In utero and Peripartum Antiretroviral Exposure as Determinant of Change in Neurocognitive Function among 6 – 10 years old HIV exposed Ugandan Children - A prospective Cohort Study

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BACKGROUND

• HEU population has at least doubled while the number of perinatally infected children has plummeted by 50%. *(UNAIDS 2017, 2018).*

• ART effectiveness for PMTCT requires these potent drugs cross the placental barrier and rise to therapeutic levels to protect the fetus from HIV-infection. *(McCormack et.al 2014)*

• Yet, peripartum ART comes with several known risks : LBW, mitochondrial and neurotoxicity.
Research Purpose

• To determine whether peripartum exposure to ART adversely affected neurodevelopmental trajectory of HIV exposed uninfected children.

• To investigate variations in this association by type of antiretroviral regimen.
Study Population: 6-10 years old Ugandan Children of HIV-infected women
Design: Prospective Cohort Study

Born 2006 to 2010 (HEU, n=101)

Peripartum ART objectively established via medical records

Neurocognitive Outcomes

1. Socio-emotional Adjustment (SEA)
2. Executive Function (EF)

No Early ART
sdNVP ± AZT
sdNVP+AZT+3TC
cART

Peripartum ART
Months 0, 6, 12
• Cognitive function was determined using structured questionnaires administered by research assistants in local Language.

• Caregivers reported behaviors consistent with EF and SEA competencies in children measured per the BRIEF and BASC-3 respectively.
Outcome Measures: SEA and Executive Function

- **Problematic SEA Composites (n=3):** measures disruptive, non-disruptive and overall level of behavioral dysfunction in children.
  - Externalizing Problems Composite
  - Internalizing Problems Composite
  - Behavioral Symptoms Index

- **Adaptive Skills Index (n=1):** measure of appropriate emotional expression/control.

- **Global Executive Function:** overall dysfunction in cognitive processes enables individuals to plan, focus attention, remember, juggle multiple tasks and appropriately inhibit irrational impulses.
Analytic Strategy

- Repeated measures multivariable analyses using PROC MIXED for each outcome. Random Effect for household of residence.
- Adjusted for: caregiver demographics, depression and behavioral factors (caregiving quality) **BUT NOT** Child-characteristics influenced by early ART exposure – e.g. LBW, prematurity and APGAR score.
- Peripartum ART related $\beta$ and 95% CIs were calculated.
- Effect Size (ES) estimated as a measure of clinical importance interpreted per Cohen Criteria: ‘small’ ($ES<|0.20|$), ‘modest’ $|0.30| \leq ES<|0.50|$, ‘large’ ($|0.50| \leq ES<|0.80|$), ‘very large’ ($ES \geq |0.80|$)
RESULTS
Figure 1: Prevalence of Peripartum ART Exposure Types Among HEU

- None: 55 (0.54)
- sdNVP/sdNVP+AZT: 22 (0.22)
- sdNVP +AZT+ 3TC: 18 (0.18)
- cART: 6 (0.06)
No difference in age-sex standardized SEA and EF by peripartum ART exposure status at study enrolment.

<table>
<thead>
<tr>
<th></th>
<th>Peripartum ART (n=46)</th>
<th>No Peripartum ART (n=55)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiver Age (Yrs, mean, SD)</td>
<td>35.4 (6.9)</td>
<td>36.3 (9.0)</td>
<td>0.596</td>
</tr>
<tr>
<td>Female Sex (n,%)</td>
<td>45 (97.8)</td>
<td>49 (89.1)</td>
<td>0.081</td>
</tr>
<tr>
<td>Biological parent (n,%)</td>
<td>43 (93.5)</td>
<td>50 (90.9)</td>
<td>0.615</td>
</tr>
<tr>
<td>Adaptive Skills Index</td>
<td>0.09 (1.1)</td>
<td>0.01 (0.97)</td>
<td>0.761</td>
</tr>
<tr>
<td>Behavioral Symptoms Index</td>
<td>0.17 (1.01)</td>
<td>-0.04 (1.03)</td>
<td>0.265</td>
</tr>
<tr>
<td>Internalizing Problems Composite</td>
<td>0.19 (0.94)</td>
<td>-0.02 (1.06)</td>
<td>0.227</td>
</tr>
<tr>
<td>Externalizing Problems Composite</td>
<td>0.27 (1.05)</td>
<td>-0.02 (1.09)</td>
<td>0.157</td>
</tr>
<tr>
<td>Global Executive Composite</td>
<td>0.10 (1.1)</td>
<td>-0.10 (1.09)</td>
<td>0.372</td>
</tr>
</tbody>
</table>
Does change in SEA and EF over 12 months vary systematically in relationship to Peripartum ART?
Figure 1: Time-Averaged Change in Adaptive Skills Index of Socio-emotional Adjustment over 12 months in relationship to Peripartum ART Type

- sdNVP/sdNVP+AZT vs. None: 0.19
- sdNVP +AZT+ 3TC vs. None: -0.53
- cART vs. None: 0.52

ART*Time, P>0.10

Z-Score Difference (95% Confidence)
Figure 1: Peripartum ART Type Related Time-Averaged Differences in Change within Problematizing Indices of Socio-emotional Adjustment over 12 months

**Internalizing Problems Index**
- sdNVP/sdNVP+AZT vs. None
- sdNVP +AZT+ 3TC vs. None
- cART vs. None

**Externalizing Problems Index**
- sdNVP/sdNVP+AZT vs. None
- sdNVP +AZT+ 3TC vs. None
- cART vs. None

**Behavioral Symptoms Index**
- sdNVP/sdNVP+AZT vs. None
- sdNVP +AZT+ 3TC vs. None
- cART vs. None

**Effect Size**
- 0.40
- 0.58
- -0.38
- 0.51
- 0.55
- -0.08
- 0.33
- 0.75
- -0.43

**ART*Time, P>0.10**

Z-Score Difference (95% Confidence)
Early Antiretroviral Exposure Related Change in Executive Function Deficit over 12 months

Source: PHAPS2- CIPHER
Age-sex standardized Executive Function Deficits Score in relationship to early antiretroviral regimen exposure among HIV exposed uninfected children
Summary of Results

• Peripartum exposure to cART was infrequent but reflective of clinical practice/policy in birth era.

• Sub-optimal peripartum ART exposure—particularly if sdNVP+AZT+3TC, predicted declines of large clinical importance in adaptive skills, elevations of large clinical importance in problematic SEA composites and elevations of large clinical importance in executive dysfunction.

• Peripartum cART exposure predicted modest increase in adaptive skills, large reductions in executive dysfunction and modest reductions in 2 of 3 problematizing SEA composites over 12 months.
Discussion & Conclusion(s)

- Small sample size is a limitation; longitudinal design and repeated assessment enhance inferential value.
- All peripartum ART exposures are not equal with respect to their long-term neurocognitive effects.
- Appropriately tailored interventions are warranted to mitigate identified neurocognitive risks in this vulnerable group of children.
- Identifying and testing effective cognitive intervention packages are a top priority to enhance long-term functional survival among HEU.
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