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-exposed uninfected (HEU) children exposed to cART (Zidovudine/Lamivudine/Lopinavir/ritonavir) 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 (FSDQ) was considered indicative of developmental delay.
Results: An FSDQ<85 was found in 8 (8.3%) of Group A participants and 15 (14.6%) of Group B participants. In univariate logistic regressions, lower income (OR=0.93, p=0.02), older infant age (OR=1.08, p=0.03), and lower birth weight (OR=0.16, p=0.0002) were associated with the probability of FSDQ <85, while group (A/B) was not (OR = 0.53, p=0.16). In the multivariable analysis, only lower birth weight (OR=0.17, p<0.001) and older age (OR=1.10, p=0.03) remained associated with FSDQ <85.
Conclusions: Our study shows no evidence of a higher proportion of delayed infants in the exposed group when compared to a similar HIV-unexposed control group. These results suggest that cART during pregnancy and prolonged breastfeeding does not impact early childhood cognitive or language development. This finding is reassuring in light of the recent substantial increase in infant cART exposure during prolonged breastfeeding. Longer term monitoring of these infants cognitive development will be important to confirm these findings.

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 regimens with which they are treated. 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 the neurocognitive development of HEU infants is not negatively impacted by antepartum antiretroviral exposure[3-5], although two studies questioned the delayed development of language with in utero Atazanavir exposure[6,7].

However the impact of a combination of antepartum and then prolonged postpartum exposure during breastfeeding is unknown. Very rapid and essential brain development occurs during the first year of life. As zidovudine and lamivudine (but not Lopinavir/ritonavir) are well secreted into breast milk[8] and cross the blood brain barrier, the impact of long term exposure of nucleoside reverse transcriptase inhibitors on the developing infant's brain is of significant concern.

As more HIV-infected mothers in developing countries are initiated on long-term cART following the rollout of new WHO protocols[9], clarifying the impact of long term exposure to cART on HEU infants is a priority.

Methods

Between June 2011 and August 2013, 200 children ages 15-36 months were recruited to participate in this double-cohort study of neurodevelopmental outcomes. All participants lived within a single district of Lusaka, Zambia

Group A HEU (HIV Exposed but uninfected):
Mothers received zidovudine 300mg/lamivudine 150mg twice daily and lopinavir 200mg/ritonavir 50mg 2 tablets twice daily, to start between gestational age (GA) 14-30 weeks until weaning was complete. A single dose of nevirapine (sdNVP) was given to all mothers in labor and to infants within 48 hours postpartum. Infants also received ZDV liquid for 7 days postpartum. Maternal cART was continued during 6 months of exclusive breastfeeding and then 6 months of complementary feeding with weaning between 12-13 months of age with mothers remaining on cART indefinitely thereafter (WHO Option B+).

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 mothers bring their children to under-5 clinics monthly from birth to 5 years for vaccinations and health promotion campaigns. Asymptomatic children were recruited from the local "under-5" clinics.

Procedure for Cognitive Assessment:
Cognition 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. Items require 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.

Results

TABLE 1. Demographic Data

	HEU (Group A) N=97	Controls (Group B) N=103	P value Group A vs B	P value Univariate analysis FSDQ<85
Infant Age (months)	22.4 (SD 5.0)	24.1 (SD 6.1)	0.03	0.03 OR = 1.08
Infant Gender (M)	52 (54%)	49 (48%)	0.39	0.49
Birth Weight (Kg)	2.91 (0.41)	3.04 (0.59)	0.07	0.0002 (OR=0.16)
Gestational age at Birth (Weeks)	38.6 (2.7)	37.8 (3.2)	0.09	0.1
Duration of Breastfeeding (weeks)	50.0 (9.0)	71.6 (24.6)	<0.0001	0.12
Maternal age	29.9 (5.5)	26.7 (6.1)	0.0002	0.5
Marital status --Single	8 [8.2%]	26 [26.3%]	0.03	0.1
--Married	82 [84.5%]	70 [70.7%]		
Maternal education <primary	8 [8.3%]	14 [14.1%]	0.18	0.19
primary	29 [30.2%]	39 [39.4%]		
secondary	44 [45.8%]	36 [36.4%]		
college	15 [15.6%]	10 [10.1%]		
Family Income/month (median kwacha) {range}	500,000 {0-7,000,000}	507,600 {0-5,922,000}	0.03	0.1

Comparison of Developmental Quotient (DQ)

UNIVARIATE	Overall N=200	HEU (Group A) n=97	Controls (Group B) n=103	P value
CAT DQ <85	*21 (10.5%)*	*10 (10.31%)*	*11 (10.68%)*	*0.93*
CLAMS DQ<85	*29 (14.6%)*	*9 (9.4%)*	*20 (19.4%)*	*0.04*
Full Scale DQ (FSDQ)<85	*23 (11.6%)*	*8 (8.3%)*	*15 (14.6%)*	*0.16*

MULTIVARIATE LOGISTIC REGRESSION for FSDQ<85	Odds Ratio	95% CI	LRT	P value
Group A/B	0.847	0.285-2.5	**0.10**	**0.76**
Monthly Household income (in 100,000 Kw)	0.95	0.83-1.01	**2.1**	**0.15**
Birth Weight (kg)	0.17	0.05-0.50	**10.7**	**0.001**
Infant age (months)	1.10	1.01-1.21	**4.6**	**0.03**

Discussion

This study is the first to assess the neurodevelopmental outcomes in HEU infants exposed to both antenatal and 1 year of postnatal ARV's as per the new WHO guidelines. We found no evidence of increased neurodevelopmental delay for children up to 36 months of age after cART exposure. This is very reassuring, especially given their longer exposure and the fact that ZDV and 3TC are well secreted in breast milk[8].

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 apparent 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 with 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 development scores.

Conclusions

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. Longer term follow-up of these infants will be important to confirm these findings.

References

1)Laughton B, Cornell M, Grove D, Kidd M, Springer PE, Dobbels E, van Rensburg AJ, Violari A, Babiker AG, Madhi SA, Jean-Philippe P, Gibb DM, Cotton MF. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. AIDS. 2012 Aug 24;26(13):1685-90
2)Alimenti A, Forbes J, Oberlander T, Money D, Grunau R, Papsdorf M, Maan E, Cole L, Burdge D. A prospective controlled study of neurodevelopment in HIV-uninfected children exposed to combination antiretroviral drugs in pregnancy. *PEDIATRICS* 2006;118:e1139.
3)Williams PL, Marino M, Malee K, Brogly S, Hughes MD, Mofenson LM. Neurodevelopment and In Utero Antiretroviral Exposure of HIV-Exposed Uninfected Infants January 18, 2010 *PEDIATRICS* Vol. 125 No. 2 February 1, 2010 pp. e250 -e260
4)Culnane M, Fowler M, Lee A, et al. Lack of long-term effects of in utero exposure to Zidovudine among uninfected children born to HIV-infected women. *JAMA.* 1999;281(2):151-157.
5)Gómez C, Archila ME, Rugeles C, Carrizosa J, Rugeles MT, Cornejo JW. [A prospective study of neurodevelopment of uninfected children born to human immunodeficiency virus type 1 positive mothers]. Rev Neurol. 2009 Mar 16-31;48(6):287-91.
6)Rice ML, Zeldow B, Siberry GK, Purswani M, Malee K, Hoffman HJ, Frederick T, Buchanan A, Sirois PA, Allison SM, Williams PL; Pediatric HIVAIDS Cohort Study (PHACS). Evaluation of risk for late language emergence after in utero antiretroviral drug exposure in HIV-exposed uninfected infants. Pediatr Infect Dis J. 2013 Oct;32(10):e406-13. doi: 10.1097/INF.0b013e31829b80ee.
7)Sirois PA, Huo Y, Williams PL, Malee K, Garvie PA, Kammerer B, Rich K, Van Dyke RB, Nozyce ML; Pediatric HIVAIDS Cohort Study. Safety of perinatal exposure to antiretroviral medications: developmental outcomes in infants. Pediatr Infect Dis J. 2013 Jun;32(6):648-55. doi: 10.1097/INF.0b013e318284129a
8)Shapiro RL, Holland DT, Capparelli E et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. J Infect Dis. 2005;192(5):720-7.
9)World Health Organization. Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. (June 2013) ISBN 978 92 4 150572 7.
10)Van der Merwe K, Hoffman R, Black V, Chersich M, Coovadia A, and Rees H. Birth outcomes in South African women receiving highly active antiretroviral therapy: a retrospective observational study. *Journal of the International AIDS Society.* 2011, 14:42
11)Wachtel RC, Shapiro BK, Palmer FB, Allen MC, Capute AJ. CAT/CLAMS: A tool for the pediatric evaluation of infants and young children with developmental delay. *Clinical Pediatrics* 1994;33:410-15.
12)O' Connor, Leppert ML, Shank TP, Shapiro BK, Capute AJ. The Capute Scales: CAT/CLAMS—A pediatric assessment tool for the early detection of mental retardation and communicative disorders. MRDD Res Rev 1998;4:14-19
13)Voigt, RG ; Brown, FR ; Fraley, JK ; et al. Concurrent and predictive validity of the cognitive adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS) and the Mental Developmental Index of the Bayley Scales of Infant Development. CLINICAL PEDIATRICS, June 2003; 42(5): 427-432
14)Wachtel RC, Tepper VJ, Houck D, McGrath CJ, Thompson C. Neurodevelopment in pediatric HIV infection. *Clinical Pediatrics* 1994;33:416-20.
15)Luciana M. Cognitive development in children born preterm: Implications for theories of brain plasticity following early injury. Dev Psychopathol 2003;15:1017-47.