

## SCHOOL-AGE CHILDREN

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### INTRODUCTION

Children with perinatal HIV infection are at-risk for neuropsychological deficits, but few studies have performed neuropsychological evaluation of African children across multiple sites in resource-poor settings where children have received well-documented anti-retroviral treatment and medical care and follow-up.

#### Principal study aims are:

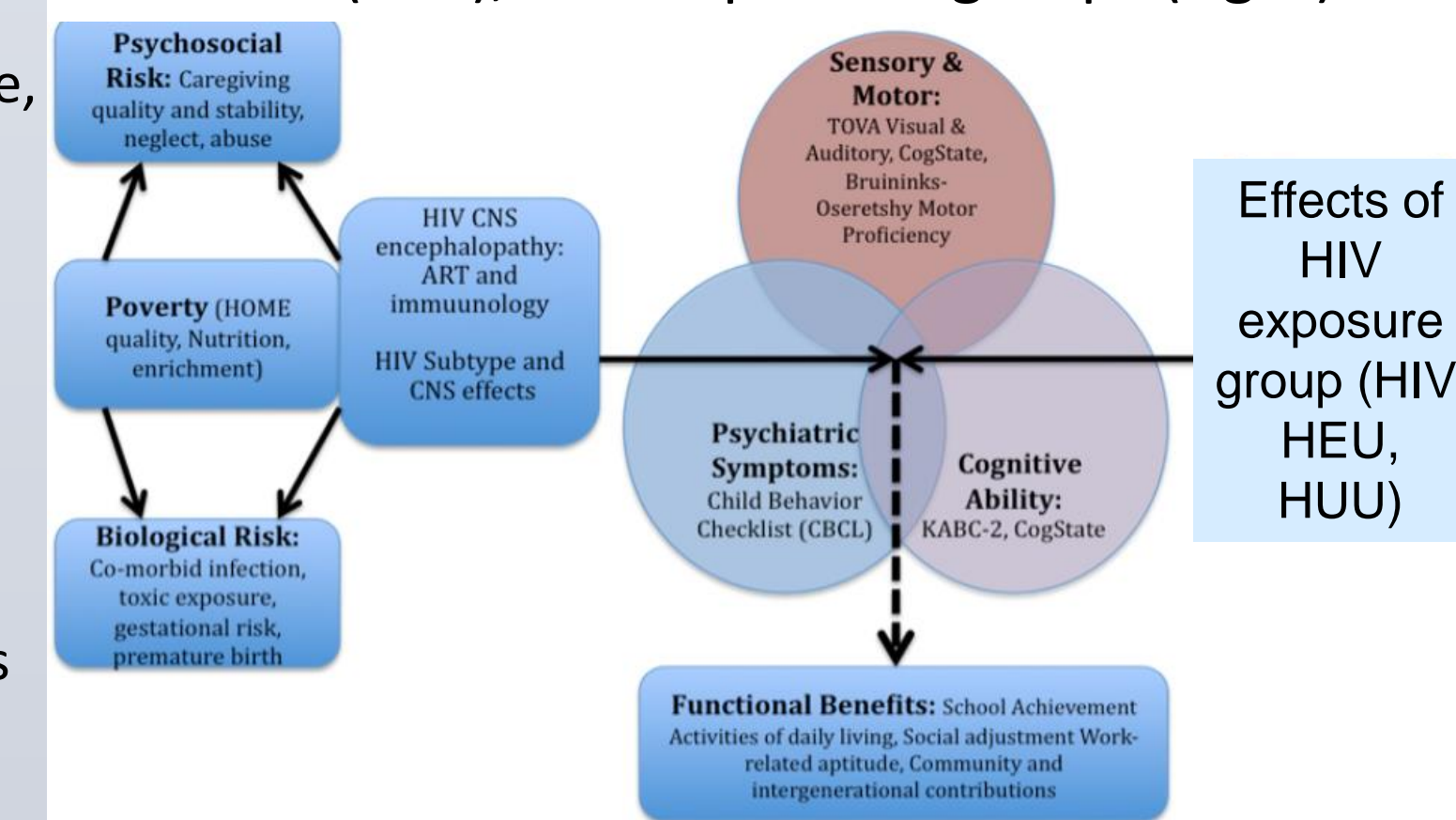
- To evaluate neuropsychological outcomes in perinatally HIV-infected (HIV), HIV-uninfected perinatally-exposed (HEU), and HIV unexposed and uninfected (HUU) children across 6 sub-Saharan sites in 4 countries.
- Compare longitudinal neuropsychological outcomes among HIV, HEU, and HUU children across sites at enrollment, 48-week, and 96-week follow-up

#### Participating P1060 Study Sites for P1104s substudy

- University North Carolina-Lilongwe CRS - Lilongwe, Malawi
- WITS RHI Research CRS – Johannesburg, RSA
- Chris Hani Baragwanath Hospital-Soweto, RSA
- FAM-CRU Tygerberg–Stellenbosch, RSA
- Makerere University – Johns Hopkins University Collaboration–Kampala, Uganda
- Parirenyatwa Hospital Family Care CRS-Harare, Zimbabwe

**METHODS:** IMPAACT P1060 compared Nevirapine (NVP) versus Lopinavir/Ritonavir (LPVr)-based ARV in children (HIV+) starting at 6 to 35 months of age. They were later enrolled for neurocognitive follow-up at 5 to 11 yrs of age, evaluating them at enrollment, 48, and 96 weeks. They were compared to age-matched HEU and HUU controls. All children were tested with the Kaufman Assessment Battery for Children (KABC), Tests of Variables of Attention (TOVA), Bruininks-Oseretsky Test of Motor Proficiency (BOT-2), and Behavior Rating Inventory of Executive Function (BRIEF). Cohorts were compared using linear mixed models adjusted for site, child's age and gender.

Figure 2. Observational Study Design for P1104s: Neuropsychological domains (center), risk factor domains (Left), HIV exposure groups (right)



**Table 1. HIV Disease Characteristics at 1104S study entry (N=246)**

Characteristic		HIV (N=246)
Age at ARV initiation, years	Median (IQR range)	1.2 (0.7, 2.1)
ARV Regimen	NRTI	1 (0%)
	NRTI+NNRTI	78 (32%)
	NRTI+PI	165 (67%)
	PI	2 (1%)
Years on ARVs	Median (IQR range)	5.8 (5.1, 6.7)
CD4%	25% or higher	239 (97%)
HIV-1 RNA	400 or less cp/ml	235 (96%)
WHO disease stage	Clinical stage III or IV	150 (61%)

**Table 2. Child and Family Characteristics at Study Entry**

	HIV (N=246)	HEU (N=183)	HUU (N=182)	P-value
Male (%)	45.1	51.9	46.2	0.35
Black African (%)	98.4	96.2	82.4	<.001
Age (mean, sd)	7.1 (1.2)	7.3 (1.6)	7.3 (1.5)	0.96
WHO BMI z-score (median; interq. range)	-0.2 (-.8,.4)	0 (-.6,.7)	-0.1 (-.7,.6)	0.08
MICS disability (median; interq. range)	5 (0,10)	0 (0,10)	0 (0,10)	<.001
Caregiver (Cgv) is biol. Mother (%)	85	99	100	<.001
Cgv completed high school (%)	29.7	30.6	36.8	0.09
Receives social grant (%)	23.6	26.9	14.8	0.02

\* Categorical variables, Chi-Square test, Continuous variables, Kruskal-Wallis test

### NEUROPSYCHOLOGY TESTS/RESULTS

#### Kaufman Assessment Battery for Children Adjusted HUU, HEU, HIV Differences (KABC-II)

**Cognitive Performance Domains**  
• Sequential Processing (working memory)  
• Simultaneous Processing (visual-spatial problem solving)  
• Learning  
• Delayed Recall  
• Planning (reasoning)

**Global Performance Indices**  
• Nonverbal Index  
• Mental Processing Index



#### Test of Variables of Attention (TOVA) visual

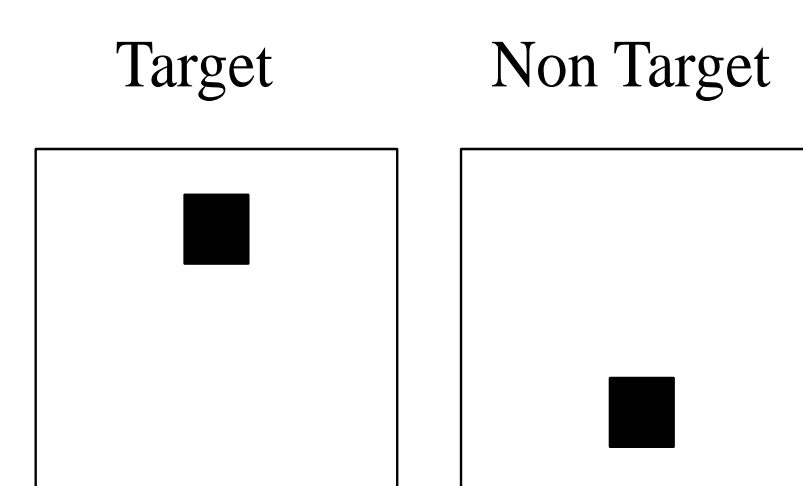
**Attention Performance Domains**  
• Percent Omission Errors  
• Response Time Variability  
• Response Time



**Impulsivity Performance Domains**  
• Percent Commission Errors

**Global Performance Indices**  
• D Prime Signal Detection  
• ADHD Index

#### Test of Variables of Attention (TOVA) Visual



#### Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition (BOT-2 short version)

- Fine Motor Precision
- Fine Motor Integrity
- Manual Dexterity
- Bilateral Coordination
- Balance
- Upper-Limb Coordination
- Speed and Agility
- Strength



#### Behavior Rating Inventory of Executive Function (BRIEF)

- The eight non-overlapping clinical scales form two broader indices:
  - Behavior Regulation (three scales) and
  - Metacognition (five scales).
- These are combined into the Global Executive Composite Index, whereby the higher the score, the greater the number of problems.
- The Parent version of the Preschool BRIEF was administered in the local language to the principal caregiver.

**Table 3: Adjusted Predicted Means (95% CI) by Group at Baseline with Changes (95% CI) from Baseline to Weeks 48 and 96 within Cohorts**

Outcome	Cohort	Week 0	Change [Week0-Week48]	P-value	Change [Week0-Week96]	P-value	Cohort P-value	Coh X Week P-value
KABC MPI	HIV	73.66 (72.34,74.98)	0.65 (-0.37,1.67)	0.21	-0.65 (-1.79,0.50)	0.27	<0.001 *	0.77
	HEU	79.55 (77.92,81.18) +	0.18 (-1.04,1.41)	0.77	-1.51 (-2.97,-0.05)	0.04 *		
	HUU	81.17 (79.55,82.78) +	0.66 (-0.72,2.05)	0.35	-1.39 (-2.89,0.11)	0.07		
BOT-2: Total score	HIV	48.07 (47.08,49.06)	-1.11 (-1.88,-0.34)	0.005 *	-0.49 (-1.26,0.27)	0.21	<0.001 *	0.09
	HEU	52.45 (51.44,53.46) +	-0.22 (-1.22,0.77)	0.66	1.28 (0.30,2.27)	0.01 *		
	HUU	52.51 (51.44,53.59) +	-0.92 (-1.83,-0.02)	0.05 *	0.27 (-0.68,1.21)	0.58		
BRIEF GEC	HIV	53.33 (51.72,54.93)	5.39 (3.91,6.87)	<0.001 *	4.43 (2.71,6.14)	<0.001 *	0.79	<0.001 *
	HEU	51.69 (50.01,53.38)	2.40 (0.78,4.02)	0.004 *	4.27 (2.68,5.87)	<0.001 *		
	HUU	50.76 (49.20,52.31) -	0.71 (-0.60,2.02)	0.29	1.58 (-0.15,3.31)	0.07		
TOVA ADHD	HIV	-0.54 (-0.90,-0.18)	-0.96 (-1.34,-0.58)	<0.001 *	-1.15 (-1.52,-0.77)	<0.001 *	<0.001 *	0.08
	HEU	0.58 (0.21,0.96) +	-0.25 (-0.65,0.15)	0.22	-0.56 (-0.96,-0.16)	0.01 *		
	HUU	0.37 (0.02,0.73) +	-0.90 (-1.29,-0.51)	<0.001 *	-1.17 (-1.59,-0.76)	<0.001 *		
TOVA D-prime Standard Score	HIV	82.92 (81.15,84.69)	-4.22 (-5.98,-2.45)	<0.001 *	-6.64 (-8.46,-4.82)	<0.001 *	<0.001 *	0.03 *
	HEU	88.47 (86.73,90.21) +	-2.23 (-4.10,-0.36)	0.02 *	-2.44 (-4.54,-0.34)	0.02 *		
	HUU	88.31 (86.63,89.99) +	-4.23 (-6.38,-2.07)	<0.001 *	-4.16 (-6.09,-2.23)	<0.001 *		

+ or - indicate HEU/HUU greater or less than HIV at week 0

\* p < 0.05 for comparisons across time within cohort and for main and interaction regression model effects

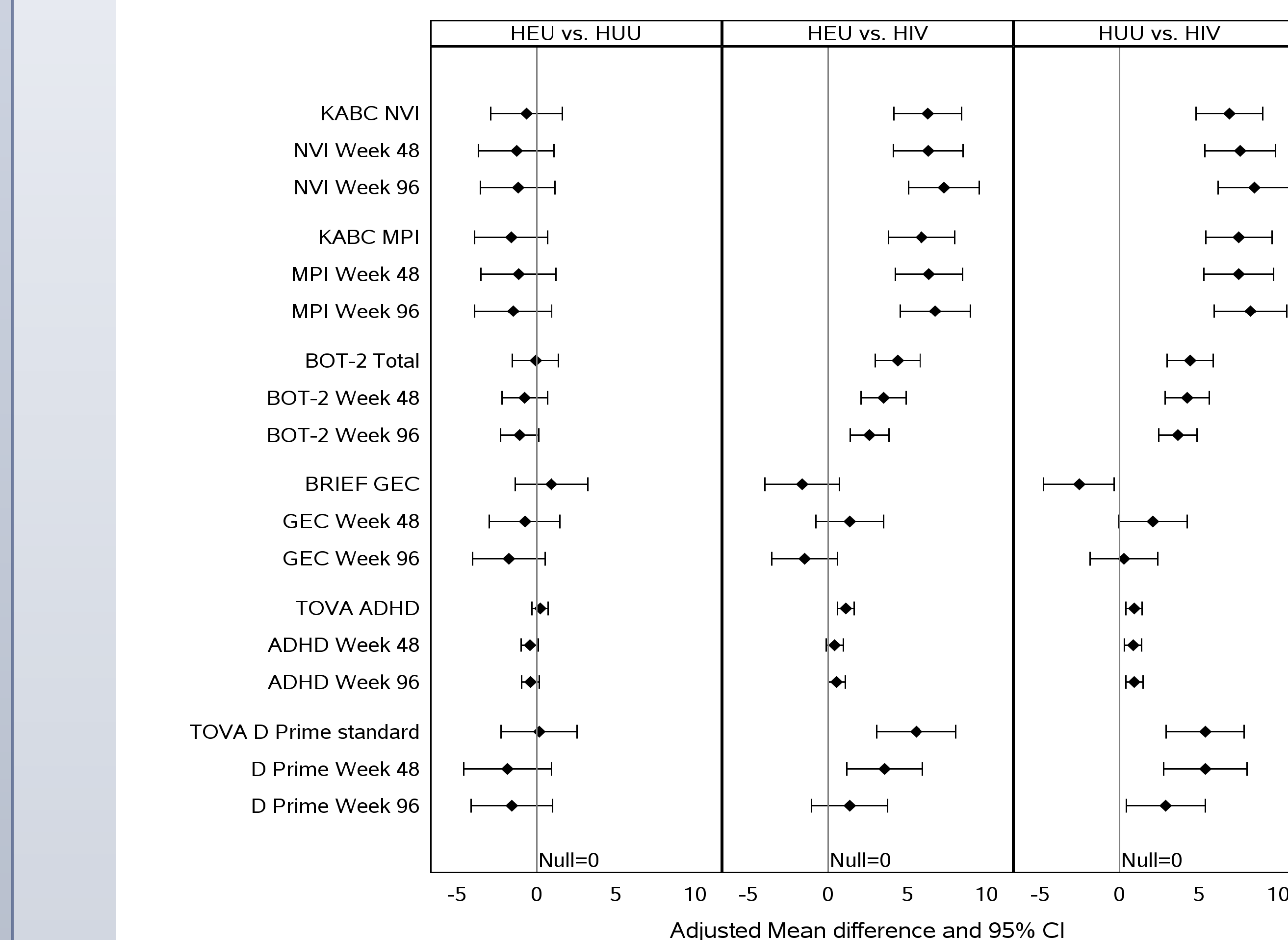
### SUMMARY NEUROPSYCHOLOGY RESULTS (see Table 4)

- For pairwise comparisons between groups, whereas the HIV group performed significantly more poorly than either the HEU or HUU groups, the HEU and HUU groups did not differ from one another (see group plots and results table for KABC-II Mental Processing Index, TOVA D prime, and BOT-2 Motor Proficiency Total).

- For the KABC Mental processing index score (MPI), the HIV group scored, on average, 5-6 points lower (~ ½ SD).

- There were significant differences among sites for the principal test outcomes, making it necessary to adjust by site when comparing the HIV, HEU, and HUU groups.

- However, HIV, HEU, and HUU between-group differences on the neuropsychological outcomes were consistent across all six study sites.



### CONCLUSIONS

- Children with HIV were significantly below HEU and HUU cohorts at all three assessment points on all principal neuropsychological outcomes, except the BRIEF (Table 3 and Forest Plot above).
- HEU and HUU cohorts were comparable on all neuropsychological outcomes (see above).
- Improvements across time points for neuropsychological outcomes were consistent among three exposure groups, except for the KABC-II Planning/Reasoning domain (see top graph above), which lagged for the HIV cohort.
- Despite 61% being Stage III or IV at diagnosis in early childhood, HIV children had excellent clinical care and robust virological suppression. Still, the HIV group had poorer neurocognitive function at all 3 assessment points, including deficits in reasoning/planning. Such deficits pose a serious risk as these children age into adolescence and make decisions on managing their disease.

### Acknowledging the P1104s Study Teams and Leadership



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