Neuropsychological outcomes in a two-year African-based pediatric observational study

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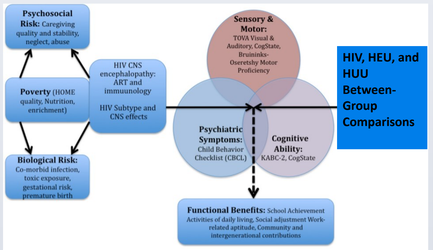
INTRODUCTION

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:

1) 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.
2) Compare initial neuropsychological outcomes among HIV, HEU, and HUU children across sites.



Participating P1060 Study Sites for P1104s

- UNC Lilongwe CRS – Lilongwe, Malawi
- Shandukani Research CRS – Johannesburg, SA
- Soweto IMPAACT CRS – Johannesburg, SA
- FAM-CRU, Stellenbosch University – Cape Town, SA
- MU-JHU Research Collaboration – Kampala, Uganda
- Harare Family Care CRS – Harare, Zimbabwe

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)	5.9 (5.1, 6.8)
CD4%	25% or higher	239 (97%)
HIV-1 RNA	400 or less cp/ml	235 (96%)

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 vars., Chi-Square test; Continuous vars., Kruskal Wallis test				

	HIV (N=246)	HEU (N=183)	HUU (N=182)	P-value *
Residential Zone				
Rural	20.7	15.8	15.9	0.63
Peri-urban	41.9	44.3	46.2	
Urban	37.4	39.9	37.9	
Running water (inside/on plot)	61.4	61.7	61.5	1.0
Refrigerator	56.1	57.9	60.4	0.67
Electricity for boiling water	67.1	67.8	60.4	0.26
Sufficient family income	27.6	27.9	32.4	0.51
* 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)

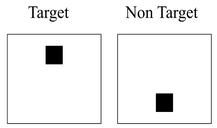
Global Performance Indices
- Nonverbal Index
- Mental Processing Index

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



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

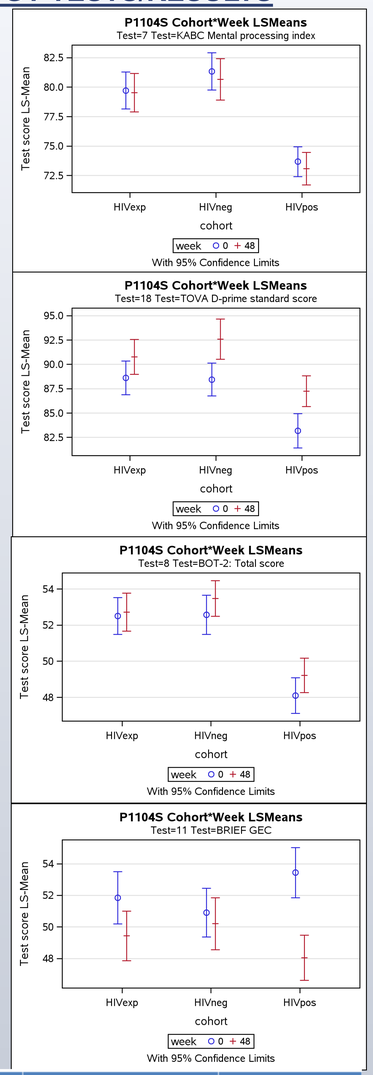
1. Fine Motor Precision
2. Fine Motor Integrity
3. Manual Dexterity
4. Bilateral Coordination
5. Balance
6. Upper-Limb Coordination
7. Speed and Agility
8. Strength

- **Total Standard Score**

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.

BRIEF Behavior Regulation Index
BRIEF Metacognition Index
BRIEF Global Executive Composite Index



Measure	Exposure	Week 0		Change from baseline		Global F test p-values	
				Wk 0 - Wk 48	P-value	Cohort	Cohort x Week
KABC MPI	HIV (HIVpos)	73.7 (72.4,75.0)		0.6 (-0.4,1.6)	0.25	<0.001	0.84
	HEU (HIVexp)	79.7 (78.2, 81.3)	+	0.2 (-1.0,1.4)	0.76		
	HUU (HIVneg)	81.4 (79.8, 82.9)	+	0.7 (-0.7,2.1)	0.33		
BOT-2	HIV	48.1 (47.1,49.1)		-1.1 (-1.9,-0.4)	0.004	<0.001	0.35
	HEU	52.5 (51.5,53.5)	+	-0.2 (-1.2,0.8)	0.69		
	HUU	52.6 (51.5,53.7)	+	-0.9 (-1.8, 0.0)	0.05		
D-Prime Standard	HIV	83.2 (81.4, 84.9)		-4.1 (-5.9, -2.3)	<0.001	<0.001	0.25
	HEU	88.6 (86.9, 90.4)	+	-2.1 (-4.0, -0.3)	0.03		
	HUU	88.4 (86.8, 90.1)	+	-4.2 (-6.3, -2.0)	<0.001		
BRIEF GEC	HIV	53.4 (51.9,55.0)		5.4 (3.9,6.9)	<0.001	0.98	<0.001
	HEU	51.9 (50.2, 53.5)		2.4 (0.8, 4.1)	0.004		
	HUU	50.9 (49.4, 52.5)	-	0.7 (-0.6,2.0)	0.29		

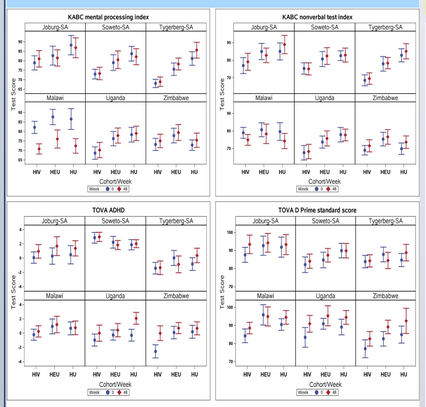
+/- p < 0.05 for pairwise comparison at week 0 between indicated cohort and HIV
Means adjusted for site, sex and age

SUMMARY NEUROPSYCHOLOGY RESULTS

- 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.

- Associations between child, caregiver, home environment characteristics and study group for KABC-II MPI scores
  - Females have about 1.3 point higher scores than males. This difference was not significant.
  - For each additional year of age, participants score about 0.3 points lower and those not yet in school score on average about 1.1 points lower. Neither difference was significant.
  - Children whose caregivers did not complete high school score about 5 points lower, while children of those who receive social grants score almost 4 points lower. Both differences were significant at p<0.001.
  - Those children with higher disability scores have lower scores; for each additional point on the disability scale, there is a decrease of 0.19 points. Those scoring higher on the developmental scale have higher scores; for each additional point there is an increase of 0.14 points. Both these results are statistically significant.

Weeks 0, 48 (blue, red) predicted standard scores (95% CI) on KABC and TOVA by exposure group and study site



MPI: mental processing index
TOVA: Tests of Variables of Attention
BOT-2: Bruininks-Oseretsky Motor Proficiency Test, 2nd edition
BRIEF: Behavior Rating Inventory of Executive Function
KABC: Kaufman Assessment Battery for Children

CONCLUSIONS

- We established the feasibility of obtaining multi-site neuropsychological measures in African children with HIV along with appropriate control comparisons; with significant performance deficits for the HIV group across all 6 sites despite language and cultural differences.
- Still, significant differences by site for our cognitive test outcomes evidence the importance of considering site-specific contextual and sampling features (e.g., adjusting between-group differences by site).
- Even with early treatment intervention through P1060, the HIV performance deficits demonstrate the need for neuropsychological monitoring and rehabilitative interventions.
- P1104s children have been assessed for a 2nd time (week 48), have now been assessed for a third time (week 96), providing a neuropsychological evaluation at several time points over a two-year period in order to further gauge the brain/behavior developmental trajectory of early and ongoing pediatric HIV treatment/care options in the African context.

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Lab Data Coordinator: Brittany White, B.S.

Final Conclusion after Years 1 & 2 of P1104s

Some . . . see things as that are and say why. Others dream things that never were and ask why not?
George Bernard Shaw

Can we do neuropsychological evaluation of pediatric HIV as a core aspect of morbidity and quality-of-life for African children as part of the IMPAACT clinical trials program? *Yes we can!*

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