Developmental outcomes and ARV exposure in HIV-exposed uninfected children

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BACKGROUND

- Over half of all HIV+ adults worldwide are female
- >1.4 million children globally and >200 children in Canada born annually to mothers living with HIV; majority are **HIV-Exposed Uninfected (HEU)**
- ARV treatment during pregnancy has greatly reduced rates of HIV vertical transmission
- Increasing proportion of HEUs are exposed to ARVs *in utero*
- Concerns of adverse developmental effects from long term ARV exposure in children exposed *in utero* persist
- Long-term effects of exposure to maternal HIV "milieu" and ARVs remain unclear

OBJECTIVES

- To compare frequencies of **neurodevelopmental disorders (NDs)** among HEU children born in BC compared to a matched HIV- unexposed control group, while adjusting for sociodemographic influences
- To examine any possible associations with exposure to maternal ARVs

METHODS

Retrospective Controlled Cohort Study

HEU: HIV-Exposed Uninfected

HUU: HIV-Unexposed Uninfected (controls)

446 **HEUs** → **1:3** matched (98%) → 1323 **HUUs**

- Born to mother living with HIV during 1990-2012
- HIV-uninfected
- Personal health number on record

Controls matched on:
- Age
- Sex
- Geocode

Datasets collected by **Population Data BC** from:
- BC Ministry of Health (Medical Services Plan **ICD 9 codes**) [1]
- Perinatal Services BC [2]
- BC Vital Statistics Agency [3]
- The Oak Tree Clinic, Vancouver, BC [4]

RESULTS

Table 1: 1990-2012 Unadjusted Odds Ratios of ND Diagnosis HEU N=446 HUU N=1323

Neurodevelopmental Disorder (ICD-9)	% HEU/HUU	Odds Ratio (OR)	95% CI[b]	P[c]
At least one ND	**30 / 13**	**2.78**	2.1, 3.6	<0.0001
Infantile Autism (299.0)	2 / 0.7	**3.01**	1.2, 7.6	0.015
Disturbance of Emotions (313.0-313.9)	9 / 3	**2.93**	1.9, 4.6	<0.001
Hyperkinetic Syndrome (314.0-314.9)	14 / 5	**3.30**	2.3, 4.8	<0.0001
Developmental Delay (315.0-315.9)	18 / 6	**3.53**	2.5, 5.0	<0.0001
Intellectual Disability (317.0-319)	-[a]	0.99	0.2, 4.9	0.99
Epilepsy (345.0-345.9)	5 / 3	1.63	0.9, 2.8	0.08
Other Conditions				
Neoplasms (140.0-239.9)	6 / 9	0.66	0.4, 1.0	0.06
Asthma (493.0-493.9)	22 / 21	**1.02**	0.8, 1.3	0.90
Preterm Birth (<37 wks GA)	20 / 7	**3.58**	2.6, 5.0	<0.0001

[a] N<6 undisclosed as per Population BC data disclosure agreement

Table 3: Unadjusted Odds Ratios: Any ND by ARV Regimen

ARV Regimen	Any ND N (%)	Total N	Odds Ratio (95% CI)	P-value
None				
0. HUU (reference)	40 (18)	226	1	<0.0001
1. HEU	32 (42)	76	**3.38** (1.92, 5.96)	
NRTIs Only				
0. HUU (reference)	25 (16)	152	1	<0.0001
1. HEU	25 (49)	51	**4.88** (2.45, 9.76)	
NRTIs + NNRTI				
0. HUU (reference)	34 (17)	201	1	<0.004
1. HEU	23 (33)	69	**2.46** (1.33, 4.55)	
NRTIs + PI (unboosted)				
0. HUU (reference)	61 (15)	398	1	<0.0001
1. HEU	44 (33)	133	**2.73** (1.74, 4.29)	
NRTIs + PI (boosted)				
0. HUU (reference)	15 (5.0)	329	1	0.16
1. HEU	9 (8.0)	112	**1.83** (0.79, 4.22)	

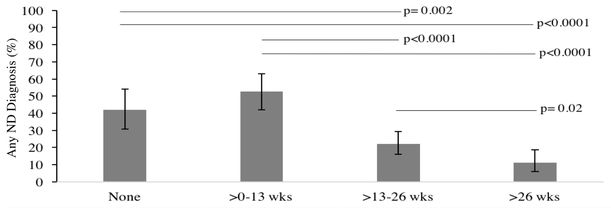
HEUs compared to HUU matched controls for each antiretroviral exposure class.

Table 2: 2000-2013 Adjusted Odds Ratios of Any ND Diagnosis Adjusted for Age at Follow Up, Sex, and Substance use/Smoking HEU N=309 HUU N=917

Crude OR Any ND(95% CI)	Variable	Any ND N (%)	Adjusted OR (95% CI)	P-value
2.25 (1.61, 3.15)	**HIV Exposure**			
	0. HUU (reference)	109 (12)	1	0.011
	1. HEU	72 (23)	**1.67** (1.12, 2.48)	
	Age at Follow Up (years)			
	0. ≤6 yrs (all reference)	39 (7)	1	<0.0001
	1. >6 yrs (all)	142 (22)	**4.47** (3.03, 6.59)	
	Sex			
	0. Female (all reference)	77 (12)	1	<0.0001
	1. Male (all)	104 (18)	**1.98** (1.41, 2.77)	
	Substance use/ Smoking (HEUs & HUUs)			
	0. None (reference)	119 (12)	1	<0.0001
	1. Either	29 (22)	**1.75** (1.34, 2.27)	
	2. Both	33 (35)	summary estimate	

Age at follow up in years. P-value calculated from Pearson chi-squared test. Crude odds ratios were calculated using Mantel-Haenszel method. Adjusted odds ratios were calculated from logistic regression.

Figure 1: Any ND Diagnosis (%) by (Any) *in utero* Antiretroviral Exposure Duration HEU N=411



ARV Duration	None	>0-13 wks	>13-26 wks	>26 wks
Any ND N (%; 95%CI)	32 (42; 31-54)	50 (53; 42-63)	36 (22; 16-29)	12 (11; 6-7)
Total N	76	95	162	107

Duration of exposure (in weeks) in HEU cohort. Univariate comparisons bars illustrate where p<0.05 only, error bars=95% CIs

SUMMARY

- **30% HEUs** in our cohort had one /more diagnoses of: autism, disturbance of emotions, hyperkinetic syndrome, developmental delay, intellectual disability, and/or epilepsy
- **HEUs** at **>2x increased risk** (p<0.0001) for **NDs** relative to controls (13%) and **>3x increased risk for preterm birth**
- **HEU** cohort had **higher** frequencies of exposure to **maternal smoking** (p<0.0001) and **alcohol consumption** during pregnancy (p<0.0001)
- **Increased risk of ND diagnosis persists in HEUs** after adjusting for follow up time, sex and exposure to maternal substance use and/or smoking relative to HUUs
- **Regardless of ARV exposure type or duration of exposure**, **HEUs** had **higher risk of ND** diagnosis compared to controls

CONCLUSIONS

- Our data suggest no direct association between ARVs and NDs within HEU children in our cohort
- BC HEU children at >2x increased risk for 4/6 NDs investigated compared to demographically matched HIV-uninfected controls
- Maternal substance use, smoking and alcohol consumption are likely underestimated for the HUU mothers in our control cohort
- Prevalence of NDs is higher in HEUs; however adverse childhood experiences and other sociodemographic factors must also be considered
- Further research needed to confirm our findings in other settings
- The findings highlight a need for holistic support for pregnant women, in addition to careful developmental monitoring of HEU children past infancy and access to early interventions

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