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

Michael Boivin¹, Miriam Chernoff², Bonnie Zimmer³, Barbara Laughton⁴, Celeste Joyce⁵, Katie McCarthy⁶, Pim Brouwers⁷, Patrick Jean-Philippe⁸, Sonia Lee⁹, Joan Coetzee⁴, Avy Violari⁵, Mark Cotton⁴, Paul Palumbo¹⁰ and the IMPAACT P1104s Study Team

¹Michigan State University, ²Harvard University, ³Frontier Science, ⁴Stellenbosch University, ⁵University of Witwatersrand, ⁶FHI360, ⁷NIH/NIMH, ⁸NIH/NIAID, ⁹NIH/NICHD, ¹⁰Dartmouth University
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, MS

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.
Lab Data Coordinator: Brittany White, B.S.
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-Saharan 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

Presentation to the 8th Annual HIV Pediatrics Workshop: Durban, RSA; 16-July-2016
<table>
<thead>
<tr>
<th>Developmental Domain</th>
<th>Tonus</th>
<th>Cognition</th>
<th>Intellect / Achievement</th>
<th>Affect Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Function</strong></td>
<td><em>Visual Spatial Memory</em></td>
<td><em>Auditory Verbal Memory</em></td>
<td><em>Central Executive Function</em></td>
<td></td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td>Learning, Sequential Processing,</td>
<td>Learning, Sequential Processing</td>
<td>Planning, Simultaneous Processing</td>
<td>Rebus and Rebus Delayed</td>
</tr>
<tr>
<td><strong>Intellect / Achievement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affect Adjustment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Kaufman Assessment Battery for Children (KABC-II)**

- Tests of Variables of Attention (TOVA)
  - Simple reaction time (RT) for correct response
  - RT Speed and Variability on Signal Detection task

**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

**Presentation to the 8th Annual HIV Pediatrics Workshop: Durban, RSA; 16-July-2016**
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
<table>
<thead>
<tr>
<th>Category</th>
<th>Potential confounders assessed in building regression models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child attributes</td>
<td>sex, age, clinical site, whether the child is in school at the time testing, WHO-BMI, Weight and Height z-scores</td>
</tr>
<tr>
<td>Caregiver attributes</td>
<td>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</td>
</tr>
<tr>
<td>Caregiving quality</td>
<td>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</td>
</tr>
<tr>
<td>Home environment</td>
<td>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</td>
</tr>
<tr>
<td>Community environment</td>
<td>A comparison of children from urban, peri-urban, and rural communities on neuropsychological outcomes</td>
</tr>
</tbody>
</table>
## Child and Caregiver Characteristics (N=611)

<table>
<thead>
<tr>
<th></th>
<th>HIV (N=246)</th>
<th>HEU (N=183)</th>
<th>HUU (N=182)</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>45.1</td>
<td>51.9</td>
<td>46.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Black African (%)</td>
<td>98.4</td>
<td>96.2</td>
<td>82.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (mean, sd)</td>
<td>7.1 (1.2)</td>
<td>7.3 (1.6)</td>
<td>7.3 (1.5)</td>
<td>0.96</td>
</tr>
<tr>
<td>WHO BMI z-score (median; interq. range)</td>
<td>-0.2 (-.8,.4)</td>
<td>0 (-.6,.7)</td>
<td>-0.1 (-.7,.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>MICS disability (median; interq. range)</td>
<td>5 (0,10)</td>
<td>0 (0,10)</td>
<td>0 (0,10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Caregiver (Cgv) is biol. mother (%)</td>
<td>85</td>
<td>99</td>
<td>100</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cgv completed high school (%)</td>
<td>29.7</td>
<td>30.6</td>
<td>36.8</td>
<td>0.09</td>
</tr>
<tr>
<td>Receives social grant (%)</td>
<td>23.6</td>
<td>26.9</td>
<td>14.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Categorical vars., Chi-Square test; Continuous vars., Kruskal Wallis test
Child and Caregiver Characteristics (cont.)

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

* 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

KABC Standard Scores

Least Squares Mean

Sequential Simultaneous Learning Planning Delayed recall Nonverbal MPI

Test

cohort HUU HEU HIV

Errorbars show 95% CIs

Presentation to the 8th Annual HIV Pediatrics Workshop: Durban, RSA; 16-July-2016
*Adjusted Raw Scale Scores on KABC-II Performance for all Study Sites

Errorbars show 95% CIs
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

<table>
<thead>
<tr>
<th>Attention Performance Domains</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Omission Errors ($P&lt;0.001$)</td>
<td></td>
</tr>
<tr>
<td>Response Time Variability ($P&lt;0.001$)</td>
<td></td>
</tr>
<tr>
<td>Response Time ($P&lt;0.001$)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impulsivity Performance Domains</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Commission Errors ($P=0.09$)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Global Performance Indices</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>D Prime Signal Detection ($P&lt;0.001$)</td>
<td></td>
</tr>
<tr>
<td>ADHD Index ($P&lt;0.001$)</td>
<td></td>
</tr>
</tbody>
</table>
Attention Performance Scores on TOVA D Prime (standardized) and ADHD index, by Study

TOVA ADHD and D-Prime

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)

Errorbars show 95% CIs
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.


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 HIVpos (N=452)

In 1104S (N=246)
- NVP Exposed (N=86)
  - NVP (N=44)
  - LVP (N=42)
- NVP Unexposed (N=160)
  - NVP (N=82)
  - LPV (N=78)

Not in 1104S (N=206)
- NVP Exposed (N=78)
  - NVP (N=38)
  - LPV (N=40)
- NVP Unexposed (N=128*)
  - NVP (N=65)
  - LPV (N=62)
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 LPV/r 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.
Presentation to the 8th Annual HIV Pediatrics Workshop: Durban, RSA; 16-July-2016
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!