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Longitudinal Trajectories of Neurocognitive Test Performance among Individuals with Perinatal HIV-Infection and -Exposure: Adolescence through Young Adulthood.

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Abstract

There are an estimated 2.1 million youth less than 15 years of age living with HIV globally (the majority perinatally HIV-infected [PHIV]) and millions more perinatally HIV-exposed uninfected (PHEU) youth who are expected to survive through adolescence and into adulthood. The transition from adolescence to young adulthood requires adaptation to more demanding social interactions, academic pressures, and individual responsibilities which each place distinct demands on neurocognitive functions. This study examined trajectories of neurocognitive test performance in the domains of processing speed (PS), working memory (WM), and executive functioning (EF) among PHIV and demographically similar PHEU youth as they age through adolescence into young adulthood. Data for this paper come from 4 time points, spanning approximately 10 years, within the Child and Adolescent Self-Awareness and Health Study (CASA). Youth age ranged from 15 to 29 years. Longitudinal linear mixed effect models were computed for each test as a function of age, PHIV status, PHIV status by age interaction. Our findings indicate that there are few differences in performance on tests of EF and WM between PHIV and PHEU youth as the age from adolescence to adulthood, though PHEU youth showed significantly better PS as they aged than PHIV youth. Future research is needed to understand these vulnerable youth's neurocognitive trajectories as a function of HIV-infection and -exposure, biological functions and psychosocial stressors.

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Declaration of Interest Statement

Nothing to declare.

Keywords

perinatal HIV; adolescence; longitudinal; working memory; executive functioning

There are an estimated 2.1 million children less than 15 years of age living with HIV globally, the majority born with PHIV, who are now expected to survive well into adulthood (UNAIDS, 2016; Woollett, 2016; Zandoni, Archary, Buchan, Katz, & Haberer, 2016). While effective scale-up of prevention of mother-to-child transmission (PMTCT) has drastically reduced the number of infants born with HIV throughout the world, there are countless numbers of children who were born to mothers living with HIV who did not acquire the virus (perinatally HIV-exposed and uninfected; PHEU), who share sociodemographic conditions similar to PHIV children, and often serve as a reference group for PHIV studies (Cohen et al., 2015). Yet, little is known about the millions of PHIV and PHEU youth's neurocognitive functioning as they age from adolescence into young adulthood. This is a critical developmental period for these youth as they must adapt to more complex and demanding social interactions, environments, academic pressures, and individual responsibilities which all place unique demands on their neurocognitive functions (Steinberg & Morris, 2001).

Neurocognitive deficits have been routinely observed in children and adults living with HIV (Heaton et al., 2010; Malee, Smith, & Mellins, 2016; Sheppard et al., 2015; Smith & Wilkins, 2014; Vance et al., 2011). PHIV and PHEU youth face multiple challenges related to a myriad of psychosocial and environmental stressors (e.g., poverty), as well as lifelong HIV and its treatment (among those with PHIV), which may affect neurocognitive functioning (Cohen et al., 2015; Wood, Shah, Steenhoff, & Rutstein, 2009). A recent meta-analysis found that the most commonly affected neurocognitive domains among PHIV youth are executive function (EF), working memory (WM), and processing speed (PS) (Phillips et al., 2016). Other cross-sectional studies have shown similar findings, as well as problems in the domains of memory, attention, motor functioning, language, and visuospatial processing, with some studies showing similar performance in these domains compared to demographically similar PHEU youth (Hoare et al., 2016; Malee, Smith, & Mellins, 2016; Nichols et al., 2016; Ruel et al., 2012; Shanbhag et al., 2005; Smith et al., 2012; Van Rie, Harrington, Dow, & Robertson, 2007). However, much less is known about PHEU adolescent and young adult outcomes. PHEU children may have lower performance on verbal and full-scale intelligence test scores as well as memory scores than matched HIV-uninfected unexposed (HUU) children, although the differences may be small with unknown long-term clinical importance (Kerr et al., 2014).

Higher-order neurocognitive functions, such as EF (e.g., problem solving, impulse control, cognitive flexibility, and abstraction) and WM, are particularly important to youth development because they are known to influence academics, pro-health behaviors (e.g., medication adherence), and transition to adulthood (Malee, Smith, & Mellins, 2016; Nichols et al., 2016). PS, the speed with which one is able to complete mental tasks, also plays an important role in higher-order functioning. PS makes information available to EF and WM,

such that EF and WM gain information quicker with faster PS (Albinet, Boucard, Bouquet, & Audiffren, 2012; Fellows, Byrd, & Morgello, 2014).

Few studies to date have examined neurocognitive functioning over time and across the developmental period of adolescence and young adulthood for PHIV and PHEU youth, and none have examined the specific neurocognitive domains of PS, WM, and EF. Two studies examined neurocognitive functioning over time among PHIV and PHEU youth, albeit only across two time points (Puthanaket et al., 2010; Malee et al., 2017). One study did not include PHEU youth and included children and adolescents (Puthanaket et al., 2010), and the other used PHEU youth only as a control group (Malee et al., 2017). This is a critical developmental period that places unique demands on neurocognitive functioning and a period when youth initiate and experiment with sexual and substance use behaviors, as well as focus on social interests and peer norms which may affect adherence to medications and other treatment requirements, retention in care, and transition from dependence on parents to self-reliance (Smith & Wilkins, 2015).

There is a need to understand longitudinal trajectories of neurocognitive development and functioning among these vulnerable and demographically similar populations who were both exposed to HIV and often ART *in utero*. Additionally, there is a need to further understand those unique features of PHIV, such as being exposed to ART from a young age (often for the entirety of their lives; some to older more toxic regimens; some with poor adherence), as well as growing up in impoverished conditions – all of which can affect the developing brain (Laughton, Cornell, Boivin, & Van Rie, 2013). Understanding neurocognitive functioning across developmental stages (e.g., from adolescence through adulthood) can help providers and researchers develop targeted interventions and understand the long-term effects of PHIV and perinatal HIV-exposure without HIV infection, as well as model neurocognitive outcomes in these vulnerable populations (Jeremy et al., 2005; Wood, Shah, Steenhoff, & Rutstein, 2009). Using data from a longitudinal cohort study based in New York City, the aim of this secondary data analysis was to examine trajectories of neurocognitive test performance in the domains of PS, WM, and EF over four time points among PHIV and demographically similar PHEU youth as they age from adolescence to young adulthood.

Method

Participants

Data were collected from participants enrolled in the Child and Adolescent Self-Awareness and Health Study (CASA), an ongoing longitudinal study investigating the mental health and risk behaviors of PHIV and PHEU youth that began in 2003 and currently has seven waves of data collection. Methods have been previously described in detail (Mellins et al., 2009). In brief, the cohort was recruited from four medical centers administering primary care services to HIV-affected families within New York City from 2003 to 2008. Inclusion criteria at baseline were (1) youth aged 9 to 16-years-old with perinatal exposure to HIV, (2) cognitive capacity to complete the initial psychosocial interview, (3) primary language English, and (4) English and/or Spanish speaking adult caregivers with legal ability to sign consent for youth participation. Among 443 eligible participants, 11% refused contact and 6% could not be contacted by the clinics. The study enrolled 340 youth (206 PHIV and 134

PHEU) and their caregivers (Table 1). Since the initial study which had one follow-up (FU) visits (baseline and FU2), six additional FUs (FU2 – FU7) have been added; FU7 is near completion. For the current study, all available data from FU4-FU7 prior to September 19th, 2018 were examined. This is when test of EF, WM, and PS tests were introduced into the study. The median time interval between FU4 and FU5 was approximately 2.20 years (*interquartile range* [*IQR*] = 1.28-2.67). The intervals between FU5 and FU6 interviews was 1.02 years (*IQR* = 0.97-1.06), and between FU6 and FU7 was 1.06 years (*IQR* = 1.01-1.14).

Procedures

Youth were interviewed at the CASAH research offices, apart from 10% of occasions occurring in participants' homes if traveling to office was difficult and privacy at home could be obtained. All interviews with youth were conducted in English, which was participants' primary language (and an inclusion criteria). Written informed parental consent and youth assent were obtained from participants 17 years of age or less and written informed consent for participants 18 years. Participants were compensated \$40 for their time and travel at each FU visit. The New York State Psychiatric Institute's Institutional Review Board granted approval for all waves of the study.

Measures

Demographics and Medical History—Demographics were collected at all visits. Those used in these analyses included youth age at each FU, sex at birth, race/ethnicity, education (including whether youth ever skipped a grade, were ever held back in school, or ever received special education), caregiver primary language (English vs. Spanish) and caregiver's relationship to youth (birth parent vs. other type of caregiver) at baseline. Hospitalization history was gathered during the psychosocial interview at each FU and total number of hospitalizations reported at each FU was used in analyses.

Viral load data for PHIV youth were obtained from their medical providers. For FU2-FU4, viral load test results from the past 3 months were obtained. For FU5-FU7 values were expanded to include viral load test results from the previous 12 months. Viral load was considered detectable if over 400 copies/mL and undetectable if under 400 copies/mL. For each participant and at each FU, the number of viral load test results varied from a single result up to 11 results, e.g., youth with more medical complications and who were sicker could have more viral load test results. At each FU, the most recent viral load test results were selected (up to 3), and the proportion of viral load test results that were detectable was computed. The proportion of detectable viral load test results were categorized into 5 levels: none 0%, 33% (1 detectable out of 3 visits), 50% (1 detectable out of 2 visits), 66% (2 detectable out of 3 visits), and all (100%).

Trail Making Test—The Trail Making Test (TMT) is a two-part instrument used to measure PS and executive EF and consists of TMT A and TMT B (Reitan, 1992). TMT A assesses PS (Reitan, 1958; Sánchez-Cubillo et al., 2009). Participants are asked to connect a series of numbered circles as quickly as possible in numerical order. TMT B assesses task-switching capabilities and dominant response inhibition associated with EF (Sánchez-Cubillo et al., 2009). Participants are presented with circles with either a letter or number,

and are asked to alternate numerically then alphabetically, connecting circles and switching between numbers and letters. TMT has been widely used in HIV research and with PHIV youth (Nichols et al., 2016). Participants are assessed based on completion times (in seconds); shorter times indicate better performance.

Digit Span Task—The Digit Span subtest of the Weschler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Wechsler, 2008) assesses verbal WM using forward and backward recall patterns. Participants are asked to recall increasing spans of digits as read by the examiner, and then in reverse order as read by the examiner. Span tasks in particular, such as this one, have been extensively empirically-validated as a reliable method for assessing working memory capacity (Conway et al., 2016). The total number of correct responses (forwards and backwards) are recorded and transformed into an age-referenced scaled score with a mean of 10 and standard deviation of three (Wechsler, 2008).

Statistical Analysis

Baseline and FU4 demographics were summarized by youth PHIV status, using means, standard deviations, counts, and percentages as appropriate. Medians and interquartile ranges are presented for characteristics with skewed distributions. Differences by youth PHIV status were tested using chi-square tests for categorical variables and t-tests (or Wilcoxon rank sum test for non-normal distributions) for continuous variables. To characterize each cognitive outcome across the study from adolescence into young adulthood, the observed mean scores across age (range 16-27 years) were plotted for three age cohorts (9 to 10, 11 to 13, and 14 to 17 years of age at baseline) and stratified by PHIV status.

Separate longitudinal linear mixed effect models with a random intercept to account for repeated measures were fit for each of the cognitive outcomes. A log-link function was used to account for the right skewed distribution of the Trails A and B outcomes and an identity link function was used for the approximately normally distributed Digit Span outcome.

Each outcome was modeled as a function of time-varying youth age at each FU (FU4 – FU7), youth PHIV status, and youth PHIV status by youth age interaction. Age was included as a time-varying covariate (instead of test performance at each FU wave) in order to estimate approximate age at which neurocognitive performance declines or improves. If the youth PHIV status by youth age interaction was significant, suggesting PHIV status moderates the association between youth age and cognitive outcomes, slope estimates within groups were computed and tested for significance. Contrasts were performed at each year in age from age 16-29 to determine at what age model-estimated mean outcome scores began to significantly differ. If the interaction was not found to be significant, the interaction term was omitted and a model with only main effects was fit. Additionally, because the observed data may suggest a non-linear trend, the interaction between PHIV status and age-squared was also tested. Thus, all models treated age as a linear term. For all outcomes, PHIV status and age to examine if cognitive performance changes differently across age by PHIV status and birth cohort.

All models were adjusted for the following covariates: caregiver primary language (English vs. not) and caregiver relationship to youth (biological parent vs. not) reported at baseline; youth ever skipped a grade, ever held back in school, or ever received special education; and the number of hospitalizations at each FU. Youth grade level was not included as a covariate since it was highly correlated with youth age. For each participant, the number of hospitalizations varied at each follow-up, therefore two terms were included in the model to represent the variation within and between participants respectively: (1) the number of hospitalizations centered on the average number of hospitalizations across all follow-ups, and (2) the average number of hospitalizations for each participant at each FU (Lalonde, 2015).

For PHIV youth, the effect of viral load was also explored as a moderator of youth age on each cognitive outcome. Viral load was considered detectable if over 400 copies/mL and undetectable if under 400 copies/mL. The 5-level categorical viral load variable was included as an interaction with youth age for each neurocognitive outcome model. All statistical tests were 2-tailed with a significance level of 5% and performed using SAS software version 9.4 (Copyright © [2003], SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA).

Results

Table 1 presents baseline sample characteristics for the original CASAH cohort (340 PHIV and PHEU youth) and the cohort characteristics at FU4 (242 PHIV and PHEU youth). PHIV and PHEU youth did not differ by age, sex at birth or race/ethnicity at CASAH baseline. PHEU were more likely to have been raised by a birth parent and more likely to have a caregiver living with HIV. At FU4, PHIV youth were about 1.5 years older, on average, than PHEU youth ($p < .001$). Data for these analyses are from EF, WM and PS scores at FU4, FU5, FU6, and FU7. None of the PHIV status by age-squared or birth cohort by PHIV status and age interactions were significant. Thus, all models were treated age as a linear term.

Figure 1 shows the observed mean and one standard deviation of performance for each cognitive outcome by PHIV status, plotted against mean age at each FU grouped by birth cohort on study entry. For example, PHIV participants who entered the study between the ages of 9 and 10 had an average log Trails A time of 3.27 seconds (SD=0.38). Average log Trails A time decreased to 3.24 seconds (SD=0.40) at FU5, 3.18 seconds (SD=0.39) at FU6, and 3.06 seconds (SD=0.27) at FU7. At FU5, FU6, and FU7, the average log Trails A time decreased to 3.24 seconds (SD=0.40, $n=34$), 3.18 (SD=0.39, $n=28$), and 3.06 (SD=0.27, $n=20$) respectively; and the average age of the cohort was approximately 19.4 (range: 18-24), 20.7 (range: 19-25), and 21.3 (range: 20-23) at each FU respectively (see Supplemental Table 1).

Processing Speed (PS)

There was a significant interaction between youth age and PHIV status ($b = 0.026$, $p = .004$) on TMT A, while adjusting for covariates (see Table 2 and Figure 2). The slope estimates for

each group (PHIV vs. PHEU) was estimated and tested for significance. With each year in age, TMT A score significantly improved (decreased time on task) in the PHEU group by 3.6% ($b = -0.036$, $p < .0001$; betas are interpreted as percent change using the formula: $e^{(b)-1} * 100\%$) and by only 1.0% in the PHIV group ($b = -0.01$; $p = .09$). Contrasts performed at each year of youth age (range: 15-29) revealed significant differences in model-estimated TMT A scores starting at age 22 and continuing until age 29 (see supplemental table 2).

Working Memory (WM)

There was no significant interaction between youth age and PHIV status ($b = 0.004$, $p = 0.95$) on the Digit Span score, while adjusting for covariates (see Figure 2). Table 2 shows the model results after removing the non-significant interaction. There was no significant main effect of PHIV status on WM ($b = -0.34$, $p = 0.31$). On average, higher (better) Digit Span scores were significantly associated with older youth age ($b = 0.07$, $p = 0.035$) and fewer number of hospitalizations ($b = -0.02$, $p < 0.001$). Lower (poorer) Digit Span scores were significantly associated with ever received special education ($b = -1.62$, $p < .001$) or ever held back a grade ($b = -0.87$, $p = .008$).

Executive Functioning (EF)

There was no significant interaction between youth age and PHIV status ($b = 0.015$, $p = .19$) on the Trail Making Test B, while adjusting for covariates (see Figure 2). Table 2 shows the model results after removing the non-significant interaction. There was no significant main effect of PHIV status ($b = 0.026$, $p = .65$). Across both the PHIV and PHEU groups, with each year increase in age, TMT B score was on average lower by 1.7% ($b = -0.017$; $p = .003$). Better (shorter time on task) TMT B scores were also significantly associated with decreases in the number of hospitalizations ($b = 0.004$, $p < .001$), whereas poorer (longer time on task) TMT B scores were significantly associated with ever received special education ($b = 0.31$, $p < .001$).

Viral Load

Among 149 PHIV youth, detectable viral load was not a significant moderator of youth age on any of the cognitive outcomes (EF: $F(4, 229) = 0.06$, $p = .99$; WM: $F(4, 235) = 0.62$, $p = .65$; PS: $F(4, 229) = 1.11$, $p = .35$).

Discussion

Overall, trajectories from our analyses indicate better performance in general as PHIV and PHEU youth age from adolescence through adulthood on our tests of EF, WM, and PS, with no significant differences between PHIV and PHEU trajectories of WM and EF. These findings are consistent with the literature suggesting that PHIV and PHEU youth perform similarly on tests in these domains (Nichols et al., 2016). However, we observed that PHEU youth significantly improved in PS as they aged. On average, PHEU youth improved by 3.5% each year in contrast to PHIV youth who did not significantly improve PS as they aged. The groups did not differ at their first PS assessment. Finally, we did not find

differences within the PHIV group on any of the tests when we accounted for the proportion of detectable viral loads in the previous year.

These results are consistent with previous longitudinal and cross-sectional research on neurocognitive functioning among PHIV children and adolescents. Malee et al. (2017) examined memory and EF among PHIV and demographically similar PHEU adolescents 12 to 17 years of age in the US across two time points two years apart. Overall, PHIV adolescents without a history of an AIDS-defining illness had similar performance to PHEU adolescents across most tests of EF. Adolescents with PHIV and a history of an AIDS-defining illness and higher peak viral load had lower performance on EF tests. Puthankit et al. (2010) examined full scale intelligent quotient scores among PHIV, PHEU and HIV-uninfected and unexposed (HUU) children in Thailand between 6-12 years of age over 30 months. They found that 79% of the PHIV children had below normal FSIQ scores and had significantly lower FSIQ scores compared to the PHEU and HUU groups at the 30-month follow-up.

Although trajectories were fairly similar across the groups (except for PS), we note that the mean WAIS-IV Digit Span scaled score for both groups was close to 8 (slightly lower for PHIV and slightly higher for PHEU) across all FUs, which is in the lower end of the normal range (or 25th percentile) of performance (Wechsler, 2008). Additionally, TMT A completion times (in seconds) for 18-25 year old PHIV (median model-estimated time = 25.4 seconds, interquartile range [IQR] = 24.9-25.9) and PHEU (median = 23.1 seconds, IQR = 21.5-24.9) groups were slightly slower (though still within one standard deviation) than the TMT A Tombaugh (2004) normative sample ($M = 22.93$, $SD = 6.87$). For TMT B, both PHIV (median = 63.9 seconds, IQR = 62.6-65.3) and PHEU (median = 62.8 seconds, IQR = 59.7-66.1) groups performed considerably slower than the Tombaugh (2004) normative sample ($M = 48.97$, $SD = 12.69$) with estimated mean completion times in both groups greater than one standard deviation below the Tombaugh (2004) normative sample.

While it is unclear as to why PHIV youth did not show similar gains in performance in PS, one possible explanation could be due to learning or practice effects. Longitudinal assessment of neurocognitive test performance with repeated use of neuropsychological tests can lead to performance improvements that occur due to repeated exposure to the tests, which can complicate the detection of neurocognitive change between testing sessions (Calamia, Markon, & Tranel, 2012). Practice effects, which have been observed in TMT A and B, can lead to improved performance (Mitrushina, Boone, Razani, & D'Elia, 2005). There is a nascent literature that has begun to examine the lack of practice effects among diseased populations as a novel approach to understanding neurocognition. For example, Darby et al. (2002) administered the same neurocognitive tests repeatedly to a group of adults with mild cognitive impairment and matched controls over the course of one day. Results were equivalent at baseline between the controls and those with mild cognitive impairment. However, only the control participants showed improvements over the testing sessions. Those with mild cognitive impairment did not show the same boost in performance with repeated testing. Similarly, Ownby et al. (2017) found that among adults living with HIV in India, practice effects were diminished among those with HIV compared to those without, particularly on tests of PS and motor functioning. Brain-involving disease processes

may interfere with the normal learning processes that occur with repeated exposure to testing. In fact, PS has been identified as an area of relative weakness among some PHIV youth compared to performance in other domains (Smith et al., 2012). Interestingly, in our analyses, both PHIV and PHEU youth did not differ significantly on their first PS test at FU4, but only the PHEU group had significantly better performance as they aged.

It is important to note some limitations of our study. The aim of the study was to examine longitudinal trajectories of neurocognitive functioning among PHIV and PHEU youth as they age from adolescence to adulthood. Neurocognitive functioning was not the primary focus of the CASAH aims, and thus we had limited measures, affecting our capacity to confirm similarities and differences across the domains assessed. Also, a third of the sample had already entered young adulthood (mean age approximately 20 years) when testing of EF, WM, and PS domains began. Furthermore, we do not have data on these tests prior to the second wave of the CASAH study and cannot examine performance at even younger ages. Fourth, we do not have data on early development, such as prenatal exposure to alcohol or other substances and early AIDS-defining illness, including histories of encephalopathy which were common in many PHIV children early in the epidemic and have been shown to impact neurocognitive functioning (e.g., Malee et al., 2017). Fifth, while it is possible there could be selection bias among participants who dropped out of the study prior to the last four FUs (i.e., 4,5,6,7), recent research from CASAH found no significant differences across enrollment characteristics (e.g. age, race, gender, income, HIV-status, caregiver type) between those retained and lost to follow-up (Abrams et al., 2018). However, participants without a psychiatric disorder in both PHIV and PHEU groups were more likely to be lost to follow-up at FU5, but this difference was only significant for PHEU participants. Finally, it is not clear how generalizable our findings are to other PHIV and PHEU youth across the US and the world. The CASAH cohort were all originally recruited from New York City and grew up in an urban environment. Access to care and education, the quality of education, levels of impoverishment and other social stressors may be very different in other contexts and countries, thus limiting the generalizability of these findings.

Despite these limitations, this is one of the first studies to examine neurocognitive functioning among PHIV and demographically similar PHEU older youth as they age from adolescence through young adulthood. Our findings indicate that both groups demonstrate better performance on tests of EF and WM as they age. It is possible that PHIV youth may not benefit as much as PHEU youth from learning or practice effects on a test of PS, which could reflect unique HIV-related effects (e.g., viral replication in the central nervous system and exposure to ART) on brain functioning.

While these results seem somewhat encouraging with respect to PHIV youth and young adults, given they demonstrated similar WM and EF skills as their matched PHEU peers, both groups, across all domains, performed lower than aged-matched normative samples (Malee et al., 2017; Nichols et al., 2016; Sirois et al., 2016; Wood, Shah, Steenhoff, & Rutstein, 2009). Further research will need to examine if the lower than national normative sample performance in these domains places these youth/young adults at risk for poor employment, academic, treatment and other key outcomes, as seen in behaviorally infected adults (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; van Gorp et al., 2007). Since

PS contributes to WM and EF efficiency, the non-significant gains in PS among PHIV youth could indicate some risk for future deficiencies in WM and EF, especially if PS declines or does not improve over time. However, continued research is needed to understand these performance trajectories as this population continues to age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Observed means of Neurocognitive Outcome Scores by HIV status and baseline child age cohort (9-10, 11-13, 14-17) across age and follow-up.

Figure 2:
Model-estimated adjusted mean plots.

Table 1:**Demographic Characteristics of CASA at Enrollment and FU4**

	Mean (SD); N (%)	Mean (SD); N (%)	Mean (SD); N (%)
Baseline (2003-2008)	Total (N=340)	PHIV (N=206)	PHEU (N=134)
Age (years)	12.58 (2.25)	12.70 (2.16)	12.40 (2.37)
Age range (years)	9-16	9-16	9-16
Female	172 (51%)	104 (51%)	68 (51%)
African American/Black	221 (65%)	135 (66%)	86 (64%)
Latino	142 (42%)	79 (38%)	63 (47%)
Caregiver Type *			
Biological Parent	167 (49%)	73 (35%)	94 (70%)
Relative	80 (24%)	59 (29%)	21 (16%)
Non-relative	93 (27%)	74 (36%)	19 (14%)
Caregiver Sex at Birth (% Female)	298 (88%)	179 (87%)	119 (89%)
Caregiver HIV Status (% HIV+) *	150 (46%)	61 (31%)	89 (69%)
Follow-up Visit 4 (2010-2015)	Total (N= 242)	PHIV (N=146)	PHEU (N=96)
Age (years) *	19.95 (2.73)	20.51 (2.66)	19.10 (2.62)
Age range (years)	15-26	15-26	15-24
Female	126 (52%)	77 (53%)	49 (51%)
African American/Black	165 (68%)	102 (70%)	63 (66%)
Latino	118 (49%)	67 (46%)	51 (53%)

* Note: We examined differences across demographic characteristics between PHIV and PHEU groups. At baseline, PHEU youth were statistically significantly more likely to have a biological parent as a caregiver ($p<.001$) and have an HIV+ caregiver ($p<.001$) than PHIV youth. At Follow-up Visit 4, the mean age of PHEU youth was statistically significantly older than PHIV youth ($p<.001$). No other statistically significant differences were found

Table 2:
Longitudinal Regression Models Predicting Neurocognitive Outcomes across Adolescence into Young Adulthood

Effect	Digit Span (N=261) ^b			Log Trails A (N=260)			Log Trails B (N=260) ^b		
	b	SE	p	b	SE	p	b	SE	p
Youth Number of Hospitalizations ^a									
Between	-0.007	0.033	0.829	0.0002	0.004	0.962	0.005	0.005	0.332
Within	-0.022	0.007	0.001	0.003	0.001	0.004	0.004	0.001	0.001
Youth Academics									
Ever in special education	-1.629	0.330	<.0001	0.173	0.040	<.0001	0.314	0.054	<.0001
Ever held back	-0.869	0.327	0.008	0.024	0.040	0.548	0.091	0.054	0.089
Ever skipped grade	-0.377	0.869	0.665	0.011	0.105	0.917	-0.092	0.142	0.518
Caregiver Characteristics									
Primary language (English vs. not)	-0.392	0.245	0.110	0.039	0.030	0.199	0.016	0.040	0.693
Relationship to Youth (Biological parent vs. not)	0.013	0.053	0.801	0.010	0.006	0.105	0.010	0.009	0.248
Youth Age	0.067	0.032	0.035	-0.036	0.007	<.0001	-0.017	0.006	0.003
PHIV Status (PHIV vs. PHEU)	-0.343	0.341	0.315	-0.449	0.195	0.022	0.026	0.056	0.647
Youth Age * PHIV Status	--	--	--	0.026	0.009	0.004	--	--	--

Note: b = beta estimate, SE = standard error, p = p-value.

^a“Between” represents the average number of hospitalizations for each youth across all available follow-up visits. “Within” represents the change in number of hospitalizations from the youth-specific average number of hospitalizations at each follow-up.

^b Model estimates are from the main effects model after removing the non-significant Youth Age

* PHIV Status interaction.