youth with HIV performed below average on tests of reading, reading comprehension, mathematical reasoning,[13,14] and receptive (picture) vocabulary, and performed more poorly than their seronegative peers.[18] Yet, early reports on achievement in seronegative peers revealed below average performance in reading, spelling, and mathematics,[14] suggesting academic deficits may be attributable to environmental, sociodemographic and/or factors other than HIV exposure.

Academic achievement is a standard by which individual success is evaluated in today's youth. Youth with HIV are expected to meet academic standards, complete high school, independently manage their HIV medical care and medications, navigate the adult healthcare system, and function in and contribute to society at-large. Thus, it is essential to understand how well these youth are achieving academically in relation to their cognitive potential, and identify protective factors and/or deficits that may mediate this relationship, to

better understand how to support and prepare PHIV youth to meet their full potential as young adults.

The primary objectives of this study were to: 1) Describe academic achievement outcomes on standardized measures for PHIV and HEU youth in comparison to each other and population norms; 2) identify predictors of achievement outcomes and evaluate whether there is a differential influence of HIV disease and disease severity on achievement outcomes among PHIV youth; and, 3) evaluate and compare the concordance/discordance between observed versus IQ-predicted achievement scores for both PHIV and HEU youth, and identify predictors of the degree of discrepancy between observed versus predicted achievement.

MATERIALS AND METHODS

Study Population

The Pediatric HIV/AIDS Cohort Study (PHACS) Adolescent Master Protocol (AMP) is a prospective longitudinal study designed to define the impact of HIV infection and antiretroviral (ARV) therapy on pre-adolescents/adolescents with perinatal HIV exposure and HIV. PHIV (n=451) and HEU (n=227) youth, age 7–16 years, enrolled in AMP at 15 PHACS sites (US and Puerto Rico). Presented herein is a subsample of AMP data to address academic achievement and cognition in youth perinatally exposed to HIV and to examine the impact of HIV on cognitive-achievement outcomes.

Procedures

AMP was approved by all sites' respective Institutional Review Boards; informed consent and assent were obtained per institutional guidelines. Analyses were limited to AMP youth with available valid Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV),[19] Wechsler Individual Achievement Test, 2nd Edition, Abbreviated form (WIAT-II-A),[20] and Woodcock-Johnson Reading Mastery-R (WRMT-R)[21] data.

Outcome Measures

Cognition—Cognitive ability was assessed at study entry by the WISC-IV,19 a standardized measure of general intellectual ability for children. The WISC-IV provides Full Scale IQ (FSIQ) and four cognitive indices: Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory, and Processing Speed. FSIQ, VCI and PRI were examined.

Achievement—The WIAT-II-A,[20] a standardized abbreviated test of achievement, was administered at study week 48. Three subtests (Word Reading, Spelling, and Numerical Operations (NO)) yield individual subtest standard scores and a global estimate of academic achievement (Total Achievement (TA)).

Two additional standardized WRMT-R[21] subtests, Word Attack (reading ability) and Word Identification (reading decoding), were evaluated at study week 24. All tests were normed

with a mean of 100 and standard deviation of 15[19–21] and were administered by experienced examiners.

Predicted Achievement—WIAT-II-A achievement scores predicted by individual observed WISC-IV index scores (FSIQ, VCI and PRI) were obtained from tables provided in the WISC-IV Integrated manual.[22] Differences between observed and predicted scores were derived to determine cognitive-achievement discrepancy values.

Covariates of Interest

Demographic and Child Health Characteristics—Child and caregiver demographic information was collected at each study visit via interview, examination, and chart abstraction, and included: child age, sex, race, ethnicity, primary language, whether child talked before age two, history of prior hospitalization, and for PHIV youth, current and nadir CD4%, current and peak VL, ARV regimen, and CDC Class[12] status, including history of encephalopathy. Caregiver demographics included education, income, and relationship to child. Prior clinical values obtained closest to/on the visit when the outcome of interest was assessed were used.

Caregiver Functioning—Caregiver health data were collected via study-specific self-report questionnaires. Caregiver IQ was assessed by the Wechsler Abbreviated Scale of Intelligence[23] administered at study week 24.

Statistical Methods

Unadjusted linear regression models were used to evaluate each potential predictor of academic achievement, including demographic characteristics, caregiver characteristics, child health, caregiver health, and for PHIV participants, HIV disease severity indices. Covariates with $p<0.20$ without substantial missing data were considered in a multivariable model, which was further reduced to covariates with $p<0.15$. HIV status was included regardless of significance level. A separate model was fit for each achievement outcome. Parameter estimates reflect the change in mean achievement score for those with versus without a particular characteristic (e.g., HIV), or each additional unit for continuous characteristics (e.g., age). SAS version 9.2 (SAS, Cary, NC), was used for all analyses.

To determine concordance/discordance of actual versus predicted WIAT-II-A achievement scores, predicted scores for TA, Word Reading, Spelling, and NO were derived based on individually obtained FSIQ, VCI, and PRI index scores per the predicted-difference method.[22] The calculated difference score reflects the discrepancy between the actual obtained score and the predicted score for individual achievement outcomes. Negative discrepancy scores indicate the observed achievement score was lower than predicted achievement (i.e., “underachievement”) as determined by the respective IQ predictor. Mean difference scores between observed and predicted achievement scores were calculated and compared between PHIV and HEU (with and without adjustment for covariates). While it is recommended to use FSIQ as the cognitive predictor of achievement,[22] it was not known whether VCI or PRI would better predict achievement outcomes in this population, thus all

three indices were examined. Linear regression models were used to identify predictors of achievement discrepancies, and to compare PHIV versus HEU, adjusting for covariates.

RESULTS

Participants

PHIV (n=295) and HEU (n=167) youth were primarily black (73%, 68%), and/or Hispanic (21%, 29%), equally female (54%, 48%), with mean age of 13.1 and 11.3 years for PHIV and HEU youth, respectively. PHIV youth were relatively healthy (median CD4 count, 683; CD4%, 32%; VL <400 copies/mL, 72%), with 80% on HAART, and median 9 years cumulative ARV experience. Of PHIV youth with history of a CDC Class C event (26%), nearly half (12%) had a prior encephalopathy diagnosis. PHIV youth were significantly older than HEU ($p<0.001$), while more HEU youth had a biological parent as their primary caregiver and came from lower income households ($p<0.001$). Relevant demographic and health data are provided in Table 1.

Comparisons with youth not included revealed that HEU youth were more likely to have both IQ and achievement data available and thus be included in this analysis ($p=0.036$), as were youth with a biological parent as their primary caregiver ($p=0.028$). Unavailability of Spanish test versions resulted in a higher percentage of non-Hispanics ($p=0.002$) included in analyses.

Achievement and Cognition Outcomes

Unadjusted analyses demonstrated that PHIV and HEU youth did not differ on WIAT-II-A Word Reading scores (mean 87.7 vs. 90.5, respectively, $p=0.074$) or Spelling (mean 90.5 vs. 91.8, respectively, $p=0.42$), but PHIV youth obtained significantly lower scores on NO (mean 82.9 vs. 88.8, $p<0.001$) and TA (mean 86.0 vs. 89.2, $p=0.04$; Figure 1). PHIV youth also had significantly lower WRMT-R subtest scores than HEU (Word Attack, mean 92.1 vs. 95.3, $p=0.033$; Word Identification, mean 89.6 vs. 93.3, $p=0.006$). PHIV and HEU youth did not differ in FSIQ (86.7 vs. 89.4, respectively, $p=0.067$) or VCI (mean 89.1 vs. 89.9, respectively, $p=0.57$), but PHIV had significantly lower mean PRI scores (91.6 vs. 94.4, $p=0.049$; Figure 1). All mean achievement and cognition scores for both PHIV and HEU youth were significantly below population mean norms ($p<0.001$).

Predictors of Academic Achievement

In adjusted models (see Table 2), no differences in achievement scores were observed between PHIV and HEU overall, indicating HIV status did not account for observed differences in unadjusted models. Factors associated with lower mean achievement scores included older child age, black race, low-income household (<$20K), lower caregiver IQ (FSIQ <85), or prior child hospitalization (Table 2). Higher mean achievement scores were observed in all domains for children who talked before age two, and for NO if their caregiver was their biological parent. Among PHIV youth, CD4 and VL did not predict achievement outcomes; however, those with CDC Class[12] C status (a prior AIDS-defining condition, including encephalopathy) had consistently lower mean achievement scores (Table 3). PHIV youth with history of encephalopathy had significantly lower achievement

scores than HEU. PHIV youth without history of encephalopathy did not differ from HEU, suggesting that encephalopathy accounted for the originally observed effect of CDC Class[12] C status in PHIV versus HEU youth (Table 3).

Discordance between observed versus predicted achievement

Unadjusted mean discrepancy scores for observed versus predicted achievement were generally negative, reflecting underachievement in almost all domains for both PHIV and HEU youth (Table 4). PHIV and HEU youth did not differ in discrepancies for TA, Spelling, or Word Reading when predicted by either FSIQ or PRI. PHIV youth had significantly larger negative discrepancies (underachievement) than HEU youth for TA when predicted by VCI. PHIV youth also had significantly larger negative discrepancies than HEU in NO, regardless of WISC-IV predictor.

Adjusted models for discrepancies between observed and predicted achievement

Although PHIV youth had a greater degree of underachievement than HEU youth in NO, age was a major predictor of achievement ($p<0.001$, all domains); older youth had poorer achievement in all domains regardless of HIV serostatus or predictor used. Although discrepancies still reflected underachievement, after adjusting for age and other covariates, PHIV and HEU youth did not differ in degree of discrepancy between actual and FSIQ-predicted achievement scores. Other significant predictors of observed-predicted score discrepancies included: being male, prior hospitalization, lower caregiver IQ, and black race. Talking before age two was predictive of better achievement outcomes. PHIV youth with encephalopathy continued to demonstrate a greater degree of underachievement even after controlling for age and other factors.

DISCUSSION

This is the first large-scale study to assess the relationship of academic achievement with cognitive outcomes in a pre-adolescent/adolescent cohort of PHIV and HEU youth. Both PHIV and HEU youth obtained global and cognitive index scores in the Low Average to Average range of intellectual functioning across domains, with mean index scores generally within one standard deviation of population norms. These findings are both encouraging and consistent with recent post-HAART reports of cognitive functioning in youth with and exposed to perinatal-HIV,[5,6,8–11] reflecting improvements in PHIV cognitive development compared to prevalent Borderline intellectual functioning observed in the pre-HAART era.[14] While PHIV and HEU youth did not differ significantly in cognitive abilities, and did not show significant impairments in academic skills, both groups performed below normative means across academic domains, likely due to demographic and genetic risk factors. In unadjusted models, PHIV youth were equivalent to HEU youth on Spelling and Word Reading but demonstrated significantly lower overall achievement, numerical skills, and WRMT-R reading and reading decoding than their HEU peers. Lower Total Achievement may reflect the significantly lower performance on Numerical Operations, which contributed to the derived TA score. With the exception of PHIV youth's numerical skills, achievement scores fell within one standard deviation of published normative means. In adjusted analyses, initially observed differences between PHIV and HEU youth, including

numerical abilities, were explained by factors other than HIV. Consistent with Franklin et al.,[16] PHIV and HEU youth do not demonstrate any profound cognitive or achievement deficits, and based on gross comparison of these global measures, appear to be achieving generally commensurate with observed IQ, which is encouraging regarding the developmental impact of HIV and HIV exposure.

A primary focus of the analyses was to assess the degree of concordance or discordance between actual and predicted academic achievement scores in PHIV and HEU youth, not reported previously. In discrepancy analyses, both PHIV and HEU youth generally underachieved relative to predicted achievement scores based on observed IQ scores across domains. In unadjusted comparisons, PHIV did not significantly differ from HEU youth in observed degree of underachievement with the exception of their performance in numerical skills (significantly lower regardless of IQ predictor). In adjusted comparisons, however, observed achievement discrepancies were associated with older child age and other non-HIV factors. After adjustment for age and other factors, no significant discrepancy in mean achievement scores remained for PHIV overall compared to HEU. Older children, regardless of HIV status, had lower achievement scores. Of added concern, PHIV youth with history of encephalopathy demonstrated significantly lower achievement than PHIV youth without encephalopathy and HEU youth, even after adjustment for age and other factors. Further, the cognitive-achievement discrepancy (specifically, underachievement) was greater for PHIV youth with prior encephalopathy compared to PHIV youth without encephalopathy and HEU.

PHIV and HEU youth demonstrate academic and cognitive skills within the Low Average to Average range of functioning. What is not well understood, however, is the impact of increasing age or why PHIV and HEU youth underachieve in relation to their predicted cognitive potential. Older youth have been living with HIV longer, may have experienced a CDC Class[12] C event at a younger age, initiated HAART at an older age, and/or experienced periods of inadequate viral suppression, placing them at higher risk for more subtle cognitive and/or academic deficits, despite current healthier status. However, age was a factor for both PHIV youth and HEU youth, thus ruling out the suspected direct impact of HIV. Alternately, age may reflect a greater indirect effect of HIV during the pre-HAART era for both PHIV and HEU children due to the greater likelihood of parental illness, death, multiple caregivers, and other HIV-related family disruptions and relocation affecting the developmental trajectory. History of encephalopathy remained significant even after adjustment for age, demonstrating the need to increase access to academic support services, from tutoring to cognitive interventions, and ongoing cognitive/achievement monitoring, even if only asking, "*Is any subject harder for you than your classmates?" Or, "Is there any subject you could be doing better in?*" particularly as these youth progress through adolescence into adulthood.

These findings illuminate the need for ongoing monitoring of both global and specific areas of cognitive and academic functioning in order to identify strengths and weaknesses, and to better understand subtle long-term cognitive sequelae for youth with HIV.[2,5,6] Non-HIV related factors must be considered, as HIV or HIV-exposure alone did not explain the differences in achievement outcomes or observed-predicted discrepancies.

In our cohort, non-HIV factors including black race, lower household income, and lower caregiver IQ, were associated with poorer achievement outcomes. The noted age effect may reflect the cumulative impact of living in poverty, and associated disruptions over time, regardless of HIV. Poverty's impact on cognition and achievement has been well documented. Exposure to an impoverished, unenriched environment results in delayed school readiness, a "learning gap" at school entry, subsequent inability to catch up with peers, and increased risk for drop out and later lower earning potential in adulthood.[24,25] In addition to environmental influences, family medical and psychiatric histories may contribute to underachievement. Parents and caregivers may avoid seeking information or requesting services for their children's academic needs if they have concerns about disclosure of HIV, or have HIV-associated or other functional limitations themselves. Psychiatric diagnoses, such as Attention-Deficit/Hyperactivity Disorder, anxiety, and mental health problems in general, have been observed among both PHIV and HEU youth[26–28] and may have a significant and cumulative impact on academic achievement over time, especially if left untreated.

Study Limitations

Cognition and achievement were evaluated at a single time point and thus cannot identify causal pathways or trends over time. Given the lack of Spanish test versions, fewer Hispanic youth were included in analyses; therefore, our sample may not be representative of all youth with PHIV or HEU. To reduce participant burden, assessments of interest were dispersed across the first year of study participation; thus, some data were collected 48 weeks apart. While data collection in AMP is comprehensive, early history, especially *in utero* maternal exposures and perinatal well-being, were reliant on medical chart abstraction, which for many was incomplete or missing, limiting our ability to evaluate the impact of early influences on later development. Finally, although a comparison sample was included, we lacked a demographically matched control sample of youth without HIV exposure.

CONCLUSIONS

Despite generally improved global cognition during the HAART era, both PHIV and HEU youth are still achieving below standardized academic normative means, albeit in the Low Average to low end of the Average range, and generally underachieving in relation to their cognitive potential for reasons other than HIV infection and/or HIV-exposure. Of greatest concern is the lower achievement observed with increased age, regardless of HIV status and disease markers, suggesting possible "plateauing" or static progression[2] of academic skill attainment during adolescence and potential risk for poor adult occupational outcomes. Lower achievement in adolescence may be a result of inadequate attention to special educational or mental health needs (falling in the "gap"), or other as yet undefined factors. To fully understand the relationship between academic achievement and cognitive abilities in these youth, additional factors that may mediate the cognition-achievement relationship need to be considered, such as the effects of language development, adaptive and behavioral functioning, and executive function, utilizing measures that are more sensitive to subtle, specific deficits than detected by global tests to date. Longitudinal studies are needed to identify causal pathways of academic deficits and resiliency, and to develop appropriate

interventions to facilitate positive academic trajectories, especially for older youth with history of early encephalopathic insult. These potentially salient mediating factors will be assessed over time in planned future analyses.

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Appendix

The following institutions, clinical site investigators and staff participated in conducting PHACS AMP in 2012, in alphabetical order: **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, Doyle Patton, Patricia Garvie; **Children's Hospital, Boston:** Sandra Burchett, Nancy Karthas, Betsy Kammerer; **Ann & Robert H. Lurie Children's Hospital of Chicago**: Ram Yogev, Margaret Ann Sanders, Kathleen Malee, Scott Hunter; **Jacobi Medical Center**: Andrew Wiznia, Marlene Burey, Molly Nozyce; **St. Christopher's Hospital for Children**: Janet Chen, Latreca Ivey, Maria Garcia Bulkley, 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, Emily Barr, Robin McEvoy; **University of Medicine and Dentistry of New Jersey:** Arry Dieudonne, Linda Bettica, Susan Adubato; **University of Miami:** Gwendolyn Scott, Patricia Bryan, Elizabeth Willen.

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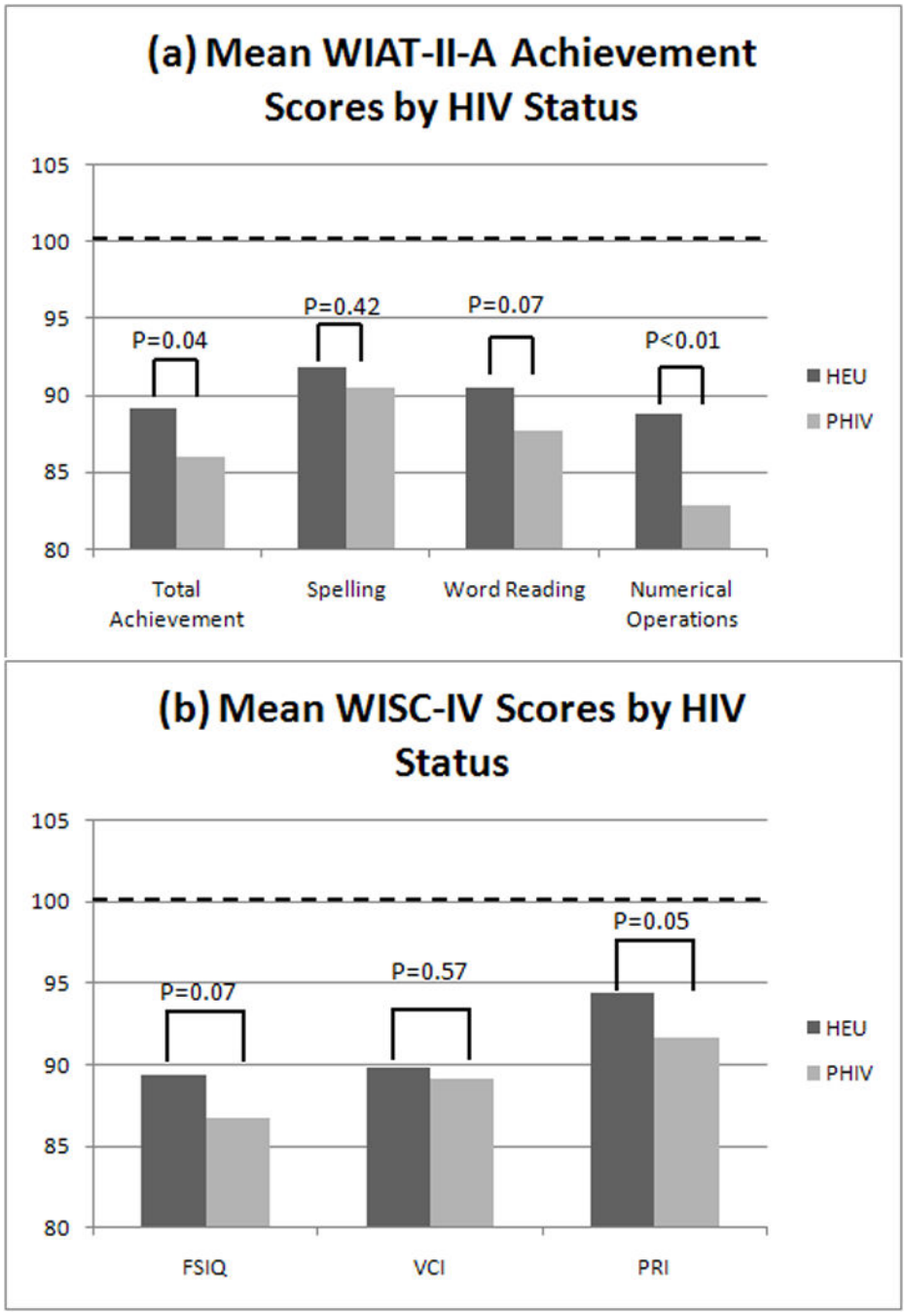

Figure 1. Mean Observed WIAT-II-A Achievement (a) and WISC-IV Cognition Index Scores (b) by HIV Status

Figure 1a) Achievement: PHIV and HEU did not differ on Spelling or Word Reading subtests, but PHIV means were significantly lower than HEU on Numerical Operations and Total Achievement; Figure 1b) Cognition: PHIV and HEU did not differ on FSIQ or VCI, but PHIV mean score was significantly lower than HEU on PRI. All achievement and cognition scores were significantly below population norm means ($p<0.001$), although still within the Low Average range of functioning.

HEU = HIV exposed uninfected; PHIV = Perinatally acquired HIV; WIAT-II-A = Wechsler Individual Achievement Test, 2nd Edition, Abbreviated; WISC-IV = Wechsler Intelligence Scales for Children, 4th Edition; FSIQ= Full Scale IQ; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index.

Table 1

Demographic and Caregiver Characteristics for AMP Youth Included in Analyses, and HIV-related Characteristics of Included PHIV Youth

Characteristic	HIV-Infected (PHIV) (n=295)	HIV-Exposed Uninfected (HEU) (n=167)	p-value
Age in years (Mean, SD)	13.1 (2.6)	11.3 (2.4)	<0.001
Male	46%	52%	0.21
Black or African American	73%	68%	0.29
Hispanic	21%	29%	0.07
Low household income	42%	60%	<0.001
Low caregiver education	25%	31%	0.28
Biological parent caregiver	47%	81%	<0.001
Caregiver IQ < 85	36%	44%	0.17
Caregiver IQ missing	21%	17%	-
Child ever hospitalized	22%	16%	0.11
Child talked before age 2	90%	92%	0.50
HIV Disease Markers			
CD4 Count, median (IQR)	683 (490, 944)	-	-
CD4%, median (IQR)	34 (25,39)	-	-
HIV VL >400 copies/mL	28%	-	-
Nadir CD4% <15%	32%	-	-
Log peak VL, median (IQR)	5.46 (4.95, 5.88)	-	-
CDC Class C diagnosis, n (%)	78 (26%)	-	-
Encephalopathy, n (%)	34 (12%)	-	-
Current ARV Regimen			
HAART with PI, n (%)	214 (73%)	-	-
HAART w/o PI, n (%)	51 (17%)	-	-
non-HAART ARV, n (%)	12 (4%)	-	-
no ARVs	17 (6%)	-	-
Cumulative years on ARVs, median, IQR	9.13 (5.65, 10.44)	-	-

PHIV = perinatally acquired HIV; HEU = HIV exposed, uninfected; SD=standard deviation; CDC= Centers for Disease Control; VL= viral load, IQR= interquartile ration; HAART= highly active antiretroviral therapy; ARV= antiretroviral.

Table 2

Final Multivariable Models of Academic Achievement (WAIT-II-A), comparing PHIV to HEU

	Total Achievement		Word Reading		Spelling		Numerical Operations	
Characteristic	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
HIV status (PHIV v HEU)	−0.59 (−3.82, 2.65)	0.72	−0.14 (−3.54, 3.26)	0.94	0.89 (−2.57, 4.35)	0.61	−2.49 (−6.32, 1.34)	0.20
Age	−1.34 (−1.92, −0.75)	<0.001	−1.61 (−2.23, −1.00)	<0.001	−0.89 (−1.52, −0.26)	0.006	−1.22 (−1.90, −0.54)	<0.001
Race (black v other)	−4.60 (−7.87, −1.34)	0.006	−5.79 (−9.22, −2.36)	<0.001	−4.33 (−7.85, −0.82)	0.016	−2.94 (−6.73, 0.86)	0.13
Household income <$20K	−3.16 (−6.19, −0.13)	0.041	−3.61 (−6.79, −0.43)	0.026	_	_	−4.76 (−8.44, −1.09)	0.011
CG Biological Parent	_	_	_	_	_	_	4.43 (0.45, 8.41)	0.029
CG FSIQ <85	−5.22 (−8.51, −1.93)	0.002	−5.83 (−9.42, −0.65)	0.025	_	_	−6.84 (−10.65, −3.03)	<0.001
Child Talked <2 yrs old	7.36 (2.32, 12.41)	0.004	9.47 (4.17, 14.77)	<0.001	8.94 (3.48, 14.41)	0.001	6.65 (0.83, 12.47)	0.025
Child ever hospitalized	−6.68 (−10.47, −2.90)	<0.001	−7.29 (−11.25, −3.31)	<0.001	−5.86 (−9.94, −1.79)	0.005	−6.19 (−10.57, −1.81)	0.006
HIV Disease Severity Measures (PHIV only)								
CDC Class C	−5.26 (−9.65, −0.87)	0.019	−4.67 (−9.35, 0.00)	0.05	−5.69 (−10.49, -.089)	0.02	−6.44 (−11.52, −1.36)	0.013
Peak VL >75K copies/mL	−4.79 (−10.51, 0.93)	0.10	_	_	_	_	−5.75 (−12.40, 0.89)	0.09
Cumulative Years on HAART	_	_	−0.40 (−0.92, 0.12)	0.13	_	_	−0.42 (−0.99, 0.15)	0.15

WIAT-II-A= Wechsler Individual Achievement Test, 2nd Ed., Abbreviated; PHIV = perinatally acquired HIV; HEU = HIV exposed, uninfected; CG= caregiver; CDC= Centers for Disease Control, FSIQ= Full Scale IQ; VL= viral load

Note: For each achievement domain, a multivariable adjusted model was fit including HIV status and the other covariates shown. The estimate reflects the mean difference in achievement scores for those with the characteristic noted versus those without, or for each one unit increase in continuous measures (e.g., age in years).

Table 3

Adjusted Mean Achievement Discrepancies in PHIV with versus without Encephalopathy Compared to HEU

	PHIV with Encephalopathy versus HEU		PHIV without Encephalopathy versus HEU	
WIAT-II-A Domain	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Total Achievement	−8.49 (−14.52, −2.47)	0.006	0.33 (−2.92, 3.59)	0.84
Word Reading	−6.69 (−13.04, −0.33)	0.039	0.62 (−2.81, 4.06)	0.72
Spelling	−7.33 (−13.86, −0.80)	0.028	1.84 (−1.65, 5.33)	0.30
Numerical Operations	−13.60 (−20.60, −6.60)	<0.001	−1.29 (−5.12, 2.54)	0.51

WIAT-II-A= Wechsler Individual Achievement Test, 2nd Ed., Abbreviated; PHIV = perinatally acquired HIV; HEU = HIV exposed, uninfected; CI= confidence interval

Each row presents the results of a separate multivariable adjusted linear regression model for a specific WIAT-II-A domain, adjusted for covariates shown in Table 3. The estimate reflects the difference in mean achievement score for those with PHIV (with or without encephalopathy) as compared to HEU.

Table 4

Unadjusted and Adjusted Mean Discrepancies in Observed versus Predicted Achievement Scores, Comparing PHIV and HEU Cohorts

Achievement Measure as Predicted by IQ Measure	Discrepancy Score Between Observed vs Predicted Achievement		Unadjusted Mean Difference between PHIV and HEU		Adjusted Mean Difference between PHIV and HEU*	
	PHIV Mean (SD)	HEU Mean (SD)	Mean Difference	P-value	Mean Difference	P-value
Predicted by FSIQ						
Total Achievement	−2.38 (10.7)	1.56 (10.0)	−0.82	0.42	1.12	0.29
Word Reading	−2.48 (12.4)	−1.66 (10.1)	−0.82	0.47	1.16	0.33
Spelling	0.22 (13.1)	−0.43 (12.0)	0.65	0.59	2.24	0.11
Numerical Operations	−7.93 (14.2)	−3.83 (12.3)	−4.11	0.002	−1.41	0.31
Predicted by VCI						
Total Achievement	−5.20 (12.5)	−2.72 (11.4)	−2.48	0.030	−0.68	0.58
Word Reading	−4.59 (13.5)	−2.28 (11.6)	−2.31	0.57	0.02	0.99
Spelling	−2.35 (14.6)	−1.59 (13.2)	−0.76	0.053	1.15	0.46
Numerical Operations	−10.5 (15.9)	−4.99 (14.1)	−5.51	<0.001	−3.07	0.05
Predicted by PRI						
Total Achievement	−8.02 (13.9)	−6.77 (11.5)	−1.25	0.30	1.18	0.37
Word Reading	−4.67 (15.7)	−4.93 (13.3)	0.26	0.85	1.22	0.41
Spelling	−7.28 (15.5)	−6.07 (12.2)	−1.21	0.35	2.14	0.19
Numerical Operations	−12.1 (16.2)	−7.75 (13.9)	−4.35	0.003	−1.44	0.36

HEU = HIV exposed uninfected; PHIV = Perinatally acquired HIV; FSIQ= Full Scale IQ; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index. WIAT-II-A = Wechsler Individual Achievement Test, 2nd Ed., Abbreviated.

*Each row is based on a separate linear regression model for difference score between observed and predicted achievement, including HIV status, age at WIAT-II-A, prior hospitalization of child, and adjusting for other covariates specific to each domain, including for: Total Achievement: caregiver tired by activities; Word Reading black race vs other, lower caregiver education (< high school), caregiver tired by activities, and child talking before age 2; Spelling male sex, household income < $20k, caregiver feeling their life is in danger, and child talking before age 2; Numerical Operations male sex, caregiver marital status, caregiver IQ<85, and caregiver difficulty with activities.