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Prospective Memory in Youth with Perinatally-acquired HIV Infection

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for the Memory and Executive Functioning Study of the Pediatric HIV/AIDS Cohort Study

Abstract

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Youth with perinatal HIV infection (PHIV) are at increased risk for neurocognitive impairment. Prospective memory (PM) is a complex neurocognitive function that has been shown to be impaired in adults with HIV disease and independently associated with poorer daily living skills, including medication non-adherence. The current study sought to determine the presence and extent of PM deficits in youth with PHIV. Participants included 173 youth with PHIV and 85 youth HIV-exposed but uninfected (PHEU), mean age 14.1 years, 75% black, 18% Hispanic. Among youth with PHIV, 26% had a past AIDS-defining condition (Centers for Disease Control and Prevention [CDC], Class C), 74% did not (non-C). Adjusted generalized estimating equation models were used to compare groups (PHIV/C, PHIV/non-C, and PHEU) on the Naturalistic Event-Based Prospective Memory Test (NEPT) and the Prospective Memory Assessment for Children & Youth (PROMACY). Secondly, subgroups defined by HIV serostatus and global neurocognitive impairment (NCI) were compared (PHIV/NCI, PHIV/non-NCI, PHEU). PHIV/C had significantly lower NEPT scores than PHEU, with decreases of 40% in mean scores, but did not differ from PHIV/non-C. PHIV/NCI had 11–32% lower PROMACY scores and 33% lower NEPT scores compared to PHIV/non-NCI (all $p < 0.05$); significantly lower scores for PHIV/NCI vs PHEU also were observed for PROMACY and NEPT indices. Findings suggest a subset of youth with PHIV (those with a prior AIDS-defining diagnosis) is vulnerable to PM deficits. The extent to which PM deficits interfere with development and maintenance of independent living and health-related behaviors during transition to adulthood requires further study.

Keywords

prospective memory; perinatal HIV; children; adolescents; executive functioning

For children and adolescents (herein referred to as “youth”) with perinatal HIV infection (PHIV), advancements in treatment and improved management of HIV-related symptomatology have led to improved quality of life and expectation of longer survival (Pizzo, 1990; Smith & Wilkins, 2015). Once considered to be significantly life-limiting, HIV disease is now viewed as a treatable chronic condition (World Health Organization, 2016). Thus as youth with PHIV progress through adolescence, they are subject to developmental expectations typical for the majority of adolescents as they prepare for adulthood. Such expectations include assuming greater independence in daily life activities, for example, completion of household chores, decision-making related to risky behaviors, management of multi-step academic or vocational projects, monitoring budgets and paying bills on time, and managing routine health care. Only recently has a sufficiently sizable cohort amassed to allow for study of adolescents and young adults with PHIV; as anticipated, initial studies already are documenting concerns regarding adaptive functioning (Garvie et al, 2014; Gosling, Burns, & Hirst, 2004; Hinkin et al., 2002; Pearlstein et al., 2014; Wolters & Brouwers, 2005), engagement in risky behaviors (Alperen et al., 2014; Elkington, Bauermeister, Brackis-Cott, Dolezal, & Mellins, 2009; Tassiopoulos et al., 2013), and nonadherence to medication regimens (Farley et al., 2008; Garvie et al, 2017; Kacanek et al., 2015; Naar-King et al., 2009; Simoni et al., 2007; Usitalo et al., 2014; Williams et al., 2006). It is therefore important to understand factors that contribute to the development of competence in managing these activities so as to better assess the capability of youth with

PHIV to take on these responsibilities and to refine intervention strategies to help support those individuals who are struggling to master those skills.

There are multiple socio-demographic and biopsychosocial factors that could contribute to or impede successful mastery of independent living skills. For individuals with HIV, one very important living skill is medication management, and good adherence relies heavily on executive functions. Although the advent of highly active antiretroviral therapy (HAART) has yielded notable improvement in the overall cognitive functioning of youth with PHIV (Garvie et al., 2014; Smith et al., 2012), those with a history of more severe HIV disease status remain vulnerable to impairment (Smith et al., 2012; Wood, Shah, Steenhoff, & Rutstein, 2009). Some increased vulnerability has also been observed among those who have had not had an AIDS-defining illness (Gongvatana et al., 2009; Jeremy et al., 2005). Among the most consistently noted vulnerabilities are aspects of executive function, such as working memory, processing speed, sequencing, organization and planning (Bisiacchi, Suppiej, & Laverda, 2000; Garvie et al., 2017; Koekkoek, de Sonnevile, Wolfs, Licht, & Geelen, 2008; Martin et al., 2006; Nichols et al., 2015; Smith et al., 2012). For example, Bisiacchi et al. (2000) showed that youth with PHIV who were neurologically asymptomatic performed more poorly on measures of sequencing, planning, inhibition, working memory, and verbal fluency compared to measures of general intelligence, language, memory, and visual-spatial ability. Further, they performed more poorly on those measures compared to PHEU youth, and it was noted that all youth with PHIV showed impairment in executive functioning regardless of disease stage. Similarly, in Koekkoek et al. (2008), measures of reaction speed, attention, visual-spatial working memory, and processing speed were the most sensitive indicators of impairment compared to measures of general intelligence which were generally within the average range for age. Performance on verbal fluency also was below national norms. In one of the largest cohort studies, Smith et al. (2012) noted that compared to PHEU youth, youth with PHIV with an AIDS-defining illness had a two- to five-times increased risk for impairment in processing speed, working memory, and perceptual reasoning.

One area of cognition that relies heavily on executive functions and is essential to medication management, but has not yet been explored in PHIV, is prospective memory (PM). PM refers to the ability to remember to carry out a future intention while engaged in a competing, ongoing activity (McDaniel & Einstein, 2007). PM is a complex, dissociable aspect of cognition that requires an individual to encode an intention (e.g., take a medication after dinner), maintain that cue-intention pairing and monitor for the cue during an ongoing activity (e.g., participating in daily routines), detect and recognize the cue (e.g., eating dinner), which triggers retrieval of the intention from retrospective memory, and finally execute the intention as planned (take medication as prescribed). PM cues are commonly classified as being event-based (e.g., taking a medication after dinner) or time-based (e.g., taking a medication in two hours), with the latter generally thought to place more demands on strategic monitoring processes (McDaniel & Einstein, 2000). PM has obvious relevance for performance of routine daily life activities including health behaviors such as medication adherence (see Zogg, Woods, Saucedo, Wiebe, & Simoni, 2012). For example, failing to remember to take certain HAART medications at the requisite time not only leads to decreased effectiveness of the regimen, but also can contribute to development of viral

resistance to some drugs (Hazra, Siberry, & Mofenson, 2010). Thus, PM plays an essential role in successfully transitioning to independent medication management.

To date, there has been relatively little research on PM in children and adolescents, and none examining youth with perinatal HIV infection. Among pediatric populations, the scant literature has suggested performance deficits in PM associated with attention deficit/hyperactivity disorder (Kerns & Price, 2001; Kliegel, Ropeter, & MacKinley, 2006), traumatic brain injury (McCauley & Levin, 2004; McCauley, McDaniel, Pedroza, Chapman, & Levin, 2009; Ward, Shum, McKinlay, Baker, & Wallace, 2007), and sickle cell disease (McCauley & Pedroza, 2010). In children with high functioning autism, performance difficulties have been indicated for time-based PM (Altgassen, Williams, Bolte, & Kliegel, 2009) but not event-based PM (Altgassen, Schmitz-Hubsch, & Kliegel, 2010). There is some suggestion that PM is related to glycemic control in children with type 1 diabetes mellitus (Osipoff, Dixon, Wilson, & Preseton, 2012).

Mild-to-moderate PM deficits are evident among adults with HIV disease and have implications for clinical care. For example, self-report of greater PM difficulties in daily life (Woods et al., 2007) and performance deficits in both time- and event-based PM are reliably found in younger (e.g., 18–24 years) (e.g., Woods et al., 2014), middle-aged (e.g., early 40s) (e.g., Carey, Woods, Rippeth, Heaton, & Grant, 2006; Martin et al., 2007), and older (e.g., mid 50s and older) (e.g., Woods, Dawson, Weber, & Grant, 2010) adults living with HIV infection. Adults with HIV-associated neurocognitive disorders (HAND) are particularly vulnerable to deficits in PM (Morgan et al., 2012; Woods et al., 2014; Zogg, Woods, Weber, Doyle, & Grant, 2011), which in turn have a unique adverse impact on different activities of daily living (e.g., Woods, Iudicello, et al., 2008), including adherence to HIV medication regimens (for a review see Zogg et al., 2012).

Youth with PHIV may have patterns of neurocognitive performance which differ from those of adults who contracted HIV through a means other than perinatal transmission. In perinatal HIV infection, the foundation and acquisition of cognitive functions could be disrupted rather than decline from a premorbid level as seen in adults with HIV. Although children may have greater CNS plasticity compared to adults in some instances, there is evidence of significant and lasting neurocognitive deficits arising from early diffuse injury (Donders & Warchausky, 2007; Ewing-Cobbs et al., 1997). Thus, the prevalence and pattern of any such PM deficits may differ from those of adults with HIV, and there also may be differences among subsets of youth with PHIV such as those who have sustained an AIDS-defining illness versus those who have not. This premise aligns with a prefrontal-lobe model of PM initially proposed by West (1996). West's model was based on work with older adults, but it has been applied to studies involving children. For example, Ward, Shum, McKinlay, Baker-Tweney & Wallace (2005) examined the impact of differing levels of cognitive impact and importance on PM performance across three groups – children (7–10 years old), adolescents (13–16 years old), and young adults (18–21 years old). Adolescents and adults showed similar PM performance levels and similar reduction in performance under conditions with high cognitive load compared to low cognitive load. However, children did not perform as well as adolescents or adults on PM tasks, and they showed a greater proportional decrease in PM performance under conditions of high cognitive load compared to low cognitive load.

Children also performed more poorly than adolescents or adults on two of three measures of executive functioning while adolescents and adults performed similarly to each other. Collectively, these results support the notion that development of PM is aligned with maturation of prefrontal lobe function.

In sum, given the unique impact of HIV on the developing brain and the importance of PM in the transition of youth with PHIV to independence, investigation of this domain in the pediatric HIV population is warranted. To this end, performance on two PM tasks was evaluated in youth with PHIV, with and without AIDS-defining conditions, and (as the reference group) youth perinatally HIV-exposed but uninfected (PHEU). In addition, subgroups defined by serostatus and global neurocognitive impairment (NCI) were compared (PHIV/NCI, PHIV/non-NCI, PHEU).

Methods

Participants

Participants for this study were enrolled in the Memory and Executive Functioning (Memory/EF) Study of the Pediatric HIV/AIDS Cohort Study (PHACS). PHACS is a prospective cohort study of the long-term effects of perinatal HIV infection and its treatments on biomedical and neurobehavioral outcomes, as previously described by Smith et al. 2012. The Memory/EF Study was designed to provide a two-year longitudinal in-depth assessment of retrospective and prospective memory and executive functioning, and their relationships to HIV disease severity as well as functional outcomes (Nichols et al., 2015). Participants were enrolled at one of eight selected urban PHACS sites throughout the United States between 2010 and 2012. Eligibility criteria included perinatal HIV infection or exposure, age 9 to <19 years at entry, enrollment in PHACS, and ability to participate in testing procedures. Because some study assessments were available only in English, adequate fluency in English was required. Analyses reported herein included youth with PHIV (n=173) and youth PHEU (n=85) who had valid baseline data for one or both of the PM memory tasks (only baseline data were used in these analyses). Institutional Review Boards (IRB) at the Harvard T.H. Chan School of Public Health and each participating Memory/EF Study site approved this project. Informed consent and age-appropriate assent were obtained for all youth participants according to local IRB guidelines.

Measures

Currently, there are no standardized, norm-referenced tests for PM in children. Therefore, our battery included two research measures of PM, one adult measure of PM with known sensitivity to HIV adapted for use with children and one previously used with children.

Prospective Memory Assessment for Children & Youth (PROMACY)—This measure was modeled after the Memory for Intentions Screening Test (MIST) (Raskin, Buckheit, & Sherrod, 2010) for the purpose of this study. As noted in the Acknowledgments, it was reproduced by special permission of the Publisher, Psychological Assessment Resources, Inc., and further reproduction is prohibited without permission from PAR, Inc. The PROMACY contains balanced PM items that include a 2-minute or 10-minute delay, a

verbal response (e.g., "In 10 minutes tell me that it is time for a break") or physical response (e.g., "When I show you a red pen, write your name on your paper"), and a time-based cue (e.g., "In 2 minutes ask me when we're going to be done") or event-based cue (e.g., "When I show you the small blue index card, write the name of your school [work] on it"). The participant must remember to perform the specified activities while working on an ongoing distractor task of word search puzzles. A recognition questionnaire is administered after all eight PM tasks have been completed to assess retrieval (encoding or consolidation) failures. Error types (no response, task substitutions, loss of content, loss of time, and place losing omissions) are coded according to standardized instructions. The PROMACY was inspired by the original adult version of the MIST which has demonstrated solid psychometrics (i.e., construct validity, test-retest reliability, inter-rater reliability, and internal consistency) (e.g., Woods, Moran, et al., 2008).

Naturalistic Event-Based ProM Task (NEPT)—See McCauley et al. (2009) and McCauley et al. (2011). This naturalistic, habitual PM task is embedded within a battery of standardized memory, executive function, attention and processing speed measures given in fixed order. In this task, the child is asked to make a specific response ("Please give me three points") each time the examiner gives the verbal cue "Let's try something different" at predetermined points during the test battery. The verbal cue is given at approximately 15-minute intervals for a total of 3 presentations. The summary score reflects a maximum of four points for each correct response, two points for giving an incorrect verbal or other response (failure of the retrospective memory component), and zero points for failing to respond to the cue. A retrospective memory (RM) score is calculated (any 4-point response is awarded 1 point toward the RM score). An Intention score also is calculated (any 4-point or 2-point response is awarded 1 point toward the Intention score).

Demographic, Caregiver, and Health Information—As part of PHACS, demographic information is collected via structured interview with the primary caregiver, including age, sex, race/ethnicity, and primary language of child, household income, and caregiver relationship to child and caregiver education. Youth medical chart abstraction provided current and peak HIV RNA viral load (VL) and age at peak VL; current, nadir and age at nadir CD4+ T-lymphocyte count and percent; Centers for Disease Control and Prevention (CDC) classification of prior AIDS defining conditions (Class C) and age at classification; diagnosis of encephalopathy and age at diagnosis; and current antiretroviral (ARV) treatment.

Other Measures—For the purpose of secondary analyses, additional data were abstracted from the Memory/EF Study, including selected subtest scores from the following age-standardized instruments: Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV; Wechsler, 2003), Delis Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001), and Wide Range Assessment of Memory and Learning – 2nd Edition (WRAML-2; Sheslow & Adams, 2003). Thirteen subtests from a battery of standardized tests assessing five ability areas were used to generate a global deficit score (see Appendix 1), which is a well-validated approach commonly used in the adult neuroAIDS literature (see Carey et al., 2004). In brief, raw scores from each test were converted into age-adjusted T-

scores using published normative standards. T-scores were then transposed into deficit scores, which ranged from 0 (T-scores >39) to 5 (T-scores <20), with higher scores representing greater levels of impairment. These deficit scores were then averaged across the battery of tests and a standard cut-point of >0.5 was applied to classify youth with PHIV with global Neurocognitive Impairment (NCI).

Design

Our primary *a priori* analyses were based on comparing youth with PHIV with a prior AIDS defining condition (CDC Class C) and youth with PHIV without such a condition to the comparison group of exposed uninfected youth, thus involving three groups (PHIV/C, PHIV/Non-C, and PHEU). As a secondary analysis paralleling the adult HIV literature on PM (see Zogg et al., 2011), youth with PHIV also were classified as having or not having NCI. Using this approach, we thus defined three groups for comparison in these secondary analyses: PHEU, PHIV without NCI (PHIV/non-NCI), and PHIV with NCI (PHIV/NCI).

Statistical Analysis

Group differences in PM functioning for each score were explored with univariate and multivariable linear regression models. Potentially confounding variables, including child demographic and caregiver characteristics, were controlled for in the multiple regression models. For all mean score outcomes, generalized estimating equation methods (GEE) were used to obtain robust (empirical) error variances. We used GEE methods as a conservative approach due to concerns about normality assumptions (i.e., PROMACY and NEPT scores had non-normal distributions, data not shown). The GEE models were used to obtain Wald chi-square tests and corresponding p-values both for individual parameters and for overall tests for categorical variables with more than 2 levels. In order to explore group differences (among the three HIV status groups and the three groups defined by HIV status and NCI status), unadjusted group means were first calculated. Next, an adjusted model was built for each outcome by including all covariates with univariate $p < 0.20$ in initial multivariable models, and retaining covariates with $p < 0.15$. Adjusted means (and mean differences between groups) along with their corresponding 95% confidence intervals (CIs) were obtained from linear regression models adjusting for these covariates. P-values < 0.05 were considered to be statistically significant. SAS (Version 9.2, SAS Institute, Cary N. C.) was used for all analyses. In some instances, the magnitude of effect was calculated using Percent Difference equation (i.e., the absolute value of the difference, divided by the average of the two groups, all multiplied by 100).

Results

Demographics & Health Characteristics

A total of 258 study participants were included as follows: PHIV/non-C (n=128), PHIV/C (n=45), and PHEU (n=85) (see Table 1). Groups did not differ with respect to race and ethnicity. Youth with history of more severe HIV disease (e.g., PHIV/C) were significantly older than PHIV/non-C and PHEU (mean age in years at study entry: 15.5, 14.5, and 12.9, respectively). Significantly fewer youth with PHIV had biological parents as primary caregivers or had caregivers with HIV disease, and more lived in higher income households.

Over two-thirds of youth with PHIV had suppressed viral load (<400 copies/mL) and CD4% 25. All but one case of encephalopathy was reported among PHIV/C. Over 85% of youth with PHIV were prescribed HAART.

Differences in Prospective Memory by HIV Status and Prior AIDS Diagnosis

In unadjusted analyses comparing the three groups, PHIV/C and PHEU differed significantly on all NEPT scores (Table 2); PHIV/C had 36–39% lower mean scores than PHEU. Further, a 40% lower mean NEPT RM score persisted after adjustment for sociodemographic covariates. In unadjusted analyses of PROMACY scores, PHIV/C and PHEU differed significantly on one of the three scores (time-based), though the difference did not remain significant in adjusted analyses. There were no significant differences observed on any NEPT or PROMACY scores when comparing PHIV/non-C and PHIV/C or when comparing PHIV/non-C and PHEU.

After adjustment, significant associations remained between PM components and HIV biomarkers (Table 3). Age at peak VL (split into three developmental periods based on literature that has shown higher risk for neurocognitive difficulties associated with AIDS-related complications occurring prior to 3–5 years of age; see Smith & Wilkins, 2015) had a similar pattern across all three PROMACY indices. Children who were 3–5 years of age at peak VL had scores 15–24% higher than children who were 5 years and 8–13% higher than children who were <3 years of age at peak VL. Children who were 3–5 years of age at Class C diagnosis had higher PROMACY event-based PM scores compared to children who were 5 years or <3 years at CDC Class C diagnosis (7% and 12%, respectively). Age at nadir CD4% was associated with all four NEPT indices; children 3–5 years at nadir CD4% had scores 48–49% higher than children who were 5 years and 39–45% higher than children who were <3 years at nadir CD4%. Higher VL at study entry was associated with lower NEPT scores, with differences ranging 38–43% across the four indices.

Differences in Prospective Memory by HIV Status and Global Neurocognitive Impairment (NCI)

Thirty-nine percent of youth with PHIV were classified as having global NCI. As expected, the subgroups (PHIV/NCI, PHIV/non-NCI, and PHEU) differed significantly in performance on both the PROMACY and the NEPT (Table 4). Specifically, PHIV/NCI performed lower on PM as compared to PHIV/non-NCI and PHEU after adjustment. These differences were significant for each of 4 primary outcomes, including the PROMACY summary score (20% and 17%, respectively), PROMACY Time-Based score (32% and 25%, respectively), PROMACY Event-Based score (11% and 10%, respectively), and NEPT RM score (33% and 47%, respectively). There were no significant PM differences between PHIV/non-NCI and PHEU after adjustment.

Discussion

“Remembering to remember” is known to be an area of vulnerability among adults with HIV and may be especially relevant to the everyday functioning and health behaviors of youth with PHIV as they transition to independence. In this first investigation of PM in youth with

PHIV, based on traditional classification approaches of disease severity, we observed modest independent effects of advanced HIV disease in performance on a naturalistic test of PM requiring habitual event-based responses (i.e., NEPT). However, HIV was not associated with difficulties performing either event- or time-based PM on a laboratory-based task adapted from the adult HIV literature (i.e., PROMACY) following adjustment for sociodemographic factors. Nevertheless, a subset of youth with PHIV – namely those youth with global neurocognitive impairment – showed large deficits across different types of PM cues on both laboratory and naturalistic tasks independent of sociodemographic factors. This latter finding is consistent with PM studies in the adult HIV literature (e.g., Carey et al., 2006; Morgan et al., 2012; Woods et al., 2014; Zogg et al., 2011) suggesting that youth with PHIV with neurocognitive impairment are susceptible to deficits in memory for future intentions (i.e., PM). Our findings add to the growing literature showing vulnerability within the broad domain of executive functioning among youth with PHIV, particularly those with greater disease severity status, and also extend support for West's (1996) prefrontal model of PM.

There are important conceptual differences between the PROMACY and the NEPT that should be considered in interpreting the sensitivity of the NEPT versus the PROMACY to PHIV/C. The NEPT is a habitual, event-based PM task that is administered in a naturalistic context in which the cue (i.e., the examiner saying “let's try something different”) is low in salience and focal to the ongoing activity (i.e., the broader evaluation procedures) and the intentions (i.e., asking for points) are not strongly semantically linked to the cue. The PROMACY, on the other hand, is a more traditional paper-and-pencil task in which the examinee is engaged in a less demanding continuous ongoing activity (i.e., a word search) to which the cues are higher in salience, non-focal (i.e., not central to the cognitive processing involved in the word search) and strategically demanding (e.g., including time-based items), but the intentions are semantically related to the cues. Thus, several explanatory possibilities exist regarding the increased sensitivity of the NEPT, which may include increased focality of the cue, the naturalistic context of the cue reducing its salience, the cognitive demands of the ongoing task or activity, and/or the lower semantic link between the cue and the intention (e.g., Woods et al., 2010). For example, McCauley and Pedroza (2010) demonstrated that enhancing the perceptual distinctiveness of event-based PM cues functionally normalized PM performance in a sample of children with sickle cell disease. Experimental studies are needed to systematically manipulate these various aspects of PM in youth with PHIV in order to gain a clearer picture of the underlying cognitive architecture of the subtle PM difficulties observed on the multifactorial tasks used in this study.

More severe and consistent PM problems were observed among youth with PHIV with global neurocognitive impairment as operationalized by performance below the average range for age based on established normative data for each instrument (which also is akin to how HAND is diagnosed clinically). Such neurocognitive subset analyses are particularly important to minimize Type II error in studies of medical populations such as HIV for whom CNS involvement is not universal. Indeed, paralleling the adult HIV literature (e.g., Doyle et al., 2015), this vulnerable subset of youth with PHIV demonstrated marked difficulties across naturalistic and lab-based PM measures, the latter of which included deficits in both event- and time-based PM. Thus, future studies might wish to determine whether or not PM

provides added value in the prediction of health behaviors (e.g., adherence) and various real-world outcomes (e.g., vocational success) in this subset of youth who evidence global neurocognitive impairment.

Age at greatest HIV severity had a number of significant associations with PROMACY and NEPT performance. However, the pattern of associations was initially somewhat puzzling. Children who had experienced their most severe disease symptoms at the age of 3 – 5 years had better PM scores than children who were either younger or older at the time of greatest disease severity. Those who were older at the time of greatest HIV insult showed the lowest PM scores. One hypothesis might be that children who are older at peak disease severity are in a period of CNS maturation that is particularly vulnerable to such insults or have less plasticity to compensate for them compared to children who are younger at peak disease severity. Another possibility is that children who were older at peak severity may have initiated HAART later and thus may have been exposed to disrupted CNS development beginning at a younger age and over a longer period of time. In perinatal HIV infection, the entire process of brain development and myelination occurs within the context of HIV. The virus enters the central nervous system (CNS) much earlier, usually before onset of severe immunocompromise and in some cases being present even in fetal tissues (Lyman et al., 1988). There is variation in age or developmental stage when the virus is most active, with differing brain structures and functions implicated at those various time points (Brouwers, van der Vlugt, Moss, Wolters, & Pizzo, 1995; Smith & Wilkins, 2015). CNS insults may be time and structure limited (Belman, 1990), a process that leads to immediate structure-specific functional deficit for those systems that have already emerged, and additional functional deficits would be noted at the time they normally would appear in the course of development. Although we adjusted for a number of demographic variables, there may be other factors we did not account for that contributed to the observed pattern. For example, the timing of HAART initiation or the specific antiretroviral drugs included in the regimen (e.g., those with greater or lesser CNS penetrance) might be important factors to consider.

In sum, PM appears to have been affected more by the degree of CNS-related effects, whatever the etiology, than simply by the presence of an AIDS-defining illness in the youth with PHIV, and the period of greatest vulnerability seems to be post-preschool age compared to infancy or toddlerhood. These results potentially offer some additional support to an idea posited by McCauley et al. (2011) that PM perhaps is more sensitive to the severity of CNS effects than to early timing of CNS injury or insult, as McCauley et al. (2009) found that there were no age-at-injury effects for PM performance, but that severity of TBI was significant. Future neuroimaging studies might more directly examine the relationship between PM and brain structure and function within the PHIV cohort, which potentially then could extend additional support for West's (1996) model.

The PM deficits observed among a subgroup of youth with PHIV have clinical implications for strategies to aid the mastery of independent life skills. One critical activity thrust upon these youth as they progress through adolescence into young adulthood is management of their own medication regimens and healthcare. Even under the best of circumstances, adherence to HAART is challenging. One feature is that it requires multiple medications with potential varied dose timing and/or dietary restrictions (Pontali, 2005). Youth have to

keep in mind a sizable amount of information as they progress through daily activities, including remembering their medication schedule, tracking the passage of time, planning for snacks and meals that meet any potential dietary requirements/restrictions, and ensuring the necessary medications are in their possession at the designated dosing times. Such activity places increased burden on PM. In the adult HIV population, PM is predictive of medication management (Woods, Moran, et al., 2008; Woods et al., 2009). Considering PM capabilities of youth with PHIV could influence decisions about the type of supports and interventions best suited to foster their overall health and long-term survival. Certainly the importance of adherence is emphasized by caregivers and clinicians, but drawing from our results, it might be more effective to focus supportive efforts on increasing the saliency of the cues.

Another consideration of transitioning through adolescence into adulthood is increased likelihood of engagement in sexual activity. In the adult HIV population, PM is predictive of behaviors that increase risk of HIV transmission (Martin et al., 2007). Similarly, PM deficits in youth with PHIV could result in not having condoms readily available for a sexual encounter, putting the sexual partner at risk for transmission. Transmission risk would be compounded further if PM deficits also contributed to poorer adherence resulting in incomplete viral suppression. Forgetting to use condoms (or to take birth control pills, for that matter) also could increase the odds of unplanned pregnancy, with compounded risk of transmitting the virus to the fetus (although this latter risk would be minimal if the mother was engaged in healthcare and adherent to ARVs in pregnancy). Interventions aimed at reducing risky sexual behavior could be better informed by considering the nature of PM in youth with PHIV. For example, Fleming, Shum, Strong, and Lightbody (2005) demonstrated that training directed at increasing awareness and promoting the use of compensatory strategies yielded benefit to PM among adults with traumatic brain injury. Alternatively, it might be that impaired retrospective memory interferes with PM, in which case a better option for intervention might involve spaced retrieval or errorless learning. If the deficit is driven by a more generalized executive dysfunction, then a focus on supporting problem-solving capacity likely would be more useful.

Limitations

There are a number of family and environmental factors that contribute to a child's cognitive development, such as poverty, in utero drug exposure, family history of learning or psychiatric illness, etc. Our analysis controlled for many of these variables given the relevance to many participants in the sample. Youth with PHEU also share some demographic factors specific to HIV disease, such as chronic illness in a family member, death of a biological parent, ostracism, and potentially adverse exposure to anti-retroviral medication in utero. These added stressors may drive cognitive vulnerability. Having a comparison sample of youth who are non-exposed, from non-HIV-affected families might have helped to better explain some of the findings. In terms of ARV treatment history among our sample, the PHIV/non-C and PHIV/C groups did not differ in regimen or in VL at study entry, nor did they differ with respect to age at greatest disease severity. However, the PHIV/C group did have an older mean age, and it is possible that there were group differences with respect to age of treatment onset, specific components of prior regimens, or past adherence. Such facets of treatment history might influence neurodevelopment and

thereby contribute to differences in PM among these youth. These complex factors were beyond the scope of this initial investigation into PM in the perinatal HIV population, but should be considered in future studies. The eight participating sites wherein this study was conducted represent all regions of the country; nonetheless, results with this sample may not generalize to all youth with PHIV and PHEU. The exclusion of non-English fluent children also limits generalizability. Finally, the PROMACY was developed specifically for this study, and although initial psychometric properties are promising, its sensitivity and specificity for the population are unknown.

Conclusions

In this initial investigation of PM in youth with PHIV, it was determined that PM deficits are not universal. Instead, findings suggest that the subset of PHIV youth with NCI appears to be vulnerable to deficits in multiple aspects of PM, independent of clinicodemographic factors. These findings mirror observations among adults with HIV infection, which show that both time- and event-based PM are adversely affected, particularly in persons with HIV-associated neurocognitive disorders (e.g., Woods et al., 2014; Zogg et al., 2011). Considering that HIV-associated PM deficits in adults are robust predictors of health-related behaviors, such as medication management (e.g., Woods et al., 2009), future work in youth may examine ways in which PM functioning may be supported or improved. For example, recent work in young adults with HIV shows that emphasizing the importance of the PM task (e.g., Woods et al., 2014), visualization of the cue-intention pairing (Faytell et al., 2015), delaying the response time of the ongoing task (Loft et al., 2014), and salient cues (Faytell et al., 2016) can improve PM performance in the lab and in daily life. The extent to which such approaches actually enhance PM in youth with HIV and in turn positively influence health outcomes in this vulnerable group remains to be determined.

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List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
CDC	Centers for Disease Control and Prevention
DKEFS	Delis Kaplan Executive Function System
EB-PM	Event-Based prospective memory
EF	Executive Function
HAART	Highly Active Antiretroviral Therapy
HAND	HIV-associated Neurocognitive Disorder
HIV	Human Immunodeficiency Virus
HIV/C	HIV infected with CDC Class C diagnosis
IRB	Institutional Review Board
NCI	global neurocognitive impairment
NEPT	Naturalistic Event-Based ProM Task
PHACS	Pediatric HIV/AIDS Cohort Study
PHEU	HIV-exposed, uninfected
PHIV	Perinatally acquired Human Immunodeficiency Virus
PM	Prospective Memory
PROMACY	Prospective Memory Assessment for Children & Youth
RM	Retrospective Memory
TB-PM	Time-Based prospective memory
VL	Viral load
WAIS-IV	Wechsler Adult Intelligence Scale, 4 th Edition
WISC-IV	Wechsler Intelligence Scale for Children, 4 th Edition
WRAML-2	Wide Range Assessment of Memory & Learning, 2 nd Edition

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Appendix

Appendix 1

Tests included in the calculation of Neurocognitive Impairment (NCI)

Domain and Test	Study group				P-Value (a)
	Total (N=258) Mean (SD)	PHEU (N=85) Mean (SD)	PHIV/non-C (N=128) Mean (SD)	PHIV/C (N=45) Mean (SD)	
Attention/Processing Speed					
Digit Span (WISC-IV/WAIS-IV)	8.23 (3.08)	8.27 (3.04)	8.53 (3.19)	7.31 (2.69)	0.072
Coding (WISC-IV/WAIS-IV)	7.63 (2.86)	7.53 (3.00)	7.91 (2.78)	7.02 (2.80)	0.190
Combined Naming/Reading (DKEFS)	8.64 (3.28)	8.74 (3.40)	9.04 (2.96)	7.33 (3.66)	0.010
Learning					
Verbal Learning (WRAML-2)	8.36 (2.71)	8.99 (2.72)	8.21 (2.73)	7.62 (2.43)	0.015
Design Memory (WRAML-2)	8.74 (2.91)	8.81 (3.06)	8.84 (2.93)	8.31 (2.59)	0.553
Memory					
Verbal Delay Recall (WRAML-2)	8.91 (2.64)	9.29 (2.89)	8.88 (2.48)	8.24 (2.49)	0.096
Design Memory Recognition (WRAML-2)	8.81 (3.07)	9.32 (3.23)	8.72 (3.02)	8.18 (2.85)	0.119
Verbal Fluency					
Letter Fluency (DKEFS)	8.43 (3.10)	8.36 (2.93)	8.74 (3.19)	7.66 (3.12)	0.132
Category Fluency (DKEFS)	9.24 (3.08)	9.62 (3.23)	9.16 (3.09)	8.70 (2.68)	0.257
Category Switching (DKEFS)	8.38 (3.10)	8.80 (3.28)	8.39 (3.03)	7.52 (2.81)	0.084
Executive Function					
Color-Word Inhibition (DKEFS)	7.82 (3.44)	8.24 (3.13)	7.99 (3.51)	6.56 (3.55)	0.021
Design Fluency Combined (DKEFS)	8.51 (2.18)	8.59 (2.08)	8.60 (2.12)	8.09 (2.50)	0.379
Twenty Questions Total (DKEFS)	8.64 (3.95)	8.06 (4.27)	8.83 (3.79)	9.18 (3.71)	0.232
(a) Analysis of Variance					

DKEFS=Delis Kaplan Executive Function System, PHEU=perinatally HIV-exposed uninfected, PHIV/C=HIV-infected with prior CDC Class C diagnosis, PHIV/non-C=HIV-infected without prior CDC Class C diagnosis, SD=standard deviation, WAIS-IV=Wechsler Adult Intelligence Scale – 4th Edition, WISC-IV=Wechsler Intelligence Scale for Children – 4th Edition, WRAML-2=Wide Range Assessment of Memory and Learning – 2nd Edition.

Table 1
Personal, Family, and HIV-related Characteristics of PHACS Memory/EF Study Participants at Entry to Study

Characteristic	Study group			P-value	
	PHEU (N=85)	PHIV/non-C (N=128)	PHIV/C (N=45)	Across all 3 groups	PHIV/C vs. PHIV/non-C
Male sex	44 (51.8%)	59 (46.1%)	16 (35.6%)	0.21	0.22
Age at entry, y (median, IQR)	12.6 (10.6, 14.6)	14.4 (12.0, 16.9)	15.6 (14.3, 17.2)	<0.001	0.03
Black Race	65 (77.4%)	95 (76.0%)	34 (81.0%)	0.80	0.51
Hispanic ethnicity	19 (22.4%)	19 (15.0%)	8 (17.8%)	0.39	0.66
Primary language is English					
Child	75 (88.2%)	120 (94.5%)	42 (93.3%)	0.24	0.78
Caregiver	70 (82.4%)	106 (83.5%)	38 (84.4%)	0.95	0.88
Caregiver black race	55 (67.9%)	74 (61.2%)	23 (57.5%)	0.10	0.08
Caregiver is biological parent	66 (77.6%)	61 (47.7%)	21 (46.7%)	<0.001	0.91
Caregiver is HS graduate	64 (75.3%)	99 (77.3%)	32 (71.1%)	0.70	0.40
Household Income <\$20,000	56 (65.9%)	50 (39.1%)	20 (44.4%)	0.002	0.79
Caregiver known HIV-infected	62 (72.9%)	50 (39.1%)	17 (37.8%)	<0.001	0.90
HIV Markers					
CD4 Lymphocyte Percent					
Entry CD4% ≥25%		99 (77.3%)	30 (66.7%)		0.16
Nadir CD4% <15%		43 (33.6%)	31 (68.9%)		<0.001
HIV RNA Viral load (VL), copies/mL					
Entry VL <400		96 (75.0%)	29 (64.4%)		0.17
Peak VL >100,000		101 (78.9%)	40 (88.9%)		0.14
Encephalopathy prior to entry		1 (0.8%)	15 (33.3%)		<0.001
Age at highest CDC stage prior to entry, median (IQR)		2.6 (0.6, 7.5)	1.4 (0.4, 4.1)		0.10
ARV regimen at entry					0.89
HAART with PI		84 (65.6%)	32 (71.1%)		
HAART without PI		28 (21.9%)	9 (20.0%)		
Non-HAART ARV		7 (5.5%)	2 (4.4%)		
Not on ARV		9 (7.0%)	2 (4.4%)		

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ARV=antiretroviral therapy, CDC=Centers for Disease Control and Prevention, HAART=highly active antiretroviral therapy, HIV=human immunodeficiency virus, PHEU=perinatally HIV-exposed uninfected, HIV/C=HIV infected with prior CDC Class C diagnosis, HIV/non-C=HIV infected without prior CDC Class C diagnosis, HS=high school, PI=protease inhibitor, VL=viral load.

P-values by Fisher's exact test for dichotomous measures, by Pearson Chi-square test for categorical measures, and Wilcoxon rank sum test for continuous measures.

Missing values (HEU, HIV/non-C, HIV/C): Black race – 1,3,3; Hispanic ethnicity, child language, caregiver language – 0,1,0; caregiver race – 4, 7, 5.

Table 2

Estimated Differences in Mean Scores for PROMACY and NEPT Prospective Memory Assessments by HIV Status and Prior AIDS Condition (CDC Class C)

Outcome	PHEU			PHIV Non-C			PHIV-C			P-value ^I	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)			
PROMACY Summary ²	36.64 (34.30,38.98)	38.32 (36.31,40.33)	37.78 (35.92,39.63)	37.34 (35.54,39.13)	39.59 (37.17,42.00)	37.57 (35.07,40.07)			0.78	none	
PROMACY Event ²	6.77 (6.36,7.19)	6.96 (6.59,7.34)	6.93 (6.64,7.22)	6.88 (6.58,7.18)	6.88 (6.38,7.37)	6.65 (6.13,7.18)			0.65	none	
PROMACY Time ²	5.44 (4.92,5.96)	5.81 (5.36,6.26)	5.66 (5.22,6.10)	5.57 (5.14,5.99)	6.32 (5.80,6.83)	5.87 (5.32,6.42)			0.61	PHIV-C > PHEU *	
NEPT EB Total ³	5.93 (4.84,7.02)	---	5.40 (4.50,6.30)	---	4.00 (2.61,5.39)	---			0.10	PHIV-C < PHEU *	
NEPT Points Total ³	4.44 (3.62,5.25)	---	3.99 (3.31,4.67)	---	3.07 (2.01,4.13)	---			0.13	PHIV-C < PHEU *	
NEPT RM Total ⁴	1.69 (1.38,2.00)	1.90 (1.58,2.23)	1.46 (1.23,1.70)	1.52 (1.26,1.78)	1.16 (0.78,1.54)	1.27 (0.86,1.69)			0.04	PHIV-C < PHEU **	
NEPT Intention ³	1.49 (1.22,1.77)	---	1.37 (1.14,1.60)	---	1.00 (0.65,1.35)	---			0.08	PHIV-C < PHEU *	

CDC=Centers for Disease Control and Prevention, CI=confidence interval, EB=event-based, NEPT=Naturalistic Event-Based Prospective Memory Task, PHEU=perinatally HIV-exposed uninfected, PHIV/C=HIV infected with prior CDC Class C diagnosis, PHIV/non-C=HIV infected without prior CDC Class C diagnosis, PROMACY=Prospective Memory Assessment for Children & Youth, RM=retrospective memory.

¹ p-value for test of equality among adjusted means across all 3 groups;

* p<0.05 for unadjusted mean scores only;

** p<0.05 for unadjusted and adjusted mean scores

² Adjusted for age at entry

³ No covariates met the criteria for inclusion in adjusted models

⁴ Adjusted for household income (>20,000) and Black race

Table 3

Association of PROMACY and NEPT Outcomes with HIV Disease Markers at Study Entry, Among Youth with Perinatal HIV Infection

Disease severity measure	Level	Unadjusted Results		Adjusted Results	
		Mean (95% CI)	P-value	Mean (95% CI)	P-Value
PROMACY Summary Score					
HIV Group by age at CDC Stage C	PHIV/C <3yr	37.80 (34.54,41.06)	0.03	37.93 (34.90,40.96)	0.61
	PHIV/C 3	42.38 (39.31,45.44)		40.02 (36.35,43.70)	
	PHIV/nonC	37.78 (35.92,39.63)		38.13 (36.39,39.86)	
Nadir CD4% at entry	< 15%	40.07 (38.18,41.96)	0.04	39.27 (37.39,41.15)	0.24
	>=15%	37.12 (35.01,39.24)		37.66 (35.70,39.63)	
Age at peak HIV viral load (years)	0-3	37.85 (35.90,39.80)	0.13	39.07 (37.39,40.75)	0.004
	3.1-5	43.50 (38.41,48.59)		43.19 (39.36,47.02)	
	5.1 or older	38.29 (35.85,40.73)		35.77 (33.04,38.50)	
PROMACY Event Score					
Age at CDC classification (years)	0-3	6.70 (6.34,7.06)	0.003	6.72 (6.38,7.06)	0.003
	3.1-5	7.56 (7.22,7.91)		7.54 (7.21,7.88)	
	5.1 or older	7.04 (6.61,7.48)		7.01 (6.56,7.45)	
Age at peak HIV viral load (years)	0-3	6.89 (6.55,7.22)	0.03	7.02 (6.72,7.32)	0.01
	3.1-5	7.63 (7.14,8.11)		7.59 (7.06,8.12)	
	5.1 or older	6.83 (6.41,7.26)		6.56 (6.07,7.05)	
PROMACY Time Score					
HIV Group by age at CDC Stage C	PHIV/C <3yr	6.04 (5.33,6.75)	0.02	6.40 (5.63,7.18)	0.39
	PHIV/C 3	6.75 (6.11,7.39)		6.31 (5.44,7.19)	
	PHIV/nonC	5.66 (5.22,6.10)		5.87 (5.47,6.28)	
Nadir CD4% at entry	< 15%	6.27 (5.77,6.76)	0.05	6.34 (5.78,6.91)	0.14
	>=15%	5.58 (5.11,6.05)		5.82 (5.39,6.25)	
Age at peak HIV viral load (years)	0-3	5.73 (5.27,6.19)	0.29	6.15 (5.72,6.58)	0.03
	3.1-5	6.88 (5.51,8.24)		7.04 (5.97,8.10)	

Disease severity measure	Level	Unadjusted Results			Adjusted Results		
		Mean (95% CI)	P-value	Mean (95% CI)	P-Value		
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NEPT EB Total							
HIV Viral load at entry (copies/mL)	>400	3.54 (2.26,4.82)	0.01	4.00 (2.66,5.34)	<.01		
	0-400	5.61 (4.70,6.53)		6.14 (5.14,7.14)			
Age at nadir CD4% (years)	0-3	5.09 (3.91,6.26)	0.10	5.39 (4.22,6.55)	0.03		
	3.1-5	7.09 (4.90,9.28)		8.36 (6.14,10.59)			
	5.1 or older	4.42 (3.33,5.52)		5.09 (3.88,6.31)			
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NEPT Points Total							
HIV Viral load at entry(copies/mL)	>400	2.62 (1.64,3.60)	0.01	2.95 (1.93,3.97)	<.01		
	0-400	4.19 (3.50,4.88)		4.57 (3.82,5.33)			
Age at nadir CD4% (years)	0-3	3.73 (2.84,4.62)	0.11	3.95 (3.07,4.76)	0.03		
	3.1-5	5.32 (3.67,6.96)		6.27 (4.60,7.94)			
	5.1 or older	3.34 (2.51,4.17)		3.84 (2.92,4.76)			
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NEPT RM Total							
HIV Viral load at entry (copies/mL)	>400	1.00 (0.64,1.36)	0.02	1.16 (0.79,1.54)	0.01		
	0-400	1.53 (1.29,1.77)		1.71 (1.45,1.97)			
Age at nadir CD4% (years)	0-3	1.44 (1.12,1.76)	0.07	1.55 (1.24,1.86)	0.02		
	3.1-5	1.91 (1.35,2.47)		2.29 (1.72,2.87)			
	5.1 or older	1.19 (0.90,1.48)		1.40 (1.08,1.73)			
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NEPT Intention Total							
HIV Viral load at entry (copies/mL)	>400	0.92 (0.59,1.25)	0.02	1.03 (0.69,1.38)	0.01		
	0-400	1.41 (1.18,1.64)		1.54 (1.29,1.79)			
Age at nadir CD4% (years)	0-3	1.30 (1.00,1.60)	0.10	1.37 (1.08,1.67)	0.03		
	3.1-5	1.77 (1.22,2.32)		2.09 (1.53,2.64)			
	5.1 or older	1.11 (0.84,1.39)		1.28 (0.97,1.58)			

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CDC=Centers for Disease Control and Prevention, CI=confidence interval, EB=event-based, NEPT=Naturalistic Event-Based Prospective Memory Task, PROMACY=Prospective Memory Assessment for Children & Youth, RM=retrospective memory.

Table 4

Estimated Differences in Mean Scores for PROMACY and NEPT Prospective Memory Assessments by HIV Status and Neurocognitive Impairment

Outcome	PHEU		PHIV/non-NCI (Not Impaired)		PHIV/NCI (Impaired)		P-value ¹	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)		
PROMACY Summary ²	36.64 (34.30,38.98)	38.54 (36.55, 40.54)	40.45 (38.86,42.04)	40.04 (38.56,41.53)	34.73 (32.02,37.45)	32.66 (30.04, 35.27)	<0.001	Impaired < not Impaired ^{**} Impaired < PHEU+ Not impaired > PHEU [*]
PROMACY Event ²	6.77 (6.36,7.19)	6.98 (6.60,7.35)	7.13 (6.83,7.42)	7.08 (6.80,7.37)	6.56 (6.11,7.01)	6.34 (5.85,6.82)	0.02	Impaired < not Impaired ^{**} Impaired < PHEU+
PROMACY Time ²	5.44 (4.92,5.96)	5.87 (5.43,6.32)	6.36 (5.98,6.73)	6.26 (5.09,6.63)	5.02 (4.40,5.64)	4.55 (3.98,5.12)	<0.001	Impaired < not Impaired ^{**} Impaired < PHEU+ Not impaired > PHEU [*]
NEPT EB Total ³	5.93 (4.84,7.02)	---	5.87 (4.88,6.85)	---	3.76 (2.61,4.92)	---	0.01	Impaired < not Impaired ^{**} Impaired < PHEU ^{**}
NEPT Points Total ³	4.44 (3.62,5.25)	---	4.36 (3.61,5.10)	---	2.82 (1.94,3.70)	---	0.01	Impaired < not Impaired ^{**} Impaired < PHEU ^{**}
NEPT RM Total ⁴	1.69 (1.38,2.00)	1.89 (1.57,2.22)	1.60 (1.34,1.86)	1.63 (1.35,1.92)	1.06 (0.75,1.37)	1.17 (0.83,1.51)	0.01	Impaired < not Impaired ^{**} Impaired < PHEU ^{**}
NEPT Intention ³	1.49 (1.22,1.77)	---	1.48 (1.23,1.73)	---	0.96 (0.67,1.25)	---	0.01	Impaired < not Impaired ^{**} Impaired < PHEU ^{**}

CI=confidence interval, EB=event-based, NCI=global neurocognitive impairment, NEPT=Naturalistic Event-Based Prospective Memory Task, PHEU=perinatally HIV-exposed uninfected, PHIV/NCI=perinatally HIV infected with global neurocognitive impairment, PHIV/non-NCI=perinatally HIV infected without global neurocognitive impairment, PROMACY=Prospective Memory Assessment for Children & Youth, RM=retrospective memory.

¹ p-value for test of equality among adjusted means across all 3 groups;

^{*} p<0.05 for unadjusted mean scores only; + p< 0.05 for adjusted means scores only;

^{**} p<0.05 for unadjusted and adjusted mean scores

² Adjusted for age at entry

³ No covariates met the criteria for inclusion in the adjusted model; p-values are for unadjusted comparison.

⁴ Adjusted for household income (>20,000) and Black race