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Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV

Stephen J. Kerr[a,b], **Thanyawee Puthanakit**[a,c,*], **Ung Vibol**[d], **Linda Aurpibul**[e], **Sophan Vonthanak**[f], **Pope Kosalaraksa**[g], **Suparat Kanjanavanit**[h], **Rawiwan Hansudewechakul**[i], **Jurai Wongsawat**[j], **Wicharn Luesomboon**[k], **Kattiya Ratanadilok**[l], **Wasana Prasitsuebsai**[a], **Kanchana Pruksakaew**[a], **Jasper van der Lugt**[a,m], **Robert Paul**[n], **Jintanat Ananworanich**[a,o], and **Victor Valcour**[p] **on Behalf of the SEARCH 012 Study Team**

[a]HIV-NAT, The Thai Red Cross AIDS Research Centre, Bangkok, Thailand [b]The Kirby Institute, University of New South Wales, Sydney, NSW, Australia [c]Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand [d]National Pediatric Hospital, Phnom Penh, Cambodia [e]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand [f]National Center for HIV/AIDS Dermatology and STDs, Phnom Penh, Cambodia [g]Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand [h]Nakornping Hospital, Chiang Mai, Thailand [i]Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand [j]Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand [k]Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand [l]Department of Juvenile Observation and Protection, Ministry of Justice, Thailand [m]The Amsterdam Institute of Global Health and Development, Amsterdam, The Netherlands [n]Department of Psychology, University of Missouri, St. Louis, MO, USA [o]SEARCH, The Thai Red Cross AIDS Research Centre, Bangkok, Thailand [p]Memory and Aging Center, Department of Neurology and Division of Geriatric Medicine, University of California, San Francisco, CA, USA

Abstract

Human immunodeficiency virus (HIV)-negative children born to HIV-infected mothers may exhibit differences in neurodevelopment (ND) compared to age- and gender-matched controls whose lives have not been affected by HIV. This could occur due to exposure to HIV and antiretroviral agents in utero and perinatally, or differences in the environment in which they grow up. This study assessed neurodevelopmental outcomes in HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) children enrolled as controls in a multicenter ND study from Thailand and Cambodia. One hundred sixty HEU and 167 HUU children completed a neurodevelopmental assessment using the Beery Visual Motor Integration (VMI) test, Color Trails, Perdue Pegboard, and Child Behavior Checklist (CBCL). Thai children (n = 202) also completed the Wechsler Intelligence Scale (IQ) and Stanford-Binet II memory tests. In analyses adjusted for caregiver education, parent as caregiver, household income, age, and ethnicity, statistically significant lower scores were seen on verbal IQ (VIQ), full-scale IQ (FSIQ), and Binet Bead Memory among HEU compared to HUU. The mean (95% CI) differences were −6.13 (−10.3

*Corresponding author: thanyawee.p@hivnat.org.

to −1.96), $p = 0.004$; −4.57 (−8.80 to −0.35), $p = 0.03$; and −3.72 (−6.57 to −0.88), $p = 0.01$ for VIQ, FSIQ, and Binet Bead Memory, respectively. We observed no significant differences in performance IQ, other Binet memory domains, Color Trail, Perdue Pegboard, Beery VMI, or CBCL test scores. We conclude that HEU children evidence reductions in some neurodevelopmental outcomes compared to HUU; however, these differences are small and it remains unclear to what extent they have immediate and long-term clinical significance.

Keywords

HIV; children; neurodevelopment; resource-limited setting

Introduction

Children infected with human immunodeficiency virus (HIV) sometimes have compromised neuropsychological functioning compared to their uninfected counterparts (Puthanakit et al., 2013). However, children whose lives have been affected by HIV (HIV exposed, uninfected, [HEU]) may show neurodevelopmental differences when compared to uninfected and unexposed children (HUU). Higher rates of mental health problems have been found among HEU compared to perinatally HIV-infected children (Malee et al., 2011). This underscores the importance of obtaining a better understanding of neurodevelopmental outcomes in HEU children. Maternal HIV immune activation may influence the developing fetal brain, as might exposure to antiretroviral therapy (ART) designed to prevent mother-to-child transmission (Sirois et al., 2013). In addition, HIV disproportionately affects those of lower socioeconomic status (Perry, 1998). Lower socioeconomic status is associated with poorer physical and psychological health outcomes in adolescents and adults (Chen & Paterson, 2006; Mani, Mullainathan, Shafir, & Zhao, 2013). Likewise, environmental stressors associated with HIV such as parental loss, illness or disability, and family economic hardship may impact on cognitive and behavioral development in HEU children (Hochhauser, Gaur, Marone, & Lewis, 2008; Mellins et al., 2011).

In the Pediatric Randomized to Early versus Deferred Initiation in Cambodia and Thailand (PREDICT; ISRCTN00234091) neurodevelopment sub-study, HEU and HUU children performed better on neurodevelopment (ND) tests compared to HIV-infected children (Puthanakit et al., 2013). The current study compared ND outcomes and sociodemographic characteristics that might influence these outcomes, in the HEU and HUU enrolled as controls in the PREDICT ND sub-study. We tested the hypothesis that neuropsychological performance would be lower in HEU versus HUU, after controlling for sociodemographic differences.

Methods

Participants

The PREDICT study was a randomized open-label trial of early versus deferred ART, in children aged 1–12 years with a CD4 between 15% and 24% and no history of AIDS-defining illness or ART use (Puthanakit et al., 2012). We conducted an ND sub-study at

seven hospitals in Thailand and two hospitals in Cambodia (Puthanakit et al., 2013), where two age- and gender-matched control groups were enrolled. The HEU children were recruited from siblings of HIV-infected children in the main study or uninfected children delivered to HIV-infected mothers at these sites. The HUU children were recruited from "well-child" clinics at the same hospital study sites. Group frequency matching was used to create age and gender similarity across both the HIV-negative group and the HIV-infected group. This was accomplished using four age bands: 2–5 years, 5–8 years, 8–11 years, and ≥11 years, based on the gender and age when the HIV-infected children first enrolled in the PREDICT ND sub-study. Children were confirmed to be HIV-uninfected by standard enzyme-linked immunosorbent assay (ELISA) for HIV. Written informed consent was obtained from the caregivers and assent from the children. This study was approved by local and National Thai and Cambodian Institutional Review Boards and the University of California, San Francisco. The Study Team is listed in the Appendix.

Procedures

Detailed test procedures have previously been described (Puthanakit et al., 2013). Briefly, the neuropsychological test battery assessed cognition using a comprehensive battery of intelligence measures and neuropsychological tests among the Thai children and selected psychomotor and behavioral tests in all children. The cognitive tests were either the Thai Psychological Association-validated versions of the Wechsler Intelligence Scale for Children (WISC-III) for children aged 6–17 years or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) for children aged 2–6 years and the Stanford-Binet II memory tests (beads/sentences in children aged 3.25–17 years and digits/objects in children aged 6–17 years). Psychomotor assessments included the Beery Visual Motor Integration (VMI) for children aged 2–17 years, Purdue Pegboard for children aged 5–17 years, and children's Color Trails for children aged 8–17 years. Behavioral assessment was conducted utilizing the Child Behavior Checklist (CBCL) for preschool (1.5–5 years) and school-age (6–18 years) children. Neuropsychologists completed the IQ and Stanford-Binet memory tests at all Thai sites. At Cambodian sites, nurses were certified by neuropsychologists to administer the psychomotor tests, after correctly administering and scoring a minimum of 10 subjects per test. The English version of CBCL was translated into Thai and Khmer and then back-translated into English to ensure accurate translation. Caregivers completed the CBCL questionnaires in their own language, rating on a three-point scale, how correct a series of statements were in describing their child's behavior. Standardized scores based on age and gender were then calculated from the raw scores. Borderline-clinical range CBCL *T* scores were calculated using normative data and indicate concerning behaviors (Achenbach & Rescorla, 2001). For the internalizing *T* scores (anxiety, depression, and somatic complaints) and externalizing *T* scores (rule breaking and aggressive behavior), as well as total problem *T* scores (the sum of all syndrome scales), borderline and clinical scores are above the 84th and 91st percentiles, respectively; for individual syndrome-scale *T* scores, borderline and clinical scores are above the 93rd and 98th percentiles, respectively. In the absence of Thai and Cambodian normative data, standardization was based on US norms. HEU and HUU children underwent a single neurodevelopmental test battery assessment. Sociodemographic data, including household income, child's area of residence, whether the parent was caregiver, and educational level of the parents or caregiver, were also collected.

Quality assurance

External quality control was performed biannually throughout the study. A test administration manual was developed prior to the start of the study (in local languages), and all individuals responsible for neuropsychological assessment completed an initial training protocol to ensure fidelity to the test manual. The manual included verbatim instructions for test administration as well as detailed instructions for data scoring. A neuropsychologist visited sites for the duration of the study to ensure compliance with the test manual and standardized data collection, and completed protocols were checked at random to ensure accurate scoring procedures were implemented. Individuals involved in neuropsychological administration were periodically required to complete an assessment under observation to ensure overall accuracy in the assessment process. As a further quality control measure, a nurse-monitor reviewed all test results before they were entered into the database.

Statistical analysis

Statistical analyses were conducted with Stata 12 (College Station, TX) with the available data considered valid by the neuropsychologist or nurse who administered the tests. Four of 206 (1.9%) Wechsler tests were considered invalid due to uncooperative behavior, and 7 of 323 (2.2%) Beery tests were excluded from analysis due to uncooperative behavior ($n = 6$) and a motor handicap ($n = 1$). Sociodemographic characteristics at the time of neuropsychological testing were compared by exposure group, using a chi-square test or *t* test as appropriate. Less than 3% of sociodemographic characteristics were missing or unknown.

For the cognitive and psychomotor tests (except Purdue Pegboard), regression models were used to compare standardized test scores. For Purdue Pegboard, the outcome variable was the number of successful pin placements by the dominant and nondominant hands. The outcome variables for CBCL were the externalizing, internalizing, and total problem *T* scores, and each of the syndrome-scale based raw scores in school-aged children (Achenbach & Rescorla, 2001). Comparisons between HEU and HUU as a reference group in unadjusted linear regression models were completed first, followed by a second model adjusting for age, ethnicity, and socio-demographic differences (educational level of caregiver, income, and parent as caregiver) between exposure groups. Gender was included in adjusted models if there were statistically significant differences observed in univariate analysis at a level of $p < 0.10$. The proportion of children classified with borderline-clinical range scores for internalizing, externalizing, total problem, and individual syndrome-scale *T* scores on the CBCL was examined between HEU and HUU children using a chi-square test. Logistic regression models were used to assess the odds ratio of having a borderline-clinical score between subject groups after adjusting for sociodemographic characteristics.

Results

Sociodemographic characteristics

One hundred sixty-six HEU (64% Thai) and 167 HUU (67% Thai) children were enrolled (Table 1). The mean (SD, range) age of all children was 7.6 (3.3, 2–15) years and 58% were female. There were no differences in age or gender between the two exposure groups ($p =$

0.5 and 0.4, respectively). More HEU children were cared for by parents (93% vs. 83%; p = 0.01). Caregivers of HEU children were less likely to have an education beyond elementary school compared to HUU children (63% vs. 33%; p = 0.001), and HEU children were more likely to be from lower than average income households than HUU children (57% vs. 34%; $p < 0.001$).

Neurodevelopmental test scores

Verbal IQ (VIQ) and full-scale IQ (FSIQ) were lower in HEU children in adjusted and unadjusted analyses (Table 2). The adjusted mean difference in VIQ in HEU versus HUU children was −6.13 (95% CI −10.3 to −1.96; p = 0.004) and −4.57 (95% CI −8.8 to −0.35; p = 0.03) for FSIQ which is comprised of VIQ and performance IQ (PIQ). These differences were very similar to those observed in the unadjusted models. In contrast, PIQ did not differ between the HEU and the HUU children by the Wechsler Scales in unadjusted and adjusted analyses.

When FSIQ was broken into quartiles, there were no differences in the proportion of children from families with below average income and children with parents as caregiver (p = 0.17 and 0.61, respectively). However, children with FSIQ in the highest quartile were more likely to have parents educated beyond elementary level (74% vs. 53%; p = 0.02).

On the Stanford-Binet Intelligence tests, Sentence Memory, Digit Memory, and Object Memory did not differ between HEU and HUU children. However, Bead Memory scores were lower in HEU children with a mean difference of −3.72 (95% CI −6.57 to −0.88) in adjusted analyses.

In both unadjusted and adjusted analyses, there were no differences between HEU and HUU in Beery VMI scores, Color Trail 1 and 2 scores, and the number of successful pin placements using the Purdue Pegboard in the dominant and nondominant hands.

Behavior problems, assessed by the CBCL, showed no differences in internalizing, externalizing, and total problem *T* scores between HEU and HUU in unadjusted and adjusted analyses (Table 2). Amongst school-age children, there were statistically significant but only slightly higher CBCL syndrome-based social problem and aggressive behavior scores in HEU children in unadjusted analyses, which were not significant in adjusted models (Table 2). Likewise, there were no observed differences in the proportion of children with borderline-clinical internalizing, externalizing, and total problem scores. The proportion of HEU and HUU children with borderline-clinical internalizing, externalizing, and total problem *T* scores in the borderline-clinical range was 18.5–18.4 (p = 0.98), 12.4–13.3 (p = 0.80), and 15.4–18.4 (p = 0.49), respectively. Amongst school-age children, there were no differences in the proportion of HEU and HUU children with borderline-clinical syndrome-based scales except in the attention domain where a higher proportion of HEU children had attention problems (6.1 vs. 0.9%, p = 0.05; Table 3). However, after adjusting for sociodemographic differences between groups in a logistic regression model, the odds of attention problems amongst HEU children were not significantly different than that observed in HUU (adjusted odds ratio 6.5 (95% CI 0.70–60.1; p = 0.1).

Discussion

As hypothesized, we found that HEU children had statistically lower Wechsler VIQ, FSIQ, and Stanford-Binet Bead Memory scores compared to HUU children, but the absolute differences were small. The Stanford-Binet tests were selected to assess memory. Although FSIQ scores were significantly lower in HEU children, only Bead Memory scores were significantly lower in HEU versus HUU children. Both Bead and Object Memory measures assess nonverbal fluid reasoning and correlate with FSIQ in normative subjects (Becker, 2003), but the correlation between Object Memory and general measures of intelligence is lower than with Bead Memory (Sattler, 1988). This may explain why Bead but not Object Memory scores were significantly lower in HEU children in our study.

No differences were observed between HEU and HUU groups in PIQ, Sentence, Digit, or Object Memory. Scores for tests assessing motor coordination, sustained attention, sequencing, and executive function did not differ between groups. There were no differences in behavior scores or proportion of children with borderline-clinical scores noted, with the exception of borderline significant differences in attention problems that did not persist after adjustment for sociodemographic factors.

Thirty-eight percent of HEU youths in a recent report from the US-based Pediatric HIV/AIDS Cohort study (PHACS) were at risk for, or currently had, clinically significant mental health problems. The odds were significantly higher in HEU compared to perinatally infected children and children with caregivers who had a psychiatric disorder (Malee et al., 2011). We found lower rates of borderline-clinical disorders in HEU children than the PHACS, and the odds of borderline-clinical scores between HEU and HUU groups were not increased after adjusting for sociodemographic factors. One possible reason for lower rates of mental health problems observed in our HEU is the age distribution of children in the two studies. Although a comparable proportion of subjects in our study was aged <12 years (77% in the PHACS vs. 87% in our study), the PHACS did not include children <7 years, and 46% of children in our study were aged <7 years when neuropsychological testing was performed. Direct comparison of the two studies is also complicated because we did not collect data on psychiatric disorders or health status of the caregivers in our study, or other home environmental factors which could potentially influence caregiver effectiveness and neuropsychological outcomes among children. For example, in the PHACS, 63% of HEU resided with single caregivers, whereas in Asia, it is common for several generations of family to live together, with an extended family network of aunts, uncles, cousins, and grandparents who can provide additional support and child supervision.

We identified lower VIQ and FSIQ in the HEU children before and after adjustment for sociodemographic covariates. Growing up in a household affected by HIV may subject children to disadvantages in the home literacy environment. In Western settings, this has been shown to contribute to disparities in reading ability amongst children attending kindergarten (Aikens & Barbarin, 2008). Within an extended family household, literacy might reasonably be consistent across generations due to economic factors limiting or facilitating access to education. In our study, 57% of HEU versus 34% of HUU resided in homes where the income was low or very low, and 66% of HEU caregivers were educated at

elementary level or had no education versus 34% of HUU caregivers. We also found a higher proportion of children with FSIQ in the highest quartile had parents or caregivers educated beyond elementary school ($p = 0.02$). It is possible that the low-income and low education levels of the caregivers are primary drivers of lower IQ and Bead Memory performance among the HEU children. Further, lower VIQ scores in HEU could be related to environmental stressors, such as parental loss or sickness, or reduced stimulation provided by parents or caregivers with lower levels of education. While HIV-positive children are regularly followed up in specialized clinics that cater to their needs, their uninfected siblings may not come in contact with health and support services.

In resource-rich settings, studies on infants ≤2 years have not identified ND delays in HEU children after adjusting for confounds (Le Doare, Bland, & Newell, 2012), however, precisely when deficits begin to manifest is not clear. Thirty-four percent of HEU youths participating in the Child and Adolescent Self-Awareness Health Study (CASAH) scored in the lowest 10th percentile on the Peabody Picture Vocabulary Test, an instrument that assesses receptive language abilities and correlates strongly with Wechsler VIQ and FSIQ scores (Brackis-Cott, Kang, Dolezal, Abrams, & Mellins, 2009). Compared to the children in our cohort, CASAH participants were older (aged from 9 years to 16 years), only 70% of CASAH participants had a parent as primary caregiver, and most were living in impoverished urban communities, likely without the extended family support that is common in Thailand and Cambodia.

The lower VIQ scores noted among HEU versus HUU children in our study may not be without consequence. Language and reading skills are critical to academic success (Ippolito, Steele, & Samson, 2008) and also for negotiating successful relationships in adolescence and adulthood. Further functional studies of this cohort of children and adolescents are in progress and will inform the degree to which the differences in IQ scores between the HEU and the HUU children in our cohort impact social functioning and resilience.

There are few studies in resource-limited settings, but in Africa, more pre-school HEU than HUU children were classified with moderate to severe cognitive, motor, and language deficits (Van Rie, Mupuala, & Dow, 2008). Differences between these groups may stem from dissimilarities in social structures and support networks, and a higher proportion of HEU children living in poverty. In support of this, 80% of the HEU children in this African study lived in households with inadequate income versus 21% in the HUU group, and 31% of HEU children had poor access to water versus 13% of HUU children. In contrast, all of the HEU and HUU in our study had access to water and health care. Nevertheless, direct comparison of the results of these studies is complicated by standardization against US norms, and scoring may be subject to cultural differences in interpretation.

Our study has a number of limitations. First, FSIQ is comprised of VIQ and PIQ, and thus, the significant difference noted in FSIQ between HIV-exposure groups is highly influenced by the difference in VIQ. Second, our study employed a cross-sectional design and children were matched for age, gender, and ethnicity; however, elucidating how these ND differences evolve over time requires robust longitudinal data. Third, we did not capture data on maternal exposure to antiretroviral agents or details about the pregnancy (such as premature

birth) that could potentially influence the developing brain. A large Pediatric AIDS Clinical Trials Group (PACTG) study did not find associations with lower scores on the Bayley Scales of Infant and Toddler Development and exposure to antiretroviral agents in utero, after adjusting for confounds (Williams et al., 2010). A more recent study also, using the Bayley Scales, reported lower mean scores in the language domain with in utero exposure to atazanavir (Sirois et al., 2013). Although our children were older than the infants in these latter two studies, the most commonly used regimens for the prevention of mother to child transmission for children in our cohort would have been zidovudine from week 34 of pregnancy, with or without single dose nevirapine or zidovudine + nevirapine + lamivudine for the youngest exposed children. At Last, we did not collect measures of caregiver cognitive function and mental and physical health status, recent stressful events in the household, or health status of other children in the household. These factors are known to influence neurocognitive function (Mellins et al., 2008) and may have contributed to the poorer neurocognitive scores observed in the HEU in our study.

Strengths of our study include a large sample size, the relative absence of maternal substance abuse, the tight quality control measures employed on a biannual basis, and the completion of the our study in a resource-limited setting where ND data are lacking.

Conclusions

This study, conducted in a resource-limited setting, demonstrates that HEU children have modest but significant reductions in VIQ, FSIQ, and Bead Memory (assessed by Stanford Binet) compared to HUU children, after adjusting for relevant sociodemographic covariates. No differences in other neurodevelopmental or behavioral outcomes were noted. These data suggest that ND is measurably different between groups; however, the differences are small and their clinical impact remains unclear. Longitudinal studies of ND outcomes in HEU are warranted to examine long-term clinical consequences.

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Appendix

SEARCH 012 team members

Bangkok

Jintanat Ananworanich, Thanyawee Puthanakit, Torsak Bunupradah, Stephen Kerr, Sasiwimol Ubolyam, Naphassanant Laopraynak, Tulathip Suwanlerk, Kanchana Prusakaew, Kattiya Ratanadilok, Varaporn Pothipala, and Kesdao Nanthapisal.

UCSF

Victor Valcour, Stephanie Catella, Akash Desai, Lauren Wendelken–Riegelhaupt, and Edgar Busovaca.

The following investigators, clinical centers, and committees participated in the Pediatric Randomized of Early versus Deferred Initiation in Cambodia and Thailand (PREDICT trial) Neurodevelopment sub-study.

Steering committee

Praphan Phanuphak, David A. Cooper, John Kaldor, Mean Chhi Vun, Saphonn Vonthanak, and Kiat Ruxrungtham.

Primary endpoint review committee

Carlo Giaquinto, Mark Cotton, and Rangsima Lolekha.

Clinical events review committee

Virat Sirisanthana, Kulkanya Chokephaibulkit, and Piyarat Suntarattiwong.

Data safety monitoring board members

Paul Volberding, Shrikant Bangdiwala, Kruy Lim, N.M. Samuel, David Schoenfeld, Annette Sohn, Suniti Solomon, Panpit Suwangool, Ruotao Wang, Fujie Zhang, Laurie Zoloth, and Dennis O. Dixon.

National Institutes of Health

Lawrence Fox, Akinlolu O. Ojumu, Jane E. Bupp, Michael Ussery, Neal T. Wetherall, Pim Brouwers, Lynne M. Mofenson, Macaya Douoguih, and Eva Petrakova.

Advisors

Matthew Law, William T. Shearer, Victor Valcour, Rober Paul, Kovit Pattanapanyasat, *Natthaga Sakulploy*, Janet M. McNicholl, Chutima Saisaengjan, and Kattiya Rattanadilok.

Clinical research sites

CIP TH001

HIV Netherlands Australia Thailand (HIV-NAT) Research Collaboration, Thai Red Cross AIDS Research Center, Bangkok, Thailand; Kiat Ruxrungtham, Jintanat Ananworanich,

Thanyawee Puthanakit, Chitsanu Pancharoen, Torsak Bunupuradah, Jasper van der Lugt, Wasana Prasitsuebsai, Stephen Kerr, Theshinee Chuenyam, Sasiwimol Ubolyam, Apicha Mahanontharit, Tulathip Suwanlerk, Jintana Intasan, Thidarat Jupimai, Tawan Hirunyanulux, Praneet Pinklow, Kanchana Pruksakaew, Oratai Butterworth, Chulalak Sriheara, Anuntaya Uanithirat, Sunate Posyauattanakul, Thipsiri Prungsin, Pitch Boonrak, Waraporn Sakornjun, Tanakorn Apornpong, Jiratchaya Sophonphan, Ormrudee Ritim, Nuchapong Noumtong, Noppong Hirunwadee, Chowalit Phadungphon, Wanchai Thongsee, Orathai Chaiya, Augchara Suwannawat, Threepol Sattong, Niti Wongthai, Kesdao Nantapisan, Umpaporn Methanggool, Narumon Suebsri, Taksin Panpuy, Pattiya Jootakarn, Kanitta Santikul, Apiwan Niyomlaksakul, and Chayapa Phasomsup.

CIP TH003

Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand; Jurai Wongsawat, Rujanee Sunthornkachit, Visal Moolasart, Natawan Siripongpreeda, Supeda Thongyen, Piyawadee Chathaisong, Vilaiwan Prommool, Duangmanee Suwannamass, Simakan Waradejwinyoo, Nareopak Boonyarittipat, Thaniya Chiewcharn, Sirirat Likanonsakul, Chatiya Athichathana, Boonchuay Eampokalap, Wattana Sanchiem, Jarunsri Pantoe, and Pintorn Prashyanusorn.

CIP TH004

Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; Pope Kosalaraksa, Pagakrong Lumbiganon, Chulapan Engchanil, Piangjit Tharnprisan, Chanasda Sopharak, Viraphong Lulitanond, Samrit Khahmahpahte, Ratthanant Kaewmart, Prajuab Chaimanee, Mathurot Sala, Thaniita Udompanit, Ratchadaporn Wisai, Somjai Rattanamanee, Yingrit Chantarasuk, Sompong Sarvok, Yotsombat Changtrakun, Soontorn Kunhasura, Sudthanom Kamollert, Jintana Singkhornard, Peerada Unprai, and Chonnikarn Udomsri

CIP TH005

Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand; Wicharn Luesomboon, Pairuch Eiamapichart, Tanate Jadwattanakul, Isara Limpet-ngam, Daovadee Naraporn, Pornpen Mathajittiphun, Chatchadha Sirimaskul, Woranun Klaihong, Pipat Sittisak, Tippawan Wongwian, Kansiri Charoenthammachoke, and Pornchai Yodpo.

CIP TH007

Nakornping Hospital, Chiang Mai, Thailand; Suparat Kanjanavanit, Maneerat Ananthanavanich, Penpak Sornchai, Thida Namwong, Duangrat Chutima, Suchitra Tangmankhongworakun, Pacharaporn Yingyong, Juree Kasinrerk, Montanee Raksasang, Pimporn Kongdong, Siripim Khampangkome, Suphanphilat Thong Ngao, Sangwan Paengta, Kasinee Junsom, Ruttana Khuankaew, Parichat Moolsombat, Duanpen Khuttiwung, Chanannat Chanrin, Maetee Wongwerapan, and Wanwisa Pansakul.

CIP TH009

Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; Rawiwan Hansudewechakul, Yaowalak Jariyapongpaiboon, Chulapong Chanta, Areerat Khonponoi, Chaniporn Yodsuwan, Warunee Srisuk, Pojjavitt Ussawawuthipong, Yupawan Thaweesombat, Polawat Tongsuk, Chaiporn Kumluang, Ruengrit Jinasen, Noodchanee Maneerat, Kajorndej Surapanichadul, Pornpinit Donkaew, Apsornsri Thanapaisan, Phornpatchara Sririindharatorn, and Arpaporn Hanpa.

CIP TH010

National Pediatric Hospital, Phnom Penh, Cambodia; Saphonn Vonthanak, Ung Vibol, Sam Sophan, Pich Boren, Kea Chettra, Lim Phary, Toun Roeun, Tieng Sunly, Mom Chandara, Chuop Sokheng, Khin Sokoeun, and Tuey Sotharin.

CIP TH011

Social Health Clinic, Phnom Penh, Cambodia; Saphonn Vonthanak, Ung Vibol, Vannary Bun, Somanythd ChhayMeng, Kea Chettra, Sam Phan, Wuddhika In vong, and Khuon Dyna.

CIPTH012

Prapokklao Hospital, Chantaburi, Thailand; Chaiwat Ngampiyaskul, Naowarat Srisawat, Wanna Chamjamrat, Sayamol Wattanayothin, Pornphan Prasertphan, Tanyamon Wongcheeree, Pisut Greetanukroh, Chataporn Imubumroong, Pathanee Teirsonsern, Nittaya Khantilapapan, Petcharat Deenarn, and Bhensiri Charoenvikkai.

Table 1

Sociodemographic characteristics of study participants.

	HIV-exposed (*N* = 160)	HIV-unexposed (*N* = 167)	Total (*N* = 327)	*p*
Mean (SD) age (years)	7.4 (3.4)	7.7 (3.2)	7.6 (3.3)	0.5
Female gender	91 (57)	98 (59)	189 (58)	0.4
Ethnicity				0.5
Thai	102 (64)	112 (67)	214 (65)	
Cambodian	58 (36)	55 (33)	113 (35)	
Primary caregiver				**0.009**
Parent	149 (93)	140 (84)	289 (88)	
Grandparent	4 (3)	18 (11)	22 (7)	
Aunt/uncle	5 (3)	8 (5)	13 (4)	
Orphanage	1 (1)	0	1	
Unknown	1 (1)	1 (1)	2	
Income				**<0.001**
Very low	10 (6)	8 (5)	18 (6)	
Low	81 (51)	48 (29)	129 (39)	
Average	58 (36)	90 (54)	148 (45)	
Above average	8 (5)	19 (11)	27 (8)	
Unknown	3 (2)	2 (1)	5 (2)	
Child attends school				0.7
No	27 (17)	24 (14)	51 (16)	
Yes	131 (82)	142 (85)	273 (83)	
Unknown	2 (1)	1 (0.6)	3 (1)	
Education of caregiver				**<0.001**
None	17 (11)	8 (5)	25 (8)	
Elementary	83 (52)	47 (28)	130 (40)	
High/vocational	47 (29)	73 (44)	120 (37)	
Bachelor	7 (4)	26 (16)	33 (10)	
Masters/Ph.D.	1 (1)	9 (5)	10 (3)	
Unknown	5 (3)	4 (2)	9 (3)	

Note: Age between groups was compared using an unpaired *t*-test; categorical variables were compared using a chi-square test or Fisher's exact test as appropriate. $p \leq 0.05$ were considered statistically significant (shown in bold font).

Table 2

Neurodevelopmental test scores in HEU and HUU.

Test (N HEU:N HUU)	HIV- exposed	HIV- unexposed	Mean difference (95% CI)	*p*	Adjusted mean difference (95% CI)	*p*
Wechsler Intelligence tests (97:105)						
Performance IQ	90.3 (14.7)	94.5 (16.0)	−4.12 (−8.39 to 0.16)	0.06	−3.68 (−8.43 to 1.08)	0.13
Verbal IQ	81.1 (13.2)	87.2 (14.7)	−6.09 (−9.98 to −2.21)	**0.002**	−6.13 (−10.3 to −1.96)	**0.004**
Full-scale IQ	85.2 (13.6)	90.3 (14.7)	−5.07 (−9.01 to −1.13)	**0.01**	−4.57 (−8.80 to −0.35)	**0.03**
Stanford-Binet Intelligence Scales						
Bead Memory (92:99)	45.3 (9.1)	49.1 (9.1)	−3.78 (−6.38 to −1.17)	**0.005**	−3.72 (−6.57 to −0.88)	**0.01**
Sentence Memory (92:99)	41.4 (5.5)	42.2 (6.3)	−0.79 (−2.49 to 0.90)	0.36	−0.60 (−2.30 to 1.11)	0.49
Digit Memory[a] (75:86)	55.3 (6.9)	55.5 (7.5)	−0.21 (−2.46 to 2.04)	0.85	−0.10 (−2.53 to 2.33)	0.94
Object Memory (75:86)	52.0 (5.8)	53.2 (7.2)	−1.18 (−3.23 to 0.86)	0.26	−0.34 (−2.61 to 1.92)	0.76
Beery VMI (154:162)	94.2 (13.2)	97.7 (16.2)	−3.46 (−6.72 to −0.19)	**0.04**	−2.74 (−6.25 to 0.77)	0.13
Color Trail (63:71)						
Color Trail 1 standard score	78.4 (17.2)	84.0 (16.4)	−5.59 (−11.33 to 0.15)	0.06	−5.91 (−12.32 to 0.51)	0.07
Color Trail 2 standard score	87.8 (13.6)	88.2 (15.4)	−0.39 (−5.39 to 4.61)	0.90	2.12 (−3.55 to 7.80)	0.46
Purdue Pegboard (successful pin placements; 119:128)						
Dominant hand	12.4 (2.7)	12.5 (2.5)	−0.15 (−0.81 to 0.52)	0.67	0.09 (−0.47 to 0.64)	0.76
Nondominant hand	11.3 (2.8)	11.6 (2.4)	−0.33 (−0.98 to 0.32)	0.32	−0.28 (−0.78 to 0.22)	0.28
Children' s Behavior Checklist (CBCL) (158:162)						
Internalizing *T* score	50.7 (10.1)	51.3 (9.2)	−0.64 (−2.77 to 1.49)	0.55	−1.84 (−4.11 to 0.45)	0.11
Externalizing *T* score	50.5 (8.7)	50.0 (8.7)	0.54 (−1.38 to 2.46)	0.58	−0.03 (−2.14 to 2.08)	0.98
Total problem *T* score	50.7 (9.3)	49.2 (9.7)	1.45 (−0.64 to 3.54)	0.17	0.46 (−1.81 to 2.73)	0.69
CBCL syndrome based scales (raw scores) in school-age children (98:109)						
Anxious/depressed	3.2 (2.8)	2.6 (2.4)	0.60 (−0.11 to 1.32)	0.10	0.47 (−0.31 to 1.25)	0.23
Withdrawn/depressed	2.0 (1.7)	1.9 (1.7)	0.08 (−0.39 to 0.56)	0.73	−0.12 (−0.65 to 0.40)	0.65
Somatic complaints	2.2 (2.3)	2.3 (2.5)	−0.12 (−0.78 to 0.53)	0.71	−0.31 (−1.04 to 0.42)	0.06
Social problems	3.3 (2.7)	2.5 (2.3)	0.81 (0.12 to 1.49)	**0.02**	0.58 (−0.18 to 1.33)	0.83
Thought problems	1.8 (2.1)	1.7 (2.3)	0.10 (−0.50 to 0.71)	0.74	0.09 (−0.57 to 0.75)	0.80
Attention problems[a]	3.2 (3.0)	2.6 (2.7)	0.65 (−0.13 to 1.43)	0.10	0.50 (−0.35 to 1.35)	0.25
Rule-breaking behavior[a]	2.2 (2.1)	2.1 (2.1)	0.08 (−0.5 to 0.65)	0.80	−0.10 (−0.74 to 0.54)	0.75

Test (N HEU:N HUU)	HIV- exposed	HIV- unexposed	Mean difference (95% CI)	*p*	Adjusted mean difference (95% CI)	*p*
Aggressive behavior[a]	5.5 (4.1)	4.5 (4.2)	1.03 (−0.11 to 2.16)	0.08	0.62 (−0.58 to 1.82)	0.31
Other problems	4.0 (2.8)	3.2 (2.8)	0.79 (0.02 to 1.55)	**0.04**	0.75 (−0.08 to 1.58)	0.08
Total raw score (sum of all raw syndrome scores)	27.5 (18.5)	23.4 (18.4)	4.11 (−0.95 to 9.16)	0.11	2.60 (−2.92 to 8.11)	0.36

Note: Adjusted mean difference is adjusted for age, parent as caregiver, caregiver education of elementary level or below and average income or above, and for ethnicity in tests completed by both Thai and Cambodian children. Linear regression was used to calculate the mean difference in test scores between HEU with HUU as a reference group. Adjusted models were adjusted for age, ethnicity, and sociodemographic differences between exposure groups (educational level of caregiver, income, and parent as caregiver). Gender was included in adjusted models if there were statistically significant differences observed in univariate analysis at a level of $p < 0.10$. $p \leq 0.05$ were considered statistically significant (shown in bold font).

[a]Also adjusted for gender.

Table 3

Percentage of children with CBCL borderline-clinical problem scores, by subject group.

Domain	HIV-exposed (*N* = 158)	HIV- unexposed (*N* = 162)	*p*
Internal *T* score	18.4	18.5	0.97
External *T* score	13.3	12.4	0.80
Total problem *T* score	18.4	15.4	0.49
CBCL syndrome based T scales (school-age children)			
Anxious/depressed	9.2	6.4	0.46
Withdrawn/depressed	11.2	12.8	0.72
Somatic complaints	15.3	16.5	0.81
Social problems	10.2	4.6	0.18
Thought problems	10.2	10.1	0.98
Attention problems	6.1	0.9	**0.05**
Rule-breaking behavior	9.8	7.3	0.63
Aggressive behavior	10.2	7.3	0.47

Note: Proportion of HEU and HUU with borderline-clinical scores was compared using a chi-square test. $p \leq 0.05$ were considered statistically significant.