Factors of risk and resilience in the neurodevelopment of children affected by HIV

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Adjunct Professor of Psychiatry
University of Michigan

HIV and Healthy Living
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BACKGROUND: Over the past three decades, the clinical presentation of HIV infection of the Central Nervous System (CNS) has evolved. Prior to widespread use of effective antiretroviral therapy (ART), more than a third of infected individuals exhibited a range of neurocognitive and motor deficits that frequently progressed to severe dementia and paralysis. However, the use of ART has significantly decreased the prevalence of severe forms of HIV-1 associated neurocognitive disorders (HAND). Studies of neurocognitive dysfunction have reported variable prevalence, ranging from 21% to 77.6%, defined primarily by mild to moderate neurocognitive impairment. HIV-associated chronic inflammation and associated neurotoxicity of long-term ART, as well as the aging of the HIV-infected population, likely influence the pathogenesis of HAND. Despite significant research efforts directed towards a better understanding of the mechanisms underlying HIV neuropathogenesis, definitive causal pathophysiology of HAND and thus effective prevention or treatment remain elusive. Furthermore, HIV therapeutic research now includes efforts to effect a cure, by eliminating or silencing HIV within infected cells, which must include efforts to target the latently infected cells within the CNS.

CONCLUSION: Prevention and treatment of the neurological complications of HIV, and eradication of persistent virus from the CNS compartment are major priorities for the HIV-CNS research. Here we give an overview of the progress of research on HIV-CNS disease, define new challenges and research areas, and highlight domestic and global priorities.

PMID: 27009096
START trial finds that early treatment improves outcomes for people with HIV
Starting at a CD4 count over 500 cells/mm³ is safer than waiting till 350 cells/mm³

• START, which opened widely in March 2011 at 215 sites in 35 countries. The trial enrolled 4685 men and women with HIV who had never taken ART.

• Half were randomised to start ART immediately and the other half deferred treatment until their CD4 cell count declined to 350 cells/mm³. Participants in the study were followed for three years.

• As of March 2015, the DSMB found 41 instances of AIDS, serious non-AIDS events or death among those enrolled in the group starting ART early, compared to 86 events in those deferring it.

• This equates to a reduction of 53% in the risk of developing serious illness or death. Concerning AIDS-defining illnesses in particular, the risk reduction was even more pronounced at 70%.
Brain Degeneration and Dementia in Sub-Saharan Africa

Part II: Selected Causes of Brain Degeneration in Uganda

4 HIV-Associated Cognitive Impairment in Sub-Saharan Africa
   Noeline Nakashua
An Understanding of Pediatric HIV Disease and Exposure Across the Life Span is Foundational to Understanding Adult HAND and Ageing
Plasticity is a double-edged sword that leads to both adaptation and vulnerability

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

From Neurons to Neighborhoods
Human brain development: The Early Critical Period

Grantham-McGregor et al Lancet, 2007; 369: 60-70
Positive Neuroplasticity across the Developmental Lifespan

Critical Period Neurodevelopment

Threshold of Neurodevelopmental Delay and Disability

Threshold for Decline/Dementia

Cognitive Reserve

Impact of Intervention to alter developmental trajectory

First 1000 days

Middle Childhood through adolescence

Successive decades of Adulthood
Background

- Pediatric HIV
  - Developmental lag
  - Neurocognitive impairment
- Effects on mother
  - Potential for compromised caregiving
White matter signal abnormality in children on CHER study

Mean age 33m

5 of 22 with on ART from 7-8W of age

Ackermann Pediatr Infect Dis J 2014; 33e
Fractional anisotropy (FA) is a measure derived from the diffusion tensor imaging that assesses the degree of anisotropic self-diffusion, i.e. the integrity of the white matter tract. The higher the FA the healthier the tract; lower FA indicates damage to its integrity. (J. Hoare, *Southern African Journal of HIV Medicine*, 2009)

- 39 HIV+ & 13 controls
  - Age & ethnicity
- 2 clusters with lower FA
- 7 clusters with increased mean diffusion
- Corticospinal
- Early interrupted had lower FA than early continuous
Child with Cerebral Malaria

Abnormal posturing, brain stem herniation, intracranial pressure.
Conclusions: NIH/Fogarty R21 prospective study of Neurocognitive Effects of CM

One in four Ugandan children >5 years old who develops cerebral malaria (CM) was cognitively impaired 2 years later.

Severity of malarial CNS infection is related to attention impairment and visual-spatial working memory.

One in five Ugandan CM children developed seizure disorder over 2-yr follow-up.
Complications associated with long-term HIV infection

- cardiovascular disease,
- diabetes,
- lung disease,
- certain cancers,
- HIV-Associated Neurocognitive Disorders (HAND), and
- liver disease (including hepatitis B and hepatitis C), among others.

Age-Associated Dementia from Vascular Disease versus Degenerative Disease (Alzheimer’s Disease)
The First 1000 Days “continuum”

- Conception
  - 270 days
  - Antenatal
- Birth
  - 365 days
  - Early Postnatal/Infancy
- 1000 days
  - 365 days
  - Early Childhood

1st 1000 days to City of Cape Town Health
Advancing Early Childhood Development: from Science to Scale 2

Nurturing care: promoting early childhood development


The Lancet, 2016
Early childhood development coming of age: science through the life course

Maureen M Black, Susan P Walker, Lia C H Fernald, Christopher T Andersen, Ann M DiGirolamo, Chunling Lu, Dana C McCoy, Günther Fink, Yusra R Shawar, Jeremy Shiffman, Amanda E Devercelli, Quentin TWodon, Emily Vargas-Barón, Sally Grantham-McGregor*, for the Lancet Early Childhood Development Series Steering Committee†

Early childhood development programmes vary in coordination and quality, with inadequate and inequitable access, especially for children younger than 3 years. New estimates, based on proxy measures of stunting and poverty, indicate that 250 million children (43%) younger than 5 years in low-income and middle-income countries are at risk of not reaching their developmental potential. There is therefore an urgent need to increase multisectoral coverage of quality programming that incorporates health, nutrition, security and safety, responsive caregiving, and early learning. Equitable early childhood policies and programmes are crucial for meeting Sustainable Development Goals, and for children to develop the intellectual skills, creativity, and wellbeing required to become healthy and productive adults.

In this paper, the first in a three part Series on early childhood development, we examine recent scientific progress and global commitments to early childhood development. Research, programmes, and policies have advanced substantially since 2000, with new neuroscientific evidence linking early adversity and nurturing care with brain development and function throughout the life course.
Sub-Saharan Africa and Children at Risk from Poverty

<table>
<thead>
<tr>
<th>Region</th>
<th>Under-5 population</th>
<th>Number stunted</th>
<th>% stunted</th>
<th>Number living in extreme poverty</th>
<th>% living in extreme poverty</th>
<th>Number at risk of not reaching developmental potential</th>
<th>% at risk of not reaching developmental potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Asia and Pacific</td>
<td>136.2</td>
<td>145.7</td>
<td>34.1</td>
<td>29.6</td>
<td>25%</td>
<td>30.2</td>
<td>18.2</td>
</tr>
<tr>
<td>Europe and central Asia</td>
<td>25.4</td>
<td>27.9</td>
<td>4.8</td>
<td>4.8</td>
<td>19%</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>56.8</td>
<td>54.1</td>
<td>9.1</td>
<td>8.0</td>
<td>16%</td>
<td>4.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Middle East and north Africa</td>
<td>32.3</td>
<td>36.5</td>
<td>8.0</td>
<td>8.6</td>
<td>25%</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>South Asia</td>
<td>171.4</td>
<td>168.1</td>
<td>80.6</td>
<td>67.6</td>
<td>47%</td>
<td>69.5</td>
<td>46.5</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>124.9</td>
<td>143.3</td>
<td>53.9</td>
<td>55.1</td>
<td>43%</td>
<td>67.5</td>
<td>72.3</td>
</tr>
<tr>
<td>Total</td>
<td>547.0</td>
<td>575.6</td>
<td>190.6</td>
<td>173.7</td>
<td>35%</td>
<td>1/4.3</td>
<td>141.8</td>
</tr>
</tbody>
</table>

Generated using updated data and methods. *Calculations for the number of children at risk of not reaching their developmental potential take into account the number of children jointly exposed to stunting and poverty. Further information regarding the estimation of this joint set is provided by Lu and colleagues.*

Table 1: Estimated number (in millions) and prevalence of under-5 children experiencing stunting or extreme poverty in 2004 and 2010.

Advancing Early Childhood Development: from Science to Scale

Early childhood development coming of age: science through the life course

Maureen M Black, Susan P Walker, Lia C H Fernold, Christopher T Andersen, Ann M DiGirolamo, Chunling Lu, Dana C McCoy, Günter Fink, Yusra R Shawar, Jeremy Shiffman, Amanda E Devereux, Quentin TWodon, Emily Vargas-Barón, Sally Grantham-McGregor, for the Lancet Early Childhood Development Series Steering Committee.
Family income, parental education and brain structure in children and adolescents


Socioeconomic disparities are associated with differences in cognitive development. The extent to which this translates to disparities in brain structure is unclear. We investigated relationships between socioeconomic factors and brain morphometry, independently of genetic ancestry, among a cohort of 1,099 typically developing individuals between 3 and 20 years of age. Income was logarithmically associated with brain surface area. Among children from lower income families, small differences in income were associated with relatively large differences in surface area, whereas, among children from higher income families, similar income increments were associated with smaller differences in surface area. These relationships were most prominent in regions supporting language, reading, executive functions and spatial skills; surface area mediated socioeconomic differences in certain neurocognitive abilities. These data imply that income relates most strongly to brain structure among the most disadvantaged children.
K.G. Noble, et al., 2015, Nature Neuroscience
Labor market returns to an early childhood stimulation intervention in Jamaica

by Paul Gertler, James Heckman, Rodrigo Pinto, Arianna Zanolini, Christel Vermeersch, Susan Walker, Susan M. Chang, and Sally Grantham-McGregor

Help as hungry children helps young adults
Supporters of early childhood interventions follow the rule “better early than late,” but so far there's been limited evidence that the rule applies to disadvantaged children in developing countries. Gertler et al. looked at the earnings of young adults in Jamaica, 20 years after, as toddlers, they were given 2 years of help from community health workers. The earnings of the treatment group caught up to those of a comparison group of well-fed children, but the control group of undernourished children that did not receive the health worker visits has lagged behind.

Science, this issue p. 998

Science
Volume 344(6187):998-1001
May 30, 2014
Early Childhood Stunting Is Associated with Lower Developmental Levels in the Subsequent Generation of Children

Susan P Walker, Susan M Chang, Amika Wright, Clive Osmond, and Sally M Grantham-McGregor

Epidemiology Research Unit, Tropical Medicine Research Institute, The University of the West Indies, Mona, Kingston, Jamaica; Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom; and Institute of Child Health, University College, London, United Kingdom

TABLE 3  Mean assessment scores for second generation child development and behavior scores by stunted and nonstunted first generation group

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Stunted (assessments, n = 71)</th>
<th>Nonstunted (assessments, n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental quotient</td>
<td>98.9 ± 12.0</td>
<td>104.7 ± 10.8</td>
</tr>
<tr>
<td>Cognitive subscale</td>
<td>91.8 ± 15.3</td>
<td>97.7 ± 14.6</td>
</tr>
<tr>
<td>Hearing-and-speech subscale</td>
<td>101.4 ± 18.3</td>
<td>108.4 ± 17.0</td>
</tr>
<tr>
<td>Hand-and-eye subscale</td>
<td>95.8 ± 14.6</td>
<td>100.3 ± 13.1</td>
</tr>
<tr>
<td>Locomotor subscale</td>
<td>106.6 ± 14.4</td>
<td>112.6 ± 12.9</td>
</tr>
<tr>
<td>SDQ total difficulties score</td>
<td>14.2 ± 5.0</td>
<td>13.3 ± 5.5</td>
</tr>
<tr>
<td>SDQ prosocial score</td>
<td>7.1 ± 2.0</td>
<td>7.2 ± 2.0</td>
</tr>
</tbody>
</table>

1 Values are means ± SDs. SDQ, Strengths and Difficulties Questionnaire.
2 SDQ was administered only for children ≥3 y of age; stunted (n = 46), nonstunted (n = 50).

TABLE 4  Mixed model regression analyses of first generation group on child development

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Unadjusted²</th>
<th>Adjusted model ¹</th>
<th>Adjusted model ²</th>
<th>Effect size (model 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>P</td>
<td>β</td>
</tr>
<tr>
<td>Developmental quotient</td>
<td>-5.64</td>
<td>(-9.75, -1.53)</td>
<td>0.008</td>
<td>-5.29</td>
</tr>
<tr>
<td>Cognitive subscale</td>
<td>-6.36</td>
<td>(-11.47, -1.26)</td>
<td>0.015</td>
<td>-5.77</td>
</tr>
<tr>
<td>Hearing-and-speech subscale</td>
<td>-6.01</td>
<td>(-12.96, 0.94)</td>
<td>0.09</td>
<td>-5.36</td>
</tr>
<tr>
<td>Hand-and-eye subscale</td>
<td>-4.10</td>
<td>(-8.66, 0.41)</td>
<td>0.07</td>
<td>-3.80</td>
</tr>
<tr>
<td>Locomotor subscale</td>
<td>-5.03</td>
<td>(-10.08, 0.01)</td>
<td>0.05</td>
<td>-4.96</td>
</tr>
</tbody>
</table>
Our Goal: A Universal Brain/Behavior Omnibus


Reducing neurodevelopmental disorders and disability through research and interventions

Michael J. Boivin1,2, Angelina M. Kakooza3, Benjamin C. Warf4, Leslie L. Davidson5,6 & Elena L. Grigorenko7
Figure 1 | Disability-adjusted life years (DALYs) for each neurological, mental health and substance-use (NMS) disorder in 2010 by age. Note the rise of NMS disorders in late childhood and adolescence, particularly depression, anxiety, alcohol and other drug-use disorders. Reprinted with permission from ref. 4.

L.L. Davidson et al., 2013 Nature
The interaction between ‘top down’ executive function and ‘bottom up’ impulsive and emotional processes in regulating social, cultural and biological challenges of adolescent development with a range of outcomes.

L.L. Davidson et al., 2013 Nature
Review article

Neurodevelopment in perinatally HIV-infected children: a concern for adolescence

Barbara Laughton, Morna Cornell, Michael Boivin and Annelies Van Rie

Corresponding author: Barbara Laughton, Children’s Infectious Diseases Clinical Research Unit, Ward J8, Tygerberg Hospital, Private Bag X3, Tygerberg 7505, South Africa. Tel: +27 21 938 4987. Fax: +27 21 938 4151. (BL2@sun.ac.za)

This article is part of the special issue Perinatally HIV-infected adolescents - more articles from this issue can be found at http://www.jiasociety.org

Review article

Understanding the mental health of youth living with perinatal HIV infection: lessons learned and current challenges

Claude A Mellins and Kathleen M Malee

Corresponding author: Claude A Mellins, New York State Psychiatric Institute, Box 15, 1051 Riverside Drive, New York, NY 10032, USA. Tel: +1-212-543-5383, Fax: +1-212-543-6003. (cam14@columbia.edu)

This article is part of the special issue Perinatally HIV-infected adolescents - more articles from this issue can be found at http://www.jiasociety.org
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-Escudero 2 · Itziar Familiar-Lopez 2
Computer Games for Cognitive Rehabilitation

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.
Caregiver Training and Nutritional Enhancement to Foster Resilience in Early Childhood

Home Visit: videotaping feeding, bathing, and shared-work incidents.
Design/Methods

• Quality of caregiving and developmental *milieu*
  – Observed MISC Interactions (OMI) video scoring
  – Modified Caldwell HOME scale

• Socio-economic status (SES) Physical Quality of
Association of caregiver quality of care with neurocognitive outcomes in HIV-affected children aged 2–5 years in Uganda

Judith K. Bass, Noeline Nakasujja, Itziar Familiar-Lopez, Alla Sikorskii, Sarah M. Murray, Robert Opoka, Jura Augustinavicius & Michael J. Boivin
Conclusions

• Compared to TAU, MISC improves
  – Overall quality of caregiving
  – Language development outcomes in HIV-infected children

• Caregiving improvement and corresponding development benefit from MISC may be mediated or modified by improved functionality for caregivers affected by HIV in resource-limited settings
Adjusted Standardized Scores: KABC-II Cognitive Performance

**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 \((P<0.001)\)

Boivin et al., 2018, *AIDS*
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, Noeline Nakasujja, Alla Sikorski, Robert O. Opoka, and Bruno Giordani

Designing and evaluating Brain Powered Games for cognitive training and rehabilitation in at-risk African children


1 Department of Psychiatry, University of Michigan, Ann Arbor, Michigan, USA
2 Departments of Neurology and Psychology and School of Nursing, University of Michigan, Ann Arbor, Michigan, USA
3 Games for Entertainment and Learning (GEL) Laboratory, Department of Media and Information, Michigan State University, East Lansing, Michigan, USA
4 Department of Statistics and Probability, Michigan State University, East Lansing, Michigan, USA
5 Department of Psychiatry, Makerere University, Kampala, Uganda
6 Departments of Psychiatry and of Neurology & Ophthalmology, Michigan State University, East Lansing, Michigan, USA

How does the neurodevelopmental trajectory established during the early critical period establish the potential for neurocognitive rehabilitative benefit in later adulthood, especially as mitigated by factors of risk and resilience across the life span?

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Speed of processing</th>
<th>Spatial syllable match memory</th>
<th>Forward word recognition span</th>
<th>Working memory</th>
<th>Narrative memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants showing improvement</td>
<td>93%</td>
<td>77%</td>
<td>91%</td>
<td>80%</td>
<td>91%</td>
</tr>
<tr>
<td>Average improvement</td>
<td>41%</td>
<td>10%</td>
<td>18%</td>
<td>13%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Data for five of six training exercises are shown; data are not available for exercise 2 (syllable identification). The ET group was able to learn to perform the tasks and showed task-specific improvements after training.
Adaptive Working Memory Training Improved Brain Function
in HIV-Seropositive Patients

Linda Chang, M.D., M.S. 1,2, Gro C. Lohaugen, Ph.D. 1,3, Tamara Andres, M.D., Ph.D. 1, Caroline S. Jiang,

Interpretations: Adaptive-WMT, but not non-adaptive-WMT, improved working memory performance in both SN and HIV-participants, and the accompanied decreased or normalized brain activation suggest improved neural efficiency, especially in HIV-LMX1A-AA-carriers who might have greater dopaminergic reserve. These findings suggest adaptive-WMT may be an effective adjunctive therapy for WM deficits in HIV-participants.
Computer-assisted Cognitive Rehabilitation (CCRT)

• Validated in resource-rich settings for neurocognitive rehabilitation of children with attention / learning difficulties, post traumatic brain injury
• Piloted in Africa post cerebral malaria
• RCT in Ugandan HIV+ children – showed benefit (KABC II)
MVC

- MVC blocks CCR5 co-receptor for HIV on CD4 T cells & macrophages
- Neurocognitive improvement in 2 prospective adult trials
- Also anti-inflammatory
- Enters CSF well


DTG

- Integrase inhibitor
- Good CNS penetration
- Small tablet
- Daily dosage
A5324 – PI Kevin Robertson

• Randomized, Double-Blinded, Placebo-Controlled Trial Comparing ART Intensification with MVC & DTG with No Intensification or Intensification with DTG Alone for Cognitive Impairment in HIV+ adults

• Current ART + P + P
• Current ART + DTG + MVC
• Current ART + DTG + P

• Protocol recruiting
Neuropsychological effects of cognitive rehabilitation in Ugandan children with HIV
To understand the causes of HIV neurocognitive disabilities across the lifespan, we need to start with an understanding of the effects of the complex web of poverty in the first 1000 days of life.

Some . . . see things as that are and say why. Others dream things that never were and ask why not? George Bernard Shaw
Acknowledgements: Funding Sources

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  – *NICHD grant RO1 HD070723* (PIs: Boivin, Bass)
  – *NIMH grant R34 MH084782* (PI: Boivin)

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Thank you!