Caregiver depression and child neuropsychological outcomes in an observational study of pediatric HIV carried out in four sub-Saharan countries

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10th HIV Pediatrics Workshop
Amsterdam, Netherlands
Maternal depression

• Depression is one of the most common mental health problems among women
  – Between 7-20% of women are affected by depression symptoms during pregnancy and for the first year of the child’s life\textsuperscript{1,2}
• HIV+ women are more likely to experience depressive symptoms than their non-HIV infected peers (19.4% vs. 4.8%)\textsuperscript{3}

\textsuperscript{1} Woolhouse et al, BJOG 2014
\textsuperscript{2} Gavin et al, Obstet Gynecol 2005
\textsuperscript{3} Morrison et al, Croat Med J, 2011
• Maternal depression affects child socio-emotional and cognitive development through the child’s development stages

• This phenomenon is largely compounded in the context of HIV/AIDS:
  – African children are at a particular disadvantage if their care depends on impoverished HIV-infected caregivers, themselves at risk for mental health problems and impaired functioning.\(^4\)
  – Compromised quality of caregiving can compound the already serious neurodevelopmental effects of HIV infection and exposure for these children.

Depression of Ugandan Moms with HIV related to their BRIEF evaluation of their children, especially if HIV infected.
Primary Study Aim

To evaluate how depressive symptoms and depression severity in mothers affects their child’s neuropsychological outcomes among three cohorts of African pre-school children from the P1104s study:

1) perinatally HIV-infected (HIV+)
2) perinatally exposed HIV-uninfected (HEU)
3) un-exposed HIV-uninfected children (HUU)
Observational Study Design for P1104s: Neuropsychological domains (center), risk factor domains (Left), HIV exposure groups (right)
P1060/P1104s Study Sites

Accrual completed on 17 December 2014, with 615 participants enrolled (246 into HIV+ cohort; 185 into HEU cohort; 184 into HU cohort)

MUJHU, Kampala, Uganda  
n=89 participants (14%)

Malawi CRS, Lilongwe, Malawi  
n=82 participants (13%)

Harare Family Care, Harare, Zimbabwe  
n=133 participants (22%)

FAM-CRU, Cape Town, South Africa  
n=142 participants (23%)

Soweto, Johannesburg, South Africa  
n=100 participants (16%)

Wits RHI Shandukani Research, Johannesburg, South Africa  
n=69 participants (11%)
Methods

- Participants (n=611 dyads) were primary caregivers and their 5-11 year old child who were HIV+, HEU, or HUU.
- Caregivers were assessed for depression symptoms with the Hopkins Symptom Checklist
  - Low score: 1-1.75
  - High score: >1.75
- 3 assessment time points: 0, 48 and 96 weeks after study intake
- Cross-sectional and longitudinal linear regression models adjusted for potential confounders
Neuropsychology Assessments

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

- Cognitive Performance Domains
  - Sequential Processing (working memory)
  - Simultaneous Processing (visual-spatial problem solving)
  - Learning
  - Delayed Recall
  - Planning (reasoning)

- Global Performance Indices
  - Nonverbal Index
  - Mental Processing Index

Test of Variables of Attention (TOVA) visual

- Attention Performance Domains
  - Percent Omission Errors
  - Response Time Variability
  - Response Time

- Impulsivity Performance Domains
  - Percent Commission Errors

- Global Performance Indices
  - D Prime Signal Detection
  - ADHD Index

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

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
  BRIEF Metacognition Index
  BRIEF Global Executive Composite Index
Validity of Neuropsychological Testing in Young African Children Affected by HIV

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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)
Distal Factors Affecting Neuropsychological Outcomes in Pediatric HIV.
Between-group differences adjusted for site, sex and age at entry, WHO height-for-age Z score, school status, caregiver relation, residential zone, length of time with caregiver, socioeconomic index, MICS disability and MICS development.
# Child and caregiver characteristics at study entry, by cohort

<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</td>
<td>52</td>
<td>46</td>
<td>0.35</td>
</tr>
<tr>
<td>Black, African (%)</td>
<td>98</td>
<td>96</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Age, years (mean (SD))</td>
<td>7.1 (1.2)</td>
<td>7.3 (1.6)</td>
<td>7.3 (1.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>&lt; 6 (%)</td>
<td>17</td>
<td>20</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>6-7 (%)</td>
<td>34</td>
<td>35</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>≥ 7 (%)</td>
<td>50</td>
<td>45</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Biological mother as caregiver (%)</td>
<td>85</td>
<td>99</td>
<td>100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caregiver with HIV (%)</td>
<td>96</td>
<td>99</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>High caregiver depression level (HSCL &gt;1.75) (%)</td>
<td>43</td>
<td>43</td>
<td>40</td>
<td>0.79</td>
</tr>
</tbody>
</table>
### Biological markers of disease among HIV+ children (N=246)

<table>
<thead>
<tr>
<th></th>
<th>HIV (N=246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at ARV initiation, years (median, interquartile range)</td>
<td>1.2 (0.7,2.1)</td>
</tr>
<tr>
<td>ARV initiated at &lt; 1 year (%)</td>
<td>44</td>
</tr>
<tr>
<td># years on ARVs prior to entry (median, IQ range)</td>
<td>5.8 (5.1,6.7)</td>
</tr>
<tr>
<td>ARV regimen HAART with PI (%)</td>
<td>67</td>
</tr>
<tr>
<td>WHO disease stage III or IV (%)</td>
<td>61</td>
</tr>
<tr>
<td>CD4 percent ≥ 25% (%)</td>
<td>97</td>
</tr>
<tr>
<td>HIV RNA cp/ml 0-400 (%)</td>
<td>96</td>
</tr>
</tbody>
</table>
### Standardized test scores at study entry, Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>HIV (N=246)</th>
<th>HEU (N=183)</th>
<th>HUU (N=182)</th>
<th>Total (N=611)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KABC MPI</td>
<td>73.2 (10.5)</td>
<td>79.1 (11.4)</td>
<td>80.9 (11.7)</td>
<td>77.3 (11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BOT-2</td>
<td>48.3 (8.8)</td>
<td>52.5 (7.6)</td>
<td>52.6 (7.8)</td>
<td>50.8 (8.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BRIEF MI</td>
<td>52.2 (13.0)</td>
<td>51.9 (12.1)</td>
<td>49.8 (10.5)</td>
<td>51.4 (12.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>BRIEF BRI</td>
<td>53.1 (13.0)</td>
<td>51.2 (12.3)</td>
<td>51.9 (11.2)</td>
<td>52.2 (12.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>BRIEF GEC</td>
<td>53.2 (13.3)</td>
<td>51.5 (12.0)</td>
<td>50.6 (10.5)</td>
<td>51.9 (12.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>TOVA ADHD</td>
<td>-0.51 (3.13)</td>
<td>0.51 (2.63)</td>
<td>0.28 (2.59)</td>
<td>0.03 (2.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TOVA D PRIME</td>
<td>82.5 (14.0)</td>
<td>88.3 (12.3)</td>
<td>87.9 (11.7)</td>
<td>85.9 (13.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Associations of caregiver depression with neuropsychological test scores at entry

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted Slope (SE)</th>
<th>P-value</th>
<th>Adjusted Slope (SE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KABC MPI</td>
<td>-1.30 (0.71)</td>
<td>0.07</td>
<td>-0.44 (0.68)</td>
<td>0.52</td>
</tr>
<tr>
<td>BOT-2</td>
<td>0.46 (0.51)</td>
<td>0.37</td>
<td>-0.57 (0.53)</td>
<td>0.28</td>
</tr>
<tr>
<td>BRIEF MI</td>
<td>7.29 (0.76)</td>
<td>&lt;0.001</td>
<td>7.08 (0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BRIEF BRI</td>
<td>5.12 (0.77)</td>
<td>&lt;0.001</td>
<td>6.02 (0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BRIEF GEC</td>
<td>6.66 (0.77)</td>
<td>&lt;0.001</td>
<td>6.98 (0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TOVA ADHD</td>
<td>0.23 (0.18)</td>
<td>0.20</td>
<td>-0.13 (0.19)</td>
<td>0.49</td>
</tr>
<tr>
<td>TOVA D PRIME</td>
<td>-0.83 (0.80)</td>
<td>0.30</td>
<td>0.73 (0.89)</td>
<td>0.41</td>
</tr>
</tbody>
</table>
Association of caregiver depression severity level with neuropsychological test scores at study entry

<table>
<thead>
<tr>
<th>Test</th>
<th>Low (0-1.75) (N=351)</th>
<th>High (&gt;1.75) (N=259)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KABC MPI</td>
<td>79.2 (77.4,80.9)</td>
<td>78.7 (76.7, 80.6)</td>
<td>0.58</td>
</tr>
<tr>
<td>BOT-2</td>
<td>51.8 (50.3,53.3)</td>
<td>51.2 (49.7, 52.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>BRIEF MI</td>
<td>48.9 (46.7,51.1)</td>
<td>56.0 (53.6,58.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BRIEF BRI</td>
<td>49.6 (47.0,52.2)</td>
<td>55.3 (52.4, 58.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BRIEF GEC</td>
<td>49.2 (46.7,51.6)</td>
<td>55.9 (53.1,58.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TOVA ADHD</td>
<td>0.01 (-0.53-0.54)</td>
<td>0.08 (-0.48,0.65)</td>
<td>0.76</td>
</tr>
<tr>
<td>TOVA D PRIME</td>
<td>87.5 (85.2,89.8)</td>
<td>87.0 (84.5, 89.6)</td>
<td>0.70</td>
</tr>
</tbody>
</table>
**KABC-II Mental Processing Index means at study entry by caregiver depression level**

<table>
<thead>
<tr>
<th>Depression level</th>
<th>HIV</th>
<th>HEU</th>
<th>HUU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted mean (95% CI)</td>
<td>Adjusted mean (95% CI)</td>
<td>Unadjusted mean (95% CI)</td>
</tr>
<tr>
<td>Low (0-1.75)</td>
<td>74.8 (73.0,76.7)</td>
<td>76.0 (74.1,77.9)</td>
<td>79.6 (77.4,81.8)</td>
</tr>
<tr>
<td>High (&gt;1.75)</td>
<td>71.1 (69.3,72.8)</td>
<td>73.4 (71.2,75.5)</td>
<td>78.5 (76.1,80.9)</td>
</tr>
</tbody>
</table>

*Adjusted models included site, sex, age at entry, caregiver relationship to child, residential zone, WHO height for age z-score, and socio-economic index*
Adjusted means and 95% confidence interval for neuropsychological outcomes over time among school-age children of varying HIV status and caregiver depression level (High >1.75, Low ≤1.75). BOT-2: Total point standard score for Bruininks-Oseretsky Test of Motor Proficiency, BRI: Behavior Regulation Index, MI: Metacognition Index, and GEC: Global Executive Composite standard scores for the Behavior Rating Inventory of Executive Function.
Conclusions

• HIV-infected children had lower cognitive performance scores than their non-infected peers
• Caregivers with higher levels of depressive symptoms reported more executive function problems in their children, regardless of the child’s HIV status
• Caregiver’s depression symptoms may have a more pronounced, negative effect on the neurodevelopment of HIV-infected children
Association between coping strategies, social support, and depression and anxiety symptoms among rural Ugandan women living with HIV/AIDS

Victoria Seffren, Itziar Familiar, Sarah M. Murray, Jura Augustinavicius, Michael J. Boivin, Noeline Nakasujja, Robert Opoka & Judith Bass

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Implications and Questions

• Identifying mothers in need of support and addressing their needs could help reduce the burden of early behavioral and cognitive problems in children

• The BRIEF assessment is a promising way to systematically assess executive functioning in children in different cultural settings
  – Possible caregiver reporting bias need to be considered

• There is a need to integrate health programs for both children and mothers
  – For example: PMCT programs for HIV+ women

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6 Familiar et al, J Learn Ind Diff 2015
Acknowledging the IMPAACT P1104s Study Leadership

**Protocol Chair:** Michael Boivin, Ph.D., M.P.H.
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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.
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