Neurodevelopment of HIV/ARV-exposed uninfected children compared to HIV-unexposed uninfected children during early childhood

Julia M. Young[1,2], Ari Bitnun[3,4], Stanley E. Read[3,4], Mary Lou Smith[1,2,5]

[1] Department of Psychology, The Hospital for Sick Children; [2] Neurosciences and Mental health Program, Research Institute, The Hospital for Sick Children; [3] Division of Infectious Diseases, The Hospital for Sick Children; [4] Department of Pediatrics, University of Toronto; [5] Department of Psychology, University of Toronto Mississauga

The authors have no conflicts of interest to disclose

Introduction & Methods

Introduction

- HIV-exposed uninfected children (HEU) may be at risk for neurodevelopmental challenges due to in utero and perinatal exposure to HIV and anti-retroviral (ARV) medications.[1]
- With the increasing numbers of HEU children worldwide, it is important to determine the potential impact of exposure to HIV and ARVs on neurodevelopmental outcomes.
- Although the literature indicates some mixed findings, there is evidence that discrepancies in cognitive abilities between HEU and HIV-unexposed uninfected (HUU) children emerge during childhood.[2]
- HEU children have demonstrated lower scores of language and cognitive measures that have been identified as early as 1 year of age as well as through adolescence.[3-6]
- The objective of the present study is to compare cognitive abilities and adaptive functioning between HEU and HUU children during the preschool and early school ages.

Methods

- 355 HEU Children were recruited from the Family Centered HIV Clinic at the Hospital for Sick Children in Toronto at 3.5 and 5.5 years of age.
- All children underwent neurodevelopmental assessments as a part of their routine care.
- Inclusion criteria included being born to a mother living with HIV, having a negative HIV status, and no known developmental or medical conditions.
- A comparison cohort of 89 HIV-unexposed uninfected (HUU) children was recruited through the community with comparable socio-demographic status.
- Demographic and maternal medical data were extracted through parent interviews and the child's medical records. (*See Table 1 and Table 2*).

Table 1. Medical variables for HEU children and mothers

	3.5 Year (N = 211)		5.5 Year (N = 144)	
Measure	N*	**N (%)**	**N***	**N (%)**
Perinatal ARV medication				
Zidovudine	205	203 (99%)	136	136 (100%)
Lamivudine	203	17 (8.4%)	133	12 (9%)
Nevirapine	203	23 (11.3%)	133	14 (10.5%)
Maternal CD4 count	***148***		**91**	
≥500		80 (54.1%)		50 (54.9%)
< 500		68 (45.9%)		41 (45.1%)
Maternal Viral Load	***192***		**120**	
< 50		162 (84.4%)		102 (85%)
≥50		30 (15.6%)		18 (15%)
ARV medication regimen	***203***		**132**	
PI-based ARV		149 (73.4%)		98 (74.2%)
NNRTI-based ARV		36 (17.7%)		19 (14.4%)
Other		15 (7.4%)		11 (8.3%)
None		3 (1.5%)		4 (3.0%)
ARV initiation	**185**		**114**	
Prior to pregnancy		87 (47.0%)		50 (43.9%)
1st trimester		54 (29.2%)		37 (32.5%)
2nd trimester		33 (17.8%)		18 (15.8%)
3rd trimester		11 (5.9%)		9 (7.9%)
IV AZT during labor	197	189 (95.9%)	133	129 (96.9%)
Medical condition	206	55 (26.7%)	138	36 (26.1%)

N*- total available data

Methods & Results

Table 2. Demographics

	3.5 Year				5.5 Year			
Mean (SD) or n (%)	**N***	**HEU**	**HUU**	**p-value**	**N***	**HEU**	**HUU**	**p-value**
Child, Maternal, and Social Factors								
Total sample size	242	211	31	-	202	144	58	-
Age	239	3.56 (0.17)	3.53 (0.21)	0.615	191	5.55 (0.38)	5.4 (0.77)	0.116
Sex (M/F)	242	107/104	11/20	0.164	202	64/80	22/36	0.490
Gestational Age	231	37.91 (2.24)	38.67 (1.79)	0.109	**180**	**37.95 (2.57)**	**39.15 (1.94)**	**<0.001**
Birthweight	229	3.04 (0.69)	3.3 (0.61)	0.042	188	3.09 (0.59)	3.2 (0.57)	0.332
In day care at 3 years	203	141 (81.9%)	21 (67.7%)	0.116	168	97 (88.1%)	48 (82.8%)	0.461
Mother employed	202	79 (45.9%)	17 (54.8%)	0.374	161	49 (46.7%)	27 (46.6%)	0.983
One parent in house	222	108 (56.5%)	13 (41.9%)	0.187	**175**	**68 (58.1%)**	**22 (37.9%)**	**0.018**
Maternal substance use	235	17 (8.3%)	2 (6.5%)	0.996	197	12(8.6%)	2 (3.4%)	0.324
Maternal education level	191				141			
High school or less		76 (47.5%)	8 (25.8%)	0.042		**41 (49.4%)**	**13 (22.4%)**	**0.012**
High school plus		84 (52.5%)	23 (74.2%)			**42 (50.6%)**	**45 (77.6%)**	
Language in home	184				146			
Only English		110 (71.9%)	24 (77.4%)	0.683		**54 (61.4%)**	**53 (91.4%)**	**<0.001**
English and other		43 (28.1%)	7 (22.6%)			**34 (38.6%)**	**5 (8.6%)**	
Region of maternal origin	237				194			
North America		33(16.0%)	8 (25.8%)	0.037		23 (15.9%)	21 (36.2%)	0.774
Africa		128(62.1%)	6 (19.4%)			81 (56.3%)	11 (18.9%)	
Carribean		19 (9.2%)	6 (19.4%)			12 (8.3%)	11 (18.9%)	
Other		26(12.6%)	11 (35.5%)			20 (13.9%)	15 (25.9%)	

* Available Data of Total HEU and HUU Sample

Neurodevelopmental Assessments

- Intellectual abilities such as Verbal IQ (VIQ), Performance IQ (PIQ), Full Scale IQ (FSIQ), General Language (GL), and Processing Speed (PRSD) were assessed by the *Wechsler Preschool and Primary Scales of Intelligence, 3rd Edition*.[7]
- Visuomotor Integration (VMI) was assessed with the *Beery-Buktenica Test of Visual Motor Integration*.[8]
- Caregiver report of adaptive behaviours (daily living skills, socialization, communication, and motor skills) were measured with the *Vineland Adaptive Behaviour Scales, 2nd Edition*.[9]

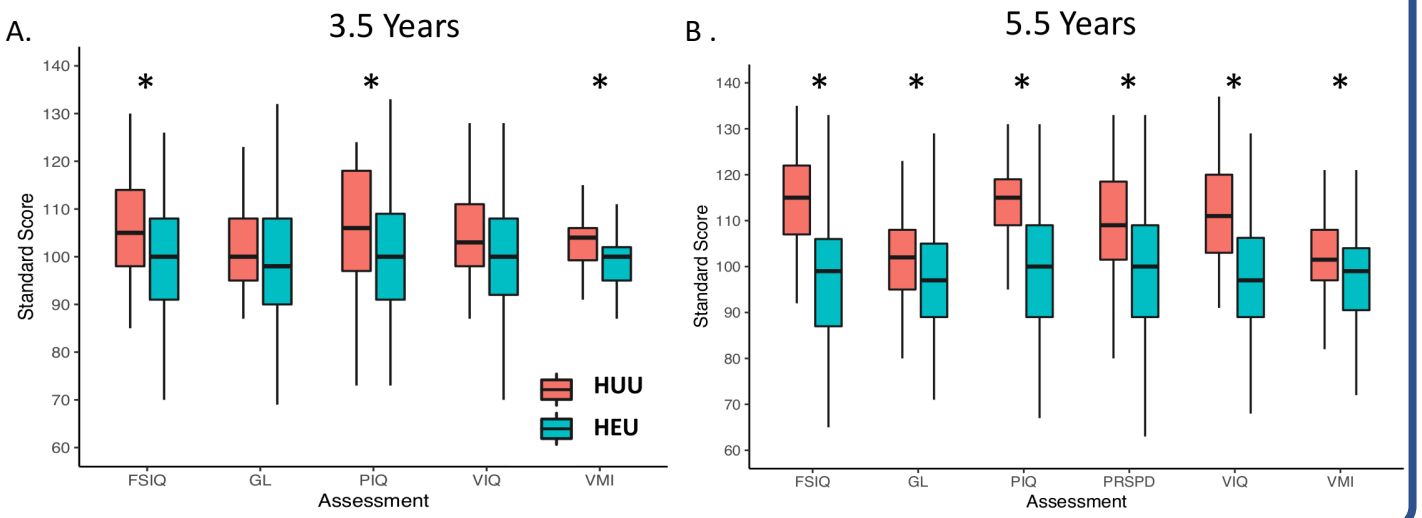
Statistical Analyses

- Demographic and neurodevelopmental variables were compared using non-parametric Kruskal Wallis tests for continuous and ordinal variables and Chi-square tests for categorical variables.
- Multiple regression analyses evaluated the influence of demographic variables on outcomes.
- Linear mixed effects models evaluated age-related developmental changes by group.
- Significance was held at $p \leq 0.01$.

Results

Figure 1. Cross-sectional Analyses

- At 3.5 years of age, HEU children scored significantly lower than HUU children on measures of FSIQ, PIQ, and VMI. (*Figure 1A*)
- At 5.5 years of age, HEU children scored significantly lower than HUU children on all neurodevelopmental measures. (*Figure 1B*)
- At both 3.5 and 5.5 years, HEU children scored significant lower on all measures of adaptive behaviour.
- At 3.5 years, children with parents who were employed achieved higher scores on FSIQ, VIQ, and adaptive measures based on multiple regression analyses.



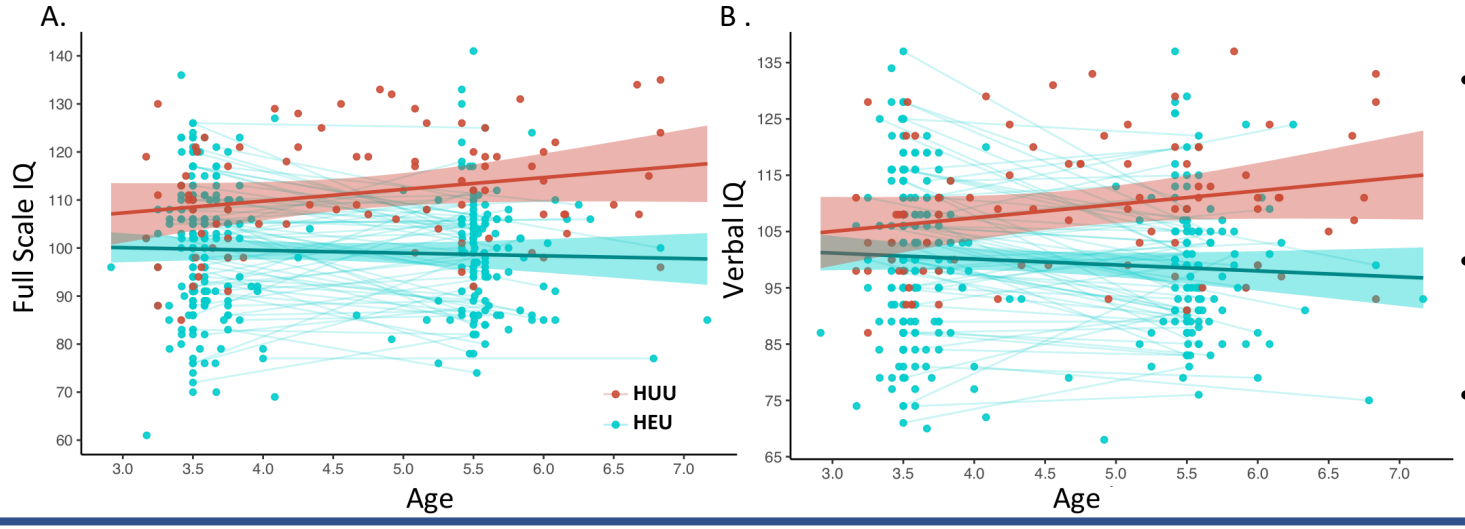


Figure 2. Analyses across age

- Across age, significant group by age interactions were present on measures of FSIQ and VIQ, indicating slower development of these skills in the HEU children. (Figure2A and 2B).
- After controlling for age, females demonstrated high scores than males on VMI and adaptive functioning.
- Modest associations were found between later onset of ARV medications during pregnancy and higher PIQ and FSIQ scores. (*Table 3*)

Results & Discussion

Table 3: LME Model with Medical Variables

	Full Scale IQ			Performance IQ		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.74	-0.15 – 1.62	0.104	0.25	-0.65 – 1.15	0.584
Age	-0.09	-0.17 – 0.00	0.062	-0.03	-0.13 – 0.08	0.602
Viral Load	-0.4	-0.79 – -0.01	0.043	-0.18	-0.56 – 0.20	0.346
ARV Regimen	-0.1	-0.38 – 0.18	0.492	-0.1	-0.38 – 0.17	0.454
ARV Initiation	**0.19**	**0.04 – 0.34**	**0.016**	**0.2**	**0.05 – 0.34**	**0.01**
Medical Conditions	0.03	-0.28 – 0.34	0.852	0.03	-0.28 – 0.33	0.856

Discussion

- HEU children demonstrated significantly lower scores on cognitive and adaptive functioning compared to HUU children at both ages.
- Gaps in verbal and overall intellectual skills widened with age between the two groups, indicating an area of vulnerability in the HEU children and highlighting the importance of ongoing follow-up.
- Slower acquisition of verbal intellectual skills as well as poorer communication skills based on caregiver report is consistent with prior literature in both resource rich and resource poor countries.[3-6]
- Females scored higher than males on measures of adaptive functioning and VMI, indicating earlier maturation in these areas.
- Maternal employment was associated with higher cognitive scores at 3.5 years, suggesting better access to resources and childcare.
- Our findings indicate that negative effects of early exposure to HIV and ARVs may not be evident until later childhood and support routine monitoring of neurodevelopment.

References

1. Evans C, Jones CE, Prendergast AJ. HIV-exposed , uninfected infants : new global challenges in the era of paediatric HIV elimination. *Lancet* 2016; 16:e92-e107.
2. McHenry MS, McAteer CI, Oyungu E, et al. Neurodevelopment in Young Children Born to HIV-Infected Mothers: A Meta-analysis. *Pediatrics* 2018; 141.
3. Rice ML, Zeldow B, Siberry GK, et al. Evaluation of Risk for Late Language Emergence after In Utero Antiretroviral Drug Exposure in HIV-exposed Uninfected Infants. *Pediatr Infect Dis J* 2014; 32:1-19.
4. Wedderburn CJ, Yeung S, Rehman AM, et al. Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort study. *Lancet Child Adolesc Heal* 2019; **3**:803-813.
5. Smith M, Puka K, Sehra R, Read SE, Bitnun A. Longitudinal development of cognitive , visuomotor and adaptive behavior skills in HIV uninfected children , aged 3 – 5 years of age , exposed pre- and perinatally to anti-retroviral medications. *AIDS Care* 2017; 29:1302-1308.
6. Kerr SJ, Puthanakit T, Vibol U, et al. Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. *AIDS Care - Psychol Socio-Medical Asp AIDS/HIV* 2014; 26:1327-1335.
7. Wechsler D. *Wechsler Preschool and Primary Scales of Intelligence, Third Edition*. San Antonio, TX: The Psychological Corporation; 2002.
8. Beery K, Buktenica N, Beery N. *Beery-Buktenica Test of Visual Motor Integration*. San Antonio, TX: The Psychological Corporation; 2010.
9. Sparrow SS, Chicchetti DV, Balla D. *Vineland Adaptive Behaviour Scales, Second Edition*. Minneapolis, MN: Pearson Assessment; 2005.

Acknowledgements

CANADIAN FOUNDATION FOR AIDS RESEARCH | FONDATION CANADIENNE DE RECHERCHE SUR LE SIDA

RBC Foundation Fondation

SickKids

Correspondence:
julia.young@sickkids.ca