Neuropsychological performance in African children with HIV enrolled in a multi-site anti-retroviral clinical trial is poorer than non-infected children at those study sites.

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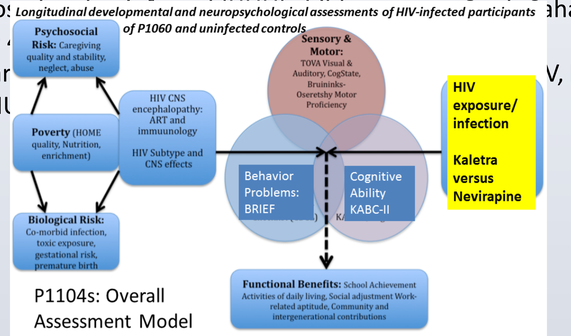
INTRODUCTION

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 unexpos… …haran sites in …
2) Compar… …V, PHEU, and PHU…



P1104s: Overall Assessment Model

Figure 1: Model of the major risk factors and developmental domains for our study children with HIV. Adapted from Walker et al., 2007 & Engle et al., 2007.

Statistical Methods

- Linear regression analyses using generalized estimating equations (GEE models) were performed to assess differences among study cohorts. Adjusted means were compared using pairwise contrasts.
- Linear regression models considered a variety of potential confounders in two steps: 1) all covariates with p < 0.20 in univariable analyses were included in a multivariable model; 2) only those covariates with p < 0.20 were retained.
- Key outcomes in each domain were used to build the final models, which were then used for others in the domain.

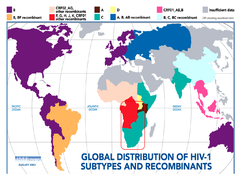
Developmental Domain	Tonus	Cognition				Intellect / Achievement		Affect Adjustment
	Motor Function	Visual Spatial Memory	Auditory Verbal Memory	Central Executive Function	Executive Reasoning	Language	Social / Emotional
Kaufman Assessment Battery for Children (KABC-II)		Learning, Sequential Processing,	Learning, Sequential Processing		Planning, Simultaneous Processing	Rebus and Rebus Delayed	
Tests of Variables of Attention (TOVA)	Simple reaction time (RT) for correct response			RT Speed and Variability on Signal Detection task			Impulsivity
Bruininks-Oseretsky Test of Motor Proficiency (BOT-2)	Gross and Fine Motor Proficiency						
Behavior Rating Inventory for Executive Functions (BRIEF)				Attention Problems	Metacognition scale		Behavior Regulation

Statistical Methods (continued)

Category	Potential confounders assessed in building regression models
Child attributes	sex, age, clinical site, whether the child is in school at the time testing, WHO-BMI, Weight and Height z-scores
Caregiver attributes	child's relationship to caregiver (biological mother or not), time spent with caregiver (less than 5 years or more), caregiver education level and employment, and whether income was mostly subsidized
Caregiving quality	UNICEF Multiple Indicator Cluster Survey (MICS-IV) disability scale (TQQ) and child development scales (caregiver report), and the caregiver Hopkins Symptoms Checklist-25 anxiety and depression scores
Home environment	source of and access to water, source of and access to fuel for heating/cooking, access to electricity and whether the family had a working refrigerator, and whether household income was sufficient for the family's needs; residential zone, e.g., urban, peri-urban or rural
Community environment	A comparison of children from urban, peri-urban, and rural communities on neuropsychological outcomes

Participating P1060 Study Sites for P1104s

1) Chris Hani Harriet Shezi clinic, Johannesburg, South Africa (Joburg); 2) Chris Hani HIV Unit, Soweto, South Africa (Soweto); 3) Tygerberg, South Africa (Tygerberg); 4) Lilongwe, Malawi (Malawi); 5) Kampala, Uganda (Uganda); and 6) Harare, Zimbabwe (Zimbabwe).



Child and Caregiver Characteristics

	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

Child and Caregiver Characteristics (cont.)

	HIV (N = 246)	HEU (N = 183)	HUU (N = 182)	P-value *
Residential Zone				
Rural	20.7	15.8	15.9	0.63
Per-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 vars., Chi-Square test; Continuous vars., Kruskal Wallis test

NEUROPSYCHOLOGY TESTS/RESULTS

Comparing the HIV, HEU, and HUU Groups on the Kaufman Assessment Battery for Children (KABC-II)

Cognitive Performance Domains
- Sequential Processing (working memory) (*P*<0.001)
- Simultaneous Processing (visual-spatial problem solving) (*P*=0.01)
- Learning (*P*<0.001)
- Delayed Recall (*P*<0.001)
- Planning (reasoning) (*P*=0.01)

Global Performance Indices
- Nonverbal Index (*P*<0.001)
- Mental Processing Index (*P*<0.001)

Test of Variables of Attention (TOVA)

Comparing the HIV, HEU, and HUU Groups on the Tests of Variables of Attention (TOVA)

Attention Performance Domains
- Percent Omission Errors (*P*<0.001)
- Response Time Variability (*P*<0.001)
- Response Time (*P*<0.001)

Attention Performance Domains
- Percent Commission Errors (*P*=0.09)

Global Performance Indices
- D Prime Signal Detection (*P*<0.001)
- ADHD Index (*P*<0.001)

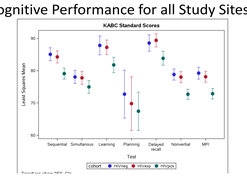
Comparing the HIV, HEU, and HUU Groups on the Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition (BOT-2 short version)

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 (*P*<0.001)**

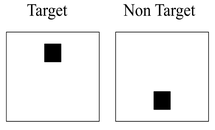
Comparing the HIV, HEU, and HUU Groups on the Behavior Rating Inventory of Executive Function (BRIEF)

- ❑ 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 (*P*=0.97)**
- **BRIEF Metacognition Index (*P*=0.07)**
- **BRIEF Global Executive Composite Index (*P*=0.34)**

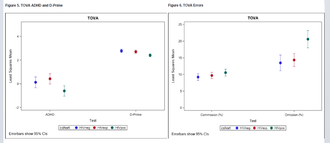
*Adjusted Standardized Scores on KABC-II Cognitive Performance for all Study Sites



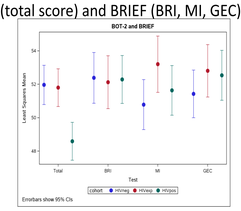
Test of Variables of Attention (TOVA) Visual



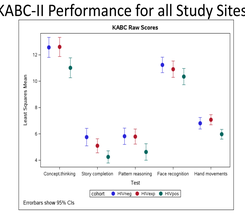
Attention Performance Scores on TOVA D Prime (standardized) and ADHD index, by Study



Standardized Performance Scores on BOT-2 (total score) and BRIEF (BRI, MI, GEC)



*Adjusted Raw Scale Scores on KABC-II Performance for all Study Sites



Summary of Principal Statistical Findings for Neuropsychological Outcomes (construct validity)

- 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.
- 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 from Years 1 of P1104s

- 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), are now being assessed for a third time (2/3 completed week 96 assessment as of June, 2016), 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.

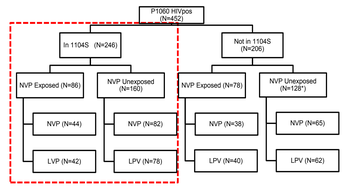
Summary of Principal Statistical Findings (continued)

- Associations between child, caregiver, home environment characteristics and study group for KABC-II MPI scores
  - Females have about 1.6 point higher scores than males.
  - For each additional year of age, participants score about 1.4 points lower and those not yet in school score on average about 3.25 points lower.
  - Children whose caregivers did not complete high school score about 2 points lower, while children of those who receive social grants score almost 4 points lower.
  - Participants living in urban areas score higher than those living in peri-urban or rural settings, the latter contrast being significant.
  - Those children with higher disability scores have lower scores; for each additional point on the disability scale, there is a decrease of 0.21 points.

Feasibility/Validity/QA of P1104s

- Between 91.5-95.6% of the cohort children completed all three tests (KABC-II, TOVA, BOT-2) in one day with high overall completion rates (TOVA 95-98%; BOT-2 and KABC close to 100%), and only 3% being invalid (KABC by cohort).
- Only 3% of entered scores were possibly invalid (KABC by cohort), mostly due to out-of-limit or extreme outlier designations. These were queried and have been corrected.
- First time a quality assurance plan involving monthly video-taping and review has been implemented in a multi-site neuropsychological study of this sort in African pediatric HIV, with scores averaging above 90% at 5/6 sites.

Limited Statistical Power for Evaluating Neuropsychological Outcomes of P1060 Treatment Arms: Exploratory Analyses Only



Secondary Study Aim from P1060 "Intent to Treat" analysis: NVP and LPV/r, in HIV-infected children (Year 1)

- In the HIV cohort, the NVP arm had lower median KABC-II Planning and Nonverbal Index scores (by 3 points each, *P*=0.04, 0.05 resp.)
- The NVP arm had lower median BOT-2 standardized scores (by 1.5 points, *P*=0.03) than the LPVr arm
- No differences between treatment arms on any other KABC-II or TOVA outcomes.

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NICHD Medical Officer: Sonia Lee, Ph.D.
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