Neurocognitive complications of HIV and its treatment in children

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2nd International Workshop on HIV Pediatrics
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Presentation Outline

1. Overview of neuropsychological effects on treatment-naïve children from the DR Congo and Uganda.

2. Preliminary findings from computer-based cognitive rehabilitation training in school-age Ugandan children with HIV (R34 MH084782 PI: Boivin).


4. Preliminary findings from caregiver-training intervention programs in very young Ugandan children with HIV (R34 MH082663 PI: Boivin).
Neuropsychological Effects of HIV in African Children

- Half of treatment-naive DR Congo children with HIV, 30 to 72 months of age, have severe mental and/or motor delay (van Rie et al., *Pediatrics*, 2008)

Follow-up Assessment of HIV Survivors – DR Congo

Presented at the 2nd International Workshop on HIV Pediatrics
16-17 July 2010, Vienna Austria
Cognitive Effects of HIV by K-ABC Subscale: Kimpese, DR Congo

Comparison of Congenital HIV Positive and Negative Children on K-ABC Subscales

Boivin et al., *Health Psychology*, 1995
K-ABC Global Performance Differences by HIV Group: DR Congo

Boivin et al., *Health Psychology*, 1995
Degree of Neurocognitive Impairment?

• Bagenda et al., (2006) concluded that treatment-naïve Ugandan children were within the normal range of performance on the K-ABC (robust survivor effect).
### Cognitive Effects of HIV by K-ABC Subscale: Kampala, Uganda

**Uganda MJ-CWRU Cohorts (Bagenda et al., Pediatrics, 2006)**

<table>
<thead>
<tr>
<th></th>
<th>HandMovSER</th>
<th>GestaltSER</th>
<th>NumberSER</th>
<th>TrianglesSER</th>
<th>WordSER</th>
<th>MatrixSER</th>
<th>SpatialSER</th>
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- Grouping Variable: ghivbay

Bagenda et al., *Pediatrics*, 2006
Predictive validity of early developmental assessment and later cognitive performance in Ugandan children (HIV positive and negative)

<table>
<thead>
<tr>
<th>Pearson correlation between BDI at 6 and 24 months and K-ABC and WRAT-3 at 8 years for Ugandan HIV Cohorts (MU-CWRU)</th>
<th>K-ABC Sequential Processing</th>
<th>K-ABC Simultaneous Processing</th>
<th>WRAT-3 Spelling</th>
<th>WRAT-3 Arithmetic</th>
<th>WRAT-3 Reading</th>
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<tr>
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</table>

*p < .05;  **p < .01;  n = 59
Research Question 1

• Do HIV+ school aged children in Uganda not currently eligible for ART demonstrate deficits relative to HIV- children? (Ruel et al., submitted for publication)

• Relevance: Would earlier treatment of immunologically intact children prevent neurodevelopmental delay or neurocognitive impairment?

• Bagenda et al., (2006) concluded that treatment-naïve Ugandan children were within the normal range of performance on the K-ABC (robust survivor effect).
Patient Characteristics: IDC Mulago Hospital

CHAMP (n= 93, ART naïve)
• (median CD4 count 655 cells/μl, CD4% (27), and plasma HIV RNA levels [4.7 log10(c/ml)]
• Median age 8.7 years
• No clinical malaria
  • all with < 3 episodes of asymptomatic parasitemia/year

U01 Malaria cohort (n=106)
• Median age 8.8 years
• No clinical malaria
  • all with < 3 episodes of asymptomatic parasitemia/year
Comparing HIV+ and HIV- Kampala Groups on KABC-2

- Memory ($P = .006$)
- Sequential Processing
- Visual-spatial ($P = .012$)
- Simultaneous Processing
- Reasoning ($P = .048$)
- Planning

*ANCOVA test. Increasing plasma HIV RNA was associated with worse performance in 6 cognitive, but no motor measures*
Test of Variables of Attention (TOVA): Visual and Auditory
Test of Variables of Attention (TOVA)

Visual

Target

Non Target
Comparing HIV+ and HIV- Groups on TOVA-visual

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
Comparing HIV+ and HIV – Groups on TOVA-auditory

D prime signal detection \((P = .58)\)
Omission Errors \((P = .19)\)
Commission Errors \((P = .90)\)
Response Time \((P = .54)\)
Response Time Var. \((P = .55)\)

*ANCOVA test on linear Studentized Residual Errors to age. SES and gender are covariates.
Comparing HIV Subtype A and D Groups on TOVA-auditory

D prime signal detection ($P = .34$)
Omission Errors ($P = .51$)
Commission Errors ($P = .35$)
Response Time ($P = .70$)
Response Time Var. ($P = .46$)

*ANCOVA test on linear Studentized Residual Errors to age. SES total as covariate.
Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition (BOT-2)

- Fine Motor Precision
- Fine Motor Integrity
- Manual Dexterity
- Bilateral Coordination
- Balance
- Upper-Limb Coordination
- Speed and Agility
- Strength
Comparing HIV+ and HIV- Groups on BOT-2

- Fine Motor Precision ($P = .22$)
- Fine Motor Integrity ($P = .23$)
- Manual Dexterity ($P = .001$)
- Bilateral Coordination ($P = .99$)
- Balance ($P = .08$)
- Upper-Limb Coordination ($P = .05$)
- Speed and Agility ($P = .002$)
- Strength ($P = .09$)

*ANCOVA test on linear Studentized Residual Errors to age. SES and Gender are covariates.
Cognitive and Developmental Testing of Children with HIV: Uganda JHSPH Cohort, Rakai (rural)

- **Between-Group Comparisons (preliminary)**
  - **6 mos to 6 yrs**: HIV-infected children (N = 187, 32% HIV) were lower on Visual Receptive ability, Receptive Language, and Expressive Language.
    - No significant differences on Gross Motor and Fine Motor.

  - **7 yrs and older**: HIV-infected children (N = 220, 28% HIV) were lower on KABC-2 Memory (Sequential Processing) and Expressive Language.

  - Use of ARV in HIV infected children was associated with a higher risk of disability (OR = 4.7, 95%CI 1.3 to 16.3)

Brahmbhatt et al., 2010; CROI annual meeting

(K01 TW007403 PI: Brahmbhatt)
KABC-2 Testing of Children with HIV: Uganda JHSPH Cohort, Rakai (rural)

• Significant differences between HIV positive and negative children on
  – Learning subscales (Atlantis, Rebus, Rebus Delayed),
  – Memory (Word Order, Hand Movements),
  – Verbal Performance (Riddles)
  – Analogous Reasoning (Patterns)

*scores adjusted for age; Bonferroni adjustment on significance levels
Neuropsychological Effects of HIV infection in School-Age Ugandan Children

• Urban and Rural HIV+ Ugandan school age children have poorer neuropsychological performance on
  – Working memory,
  – Visual-spatial processing,
  – Visual attention (vigilance)
  – Motor performance.
Why HAART is not enough to restore neurocognitive decline in children

- If medical support is started early in a young child with HIV, that child can make significant motor and possibly cognitive recovery (Van Rie et al., JAIDS, 2009).
- Six months of HAART did not significantly change the prevalence or extent of neurocognitive deficits in HIV-infected children (Smith et al., 2008).
- Poor neuropsychological functioning correlated with higher viral loads in HIV-infected children; treatment with anti-retroviral therapy did not result in significant improvement in these measures (Jeremy et al., 2005).
Background

Research Questions:

1) Is computerized cognitive rehabilitation therapy (CCRT) feasible and effective for these children?

2) Can we document the cognitive benefit using a computerized neuropsychological screening assessment?

Boivin et al., Neuropsychology, in press
Neurocognitive CCRT Benefits in Treatment of CNS Infectious Disease
CogState Computerized Assessment (pre- and post-training)

Captain’s Log
CCRT Training
CM: 16 sessions
HIV: 10 sessions

Presented at the 2nd International Workshop on HIV Pediatrics
16-17 July 2010, Vienna Austria
You will see a number of different objects. Each object has a match. Look carefully and find its exact match. Remember where the matches are located on the board. These objects will then be hidden behind some doors. Click on the doors to uncover each pair of objects that matches. If you do not find a match, then you must wait for the doors to close before making another choice. You must be both accurate and quick to win.
Mouse Hunt - 1 (Diamond/Medium)

Watch the pictures of the bears and rhinos. When one appears that is the SAME color as the border, click the mouse as quickly as you can.
CogState design: Computer testing using playing card stimuli
(culturally neutral, minimal language, game-like)
www.cogstate.com

Is it there? (detecting)
Is it red? (identifying)
Is it the same as the one before? (working memory)
Was it already presented? (memory)

• Measures the speed, accuracy and consistency of responses
• Little practice effect.
• Sensitivity but not specificity,
• Good scientific validation
Tap on the tiles to find the hidden pathway.

Start at the top left and move one tile at a time.
Groton Maze Chase Task

• The subject is shown a 10 x 10 grid of tiles on a computer touch screen.
• As the target moves, “chase” it by tapping on the tiles one at a time.
Groton Maze Learning Task

- Move one tile at a time (start at upper-left), toward the goal tile (bottom right).
- Trial-and-error learning of the 28-step hidden pathway though the maze on the basis of step-by-step feedback (right or wrong move).
Results of CCRT Intervention on Cogstate Performance

Compared to the CM control group, the CM treatment group had significantly greater gains on Groton Maze Learning ($P < .001$) and Maze Chase (visual-spatial tracking) ($P < .001$) (upper graphs). The HIV treatment group also had significantly greater gains on Maze Learning ($P = .013$) and Maze Chase ($P = .034$) (lower graphs).
Cerebral Malaria and HIV CCRT Pilot Studies: Interpretation

Just 16 (CM) or 10 (HIV) sessions of Captain’s Log CCRT training can significantly improve visual-motor tracking and maze learning due to

1) Psychosocial support (CBCL Benefit)
2) Computer experience
3) Cognitive skills training
KABC-2 Simultaneous Processing (Visual-Spatial)

Mean Raw Score Improvement (pre and post 5 weeks)

<table>
<thead>
<tr>
<th>CCRT Intervention Group</th>
<th>No CCRT</th>
<th>CCRT Training</th>
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</thead>
<tbody>
<tr>
<td>ON HAART?</td>
<td>no</td>
<td>yes</td>
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</table>

Error Bars: +/- 2 SE

ANCOVA $F_{A*B} \quad P = .005$

<table>
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<th>ART treatment by CCRT training: &gt;5 yrs</th>
<th>ART</th>
<th>No-ART</th>
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<tbody>
<tr>
<td>CCRT</td>
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<td>19</td>
</tr>
<tr>
<td>No-CCRT</td>
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</tr>
</tbody>
</table>

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Computerized Cognitive Rehabilitation Training (CCRT) for Enhancing Cognitive Ability in Ugandan Children with HIV

Figure 3: Model of Neuropsychological Benefits of Captain's Log and RoboMemo Training for School-Age HIV Children

- ARV Treatment
- Medical Support
- HIV Clinical Stability
- HHCV Nutritional Medical Support
- HIV Viral Load
- CD4/CD8 Activation
- Brain Pathogenesis
- TOVA Attention
- Attention
- Captain's Log RoboMemo Training
- Cognitive Ability
- Working Memory
- KABC-2 Learning Reasoning
- Home Quality
- KABC-2 Memory
- Educational Quality
- Quality of Home Envir.
- Source of Caregiving
- SES Material Possessions
Neuropsychological effects of cognitive rehabilitation in Ugandan children with HIV
Kayunga Children with HIV >5 Yrs old
N=150

Pre-Test:
KABC-2, TOVA, BOT2, CogState, CBCL

Random Assignment

Captain’s Log
24 Sessions over 8 Weeks
N=50

Passive Control
No computer training or games
N=50

Captain’s Log Locked
24 Sessions over 8 Weeks
N=50

Post-Test:
KABC-2, TOVA, BOT2, CogState, CBCL

3-Month Follow-Up:
KABC-2, TOVA, BOT2, CogState, CBCL

R34 MH084782 PI: Boivin

Presented at the 2nd International Workshop on HIV Pediatrics
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The four principal components of negative (red) and positive (blue) neuroplasticity in the neuropsychological benefits of CCRT treatment of HIV.

Presented at the 2nd International Workshop on HIV Pediatrics
16-17 July 2010, Vienna Austria
Conclusions & Future Directions

• CCRT can improve computer-based visual-spatial tracking and learning in African children at risk from CNS infection and injury.

• Future CCRT will include a “computer games” active control group.

• Future CCRT will include the assessment of functional gains in school and at home.

• Internet and mobile-based CCRT allow remote neuropsychological assessment and rehabilitative treatment access in resource poor settings.
Summary 2

• HIV Subtype A is associated with poorer neuropsychological performance (visual spatial processing and TOVA impulsivity), compared to Subtype D in treatment-naïve Ugandan children.
Model for difference in neurovirulence of subtypes A and D

Subtype A: More CCR5-tropic

Subtype D: More CXCR4-tropic

*R5-HIV more efficient replication in CNS

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"Spock's Brain"

The Enterprise is raided by an alien force, who steal Spock's brain, leading Kirk and McCoy in a desperate race to retrieve it.
Students in the Andean village of Arahuay, Peru, using computers supplied by the organization One Laptop Per Child. http://www.nytimes.com/2008/01/05/technology/05laptop.html

Also, Intel/Microsoft World Ahead Classmate PC (Generation 4) at $500 with serious games by Warner Brothers (US-AID/PEPFAR Kenya program).
The Public Health Feasibility of CCRT in Resource-Poor Settings

Some . . . see things as they are and say why - I dream things that never were and say why not.

George Bernard Shaw
“Plasticity is a double-edged sword that leads to both adaptation and vulnerability”

From Neurons to Neighborhoods
Shonkoff, J. P. & Phillips, D. A. (Eds.),
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.
The effects of maternal HIV disease on quality of caregiving and subsequent child development
Neurocognitive Effects of Compromised Caregiving in African Children with HIV

HIV positive < HIV exposed < HIV nonexposed

- Boivin et al., *Health Psychology*, 1995
- Van Rie et al., *Pediatrics*, 2008
The beginning of an idea to evaluate the neurodevelopmental benefits of early childhood intervention for at-risk African children.

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Pnina S. Klein

Bar-Ilan University, Ramat-Gan, Israel

Michael J. Boivin

Indiana Wesleyan University, Marion, USA
Study aims

• In very young Ugandan children with HIV are there developmental differences between those on caregiver training intervention (MISC) and those who are not?
• A 2\textsuperscript{nd} study aim is to evaluate the developmental and behavioral benefits of HAART treatment (Triomune: Lamivudine, Stavudine, Niverapine) of younger HIV infected Ugandan children.
What is MISC?

• MISC sensitizes mothers to the positive aspects of their current childrearing interactions.
• It begins by asking parents/caregivers what outcomes they hope to achieve.
• It raises parental awareness of the child’s emotional and cognitive needs, and awareness of the impact of parental/caregiver interactive behavior.
• It is facilitative, and does not rely on outside resources or materials.
• It can be implemented with most children in a variety of contexts where caregiver/child interactions naturally take place.
MISC begins by asking parents/caregivers what outcomes they hope to achieve. What are their dreams for their children, and how do they plan to achieve those?
To Seek Information
Beyond Sensory
To Explore, To Ask
To Seek Adult Help

To Think Before Doing
To Organize & plan

Regulating
Rewarding
Expanding
Affecting
Focusing
It’s worthwhile to act / I can do
I’m with you / I’m safe
I love you / I’m loved

To Search Meaning & Excitement
To Seek Clarity of Perception

Physical Closeness
Sharing of Joy
Smiles
Emotional Development
Vocalizations
Eye Contact

ABC of Love

Mutual Engagement

Basic Messages

Basic Elements Of Mediation

Mutual Attention

Touch
Turn-Taking
Physical Closeness

Reciprocity
MISC interventions seek to enhance executive functions (and neuropsychological outcomes) through caregiver interactions
Results

• Children on HAART treatment performed significantly worse on:
  – Mullen fine motor skills
  – Mullen receptive language
  – Mullen expressive language
  – ECVT attention

• Children on HAART treatment performed significantly better on:
  – CBCL internalizing symptoms
Comparison of MISC and Control children on developmental outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect</th>
<th>$P$-values</th>
<th>Observed Power</th>
<th>$P$-value</th>
<th>Observed Power</th>
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<tr>
<td>Mullen Visual/Receptive skills</td>
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MISC Training and Caregiver EWB

• MISC training sessions were significantly related to fewer symptoms on HSCL (depression: $r = -0.28, P = 0.006$; anxiety: $r = -0.36, P = .001$).

• As a group, about 20% of the caregivers had HSCL scores high enough to be predictive of a clinical diagnosis of depression.

• The percentage being more than double for HIV-positive mothers serving as caregivers in the present study.
Gains on Color-Object Association Test for MISC and non MISC Groups

Improvements for MISC and non MISC on COAT Memory Total Group

Covariates appearing in the model are evaluated at the following values: age = 3.9607, sex = 1.4419, sestotal = 2.8837
Implications

• In the future, treatment of HIV-infected children should include HAART as soon as possible
• Treatment with HAART should also be complimented with interventions to enhance development, such as our Mediational Intervention for Sensitizing Caregivers (MISC) intervention
Acknowledgements

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