

A Neuropsychological Trajectory of Pediatric HIV: P1104s Week 0, 48, and 96 Preliminary Findings



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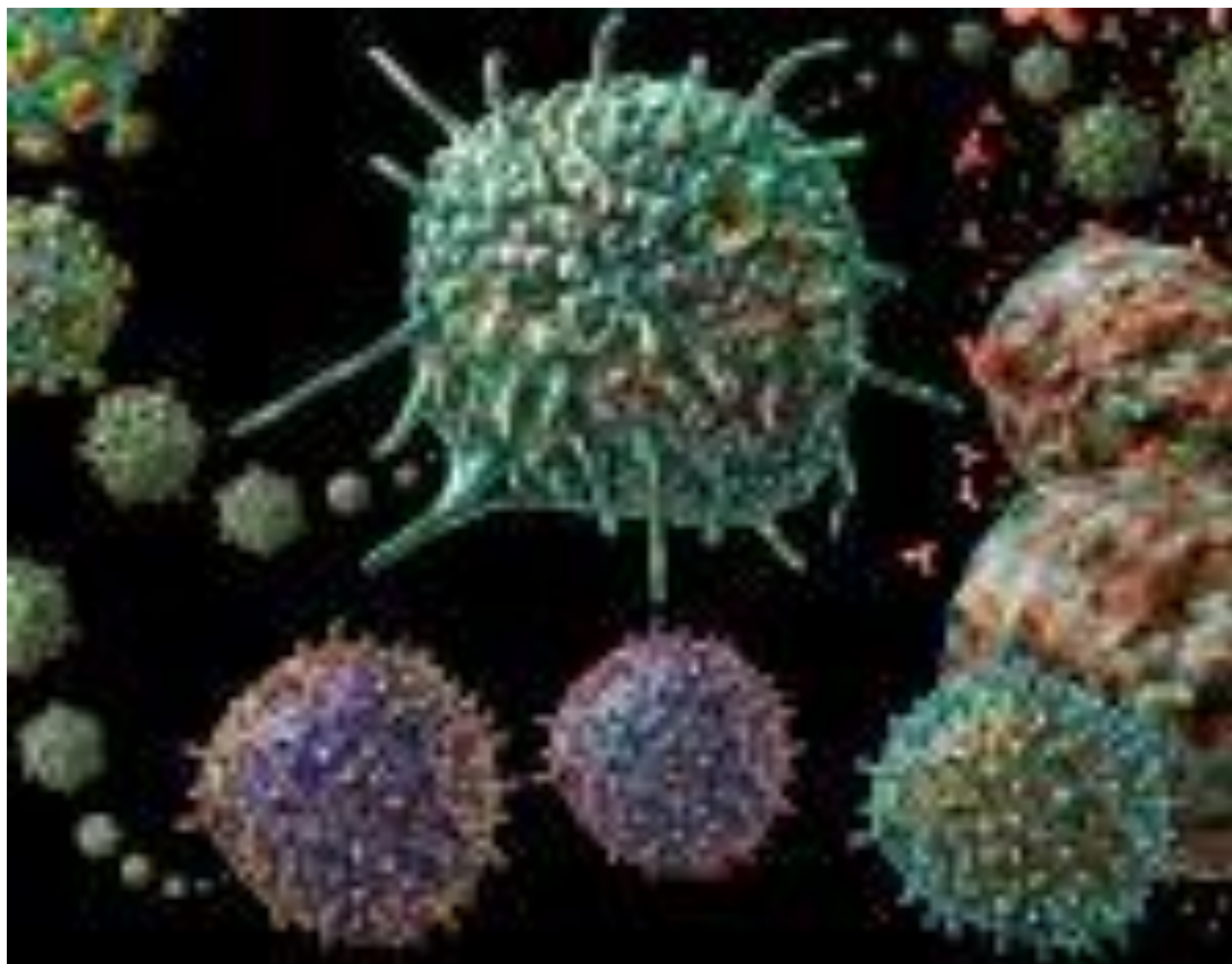
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Washington DC, May 31, 2017



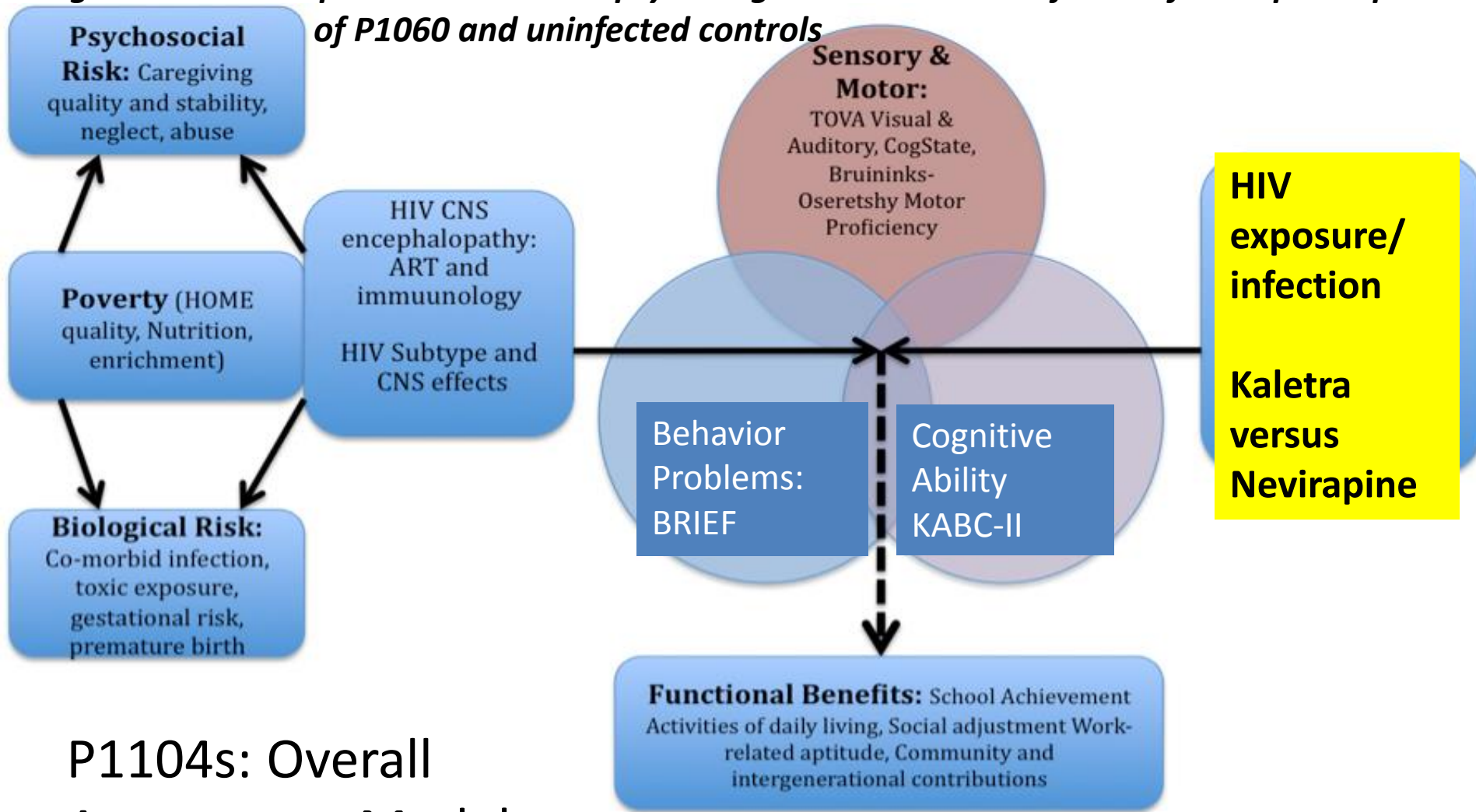
Principal Study Question: What are the neuropsychological effects of pediatric HIV disease and treatment in African children?



Presentation to the Complications & Comorbidities
Committee at IMPAACT Annual Meeting, May 31, 2017



Longitudinal developmental and neuropsychological assessments of HIV-infected participants of P1060 and uninfected controls

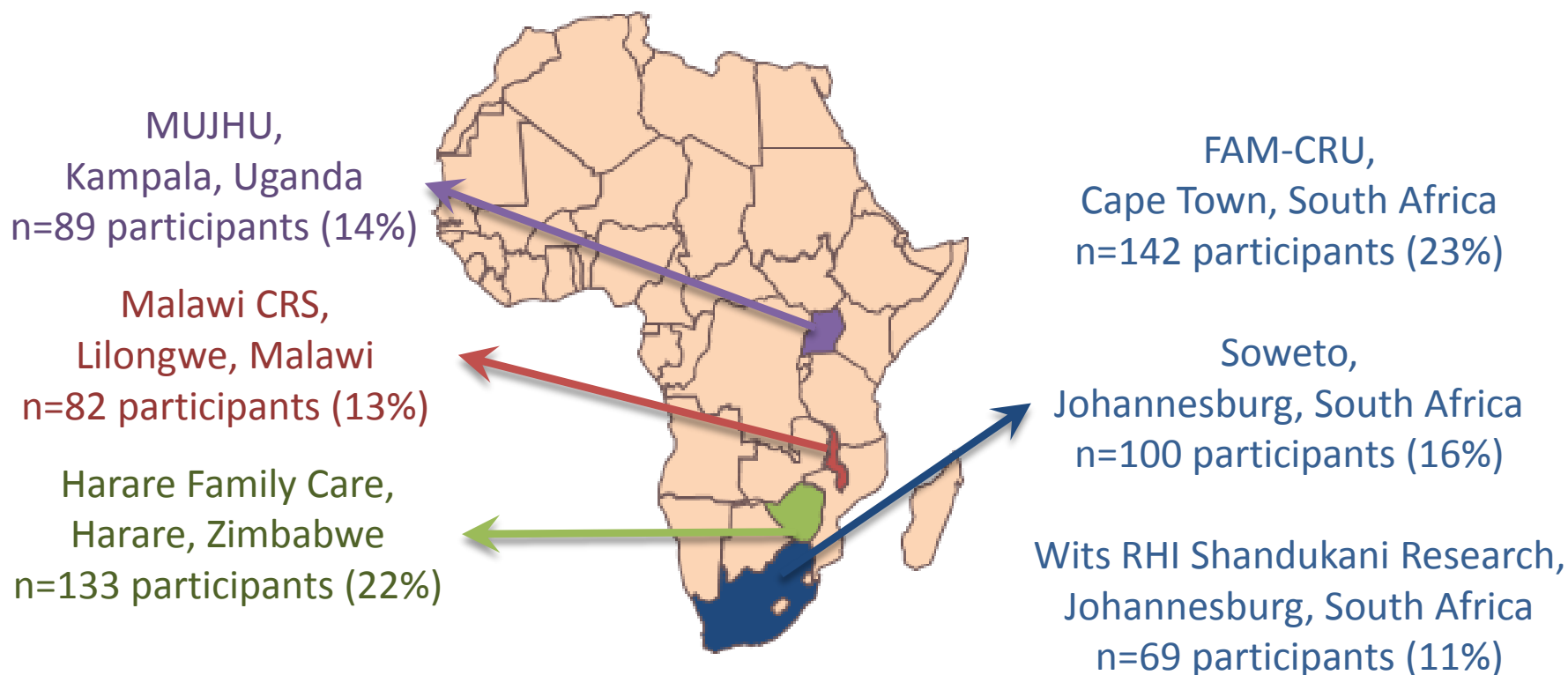


P1104s: Overall Assessment Model

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.

P1060/P1104s Study Sites

Accrual successfully completed on 17 December 2014, with 615 participants enrolled
(246 into HIV+ cohort; 185 into HIV-exposed cohort; 184 into HIV-unexposed cohort)



Study Aims and Successes

Study Aim

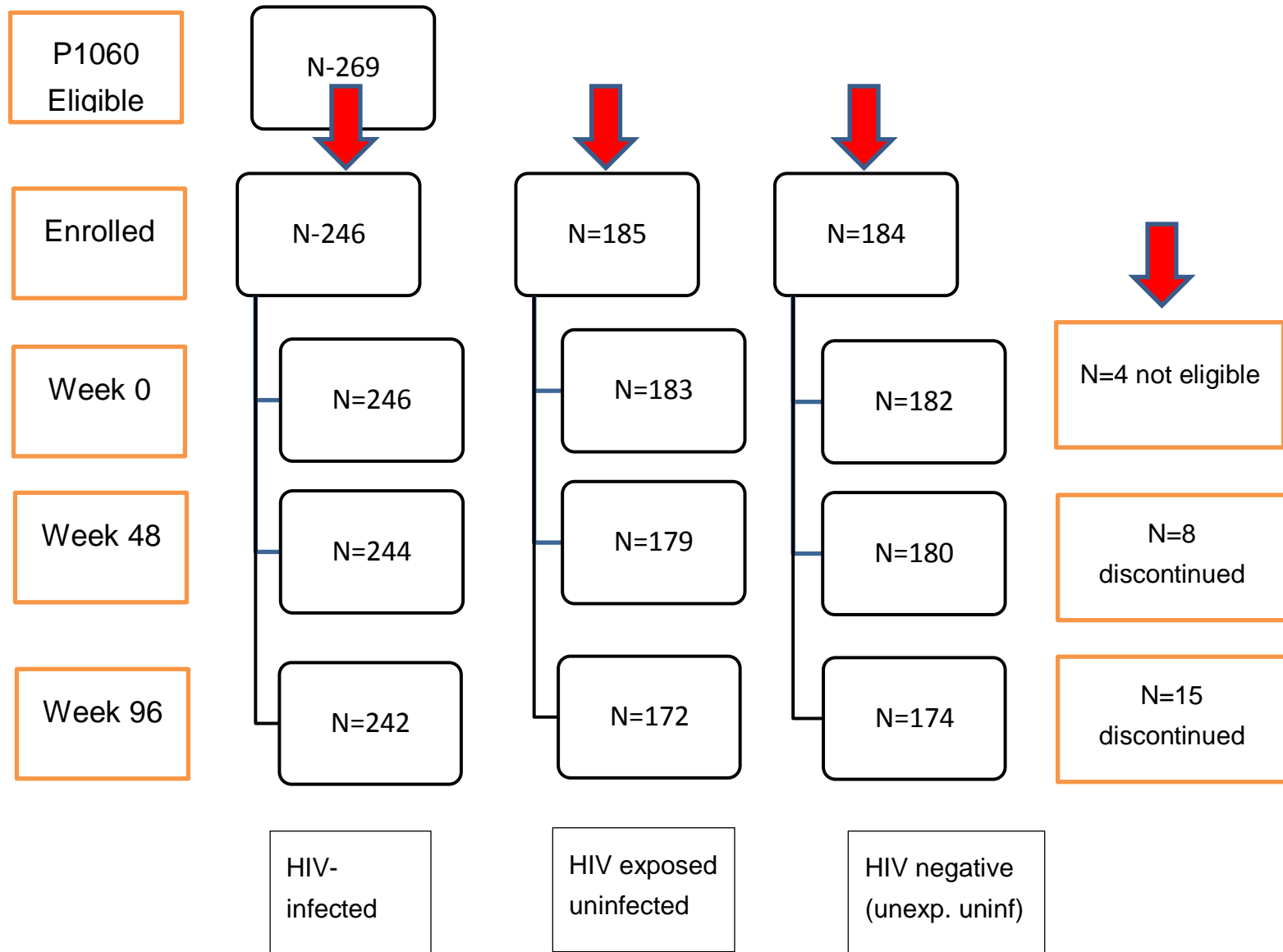
- Assess the feasibility, reliability, and validity of administering neuropsychological assessment battery among HIV-infected, HIV-exposed, and HIV-unexposed children

Excellent Retention Throughout the Study

Week 0	615 (100%)
Week 48	603 (98%)
Week 96	588 (96%)

4 participants were found to be ineligible and were replaced during study accrual; a total of 23 participants did not complete the study

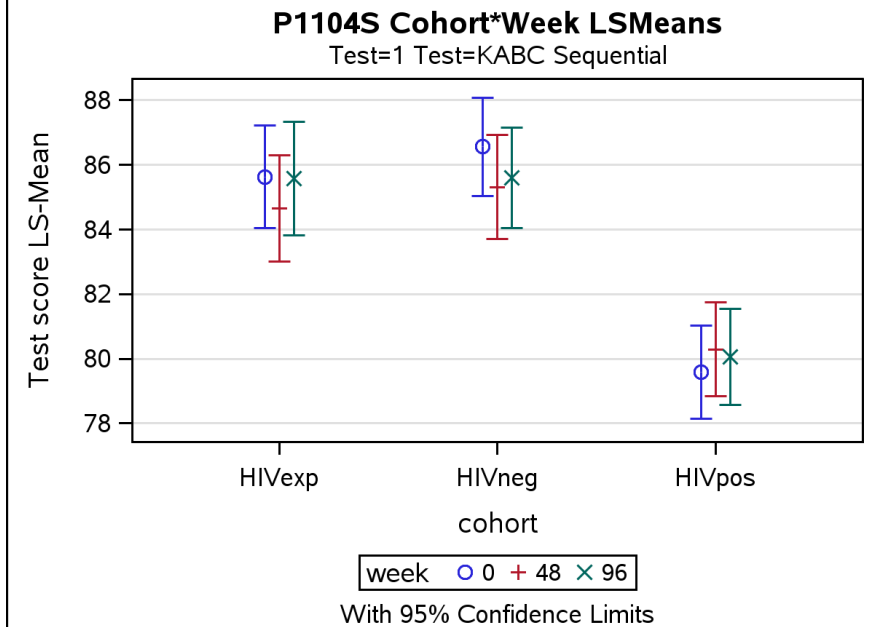
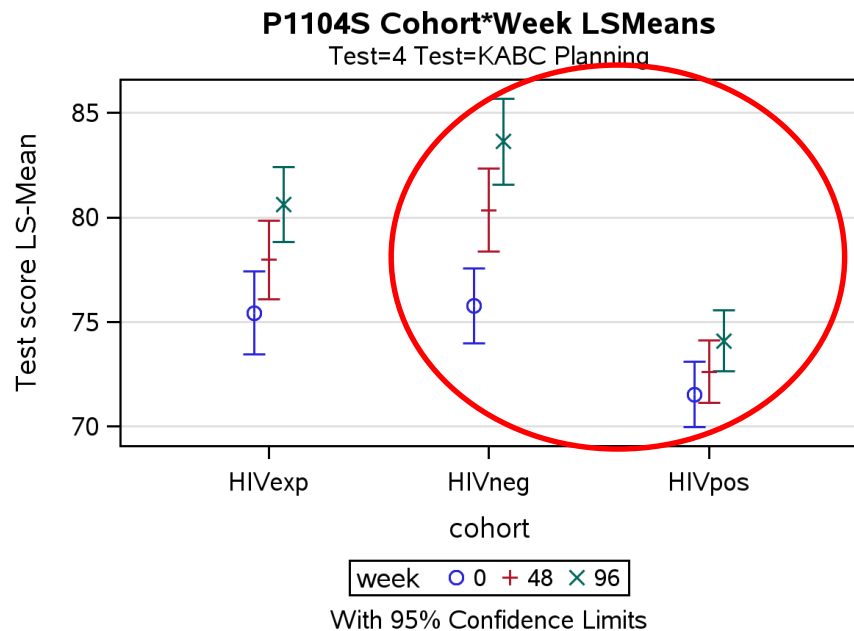
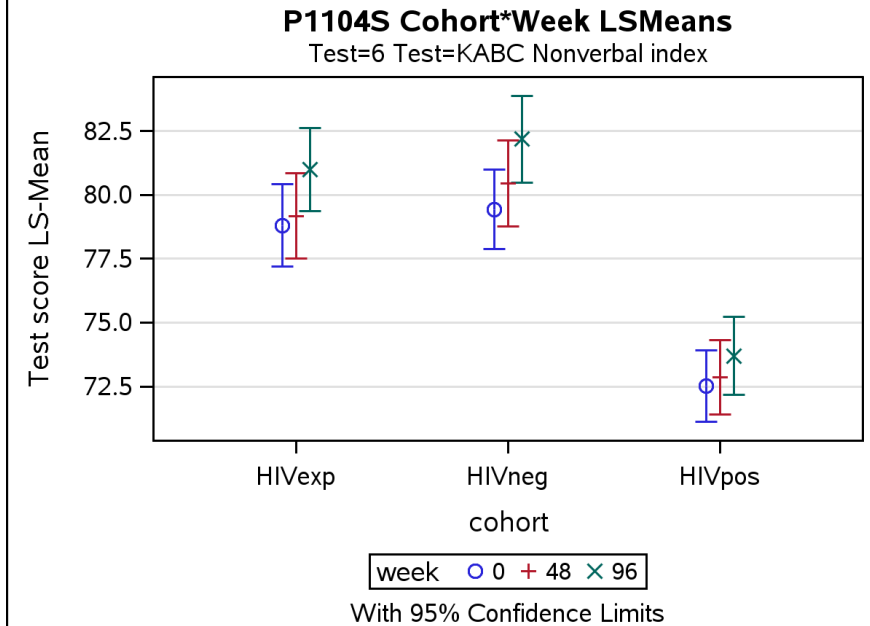
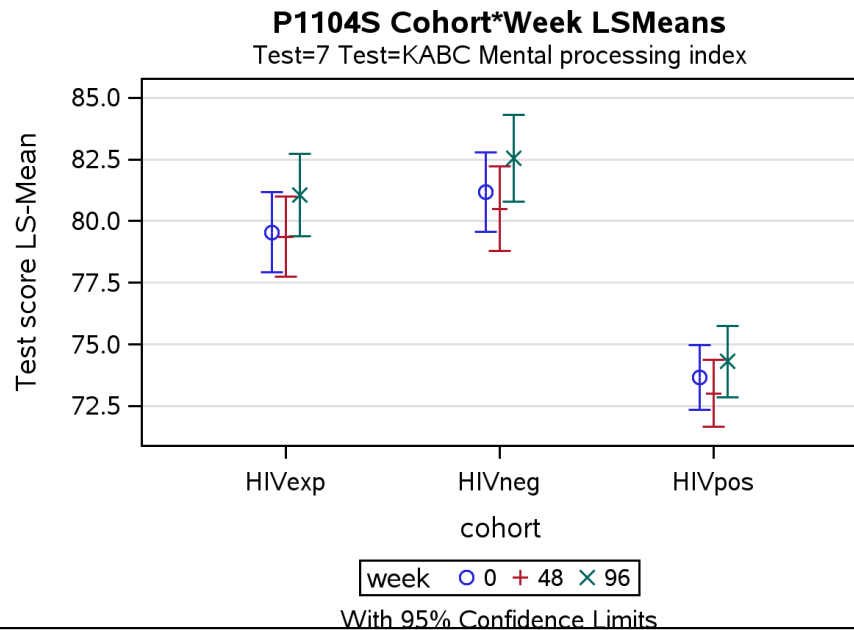
Figure 1. Eligible, enrolled and observed participants at each study week.



Comparing HIV+, HEU, HUU Groups on KABC-2 (P1104s Weeks 0, 48, 96)

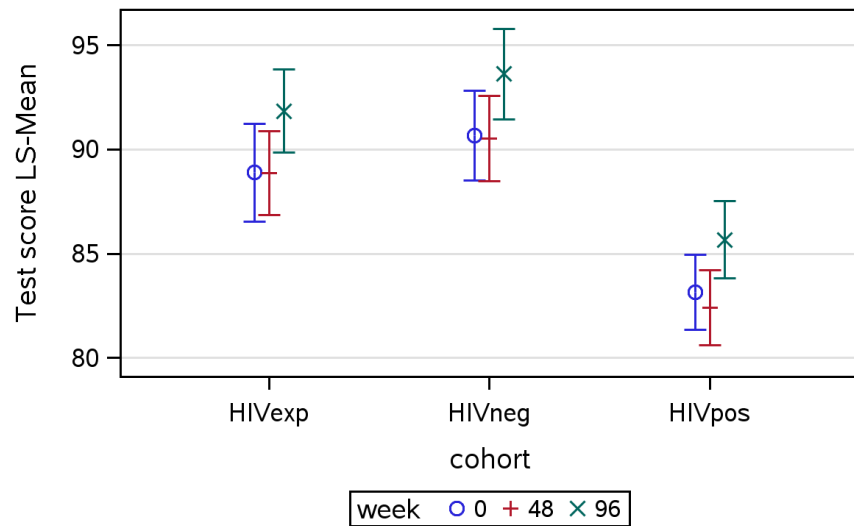
<u>Global Performance</u>	<u>Cohort</u>	<u>Cohort x Week</u>
• Mental Processing Index	$P < 0.001$	$P = 0.77$
• Nonverbal Index	$P < 0.001$	$P = 0.46$
• Planning/Reasoning	$P < 0.001$	$P = 0.001$
• Learning	$P < 0.001$	$P = 0.99$
• Memory	$P < 0.001$	$P = 0.16$
• Visual Spatial Analysis	$P < 0.001$	$P = 0.13$





P1104S Cohort*Week LSMeans

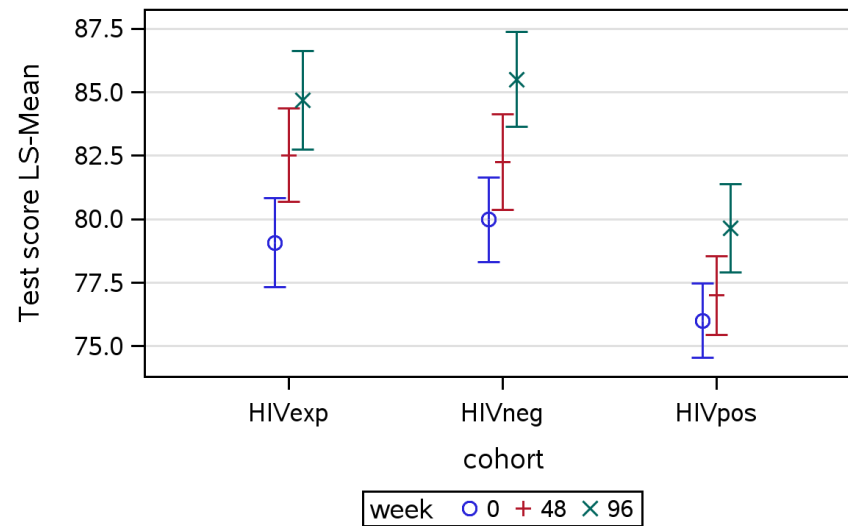
Test=3 Test=KABC Learning



With 95% Confidence Limits

P1104S Cohort*Week LSMeans

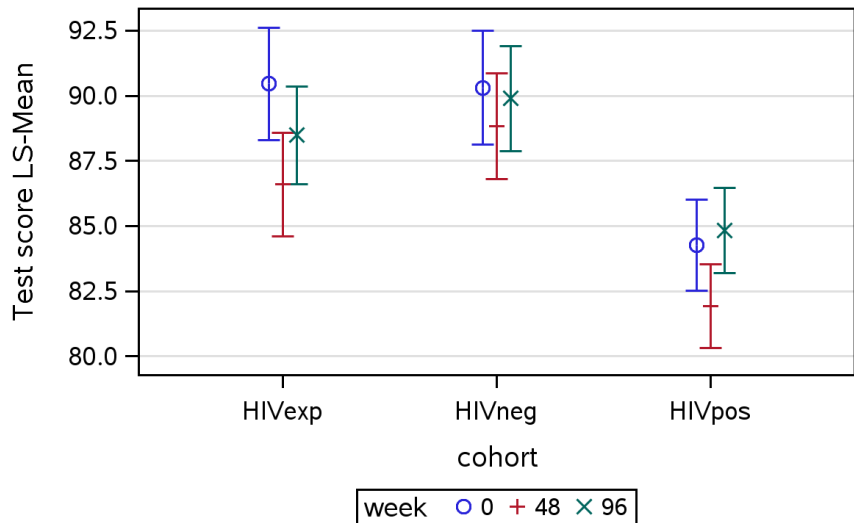
Test=2 Test=KABC Simultaneous



With 95% Confidence Limits

P1104S Cohort*Week LSMeans

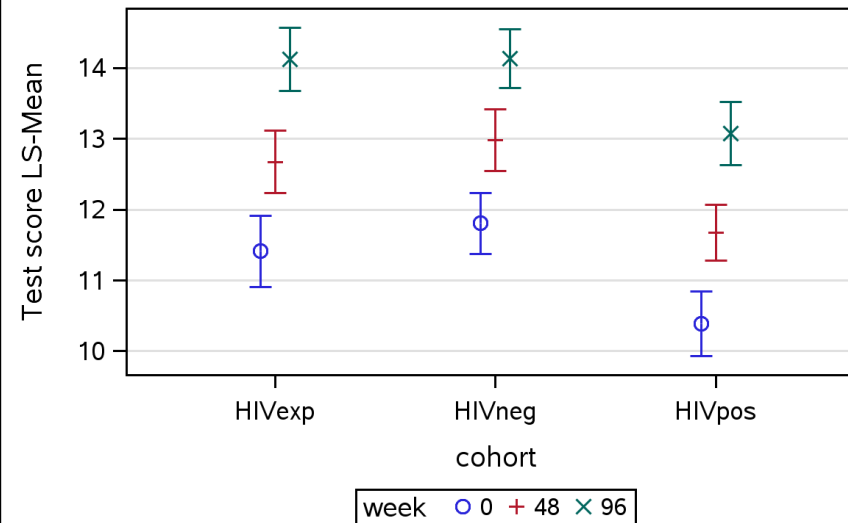
Test=5 Test=KABC Delayed recall



With 95% Confidence Limits

P1104S Cohort*Week LSMeans

Test=24 Test=KABC Face recognition raw score



With 95% Confidence Limits

Test of Variables of Attention (TOVA)

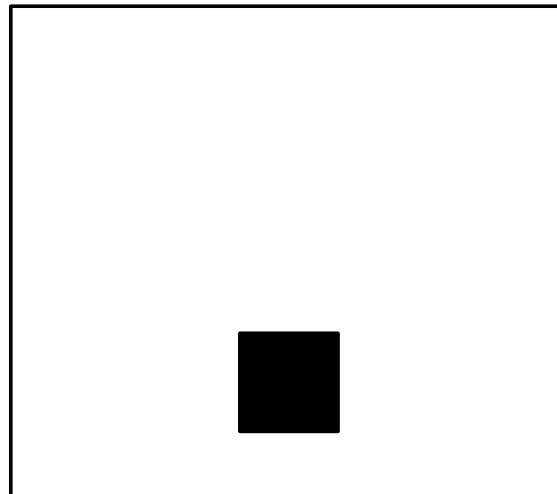
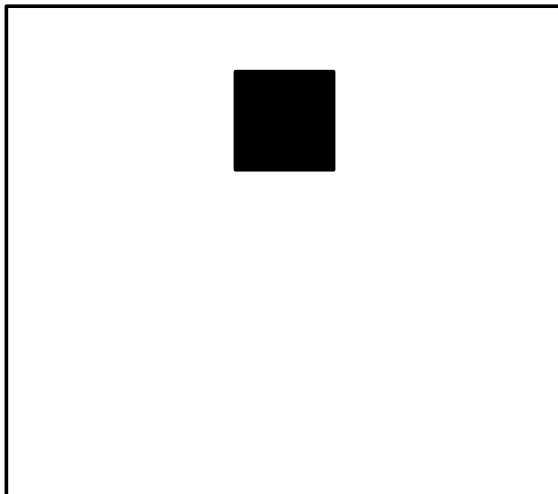


Comparing HIV+, HEU, HUU Groups on TOVA (P1104s Weeks 0, 48, 96)

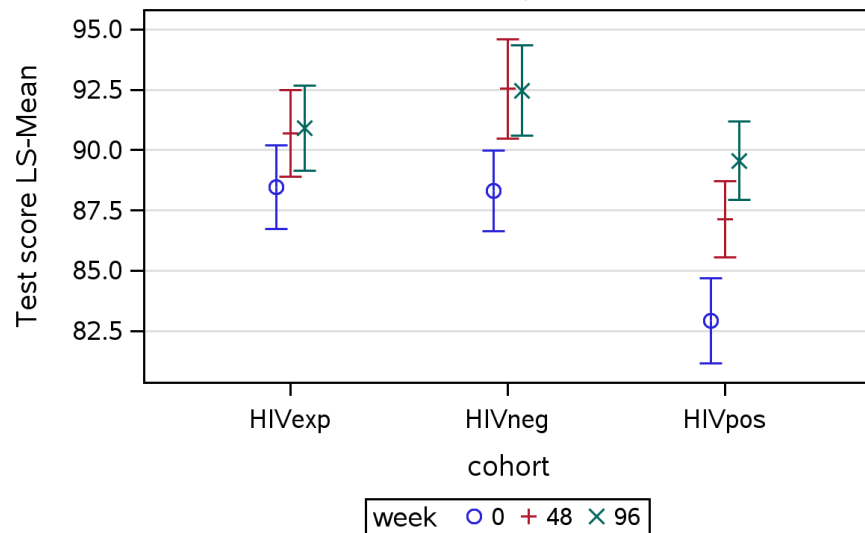
<u>Global Performance</u>	<u>Cohort</u>	<u>Cohort x Week</u>
• D Prime Standard	P<0.001	P=0.03
• Omission Errors %	P<0.001	P=0.004
• Response Time Variability	P<0.001	P=0.03
• Commission Errors %	P=0.16	P=0.56
• ADHD Diagnostic Index	P<0.001	P=0.08

Target

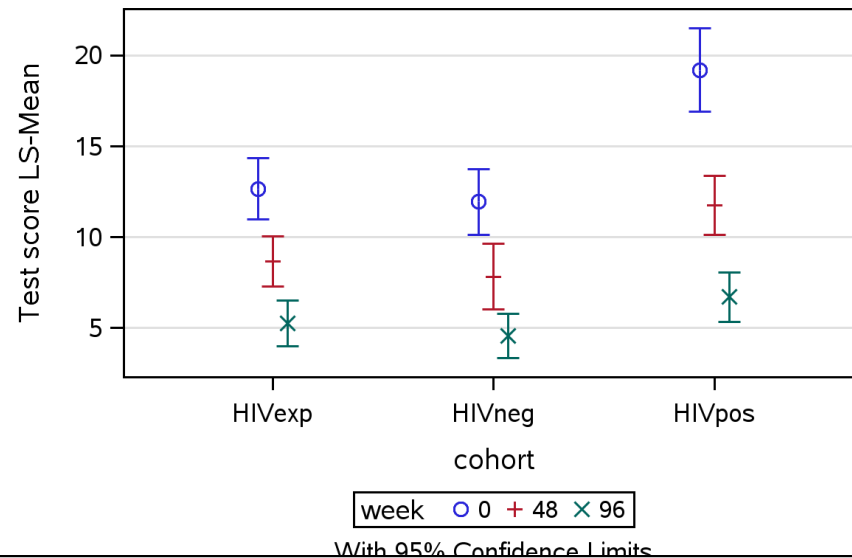
Non Target



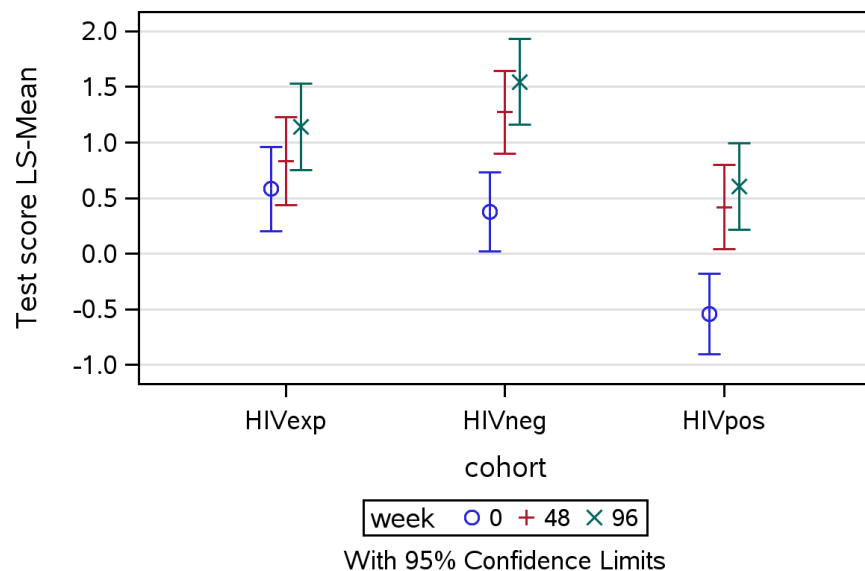
P1104S Cohort*Week LSMeans
Test=18 Test=TOVA D-prime standard score



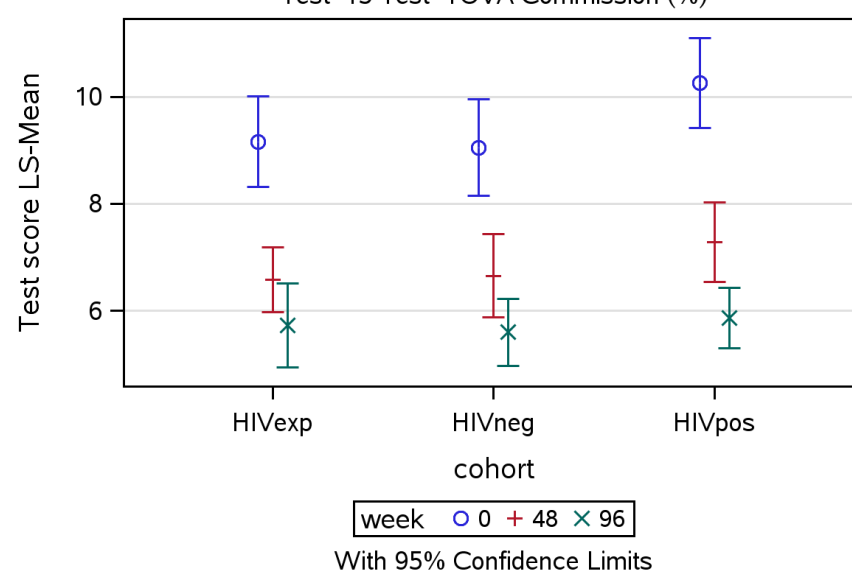
P1104S Cohort*Week LSMeans
Test=16 Test=TOVA Omission (%)



P1104S Cohort*Week LSMeans
Test=12 Test=TOVA ADHD



P1104S Cohort*Week LSMeans
Test=15 Test=TOVA Commission (%)

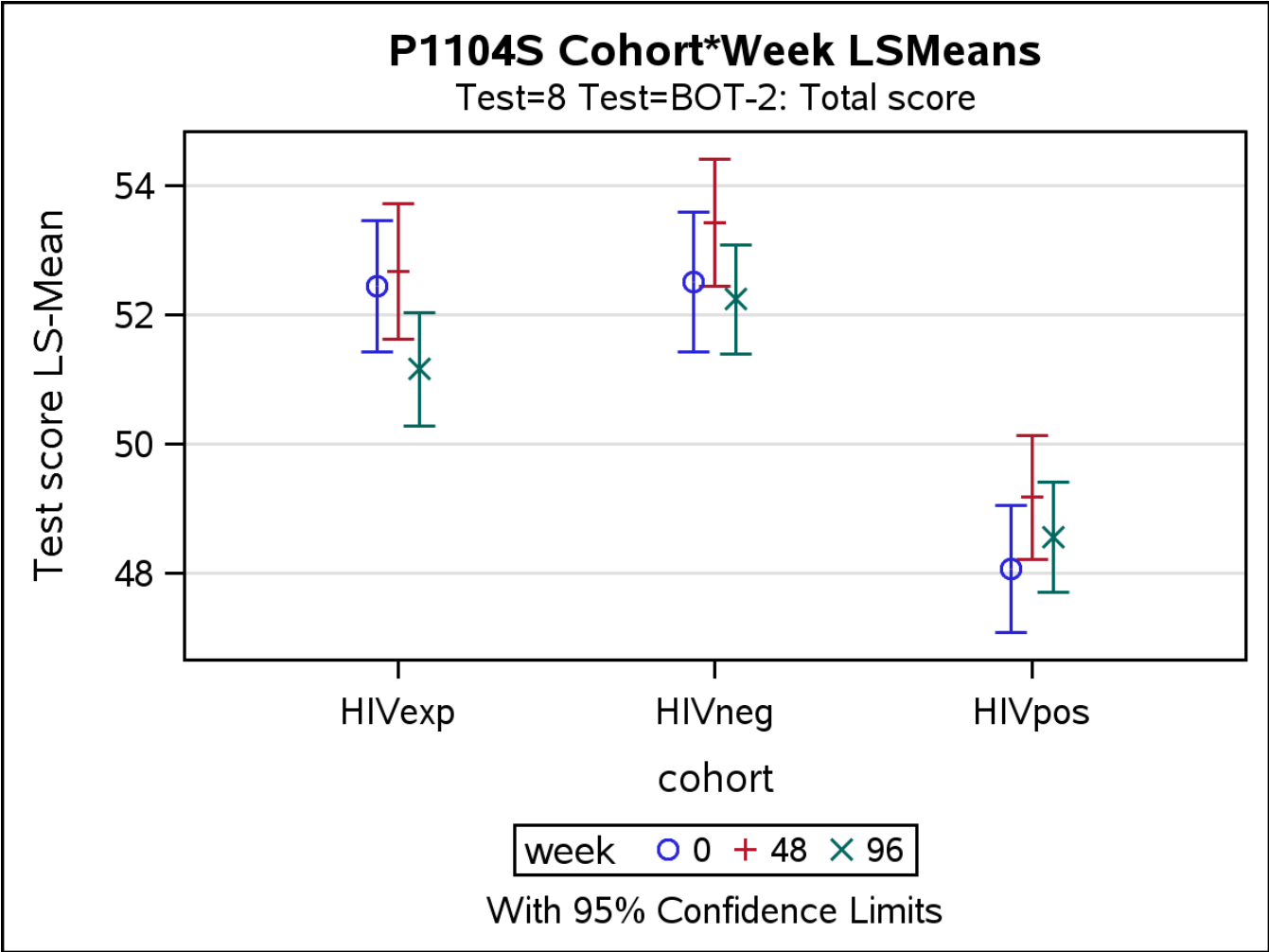


Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition (BOT-2 short version)

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



Bruininks-Oseretsky Test of Motor Proficiency, 2nd ed short form BOT-2



Global Performance

Cohort

Cohort x Week

BOT-2 Total Standard Score

P<0.001

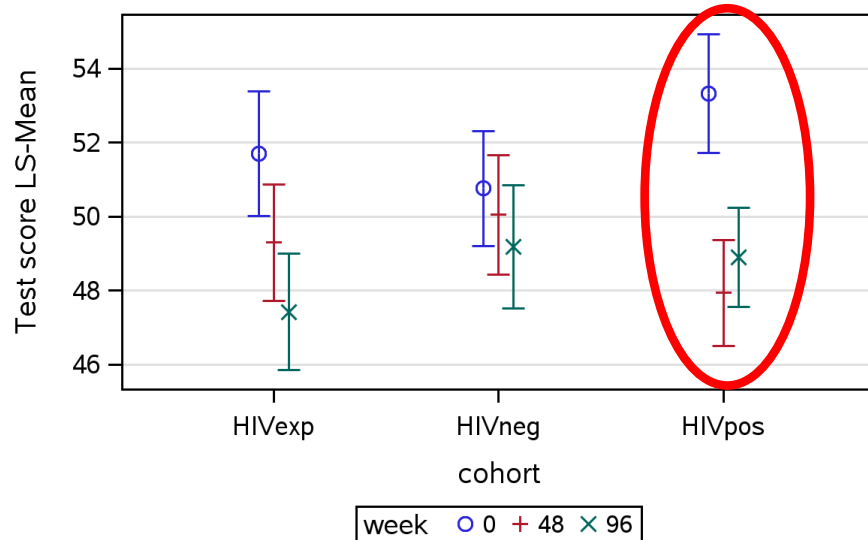
P=0.09

Behavior Rating Inventory of Executive Function (BRIEF)

- The eight non-overlapping clinical scales form two broader indexes:
 - Behavior Regulation (three scales) and
 - Metacognition (five scales).
- A Global Executive Composite score is also produced.
- The BRIEF was translated into the local languages for administration to the mother or principal caregiver of the child.

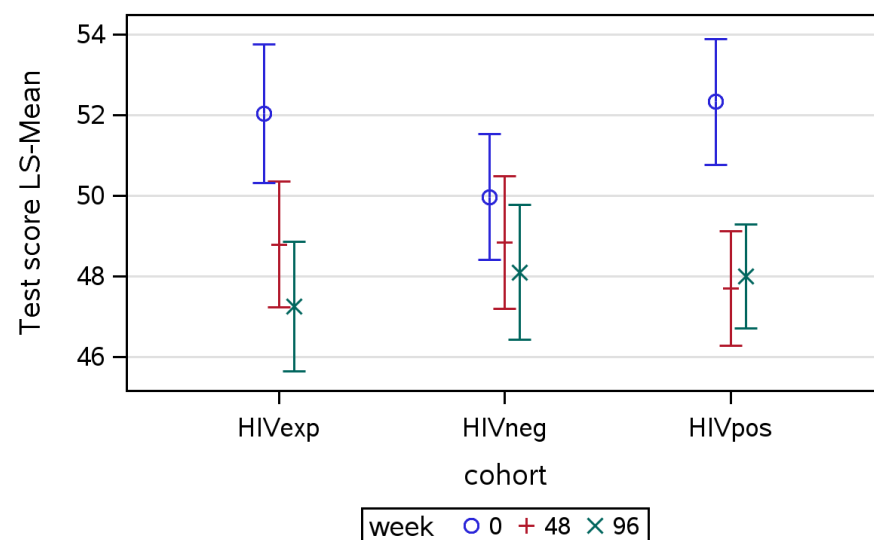
P1104S Cohort*Week LSMeans

Test=11 Test=BRIEF GEC



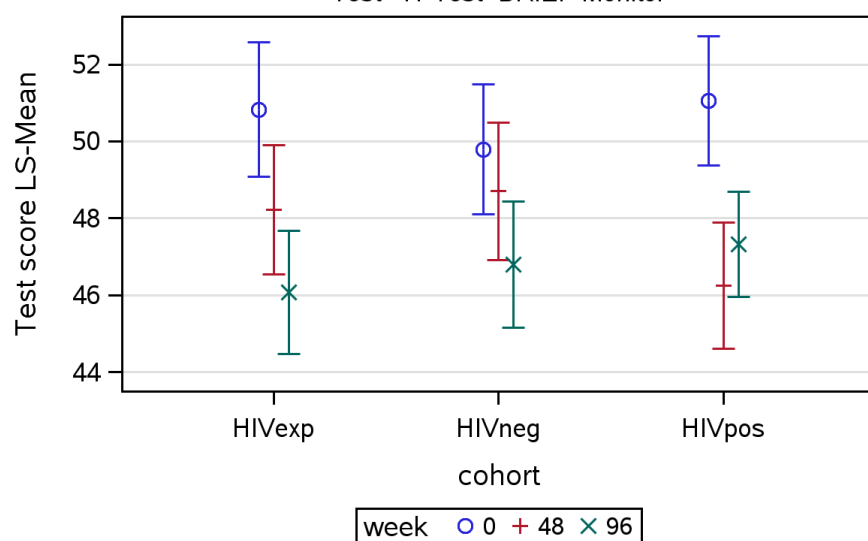
P1104S Cohort*Week LSMeans

Test=10 Test=BRIEF MI



P1104S Cohort*Week LSMeans

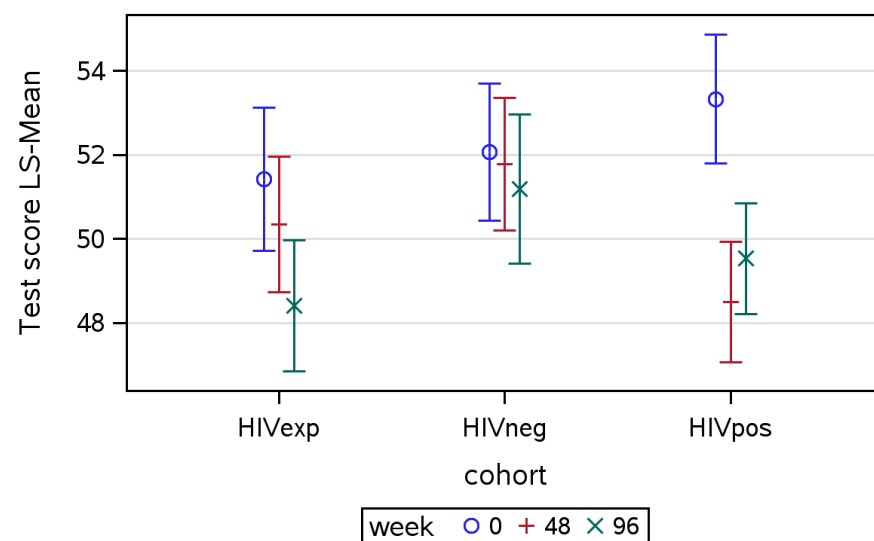
Test=41 Test=BRIEF Monitor



With 95% Confidence Limits

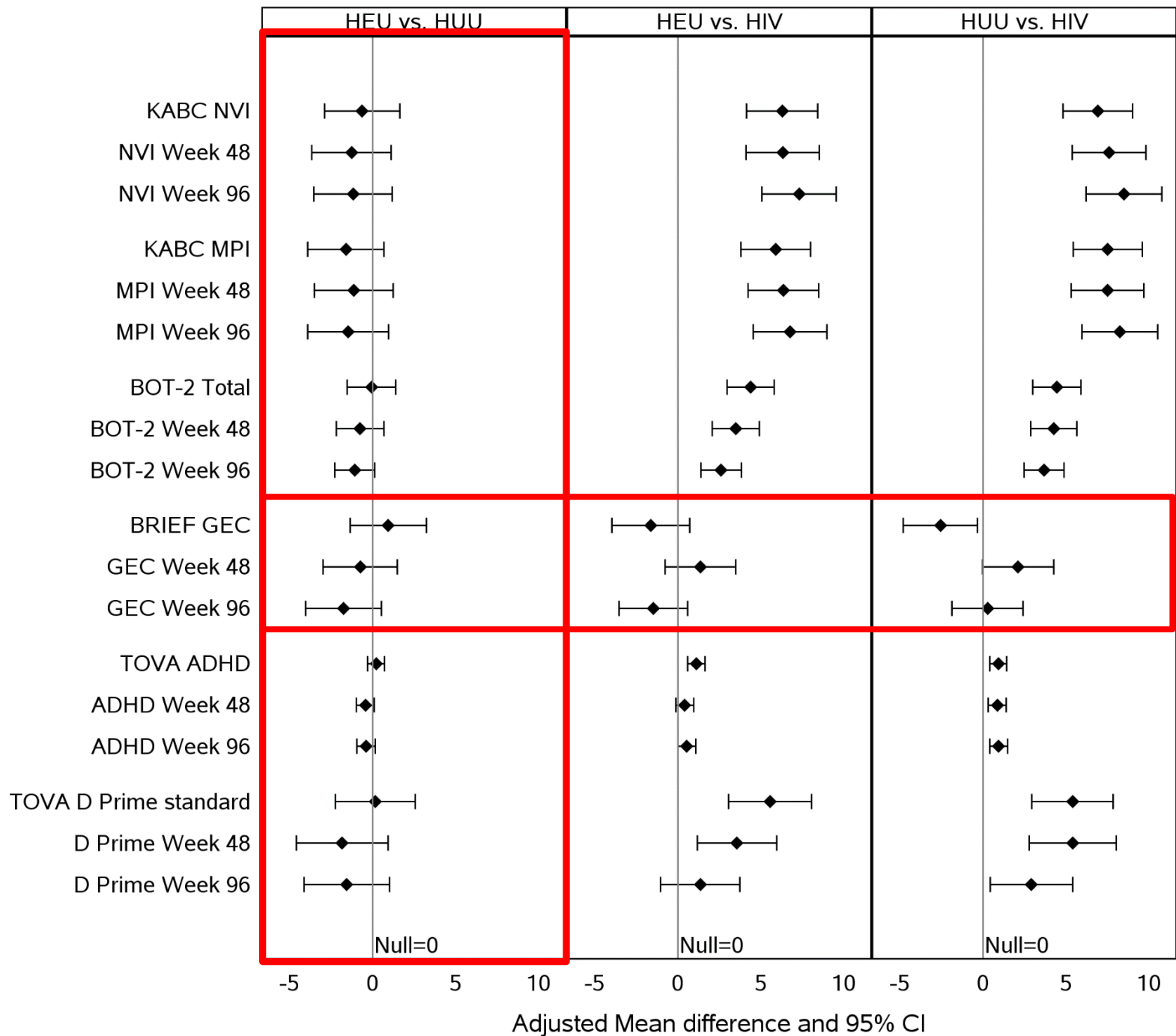
P1104S Cohort*Week LSMeans

Test=9 Test=BRIEF BRI



With 95% Confidence Limits

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



Kampala MUJHU/GHU IMPAACT and PROMISE NeuroDev Testing QA
Assessment Center Team (Left to Right: Ssesanga Titus Kisa, Mary Nyakato,
Namukooli Jackie Lydia , Agatha Kuteesa, M.J. Boivin



Conclusions from Weeks 0, 48, 96 of P1104s

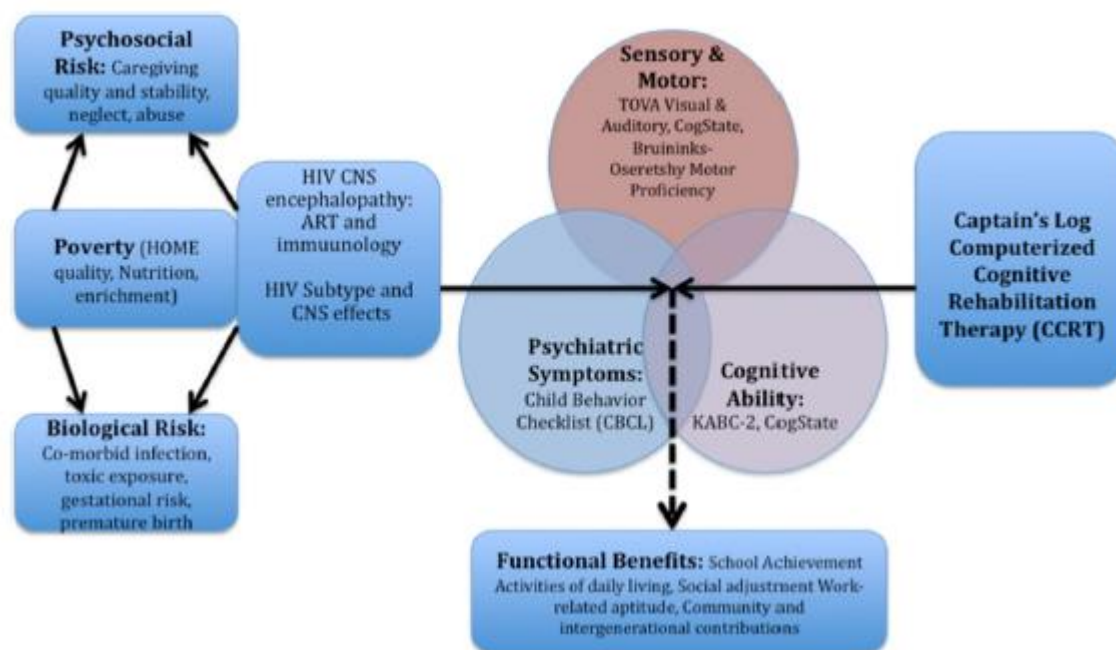
- Children with HIV were significantly below HEU and HUU cohorts at all three assessment points on all principal neuropsychological outcomes, except the BRIEF.
- HEU and HUU cohorts comparable on all neuropsychological outcomes.
- Improvements across time points for neuropsychological outcomes consistent among three exposure groups, except for the KABC-II Planning/Reasoning domain (Executive Function), which lagged behind for the HIV cohort.
- Above pattern of findings mostly consistent across all six individual study sites, although overall performance levels differed among study sites.

P1104s Publications Plan (revised 23NOV16)

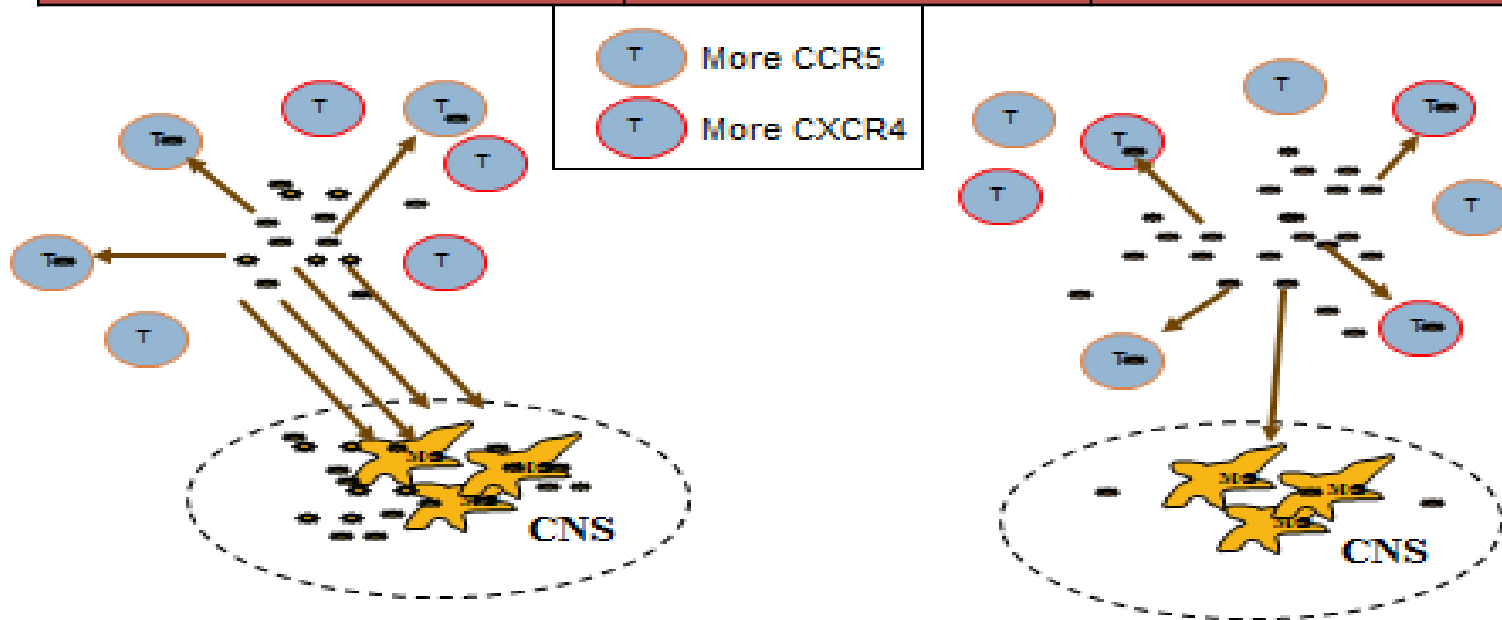
Priority	Timeline for Submission to IMPAACT	Study Objectives	Proposed Manuscript	Proposed Lead Author	Proposed Lead Statistician
1	Primary draft by January 2017	Primary Objectives 1 and 2	Week 0 baseline findings	Linda Barlow-Mosha with Sonia Lee, Pim Brouwers, Barbara Laughton and Michael Boivin	Miriam Chernoff
2	Primary draft by January 2017	N/A	Quality Assurance	Mary Nykato, Agatha Kuteesa with Horacio Ruiseñor, Joan Coetzee	Miriam Chernoff
3	Q2 2017	Primary Objective 1	Validity, feasibility, and reliability for Weeks 0, 48, and 96	Miriam Chernoff, Barbara Laughton, Lee Fairlie, Mmule Ratswana	Miriam Chernoff
4	Q3/Q4 2017	Primary Objective 2	Repeated Measures Week 48 and Week 96 findings	Michael Boivin, Celeste Joyce, Barbara Laughton, Sonia Lee, Pim Brouwers	Miriam Chernoff
5	Q3/Q4 2017	Primary Objective 2	P1104s contextual predictive factors – child, caregiver, and environmental factors	Itziar Familiar, Portia Kamthunzi, Hermien Gous, Nasreen Abrahams and Miriam Chernoff	Miriam Chernoff
6	Q1/Q2 2018	Secondary Objectives 2 and 3	P1060 subgroup findings, intent-to-treat, and treatment based analyses; clinical predictive factors	Paul Palumbo with Mutsa Bwakura Dangarembizi, Avy Violari, Patrick Jean-Philippe, Mark Cotton and Michael Boivin	Miriam Chernoff
7	Q3 2018	Secondary Objective 1	Age-adjusted outcomes for local norms versus standard scores	Miriam Chernoff with Pim Brouwers, Sonia Lee and Michael Boivin	Miriam Chernoff
8	TBD	N/A	Preliminary evaluation of neuropsychological outcomes for HIV-1 clade subtypes A, D, and C	Horacio Ruiseñor, Patrick Jean-Phillippe, Paul Palumbo, Avy Violari, Mark Cotton	Miriam Chernoff

CNS Impact of Perinatal HIV Infection and Early Treatment: the Need for Behavioral Rehabilitative Interventions Along with Medical Treatment and Care

Michael J. Boivin^{1,2} • Horacio Ruiseñor-Escudero² • Itziar Familiar-Lopez²



Arms	Required (N)	Planned (N)*
Arm 1: SOC	47	59
Arm 2: SOC + MVC	47	59
Arm 3: DTG#	47	59
Arm 4: DTG + MVC#	47	59
Controls: HEU & HU	47 (24 HEU / 23 HU)	59 (30 HEU / 29 HU)
Total	235	295



**R5-HIV more efficient replication in CNS*

Acknowledging the P1104s Study Leadership

Protocol Chair:	Michael Boivin, Ph.D., M.P.H.
Study Statistician:	Miriam Chernoff, Ph.D.
Data Manager:	Bonnie Zimmer, B.S.
NIAID Medical Officer:	Patrick Jean-Philippe, M.D.
NICHD Medical Officer:	Sonia Lee, Ph.D.
NIMH Medical Officer:	Pim Brouwers, Ph.D.
Clinical Trials Specialists:	Katie McCarthy, MPH, J.L. Ariansen, MPH
Study Investigators:	Paul Palumbo, M.D., Avy Violari, M.D., Mark Cotton, M.D., Barbara Laughton, M.D.
Site Representatives:	Linda Barlow-Mosha, Nasreen Abrahams, Lee Fairlie, Hermien Gous, Portia Kamthunzi, Mutsa Bwakura-Dangarembizi,
Assessment Center Personnel:	Agatha Kuteesa, Ssesanga Titus Triks, Mariah Namubiru Kateete
SOP development:	Mary Nyakato (University of Chester, UK)
Field Representative:	Joan Coetzee, C.P.N.
Laboratory Data Coordinator:	Brittany White, B.S.

We acknowledge and appreciate the faithful efforts of the study site staff in accomplishing P1104s



MU-JHU, Uganda



UNC Lilongwe, Malawi



PHRU SOWETO, RSA



SHANDUKANI, RSA



FAM-CRU, Cape Town, RSA



HFC, Zimbabwe

Final Conclusion from 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!*