# Cognitive Function and Neurodevelopmental Outcomes in HIV-infected Children Older Than 1 Year of Age Randomized to Early Versus Deferred Antiretroviral Therapy: The PREDICT Neurodevelopmental Study

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**Background:** We previously reported similar AIDS-free survival at 3 years in children who were >1 year old initiating antiretroviral therapy (ART) and randomized to early versus deferred ART in the Pediatric Randomized to Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) study. We now report neurodevelopmental outcomes.

**Methods:** Two hundred eighty-four HIV-infected Thai and Cambodian children aged 1–12 years with CD4 counts between 15% and 24% and no AIDS-defining illness were randomized to initiate ART at enrollment ("early," n = 139) or when CD4 count became <15% or a Centers for Disease Control (CDC) category C event developed ("deferred," n = 145). All underwent age-appropriate neurodevelopment testing including Beery Visual Motor Integration, Purdue Pegboard, Color Trails and Child Behavioral Checklist. Thai children (n = 170) also completed Wechsler Intelligence Scale (intelligence quotient) and Stanford Binet Memory test. We compared week 144 measures by randomized group and to HIV-uninfected children (n = 319).

**Results:** At week 144, the median age was 9 years and 69 (48%) of the deferred arm children had initiated ART. The early arm had a higher CD4 (33% versus 24%, P < 0.001) and a greater percentage of children with viral suppression (91% versus 40%, P < 0.001). Neurodevelopmental scores did not differ by arm, and there were no differences in changes between arms across repeated assessments in time-varying multivariate models. HIV-infected children performed worse than uninfected children on intelligence quotient, Beery Visual Motor Integration, Binet memory and Child Behavioral Checklist.

**Conclusions:** In HIV-infected children surviving beyond 1 year of age without ART, neurodevelopmental outcomes were similar with ART initiation at CD4 15%–24% versus <15%, but both groups performed worse than HIV-uninfected children. The window of opportunity for a positive effect of ART initiation on neurodevelopment may remain in infancy.

**Key Words:** HIV, children, antiretroviral therapy, neurodevelopment, resource-limited settings

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HIV afflicts greater than 3 million children worldwide[1], yet our scientific understanding of the effects of timing of antiretroviral therapy (ART) on neurodevelopmental outcomes of these children is limited. Although ART decreases rates of encephalopathy, a most severe form of HIV-associated brain insult, chronic neurobehavioral deficits remain prevalent resulting in impairments in cognition, executive and adaptive functioning and school performance.[2–9] Studies from developed and developing countries

have reported poorer neurocognitive functioning in HIV-infected children compared with their HIV-uninfected peers with greater impairments observed in children with severe HIV symptoms and immune suppression. These studies are mainly cross-sectional and observational in nature and invariably include children who initiated ART with advanced HIV disease, limiting their ability to adequately assess timing of ART on neurocognitive outcomes.[3–5,7,9–11] There are 2 randomized studies assessing timing of ART on these outcomes. The Children with HIV Early Antiretroviral Therapy study performed neurodevelopment testing in a subset of infants and reported superior neurocognitive outcomes in those randomized to early ART versus deferred ART.[12] Our study, PREDICT, assesses a similar randomized strategy in older Thai and Cambodian children.[13]

Thailand and Cambodia are among countries in Asia with the highest HIV prevalence: 1.3% in Thailand and 0.5% in Cambodia. At year end 2009, Thailand had 530,000 adults and 20,000 children living with HIV, whereas these numbers for Cambodia were 63,000 and 1120.[1,14,15] Treatment policies in both countries have evolved over time from recommending ART based on moderate to severe HIV symptoms and/or immune suppression in the early 2000s when the PREDICT study was conceived to the current policy that is recommending earlier ART initiation similar to that in developed countries.[14,16,17]

Treatment guidelines now recommend ART in all infants as soon as their HIV is confirmed, without regard to immunologic status.[18,19] In reality, the number of infected children diagnosed with HIV and started on ART during infancy is troublingly low.[20–22] This raises the question of how best to care for these older children, where guidelines are more similar to that of adults and based on immunocompromise or symptoms. The PREDICT study was designed to assess timing of ART on AIDS-free survival in children who survived and entered into care after infancy. After 3 years, children who were randomized to starting ART at CD4 15%–24% and those who waited until CD4 was <15% had similarly high rates of AIDS-free survival (97.9% and 98.7%, respectively).[13] The current analysis compared cognitive functioning and neurodevelopmental outcomes between randomized arms. We hypothesized that children given early ART would have better cognitive function and neurodevelopmental outcomes at week 144 compared with those deferring ART. We included 2 HIV-uninfected control groups, 1 exposed and the other unexposed to HIV. The HIV-exposed group serves as a control group without HIV but with similarly compromised socioeconomic status and exposed in-utero to HIV and its associated immune, virologic and treatment effects, whereas the HIV-unexposed group serves as a control group without HIV or HIV exposure and compromised socioeconomic status. These control groups aid our understanding of HIV and socioeconomic effects on neurodevelopmental outcomes.

## MATERIALS AND METHODS

### Participants

Between 2006 to 2011, we conducted the PREDICT study, a multicenter randomized, open-label trial of early versus deferred ART in children aged 1–12 years with CD4 15%–24%, no history of AIDS-defining illness and no prior ART (ISRCTN00234091)[13] (Fig. 1).
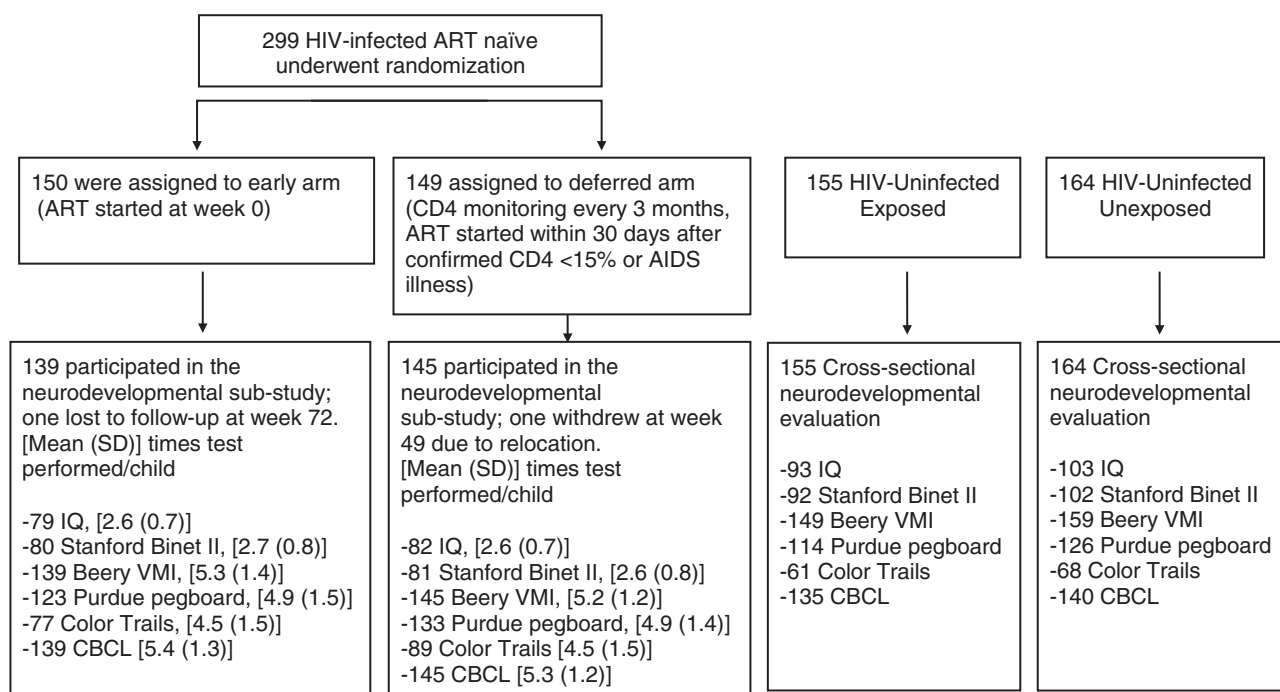


**FIGURE 1.** Study design, patient disposition and numbers completing each neurodevelopmental test. The number of children who underwent each test in each of the 4 study groups is shown. For the HIV-infected children in the early and deferred ART study arms, the mean (SD) of the number of tests performed during the study period is also shown. The cognitive and behavior assessments include 1) The intelligence tests: Wechsler Intelligence Scale for Children-III (age 6 to 17 years) or the Wechsler Preschool and Primary Scale of Intelligence-III (age 2 to 7.25 years); 2) The Stanford Binet II memory test (Beads/Sentences for age 3.5 to 17 years; Digits/Objects for age 6 to 17 years); 3) Beery Visual Motor Integration Test (age 2 to 17 years); 4) Purdue Pegboard (age 5 to 17 years); 5) Children's Color Trails (age 8 to 17 years); 6) the Child Behavior Checklist (age 2 to 18 years).

This neurodevelopmental substudy began 2 years after starting enrollment, and was conducted between 2008 and 2011. Participants were recruited from 7 sites in Thailand and 2 sites in Cambodia. We enrolled two age- and gender-matched HIV-uninfected control groups from the PREDICT sites: HIV-unexposed and HIV-exposed children. Matching for age was accomplished using 4 age bands: 2–5 years, 5–8 years, 8–11 years and ≥11 years old, based on the age when the HIV-infected child first enrolled in the neurodevelopmental substudy. Written informed consent was obtained from the caregivers before enrollment.

## Randomizations

The HIV-infected children were randomly assigned to either initiating ART at CD4 15%–24% (early arm) or initiating ART when CD4% was <15% or a CDC category C event developed (deferred arm). In December 2008, the CD4 threshold for children aged 1–3 years was modified to CD4 <20% based on local treatment guidelines changes. Randomization was stratified by research site and history of nevirapine exposure for preventing mother-to-child HIV transmission, and managed from the trial coordinating center (HIV-NAT in Bangkok, Thailand) using a computerized system.

## Procedures

Our primary objective was to determine neurodevelopmental outcomes at week 144 in early versus deferred ART children. The secondary objective was to compare these outcomes between the HIV-infected children in PREDICT and their HIV-uninfected peers. We assessed a range of behavioral and cognitive abilities, which are at risk for HIV-associated impairment using standardized tests that were in use in Thailand and Cambodia and which have good validity and reliability in their original form. Neuropsychological tests that required attention, tapping memory, psychomotor speed and processing speed were selected for administration in this study as these cognitive domains are frequently impaired among HIV-infected individuals. Furthermore, measures that tap these cognitive constructs are relatively brief to administer and score and they minimize language responses. Finally, the selected neuropsychological measures allowed straightforward translation of instructions as well as appropriate methods to ensure data fidelity through staff training and efficient monitoring of accuracy in test administration and scoring. HIV-infected children underwent age-appropriate psychomotor and behavioral assessments every 6 months and cognitive tests annually. The Cambodian sites performed only the psychomotor and behavioral measures; the Intelligence and Memory tests were not administered. The cognitive tests were either the Thai-version of the Wechsler Intelligence Scale for Children-III (age 6 to 17 years) or the Wechsler Preschool and Primary Scale of Intelligence-III (age 2 to 7.25 years), and the Stanford Binet II memory test (Beads/Sentences for age 3.5 to 17 years; Digits/Objects for age 6 to 17 years). The psychomotor assessments were Beery Visual Motor Integration (age 2 to 17 years), Purdue Pegboard (age 5 to 17 years) and Children's Color Trails (age 8 to 17 years). Thai versions of Wechsler Intelligence Scale for Children-III, Wechsler Preschool and Primary Scale of Intelligence-III and Stanford Binet II memory tests were available and widely used in Thailand, and have been validated by the Thai Psychologist Society. The assessments were completed by psychologists at all Thai sites. For the fine motor tests (Berry Visual Motor Integration, Purdue Pegboard and Color Trails), the English instructions were translated into Thai and Khmer by bilingual translators. Trained nurses were certified to administer these tests by experienced Thai and US neuropsychologists after correctly performing and scoring a minimum of 10 subjects per test. External quality assurance review by a US neuropsychologist was performed several times over the course of the study. The Child Behavior Checklist (CBCL) was completed by primary caregivers to assess behavioral problems at all sites (age 2 to 18 years), using the preschool (18 months to <6 years) and school-aged (age 6–18 years) forms. The English version of CBCL was translated into Thai and Khmer, and then back translated into English to ensure accurate translation. Between 2010 and 2011, the HIV-uninfected controls (155 born to HIV-infected mothers ["exposed"] and 164 born to HIV-uninfected mothers ["unexposed"]) underwent a 1-time neurodevelopmental assessment using the same tests. HIV-uninfected/exposed children were recruited from siblings of HIV-infected children and from children delivered to HIV-infected mothers at the study sites. HIV-uninfected/unexposed children were recruited from well-child clinics in the same hospitals. In the HIV-infected children, first-line ART consisted of zidovudine, lamivudine and nevirapine. A protease inhibitor (lopinavir/ritonavir or nelfinavir) was substituted for nevirapine in children with prior exposure to nevirapine as part of preventing mother-to-child HIV transmission (nelfinavir was not used after September 2007).[16] The protocol received approval from the Thai and Cambodian National, and local Institutional Review Boards.

## Statistical Analysis

Analyses were conducted with Stata 11.2 (Stata Corporation, College Station, TX). All analyses used available data that was considered valid by the psychologist who conducted the test. Apart from Perdue Pegboard and CBCL, the outcome variables for statistical comparison in primary analysis were the neurodevelopment scaled scores, standardized against US norms. Internal, external and total problem age and gender adjusted T scores were used as the outcome variable in the CBCL models. For the Purdue Pegboard, regression models compared the number of successful peg placements adjusting for age and gender because standardized scores were not available. The unadjusted mean difference in each standardized neurodevelopmental test score between the early and deferred arms were compared at week 144. For comparisons between the HIV-infected and uninfected groups, early and deferred data were combined because there was no difference between arms, and mean differences were adjusted for sociodemographic characteristics. In addition to comparing the mean CBCL internalized, externalized and total problem T scores, we assessed the proportion of children with CBCL syndrome-based subscale T scores in the borderline/clinical ranges (T ≥ 65) and assessed whether this was different in school-age children aged 6–11 years versus those aged ≥12 years. We then made comparisons of the mean full scale intelligence quotient (IQ) in children with borderline/clinical syndrome T scale scores against those with scores in the normal range, within these age groups. Three sensitivity analyses were conducted. First, we compared the change in neurodevelopmental scores from the first to the last evaluation by treatment arm and among children in the deferred arm who initiated treatment versus those who did not. Second, changes in neurodevelopmental scores for 39 early and 32 deferred children who had an assessment at the time of randomization were compared. Third, we used a multivariable random effects regression panel model to compare the neurodevelopmental scores at each study visit between the early and the deferred arms over the entire duration of follow-up. In univariate analyses, we assessed the contribution of age, gender, CD4% and $\log_{10}$ HIV RNA at each visit, the educational level of the caregiver, income level and whether the child lived with family. Factors significant in univariate analysis at $P < 0.2$ were included in the multivariable models. Years from the first to last test, the first score, whether the child was on ART at the time of the test and treatment arm were adjusted for in each model.

**TABLE 1.** Demographics, Socioeconomics and HIV-related Characteristics

| | HIV Infected (at Week 144 of PREDICT) | | HIV Uninfected | |
| --- | --- | --- | --- | --- |
| | Early ART (n = 139) | Deferred ART (n = 145) | HIV Exposed (n = 155) | HIV Unexposed (n = 164) |
| Demographic and socioeconomic characteristics | | | | |
| Median age | 9 yr | 9 yr | 7 yr* | 7 yr* |
| Age, n | | | | |
| <5 yr | 14 | 13 | 40* | 38* |
| 5–12 yr | 106 | 106 | 96 | 112 |
| >12 yr | 19 | 26 | 19 | 14 |
| Female | 51% | 64% | 57% | 58% |
| Thai | 60% | 59% | 63% | 66% |
| Father or mother as primary caregiver | 65% | 64% | 93%* | 87%* |
| Caregiver education; high school/bachelor | 43% | 43% | 34% | 65%* |
| Low/very low income | 59% | 66% | 58% | 35%* |
| HIV-related characteristics | | | | |
| CDC N:A:B | 1:61:38% | 1:63:36% | | |
| Time on ART (wk) | 144 wk | 48% on ART for a median of 81 wk | | |
| Median current CD4% | 33% | 24%* | | |
| Median current CD4 count (cells/mm³) | 978 | 653* | | |
| Median %CD4 nadir | 18% | 15%* | | |
| %HIV RNA <50 copies/mL | 91% | 40%* | | |

Characteristics at time of primary neurocognitive endpoint (week 144 of PREDICT) are shown here for the HIV-infected children in the randomized early and deferred ART arms. The 2 HIV-uninfected groups had a cross-sectional neurodevelopmental assessment, and their characteristics at time of enrollment are included.

The significant *P* values for the demographic and socioeconomic characteristics denote significant differences between each of the HIV-uninfected groups with the combined HIV-infected groups. Exceptions are caregiver's education and low/very low income in which only the HIV-unexposed uninfected group is significantly different to the other 3 groups. For HIV-related characteristics, the *P* value denotes significant differences between the early and deferred HIV-infected arm.

*\*P* value <0.001.

## RESULTS

### Demographic Characteristics

Between March 2006 and September 2008, 455 children were screened and 300 HIV-infected children (180 Thai and 120 Cambodian) enrolled in the main PREDICT study. Of these, 284 HIV-infected children participated in this neurodevelopmental substudy (139 in the early arm and 145 in the deferred arm). Three hundred nineteen age-matched HIV-uninfected children including 155 HIV-exposed and 164 HIV-unexposed were enrolled as controls. The number of children who underwent each test and number of repeat tests are also shown in Figure 1. The numbers of assessments before week 144 were not different between the early and the deferred groups, whereas the HIV-uninfected groups had only a single assessment. The HIV-infected early and deferred arms were similar in age (median age 9 years), gender (58% female), ethnicity (60% Thai) and socioeconomic status at entry and study week 144 (Table 1). Only 48% of the deferred arm children initiated ART and had a lower median duration of ART. At week 144, the early arm had higher CD4%, CD4 count and HIV RNA <50 copies/mL as well as CD4 nadir (all *P* < 0.001). ART regimens were zidovudine/lamivudine/nevirapine (n = 141), zidovudine/lamivudine/lopinavir (n = 25) and others (n = 42). The HIV-uninfected controls were 2 years younger than the infected children at week 144. The gender and ethnicity of the infected and uninfected children were similar. The HIV-exposed, uninfected group more closely resembled the HIV-infected children for caregiver's education and income (Table 1).

### Cognitive and Intellectual Function

For all cognitive tests, the test scores and mean difference in test scores did not differ by study arms (Fig. 2 and Table 2). Specifically, the mean (standard deviation [SD]) scores did not significantly differ between the early and deferred arms for full-scale IQ, verbal IQ, performance IQ and processing speed quotient. However, all mean scores were lower than those of HIV-uninfected controls (*P* < 0.001). The Stanford Binet II memory mean (SD) scores for beads, sentences and digits did not differ by randomized arms though the deferred arm had a marginally higher score for objects (mean 52 versus 50, *P* = 0.04). The sentence and digit memory scores were lower in the HIV-infected children compared with uninfected controls (*P* ≤ 0.01) (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/B428).

The mean (SD) Beery Visual Motor Integration score did not differ by early versus deferred arm, but were lower than that from the HIV-uninfected control groups (*P* < 0.001) (Table 2 and Fig. 3). The mean (SD) Color Trails 1 and 2 scores were not different across the 4 groups. For Color Trails 1, the mean (SD) scores were 79 (17) for the early arm, 80 (14) for the deferred arm, 78 (17) for the HIV-uninfected/exposed and 83 (17) for the HIV-uninfected/unexposed children (*P* > 0.05). For the Color Trails 2, the mean (SD) scores were 86 (15) for the early arm, 88 (13) for the deferred arm, 88 (14) for the HIV-uninfected/exposed and 87 (16) for the HIV-uninfected/unexposed children (*P* > 0.05). The mean (SD) scores for Purdue Pegboard dominant hand were the same in the early and deferred arms (14 [3] in both), and the mean score for the nondominant hand was not significantly different in the deferred compared with the early arm (13 [3] versus 12 [3], respectively). For both of these scores, the HIV-infected children performed better than the HIV-uninfected controls (Table 2, *P* < 0.05).

The early and deferred children had similar mean (SD) T scores on the CBCL, with total problem scores of 51 (10) versus 52 (9), externalized problem scores of 53 (9) versus 53 (10) and internalized problem scores of 52 (10) versus 53 (9), but they had higher total and externalized problem scores when compared with the HIV-uninfected/exposed (total score 50 [9] and externalized score 51 [8], *P* < 0.05) and the HIV-uninfected/unexposed (total
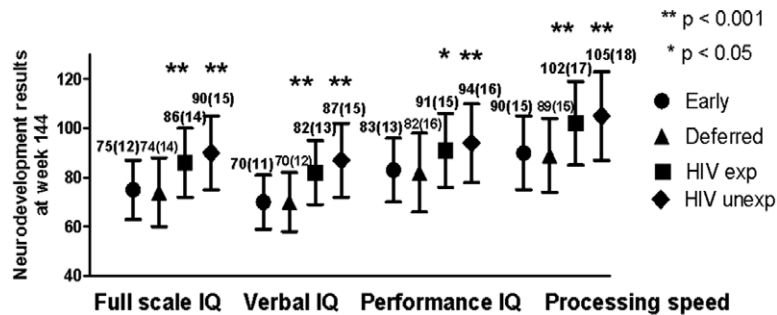
**FIGURE 2.** IQ comparison between the HIV-infected children (early versus deferred ART arms) at week 144 of PREDICT and the HIV-uninfected (HIV exposed and unexposed) control group children. Mean (SD) scores are shown. *P* values for the comparison between PREDICT children and the uninfected HIV-exposed and HIV-unexposed controls have been adjusted for parent as caregiver, educational level of caregiver and income. The IQ tests included Wechsler Intelligence Scale for Children-III (age 6 to 17 years) or the Wechsler Preschool and Primary Scale of Intelligence-III (age 2 to 7.25 years). The number of children in each group: HIV-infected/early ART arm (n = 79), HIV-infected/deferred ART arm (n = 82), HIV-uninfected/exposed (n = 93) and HIV-uninfected/unexposed (n = 103). *P* value represents significant differences between each of the HIV-uninfected groups relative to the combined early and deferred groups.

score 49 [10] and externalized score 50 [9], *P* < 0.05) groups. The externalized, internalized and total problem T scores >60 typically suggest behavioral problems in the borderline clinical range. This cutoff was met on total score for 16%, 20%, 16%, 15% (*P* = 0.6) in early arm, deferred arm, HIV-uninfected/exposed and uninfected/unexposed, respectively (22%, 19%, 13%, 11% [*P* = 0.04] for externalized and 22%, 19% 16%, 17% [*P* = 0.6] for internalized scores).

For HIV-infected children, the proportion of 188 children aged 6–11 with CBCL Syndrome scale T scores in the borderline/clinical problem range was not significantly different to 42 children aged ≥12. However, although no significant differences in full-scale IQ were noted in the younger children with borderline/clinical problem syndrome T scores, older children with borderline/clinical problem T scores in several syndrome scales had significantly lower full-scale IQs in several domains. The mean difference

**TABLE 2.** Mean Differences (95% CI) in Neurodevelopmental Test Score at Week 144 Between Deferred and Early Treatment Arms, and Between All HIV-infected PREDICT Children Versus the HIV-exposed/uninfected and HIV-unexposed/uninfected Controls

|  | Deferred versus Early | | Predict versus Exposed* | | Predict versus Unexposed* | |
|---|---|---|---|---|---|---|
|  | Differences 95% CI | *P* | Differences 95% CI | *P* | Differences 95% CI | *P* |
| **IQ** | | | | | | |
| Full-scale IQ | −0.78 (−5.02, 3.46) | 0.72 | −9.03 (−13.04, −5.01) | <0.001 | −12.45 (−16.91, −7.98) | <0.001 |
| Verbal IQ | −0.15 (−3.95, 3.65) | 0.94 | −9.25 (−12.91, −5.58) | <0.001 | −14.85 (−19.06, −10.64) | <0.001 |
| Performance IQ | −0.42 (−5.12, 4.27) | 0.86 | −6.71 (−11.15, −2.28) | 0.003 | −9.04 (−13.95, −4.13) | <0.001 |
| Processing speed quotient | −0.5 (−5.57, 4.56) | 0.84 | −10.15 (−15.17, −5.13) | <0.001 | −12.99 (−18.48, −7.50) | <0.001 |
| **Binet memory** | | | | | | |
| Beads | −2.04 (−4.68, 0.6) | 0.13 | −0.71 (−3.27, 1.86) | 0.59 | −2.18 (−4.93, 0.58) | 0.12 |
| Objects | 2.27 (0.17, 4.38) | 0.04 | 0.03 (−2.03, 2.09) | 0.98 | −0.68 (−3.04, 1.67) | 0.569 |
| Digits | −0.31 (−2.35, 1.73) | 0.77 | −2.70 (−4.78, −0.63) | 0.01 | −4.08 (−6.39, −1.76) | 0.001 |
| Sentences | −0.29 (−1.84, 1.25) | 0.71 | −2.39 (−3.93, −0.85) | 0.002 | −4.03 (−5.96, −2.11) | <0.001 |
| **Fine motor** | | | | | | |
| Beery visual motor integration | 1.01 (−2.3, 4.32) | 0.55 | −8.41 (−11.25, −5.57) | <0.001 | −10.56 (−13.72, −7.39) | <0.001 |
| Color Trail 1 standard score | 1.1 (−3.99, 6.2) | 0.67 | 0.66 (−4.54, 5.85) | 0.80 | −0.81 (−6.46, 4.83) | 0.78 |
| Color Trail 2 standard score | 2.33 (−2.26, 6.91) | 0.32 | −0.15 (−4.74, 4.45) | 0.95 | 2.49 (−2.73, 7.71) | 0.35 |
| Purdue pegboard dominant hand pin placements† | 0.12 (−0.39, 0.63) | 0.64 | 0.98 (0.49, 1.46) | <0.001 | 0.74 (0.24, 1.24) | 0.004 |
| Purdue pegboard nondominant hand pin placements† | 0.24 (−0.29, 0.76) | 0.37 | 0.79 (0.30, 1.28) | 0.002 | 0.48 (−0.01, 0.97) | 0.06 |
| **Behavior** | | | | | | |
| CBCL total problem T score | 0.91 (−1.33, 3.14) | 0.42 | 0.94 (−1.10, 2.99) | 0.37 | 2.35 (0.21, 4.49) | 0.03 |
| CBCL internalized problem T score | 0.99 (−1.18, 3.16) | 0.37 | 1.92 (−0.13, 3.98) | 0.066 | 0.85 (−1.20, 2.89) | 0.42 |
| CBCL externalized problem T score | 0.01 (−2.17, 2.2) | 0.99 | 2.44 (0.47, 4.41) | 0.015 | 3.25 (1.20, 5.30) | 0.002 |

*Significant differences are between each of the HIV-uninfected groups relative to the combined early and deferred groups. Comparisons with HIV-uninfected control groups are adjusted for differences between groups (parent as caregiver, educational level of caregiver and income).

†Purdue Pegboard pin placements are raw scores adjusted for age and gender.
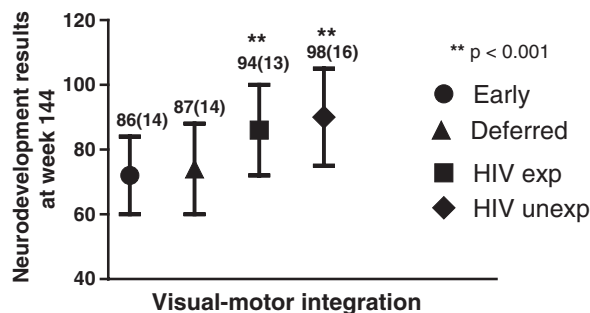
CI indicates confidence interval.

**FIGURE 3.** Results from the Beery Visual Motor Integration test that given to all children in the study.

in full-scale IQ in children with abnormal versus normal scores (95% confidence interval; $P$) were –12.4 (–24.7 to –0.2; $P = 0.048$) for anxious/depressed and aggressive behavior and thought problems, and –15.3 (–28.0 to –2.6; $P = 0.03$) for attention problems. For the HIV-uninfected children, no significant differences in full-scale IQ were observed between children with or without borderline/clinical problems in the 6–11 or 12–18 year age brackets; however, power to make comparisons in the older age group was limited due to smaller sample size.

Sensitivity analyses showed no differences in neurodevelopmental outcomes at week 144 among 3 groups of HIV-infected children: early arm (n = 139), deferred arm children who did not start ART (n = 75) and deferred arm children who did start ART (n = 64). The change in scores from first to last test also did not differ by arm (data not shown). In multivariable random effects models of change from first test over total study follow-up, no differences were noted between the treatment arms (Table, Supplemental Digital Content 2, http://links.lww.com/INF/B430) and $P$ values for differences in neurodevelopmental scores in the deferred versus early arms over all follow up. Due to delay in starting the neurodevelopmental substudy, only 39 early and 32 deferred children had assessment at the time of randomization. Among these 71 children, no differences were noted in change of scores for all tests from baseline to week 144.

## DISCUSSION

This study demonstrated that regardless of whether children age ≥1 year started ART at CD4 15%–24% or deferred ART until CD4 was <15%, the IQ, memory, psychomotor and behavioral outcomes did not differ at 3 years after study entry, despite the early ART arm achieving higher CD4 levels and viral suppression. Nevertheless, the HIV-infected children performed worse on cognitive and neurodevelopmental tests compared with their HIV-uninfected (HIV-exposed and unexposed) peers. Our data suggest that cognitive and developmental deficits in HIV-infected children occur earlier than 1 year of life and they do not improve with initiation of ART.

These data complement those from the Children with HIV Early Antiretroviral Therapy study, which showed better neurodevelopment in infants aged 10–15 months treated with ART before 3 months of age compared with those who deferred ART until CD4 criteria were reached (CD4 ~ 25%). Moreover, infants who started early on ART performed similarly to HIV-unexposed, uninfected infants.[12] Other studies suggest that HIV-infected children who initiated treatment a few years later, during preschool, did not achieve the same levels of cognition as their healthy peers.[11] School aged, ART-naive Ugandan HIV-infected children with similarly high CD4 levels as children in this study also demonstrated poorer cognition compared with those who

were uninfected.[23] These data, together with ours, suggest that insult to the central nervous system (CNS) occurs very early in the life of infected infants and thus that the optimal window of opportunity for neuroprotection through ART initiation remains early in infancy.

Our children responded well to ART with a significant rise in CD4 and fall in HIV RNA; however, their neurocognitive scores changed little over time. Additionally, the changes were similar between children who initiated and did not initiate ART. Detailed analysis using random effects models of change showed no difference between the early and deferred arms for all tests over the entire study duration. This provides evidence for an irreversible but nonprogressive HIV brain insult even in the presence of successful ART when ART is initiated in older children.[3,5,10] Improvement in cognition in children after ART has been observed by some[2,6,24] but not others.[3] It is hypothesized to be related to a decrease of inflammation and HIV viral burden in the CNS as well as possibly some general health improvements. Difference may also be due to severity of disease upon ART initiation. In our work, children never developed advanced immune compromise by study design. Consistent among studies, some degree of chronic neurocognitive impairment generally persists.[2,6,10,24,25] The statistical significant findings of better Purdue Pegboard scores in the HIV infected versus uninfected are clinically insignificant, and could be due to data variability and/or learning/practice effects from repeat testing in the HIV-infected children. Aside from Purdue Pegboard where we used age and gender adjusted raw scores for analysis, we used US norms to obtain scaled scores for the other neurodevelopment tests due to the lack of Thai and Cambodian norms. By using the same method for all 4 groups of children, we partially mitigate the bias for interpretation. As the obtained serial scores for the HIV-infected children did not significantly change during the course of the study, it suggests that the outcome comparison of this group with HIV-uninfected children who were 2 years younger is valid.

Cognitive function is critical for maturing perinatally HIV-infected children to assimilate into society.[4,26] The HIV-infected children in this study demonstrated impairments in a wide range of abilities including intelligence, memory and eye–hand coordination, which could place them at a disadvantage in the current fast-pace and competitive world.[27] Furthermore, poor cognition and memory are associated with learning and behavioral problems.[25] Compared with the HIV-uninfected controls, our HIV-infected children had more interruptive and hyperactive behaviors. In addition, HIV-infected adolescents with borderline/clinical ratings of anxious/depression, thought problems, attention problems and aggressive behaviors had significantly poorer full-scale IQ scores. These behavioral consequences are likely to critically impact their transition into adulthood.[4,7,27] Additionally, HIV preferentially affects the prefrontal cortex of the brain, an area critical for executive function and ability to perform complex tasks.[4,5] Deficits associated with damage to these areas may only be identified in late adolescents and young adulthood when the functions associated with the prefrontal lobes become critical for optimal functioning, also known as growing into a deficit.[28] Low socioeconomic status could further impedes their success, as this alone can adversely affect cognition.[29] Although the HIV-uninfected children had similarly low income and primary caregivers with low education as those infected with HIV, they exhibited superior neurodevelopmental outcomes, which suggests a dominant negative effect of HIV infection on the brain. The contribution of family, social and economic factors on neurodevelopment is however complex, and our study did not perform in depth evaluation of important factors such as resilience, child–caregiver relationship, social and family

support, stigma, life stresses and mental health. These issues warrant future investigations.

Governments and public health systems face challenges with scaling up HIV diagnostics and treatment for HIV-infected infants. In 2010, the World Health Organization issued a recommendation, based on the Children with HIV Early Antiretroviral Therapy results,[30] that HIV diagnosis for HIV-exposed and ART for HIV-infected infants should be instituted during the first few months of life.[18] Each year, around 400,000 infants are newly infected with HIV, most living in sub-Saharan Africa.[1] Due to limited infrastructure and resources, fewer than half of these infants are being identified and treated in the first year of life.[20–22] This missed opportunity for early ART has led to a crisis of information regarding how to approach aging-up HIV-infected children who are clinically asymptomatic without ART after 2 years of age. Our data suggest that with close CD4 monitoring, deferring ART to CD4 <15% in older children who are well did not lead to worse AIDS-free survival,[13] cognition or neurodevelopment. However, deferring ART was associated with lower CD4 and higher viral replication, which could potentially lead to neuroinflammation and damage.

The randomized design of our study is a major strength; however, there are some limitations. The lack of baseline neurodevelopmental assessment in a substantial number of children limits our ability to measure changes in neurodevelopmental scores from before treatment initiation. The random effects model estimating changes over time utilizing all data points however does allow us to evaluate longitudinal growth in neurocognitive function. Our population includes mainly older children, limiting relevance to younger children who may be at greater risk for HIV-associated brain injury.[8,9,24] However, our population is unique in that it generally lacks maternal illicit drug use, which often confounds reports from developed countries.[31] We partially controlled for non-HIV confounders with comparative data from HIV-uninfected both exposed and unexposed to HIV.

In conclusion, in HIV-infected children surviving beyond age 1 year without ART, neurodevelopmental outcomes were similar with ART initiation at CD4 15%–24% versus <15%, but both groups performed worse than HIV-uninfected children. The results suggest that the window of opportunity to prevent neurobehavioral deficits remains in the first year of life. We continue to follow these children beyond 3 years after randomization into the early versus deferred arms and have incorporated neuroimaging to capture effects of ART timing on brain growth and integrity. As children may age into their deficits, it will be important to determine how HIV and ART timing influence long-term neuropsychological, behavioral and psychiatric outcomes to enable identification of interventions to improve outcomes. These data may pivotally inform this issue and impact on future treatment guidelines.

## APPENDIX

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

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