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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IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Acknowledging the P1104s Study Leadership

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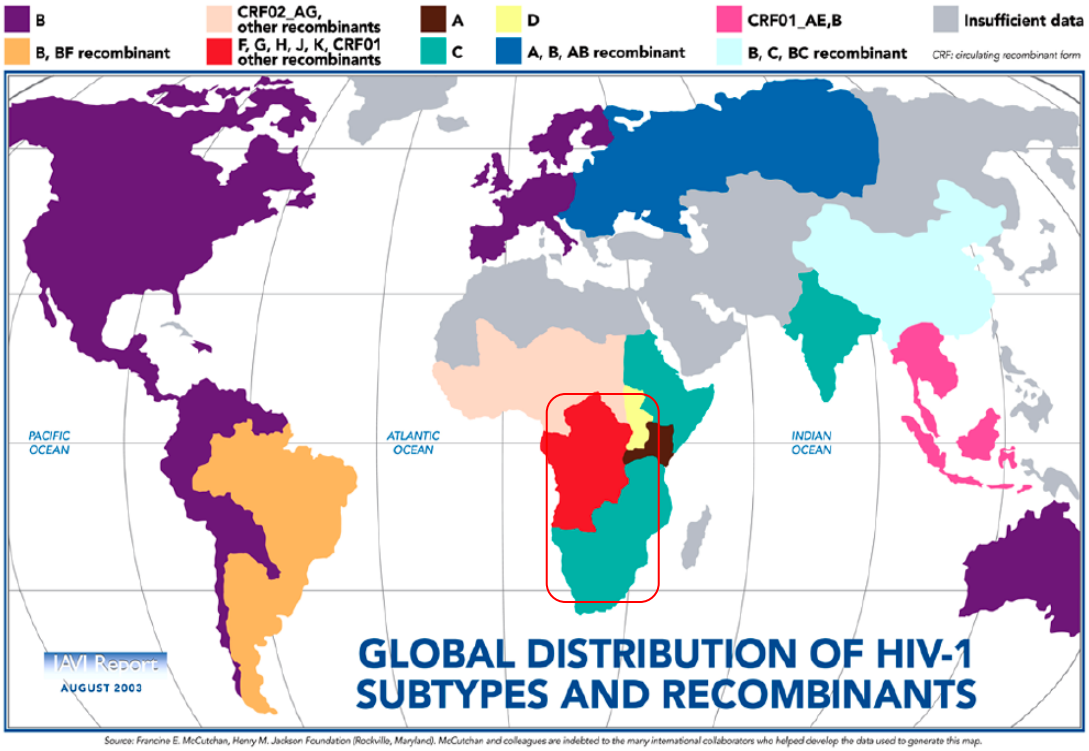
P1104S Primary Objectives

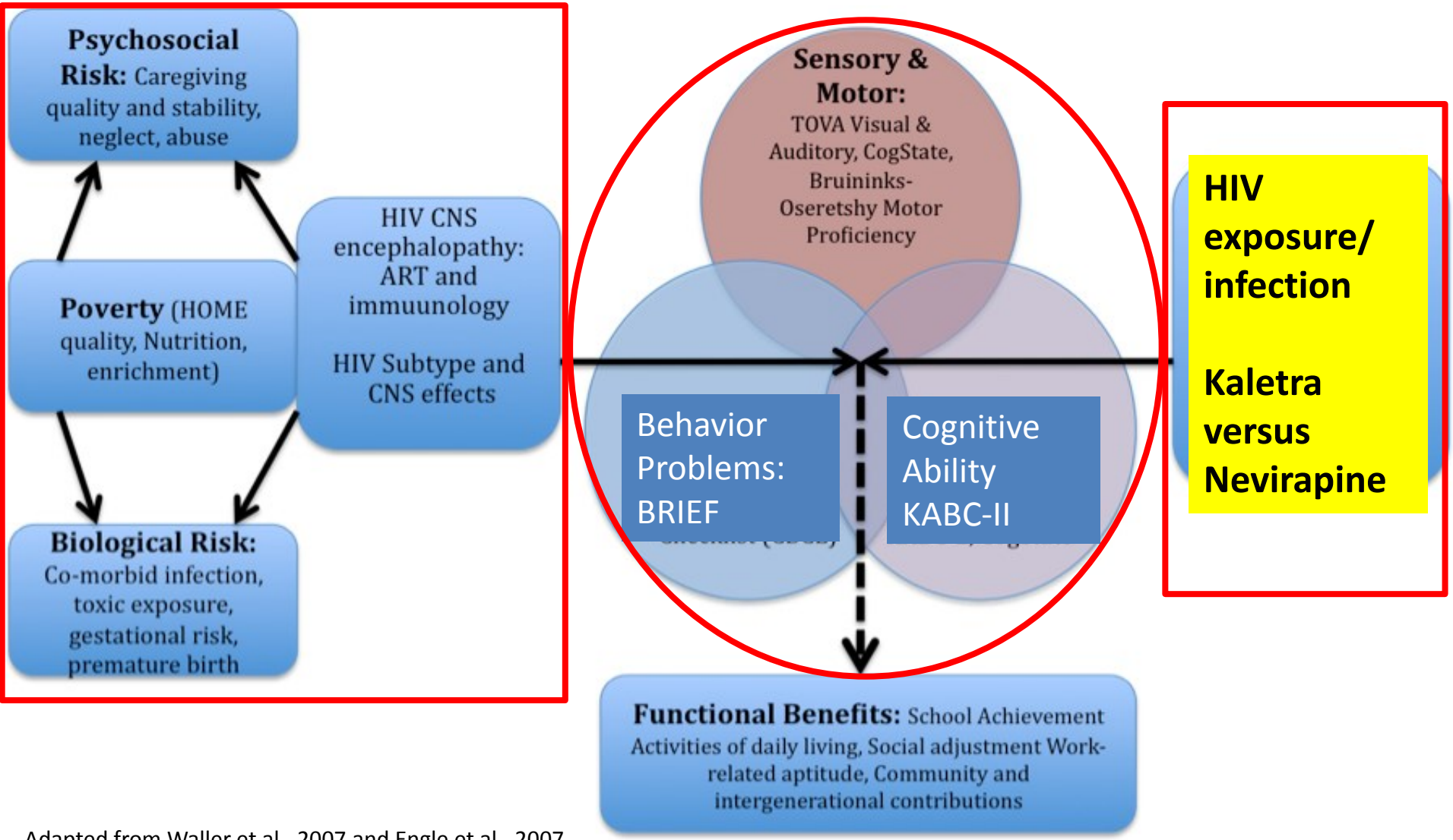
1. To assess the feasibility, reliability, validity of administering a neuropsychological assessment battery in HIV-infected (HIV), HIV-uninfected perinatally-exposed (HEU), and HIV-uninfected non-perinatally-exposed (HUU) children 5 to 11 years of age at clinical sites in resource-limited settings in sub-Sahara Africa.
2. To compare neuropsychological outcomes between the perinatally HIV, HEU and HUU children cross-sectionally and longitudinally with 3 assessments over two years.

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



Overall Assessment Model



Adapted from Waller et al., 2007 and Engle et al., 2007

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

- Linear regression analyses compared differences among study cohorts using generalized estimating equations (GEE models)
  - Adjusted means were compared using pairwise contrasts
  - Only covariates with $p < 0.20$ in univariable analyses were included in a multivariable model; $p < 0.20$ required to retain effect in final model.

- Key outcomes in each domain were used for final models, which were then used for other related outcomes in the domain

Statistical Methods (contd)

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

Child and Caregiver Characteristics (N=611)

	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				

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

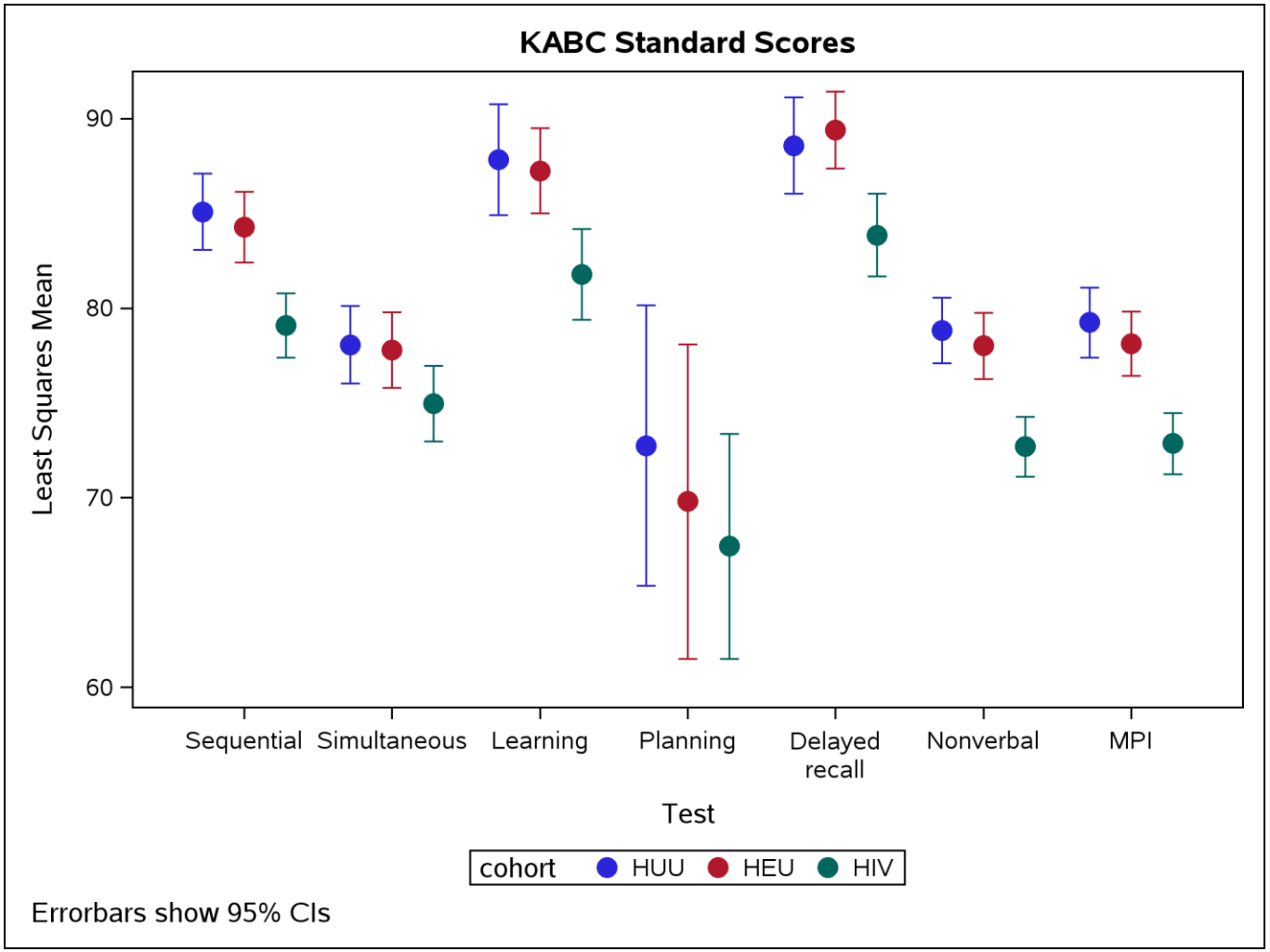
Cognitive Performance Domains

- 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)

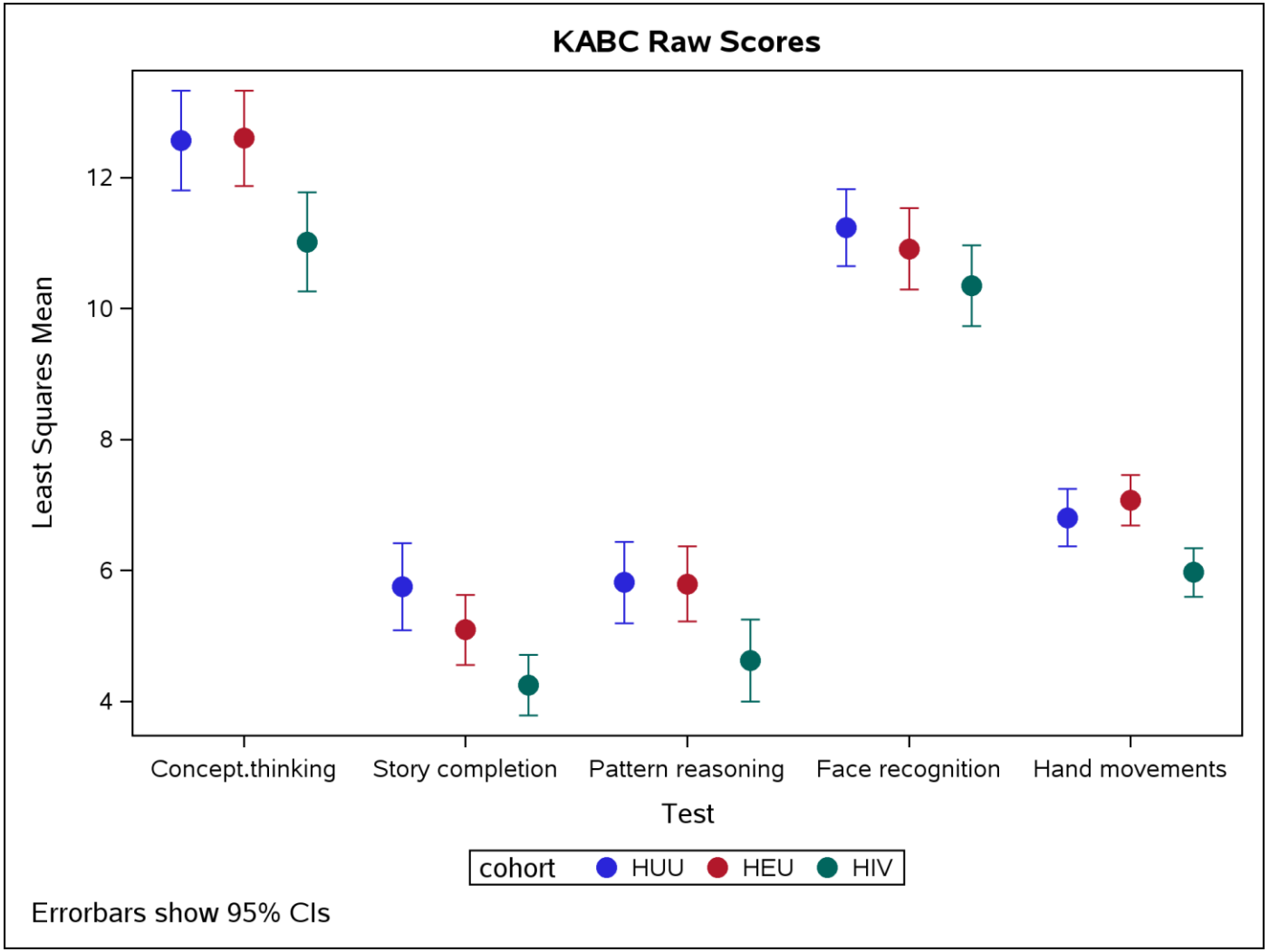
Global Performance Indices

- Nonverbal Index (*P*<0.001)
- Mental Processing Index (*P*<0.001)

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



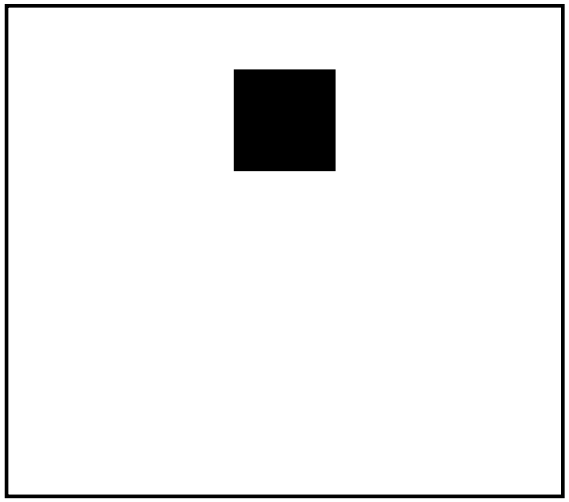
*Adjusted Raw Scale Scores on KABC-II Performance for all Study Sites



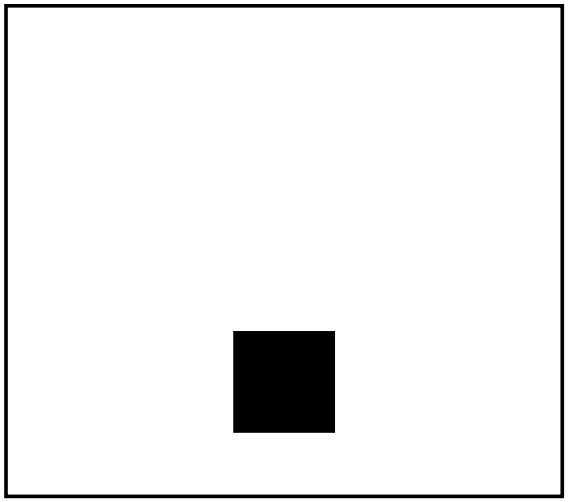
Test of Variables of Attention (TOVA) visual

Test of Variables of Attention (TOVA) visual

Target



Non Target



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

Attention Performance Domains

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

Impulsivity Performance Domains

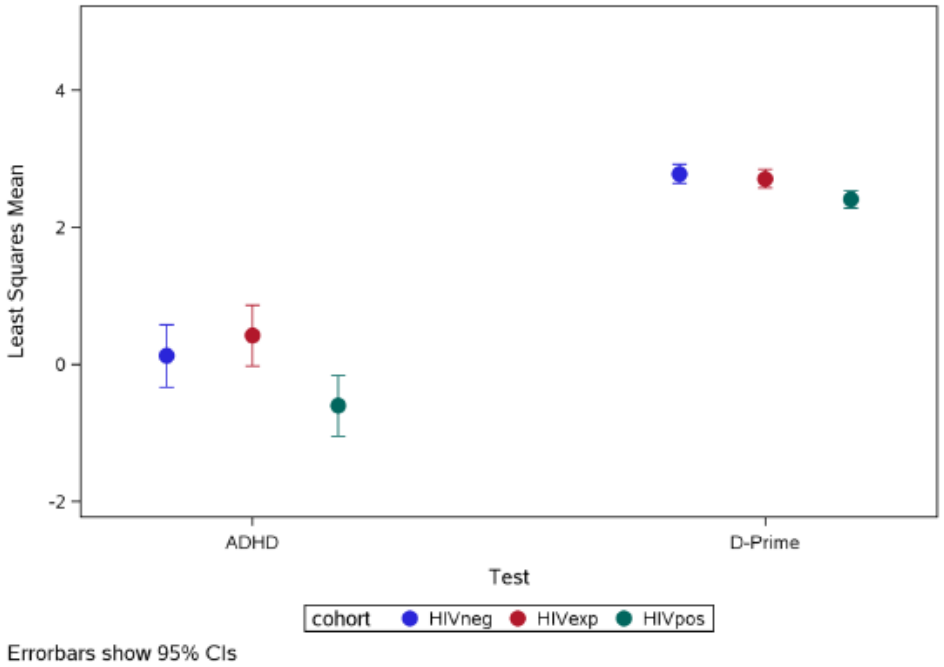
- Percent Commission Errors (*P*=0.09)

Global Performance Indices

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

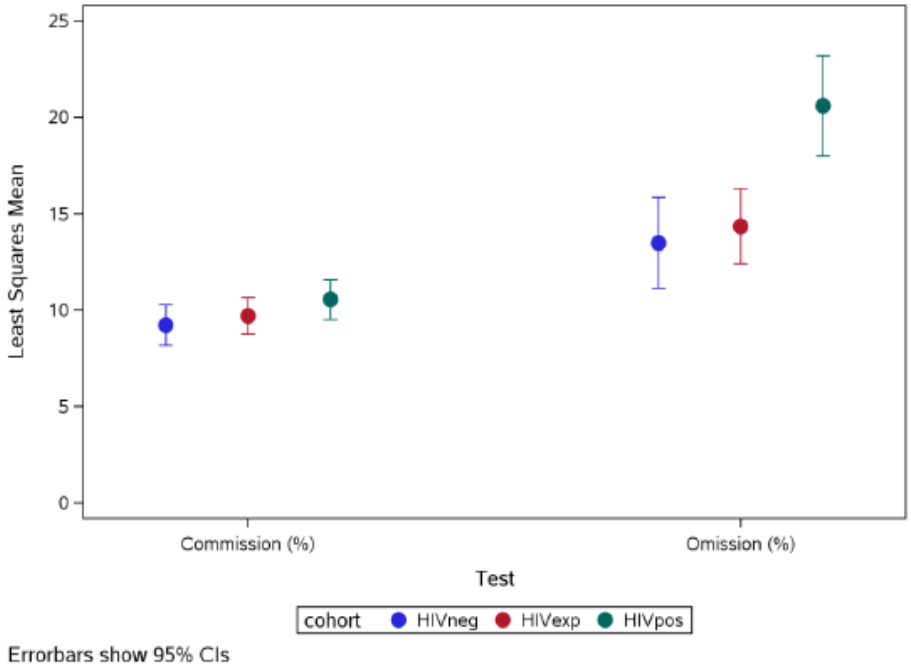
Attention Performance Scores on TOVA D Prime (standardized) and ADHD index, by Study

TOVA ADHD and D-Prime



Errorbars show 95% CIs

TOVA Errors



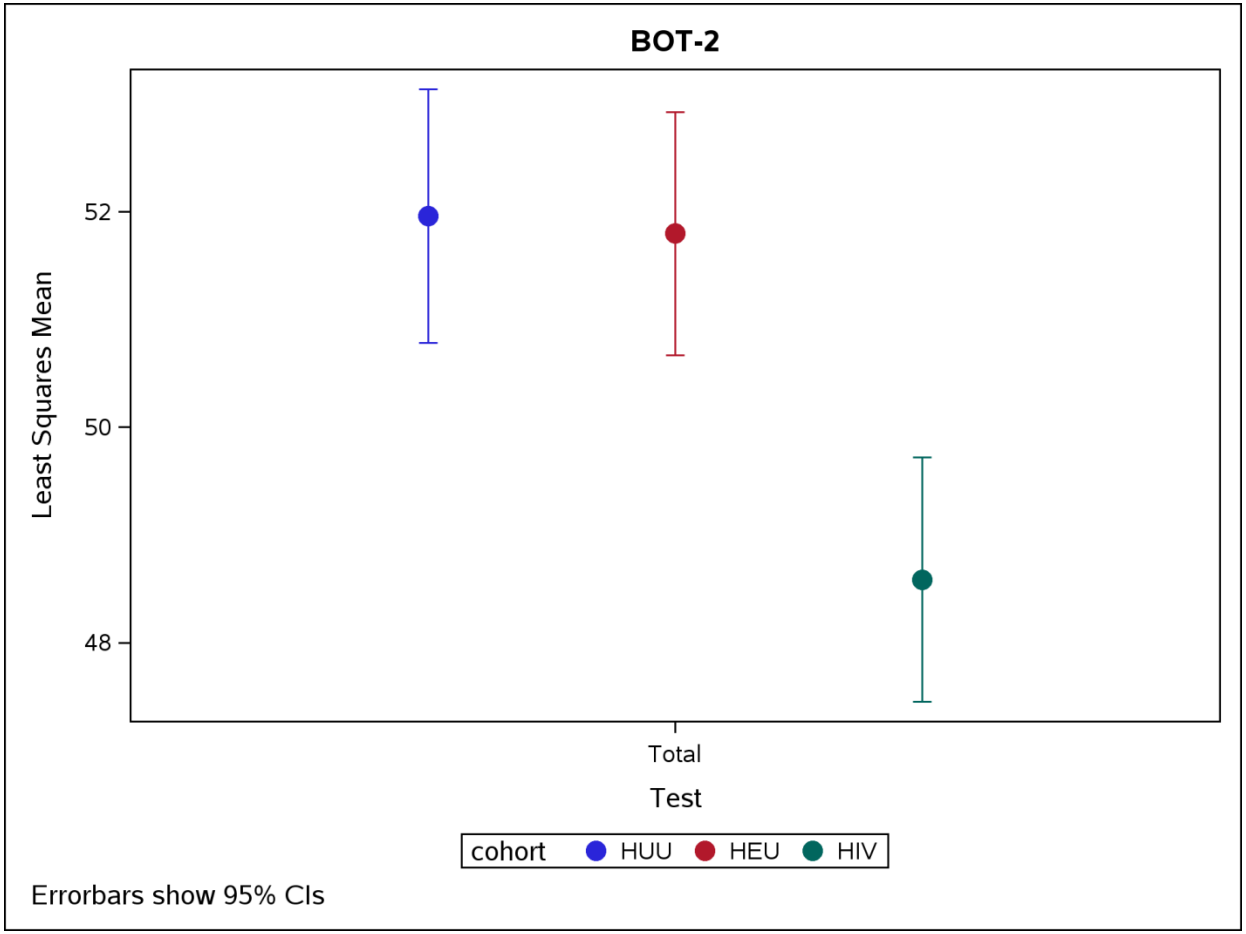
Errorbars show 95% CIs

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)**

Standardized Performance Scores on BOT-2 (total score)



Behavior Rating Inventory of Executive Function (BRIEF)

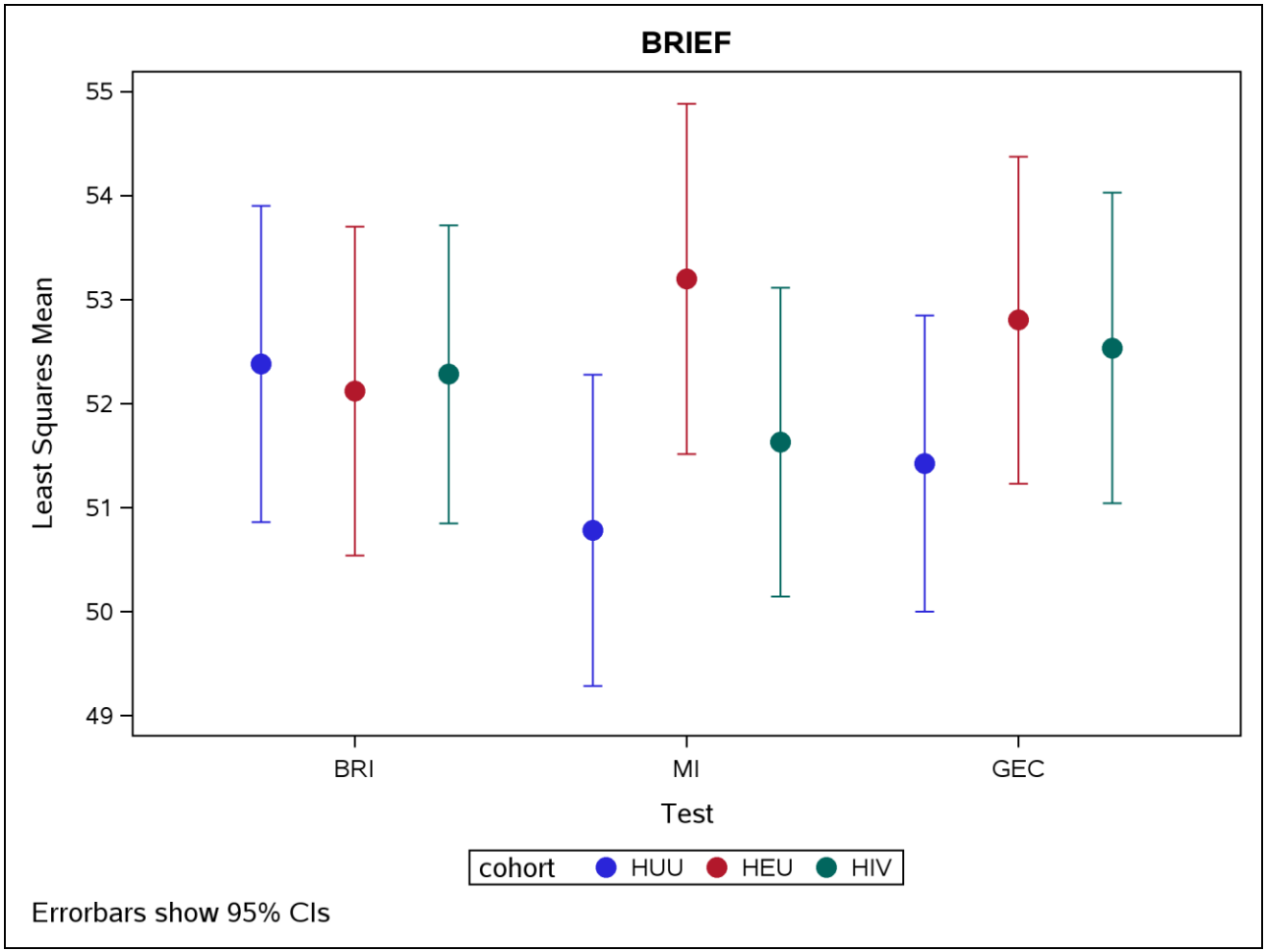
- The eight non-overlapping clinical scales form two broader indices:
  - Behavior Regulation (three scales) and
  - Metacognition (five scales).
- These are combined into the Global Executive Composite Index, whereby the higher the score, the greater the number of problems.
- The Parent version of the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

BRIEF Behavior Regulation Index (*P*=0.97)

BRIEF Metacognition Index (*P*=0.07)

BRIEF Global Executive Composite Index (*P*=0.34)

Standardized Performance Scores on BRIEF (BRI, MI, GEC)



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.

Summary of Principal Statistical Findings (cont'd)

- 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.

Pediatr Infect Dis J. 2014 Aug;33(8):846-54. doi: 10.1097/INF.0000000000

Predictors of virologic and clinical response to nevirapine versus lopinavir/ritonavir-based antiretroviral therapy in young children with and without prior nevirapine exposure for the prevention of mother-to-child HIV transmission.

Lindsey JC[1], Hughes MD, Violari A, Eshleman SH, Abrams EJ, Bwakura-Dangarembizi M, Barlow-Mosha L, Kamthunzi P, Sambo PM, Cotton MF, Moultrie H, Khadse S, Schimana W, Bobat R, Zimmer B, Petzold E, Mofenson LM, Jean-Philippe P, Palumbo P; P1060 Study Team.

Author information

Abstract

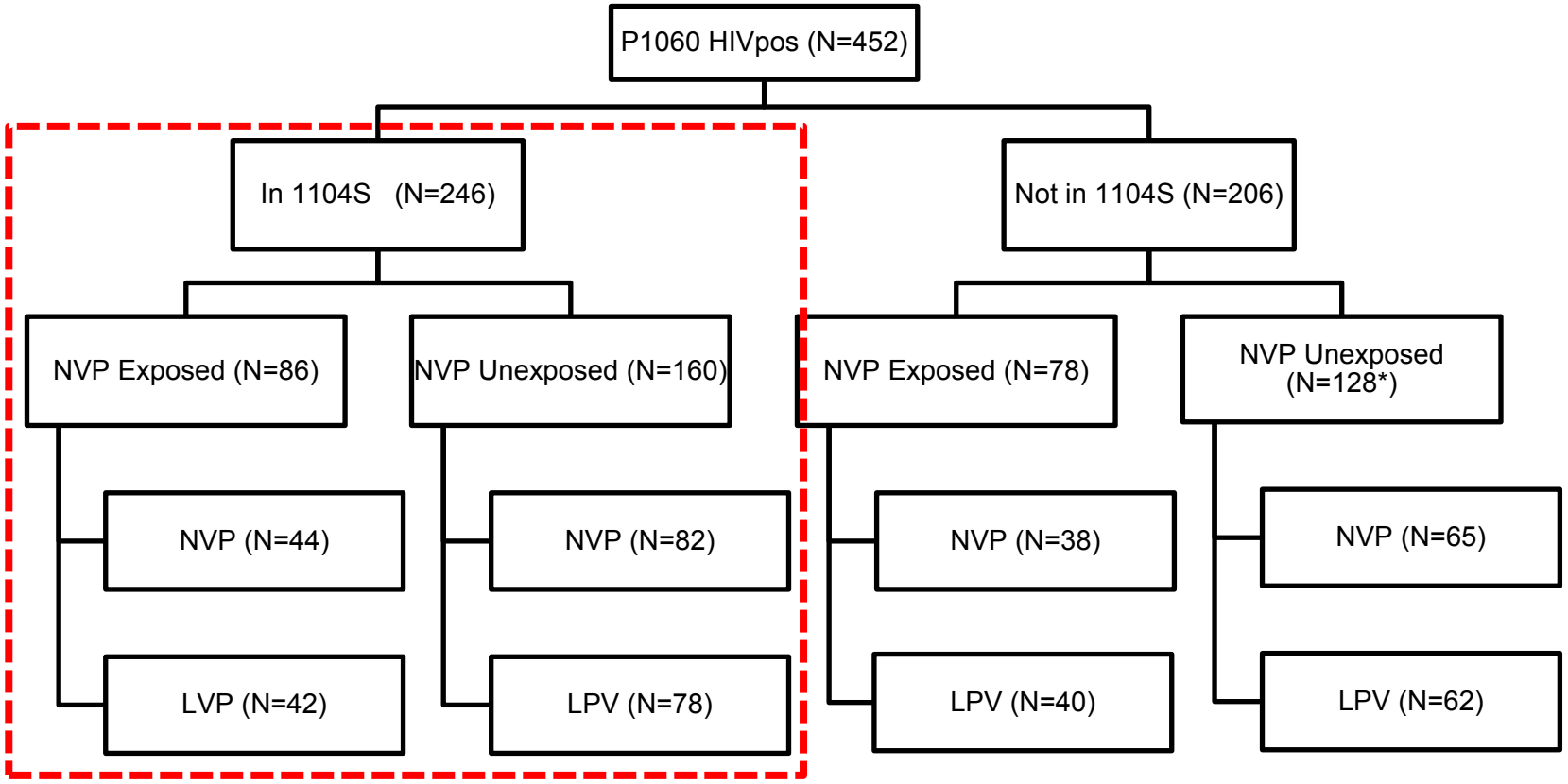
BACKGROUND: In a randomized trial comparing nevirapine (NVP)-based versus lopinavir/ritonavir (LPV/r)-based antiretroviral therapy (ART) in HIV-infected children [primary endpoint discontinuation of study treatment for any reason or virologic failure by week 24] aged 2 months to 3 years, we assessed whether clinical, virologic, immunologic and safety outcomes varied by prior single-dose NVP exposure (PrNVP) for prevention of mother-to-child HIV transmission and other covariates.

METHODS: Efficacy was assessed by time to ART discontinuation or virologic failure, virologic failure/death and death; safety by time to ART discontinuation because of a protocol-defined toxicity and first ≥ grade 3 adverse event; immunology and growth by changes in CD4%, weight/height World Health Organization z-scores from entry to week 48. Cox proportional hazards and linear regression models were used to test whether treatment differences depended on PrNVP exposure and other covariates.

RESULTS: Over a median follow up of 48 (PrNVP) and 72 (no PrNVP) weeks, there was no evidence of differential treatment effects by PrNVP exposure or any other covariates. LPV/r-based ART was superior to NVP-based ART for efficacy and safety outcomes; however, those on NVP had larger improvements in CD4%, weight and height z-scores. Lower pretreatment CD4% and higher HIV-1 RNA levels were associated with reduced efficacy, lower pretreatment CD4% with shorter time to ART discontinuation because of a protocol-defined toxicity, and no PrNVP with shorter time to first grade ≥ 3 adverse event.

CONCLUSIONS: Differences between LPV/r and NVP ART in efficacy, safety, immunologic and growth outcomes did not depend on PrNVP exposure, prior breast-feeding, sex, HIV-1 subtype, age, pretreatment CD4%, HIV-1 RNA or World Health Organization disease stage. This finding should be considered when selecting an ART regimen for young children.

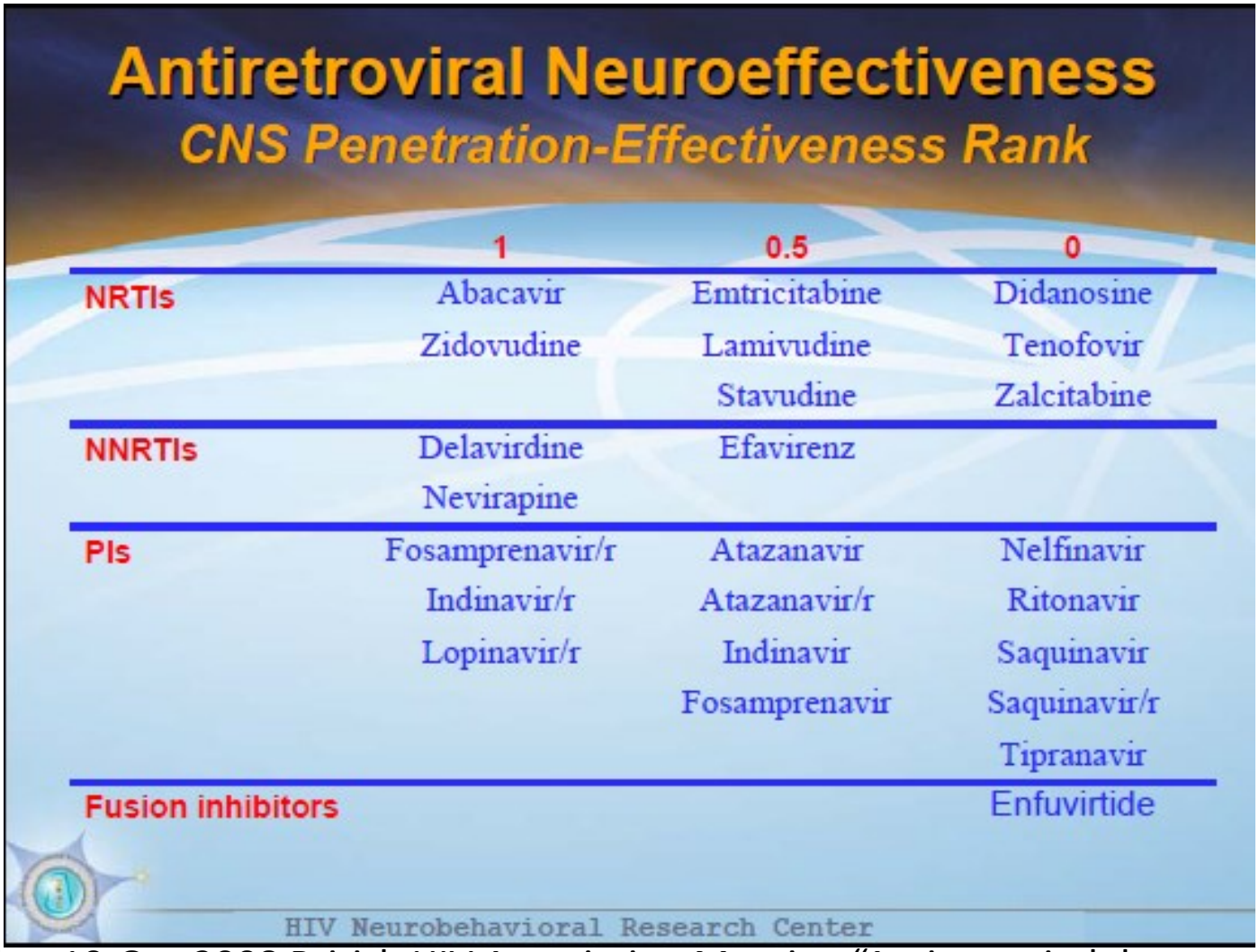
Limited Statistical Power : Exploratory Analyses Only



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.

Neuropsychological outcomes in response to the CNS pharmacokinetics, pharmacodynamics, and pharmacogenetics of cARV treatment options



Scott Letendre, 10-Oct-2008 British HIV Association Meeting "Antiretroviral drug penetration into the central nervous system: implication for HIV control"

Conclusions from Year 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.

Kampala MU-JHU

UNC Lilongwe Malawi

PHRU SOWETO, RSA

SHANDUKANI, Jhburg, RSA

FAM-CRU, Cape Town, RSA

UZ CRC, Zimbabwe

Final Conclusion after Years 1 & 2 of P1104s

Some men 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!*