P1104s Week 0 and 48 Preliminary Findings

Michael J. Boivin, PhD, MPH
Professor of Psychiatry and Neurology & Ophthalmology
Michigan State University, East Lansing, Michigan, USA

Miriam Chernoff, PhD
Senior Biostatistician, Center for Biostatistics in AIDS Research
Harvard T.H. Chan School of Public Health

Washington DC, June 13, 2016
Principal Study Question: What are the neuropsychological effects of pediatric HIV disease and treatment in African children?
Longitudinal developmental and neuropsychological assessments of HIV-infected participants of P1060 and uninfected controls

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.
P1104S Primary Objectives

1. To assess the a) feasibility, b) reliability, and c) validity of administering a neuropsychological assessment battery in 1) HIV-infected (HIV), 2) HIV-uninfected perinatally-exposed (HEU), and 3) HIV-uninfected non-perinatally-exposed (HUU) children 5 to 11 years of age at clinical sites in resource-limited settings in sub-Saharan Africa.
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).
Study Aim 1) To assess the a) feasibility, b) reliability, and c) validity of administering a neuropsychological assessment battery in 1) HIV-infected (HIV), 2) HIV-exposed/uninfected (HEU), 3) HIV-unexposed/uninfected (HUU).

- Accrual to P1104S was completed on December 17, 2014. In all, 615 participants were enrolled at six research sites, 246 into the HIV cohort, 185 into the HEU and 184 into the HUU cohorts.
- Four participants were found to be ineligible and were replaced during study accrual.
- Six hundred and three participants completed the week 48 visit (98% retention).
- Reasons for not having a week 48 visit/dropping from the study included being untestable (1), being unable to get to clinic (3), parent being unwilling to adhere to study protocol (3), parent withdrawing consent (1). Four were from the HEU group, two from HUU, and two from the HIV group.
Comparing HIV+ and HIV- Groups on KABC-2 (Ruel et al., 2012)

- Memory ($P = .008$)
- Visual-spatial ($P = .02$)
- Learning ($P = .06$)
- Reasoning ($P = .12$)

*ANCOVA test on linear Studentized Residual Errors to age. SES and Gender as covariates.*
Test of Variables of Attention (TOVA)
Test of Variables of Attention (TOVA)

Visual

Target

Non Target
Comparing HIV+ and HIV- Groups on TOVA

D prime signal detection \( (P = .87) \)
Omission Errors \( (P = .37) \)
Commission Errors \( (P = .35) \)
Response Time \( (P = .005) \)
Response Time Var. \( (P = .24) \)
ADHD Score \( (P = .03) \)

*ANCOVA test on linear Studentized Residual Errors to age. SES and Gender as covariates
Bruininks-Oseretsky Test of Motor Proficiency, 2\textsuperscript{nd} 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 indexes:
  - Behavior Regulation (three scales) and
  - Metacognition (five scales).

- A Global Executive Composite score is also produced.

- The scales include the behavior/cognitive functions of Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor.

- The BRIEF was translated into the local languages for administration to the mother or principal caregiver of the child.

- It can be easily administered by pediatric research nurses in the clinic setting.
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<th>Developmental Domain</th>
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<th>Intellect / Achievement</th>
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<td>Planning, Simultaneous Processing</td>
<td>Rebus and Rebus Delayed</td>
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<td>Attention Problems</td>
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**Kaufman Assessment Battery for Children (KABC-II)**

**Tests of Variables of Attention (TOVA)**

**Bruininks-Oseretsky Test of Motor Proficiency (BOT-2)**

**Behavior Rating Inventory for Executive Functions (BRIEF)**

**IMPAACT**

International Maternal Pediatric Adolescent AIDS Clinical Trials Network
HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children

Michael J. Boivin\textsuperscript{a}, Theodore D. Ruel\textsuperscript{b}, Hannah E. Boal\textsuperscript{c}, Paul Bangirana\textsuperscript{d}, Huyen Cao\textsuperscript{e}, Leigh A. Eller\textsuperscript{f}, Edwin Charlebois\textsuperscript{g}, Diane V. Havlir\textsuperscript{h}, Moses R. Kamya\textsuperscript{i}, Jane Achan\textsuperscript{j}, Carolyne Akello\textsuperscript{i} and Joseph K. Wong\textsuperscript{k}

\textbf{Background:} HIV-subtype D is associated with more rapid disease progression and higher rates of dementia in Ugandan adults compared with HIV-subtype A. There are no data comparing neuropsychological function by HIV subtype in Ugandan children.

\textbf{Design:} One hundred and two HIV-infected antiretroviral therapy (ART) naive Ugandan children 6–12 years old (mean 8.9) completed the Kaufman Assessment Battery for Children, second edition (KABC-2), the Test of Variables of Attention (TOVA), and the Bruininks–Oseretsky Test for Motor Proficiency, second edition (BOT-2). Using a PCR-based multiregion assay with probe hybridization in five different regions (gag, pol, vpu, env, gp-41), HIV subtype was defined by hybridization in env and by total using two or more regions. Analysis of covariance was used for multivariate comparison.

\textbf{Results:} The env subtype was determined in 54 (37 A, 16 D, 1 C) children. Subtype A and D groups were comparable by demographics, CD4 status, and WHO stage. Subtype A infections had higher log viral loads (median 5.0 vs. 4.6, \(P = 0.02\)). Children with A performed more poorly than those with D on all measures, especially on KABC-2 Sequential Processing (memory) (\(P = 0.01\)), Simultaneous Processing (visual–spatial analysis) (\(P = 0.005\)), Learning (\(P = 0.02\)), and TOVA visual attention (\(P = 0.04\)). When adjusted for viral load, Sequential and Simultaneous Processing remained significantly different. Results were similar comparing by total HIV subtype.

\textbf{Conclusion:} HIV subtype A children demonstrated poorer neurocognitive performance than those with HIV subtype D. Subtype-specific neurocognitive deficits may reflect age-related differences in the neuropathogenesis of HIV. This may have important implications for when to initiate ART and the selection of drugs with greater central nervous system penetration. © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins

\textit{AIDS} 2010, 24:1163–1170

Presentation to the Complications & Cormorbidities Committee at IMPAACT Annual Meeting, June 13, 2016
Feasibility of P1104s substudy

- 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 the P1060 children enrolled in P1104s proved untestable at baseline due to profound neurodisability.
Personal, caregiver and home environment characteristics

- Biometric scores were lower for the HIV children at entry compared to the two control groups and disability scores were higher; otherwise the groups were well matched on age, sex, school enrollment status.
- Fewer HIV children had biological mothers as caregivers and fewer of that group had siblings enrolled in the study and caregivers of that group had less formal education compared to the other two groups. Length of caregiving time was similar across the groups. Caregivers in the HIV and HEU group were largely HIV-infected in contrast to the HUU group, for which none of the caregivers had HIV.
- Caregivers of all three study groups had comparable HSCL anxiety and depression mean scores.
- Fathers play more of a role in the economic well-being of the household in the HUU and HEU groups compared to HIV, while social grants are more prominent in the HEU and HIV groups.
- Only about one third of families feel they have sufficient means to meet their needs, and this is comparable across groups.
- Residential zones and socioeconomic indicators related to fuel and water sources and refrigeration are comparable across study groups.
- Most HIV children were at WHO Stage 3 at study entry, their HIV disease is well controlled according to CD4% and VL measures.
Validity of P1104s substudy testing

• Careful review of all CRF “Possible Invalidity” of testing results flags and comments by *ad hoc* P1104s team for data validity and analysis.

• Bonnie Zimmer at Frontier Science added range of score limits for all test scores.

• 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.
## Fully Adjusted Mixed Model Results - Intraclass Correlations Week 0 to 48

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICC</th>
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<tbody>
<tr>
<td>1 KABC Sequential</td>
<td>0.65</td>
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<tr>
<td>2 KABC Simultaneous</td>
<td>0.61</td>
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<tr>
<td>3 KABC Learning</td>
<td>0.48</td>
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<tr>
<td>4 KABC Planning</td>
<td>0.67</td>
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<tr>
<td>5 KABC Delayed recall</td>
<td>0.34</td>
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<tr>
<td>6 KABC Nonverbal index</td>
<td>0.69</td>
</tr>
<tr>
<td>7 KABC Mental processing index</td>
<td>0.67</td>
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<tr>
<td>21 KABC Conceptual thinking raw score</td>
<td>0.41</td>
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<tr>
<td>22 KABC Story completion raw score</td>
<td>0.66</td>
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<tr>
<td>23 KABC Pattern reasoning raw score</td>
<td>0.51</td>
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<tr>
<td>24 KABC Face recognition raw score</td>
<td>0.37</td>
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<tr>
<td>25 KABC Hand movements raw score</td>
<td>0.47</td>
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</tbody>
</table>

*Note: Results adjusted for site, sex, age at entry and covariates with p < 0.20*
*Adjusted Standardized Scores on KABC-II Overall Cognitive Performance, all Study Sites

*Note: Results adjusted for site, sex, age at entry and covariates with p < 0.20 (child in school, caregiver education obtained, caregiver receiving social grant, housing quality, physical growth, caregiver emotional wellbeing, MICS4 Child Development Score, MICS4 Child Disability Score)
*Adjusted Standardized Scores on KABC-II Overall Performance by Study Site

*Note: Results using linear mixed model regression with restricted maximum likelihood estimation and robust fixed effect error estimates, adjusting for research site, entry age, sex and HIV status group (study group).
Attention Performance Scores on TOVA D Prime (standardized) and ADHD index, by Study Sites (adjusted by site and exposure group)

*Note: Results using linear mixed model regression with restricted maximum likelihood estimation and robust fixed effect error estimates, adjusting for research site, entry age, sex and HIV status group (study group).
Standardized Performance Scores on BOT-2 (total score) and BRIEF (Global Executive Composite) by Study Sites

*Note: Results using linear mixed model regression with restricted maximum likelihood estimation and robust fixed effect error estimates, adjusting for research site, entry age, sex and HIV status group (study group).
KABC-II Between-Group Results

• There were statistically significant study group effects for all KABC measures, in which the HIV group scored lower than the HEU and HUU groups.

• Time effects were significant in all but three of the KABC global performance measures (learning, nonverbal index, mental processing index).

• Two each of the scaled and raw scores (sequential, planning, story completion, hand movements) showed assessment time (week 0 and 48) by group (HIV, HEU, HUU) interactions.

• The interaction effect was significant for the planning/reasoning subtest outcomes (HUU improved more between weeks 0, 48), and also the raw hand movement scores in the fully adjusted model.
Group by Time Interaction Effect: KABC-II Planning

**P1104S Cohort*Week LSMeans**
Test=4 Test=KABC Planning

**Test score LS-Mean**

- HIVexp
- HIVneg
- HIVpos

*With 95% Confidence Limits*

**P1104S Cohort*Week LSMeans**
Test=22 Test=KABC Story completion raw score

**Test score LS-Mean**

- HIVexp
- HIVneg
- HIVpos

*With 95% Confidence Limits*

**P1104S Cohort*Week LSMeans**
Test=21 Test=KABC Conceptual thinking raw score

**Test score LS-Mean**

- HIVexp
- HIVneg
- HIVpos

*With 95% Confidence Limits*

**P1104S Cohort*Week LSMeans**
Test=23 Test=KABC Pattern reasoning raw score

**Test score LS-Mean**

- HIVexp
- HIVneg
- HIVpos

*With 95% Confidence Limits*
A preliminary examination of the construct validity of the KABC-II in Ugandan children with a history of cerebral malaria


a Department of Psychiatry, Makerere University School of Medicine, Kampala, Uganda
b Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden
c Neuropsychology Section, Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
d Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA
e Department of Pediatrics and Child Health, Makerere University School of Medicine, Kampala, Uganda
f Institute of Clinical Neurosciences, Department of Psychiatry, Gothenburg University, Gothenburg, Sweden
g Center for Cognitive Therapy, Gothenburg, Sweden
h International Neurologic and Psychiatric Epidemiology Program, Michigan State University, East Lansing, MI, USA

Abstract

Background: Several diseases and adverse conditions affect the cognitive development of children in Sub-Saharan African. There is need to assess these children to determine which abilities are affected and the severity of the damage so as to plan interventions accordingly. However most psychological tests developed in the West have not been validated in this region making it impossible to know whether they measure what they were intended to in African children.

Objective: To examine the construct validity of the Kaufman Assessment Battery for Children, Second Edition (KABC-II) in Ugandan children.

Methods: Sixty five Ugandan children aged 7 to 16 years (Mean=9.90, SD=2.46) were tested using the KABC-II 44.59 months (SD=2.82) after an episode of cerebral malaria. The KABC-II scales of Sequential Processing, Simultaneous Processing, Planning and Learning were administered. In order to identify which factors result from administering the KABC-II in these children, factor analysis using principal component analysis with Varimax rotation was applied to the subtests making up the above scales.

Results: Five factors emerged after factor analysis comprising of subtests measuring Sequential Processing, Simultaneous Processing, Planning and Learning. The fifth scale comprised of subtests measuring immediate and delayed recall.

Conclusion: This preliminary study in Ugandan children shows the KABC-II to have good construct validity with subtests measuring similar abilities loading on the same factor. The KABC-II can be used in assessing Ugandan children after a few modifications. Further analysis of its psychometric properties in Ugandan children is required.

Key Words: neuropsychology, cross-cultural, Africa, children, validation

African Health Sciences 2009, 9(3): 186-192
P1104s KABC-II Construct Validity

• Participants with biological mothers as caregivers scored three points higher than those without.

• Participants with caregivers who had completed high school scored five points higher than those without even a primary school degree.

• Those participants whose household received social grants scored 2 points lower.

• Those living in rural areas scored almost five points lower.

• In addition, access to electricity, tap water and having a refrigerator in the house were associated with better mental processing scores.

• Having incomes sufficient for the needs of the households were also associated with higher mental processing scores.

• Caregiver mental health was not associated with mental processing scores; however, children with higher MICS disability scores had lower mental processing scores while those with higher developmental scores had higher mental processing scores.

• Of all the covariates included in the multivariable model, which showed significant associations with the mental processing index in the univariate models, only being in school at the time of the KABC testing was attenuated after adjustment and no longer was significant.
The “Shadow” Study Aims: Feasibility of a Neuropsychology Quality Assurance Plan

• Major components: a) monthly evaluation of videotaped KABC-II administration by each site tester b) monthly review of testing SOPs c) monthly group review of testing videos by site testing team using QA evaluation rubric

• Assessment center personnel for P1104s: Agatha Kuteesa, Ssesanga Titus Kisa (MU-JHU and GHU: Kampala)

• First time such a quality assurance plan has been implemented in a multi-site neuropsychological study of this sort in African pediatric HIV
KABC-II SCORING RUBRIC FOR THE P1104s STUDIES.

INSTRUCTIONS: Please indicate whether the tester is poor, adequate, good or excellent at each evaluative category. After each category, give a comment explaining reasons for score obtained. A general comment at the end of the evaluative process should be given on the entire administration process in which a tester’s shortcomings or mistakes will be corrected and also the way forward given.

TESTER’S CODE: ________________ CHILD’S ID: ________________ SITE CODE: ________________ DATE VIDEO WAS DONE: ________________ DATE VIDEO WAS SCORED: ________________ DATE FEEDBACK WAS SENT: ________________

SCORING KEY: 0=Poor (Inefficiency, lack of or little knowledge), 1=ADEQUATE (acceptable performance or basic knowledge), 2=GOOD (satisfactory or desired performance, has required qualities) AND 3=EXCELLENT (outstanding, distinctive, flexibility and creativity of tester.)

<table>
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<tr>
<th>KABC-II SCALES</th>
<th>EXPLANATION OF SCALE</th>
<th>COMMENTS</th>
<th>EASEL/MATERIAL MANAGEMENT</th>
<th>COMMENTS</th>
<th>TESTER FAMILIARITY WITH SCALE</th>
<th>COMMENTS</th>
<th>EFFICIENCY/FLUIDITY OF ADMINISTRATION</th>
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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)
Year 1 & 2 Results for P1104s QA Program

• All active testers at all of the sites are presently submitting KABC-II testing videos for evaluation monthly.

• The KABC-II evaluation rubric score (0 to 100%) is now averaging above 90% for 5 of the 6 sites.

• All testers have displayed significant improvements in their overall rubric scores from initial to later submissions of videos.
Secondary Study Aim from P1060 “Intent to Treat” analysis: NVP and LPV/r, in HIV-infected children.

For Week 0, there were no differences for any of the P1104s neuropsychology outcomes among the HIV+ cohorts treated with either NVP or Lopinavir/Ritonavir (intent to treat for a subgroup of P1060).
Limited Statistical Power for Evaluating Neuropsychological Outcomes of P1060 Treatment Arms: Exploratory Analyses Only


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 or 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.
Conclusions from Years 1 and 2 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, the significant group-by-site interaction effects for 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 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.
Neuropsychological effects of cognitive rehabilitation in Ugandan children with HIV
A Randomized Controlled Trial to Evaluate if Computerized Cognitive Rehabilitation Improves Neurocognition in Ugandan Children with HIV

Michael J. Boivin,1 Noeline Nakasujja,2 Alla Sikorskii,3 Robert O. Opoka,4 and Bruno Giordani5

Abstract

Objectives: Clinically stable children with HIV can have neuromotor, attention, memory, visual–spatial, and executive function impairments. We evaluated neuropsychological and behavioral benefits of computerized cognitive rehabilitation training (CCRT) in Ugandan HIV children.

Design: One hundred fifty-nine rural Ugandan children with WHO Stage I or II HIV disease (6 to 12 years; 77 boys, 82 girls; M = 8.9, SD = 1.86 years) were randomized to one of three treatment arms over a 2-month period.

Methods: The CCRT arm received 24 one-hour sessions over 2 months, using Captain's Log (BrainTrain Corporation) programmed for games targeting working memory, attention, and visual–spatial analysis. These games progressed in difficulty as the child's performance improved. The second arm was a "limited CCRT" with the same games rotated randomly from simple to moderate levels of training. The third arm was a passive control group receiving no training. All children were assessed at enrollment, 2 months (immediately following CCRT), and 3 months after CCRT completion.

Results: The CCRT group had significantly greater gains through 3 months of follow-up compared to passive controls on overall Kaufman Assessment Battery for Children–second edition (KABC-II) mental processing index (p < .01), planning (p = .04), and knowledge (p = .03). The limited CCRT group performed better than controls on learning (p = .05). Both CCRT arms had significant improvements on CogState Groton maze learning (p < .01); although not on CogState attention/memory, TOVA/impulsivity, or behavior rating inventory for executive function and child behavior checklist (psychiatric behavior/symptom problems) ratings by caregiver.

Conclusions: CCRT intervention can be effective for neurocognitive rehabilitation in children with HIV in low-resource settings, especially in children who are clinically stable on ARV treatment.
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 (FHI360): 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 Coordinators: Linda Barlow-Mosha, Nasreen Abrahams, Lee Farleigh,
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.
Kampala MU-JHU

**Front Row, LEFT TO RIGHT:** Linda Mosha-Barlow, Dorothy Nansikombi, Enid Kabugho, Margaret Mugenyi, Amos Bazira, Rose Mary Namwanje, Gladys Kasangaki

**Back Row:** Zam Zinda, Agatha Kuteesa, Mary Nyakato, Robinah Mudondo, Barbara Nakirya Musoke, Bertha Birungi
UNC Lilongwe Malawi

FRONT Left to Right: Angella Mwaipape, Noel Mumba, Gabriel Malunga, Steve Mphonda, Portia Kamthunzi, Lawrence Chaduka, Nelecy Chome, Towera Banda, Patricia Thindwa, Mary Chindevu; Back Row: Alfred Jaulani, Tiwonge Kamvaunamwali, Joanna Ali, Vincent Chirambo, Mary Chiunda, Dumisani Nkunika
PHRU SOWETO, RSA

Back row from left- Project Manager Nasreen Abrahams, Dr Mandisa Nyati, Dr Sylvia Dittmer, Dr Haseena Cassim, Fieldworker Lindiwe Hlomuka,  
Front row from left- Study psychologist Nkgari Given Leshabane, Study nurse Jackie Brown, Study co-ordinator Hilda Ndiweni, Neuropsychologist Celeste Joyce
SHANDUKANI, Johannesburg, RSA

Back row: Mhleli, Phatho, Hermien, Israel  Middle row: Lee Fairlie, Matsgediso, Princess, Mapule, Janet, Gurpreet, Marcia  Front row: Zinhle, Mmule, Sam
Back row: Felicity (tester), Anelma (Study-nurse), Marisa (doctor), Thandi (Tester), Charise (Data-manager), Hombakazi (Tester), Kaylee (Tester), Joan (Project Manager), Nwabisa (Counselor), Mercia (doctor), Naomi (Study-nurse), Merlissa (Data-capturer), Uninnie (Data-capturer, Candice (Data-capturer).

Front Row: Maylene (Quality Assurance sister), Barbara (Doctor), Lilly (Study-nurse), Marie (counsellor), Warren (data-capturer), Lindee (Study-coordinator), Kurt (laboratory-assistant).
Presentation to the Complications & Cормorbidities Committee at IMPAACT Annual Meeting, June 13, 2016
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!