Neurocognitive Development of HIV Exposed but Uninfected Infants After Long Term Antiretroviral Drug Exposure

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Abstract

Objective: To determine whether there is a higher risk for neurodevelopmental delay amongst HIV-unexposed infants (HEU) children exposed to cART (Zidovudine Lamivudine, Nevirapine/Tenofovir) in utero and during one year of breastfeeding (WHO Option B+), compared to children born to HIV-uninfected mothers.

Design: Children aged 15-36 months were recruited to this prospective cohort study from Lusaka, Zambia.

Methods: Group A (exposed, n=97) and Group B (control, n=103) children were assessed on their non-verbal problem-solving and language skills using the standardized Capute Scales. A score <85 on the Capute Full Scale Developmental Quotient (DQ) was considered indicative of developmental delay.

Results: An FSDQ <85 was found in 8.3% of Group A participants and 15.4% of Group B participants. In univariate logistic regressions, lower Income (OR=0.03, p=0.03), higher infant age (OR=1.08, p=0.03), and lower birth weight (OR=0.16, p=0.03) were associated with the probability of FSDQ <85, while Group A was not OR (OR=0.50, p=0.16). In the multivariable analysis, only lower birth weight (OR=0.17, p=0.01) and older age (OR=1.01, p=0.03) remained associated with FSDQ <85.

Discussion

This study is the first to assess the neurodevelopmental outcomes in HEU infants in both antenatal and 1 year of postnatal ART’s as per the new WHO guidelines. We found no evidence of increased neurodevelopmental delay for children up to 36 months of age after exposure. This is very reassuring, especially given their longer exposure and the fact that ZDV and 3TC were well tolerated in breast milk feeding.

The association between older infant age and both FSDQ and CAT DQ scores <85 could reflect a limitation of the assessment tool which may have reduced sensitivity for developmental delay at lower ages. It is also possible that as children get older, deficits are in more complex skills that are not seen in earlier stages of development[15]. These possibilities imply that longer term follow up studies looking at older children may be required to assess whether deficits emerge in further development in HEU children.

Lower birth weight was also associated with an increased risk of scoring <85 on all 3 outcomes, as could be expected based on literature of low birth weight children. Despite the fact that our HEU group had lower birth weight, this did not translate into lower developmental scores.

Conclusion

We did not identify a higher prevalence of neurocognitive delay in HEU infants compared to unexposed controls despite antepartum and 1 year of postpartum cART exposure. This data is reassuring for the rollout of new WHO breastfeeding protocols. Long term studies with these infants will be important to confirm these findings.

References


Introduction

Developmental delay has been found in HIV positive infants taking cART when compared to HEU infants; however it has been difficult to clarify how much of this effect may be related to HIV infection of the brain versus a potential adverse drug effect of the ARV therapy that they are treated with. In fact early antiretroviral therapy may be protective for the neurological development of HIV-infected infants [1]. Although a small study suggested that HEU infants (n=39) had lower development scores than non-exposed infants who were children of Hepatitis C positive mothers (n=24), this difference was no longer present when controlled for maternal substance use[2]. Other studies suggest that cART during pregnancy and breastfeeding does not impact early childhood cognitive or language development. This finding is reassuring in light of the substantial increase in infant ART exposure during prolonged breastfeeding. Longer term monitoring of these infants cognitive development will be important to confirm these findings.

Methods

Group B Controls: Infants recruited to Group B were children of HIV-negative mothers living in the same community as the Group A participants. Zambian child health guidelines recommend that all infants bring their children to under-5 clinics monthly from birth to 5 years for vaccinations and health promotion campaigns. Asymomatic children were recruited from the local “under-5” clinics.

Procedure for Cognitive Assessment: Cognitive and language was assessed with the Capute CAT/CLAMS[10]. The CAT measures non-language based problem solving abilities and the CLAMS measures language based problem-solving abilities and language comprehension/expression. The CAT/CLAMS was administered in the presence of an adult under demonstration and/or parental report[11]. The scale has been well correlated to the cognitive and language aspects of the Bayley Scales of Infant Development-2nd Edition (BSID-II) in two pediatric studies[12,13], as well as a neurodevelopmental assessment of children at risk for neurological complications of AIDS[14]. The Capute Scales was selected as the primary outcome due to its ease and brevity of administration. A score <85 is associated with developmental delay. A Full Scale Developmental Quotient (FSDQ) <85 was the primary outcome measure.

TABLE 1. Demographic Data

| Variable                  | Group A | Group B | P value | Group A vs Control B | P value
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<tr>
<td>Infant Age (months)</td>
<td>22.4</td>
<td>24.1</td>
<td>0.03</td>
<td>OR = 0.89</td>
<td>0.847</td>
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<tr>
<td>Infant Gender (M)</td>
<td>52.5%</td>
<td>49.8%</td>
<td>0.39</td>
<td>0.49</td>
<td></td>
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<tr>
<td>Birth Weight (kg)</td>
<td>2.91</td>
<td>3.04</td>
<td>0.07</td>
<td>0.302 (OR=0.19)</td>
<td></td>
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<tr>
<td>Duration of Breastfeeding (weeks)</td>
<td>50.2 (6.0)</td>
<td>71.6 (24.6)</td>
<td>&lt;0.0001</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td>29.9</td>
<td>26.7</td>
<td>0.0002</td>
<td>0.05</td>
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References

