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First trimester exposure to newer antiretroviral agents and congenital anomalies in a U.S. cohort

Kelly Fung[1], Sonia Hernandez-Diaz[1], Rebecca Zash[2], Ellen G. Chadwick[3], Russell B. Van Dyke[4], Carly Broadwell[1], Jennifer Jao[3], Kathleen Powis[1,5], Lynn M. Yee[3], and **Paige L. Williams**[1] for the Pediatrics HIV/AIDS Cohort Study (PHACS)

[1]Harvard T.H. Chan School of Public Heath, Boston, MA, [2]Beth Israel Deaconess Medical Center, Boston, MA, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Tulane University School of Medicine, New Orleans, LA, [5]Massachusetts General Hospital, Boston, MA

— BACKGROUND —

- Rapid development and roll-out of newer ARVs make it critical to assess safety in pregnancy and among children with fetal exposure.
- More evidence from population-based studies on the association between newer ARV agents and congenital anomalies is needed.

— METHODS —

Study Design

- We evaluated the association between first trimester exposure to newer ARVs and major congenital anomalies among infants enrolled in the U.S.-based prospective Surveillance Monitoring for ART Toxicities (SMARTT) study and born to persons living with HIV between 2012-2022.
- First trimester exposures to ARVs were abstracted from maternal medical records.
- Investigators classified anomalies using the Metropolitan Atlanta Congenital Defects Program (MACDP) classification system.

Statistical Methods

- Generalized estimating equation (GEE) models were used to estimate the odds ratio (OR) and confidence interval (CI) of major congenital anomalies comparing infants exposed to each ARV vs. infants unexposed to that ARV.
- Models were adjusted for infant birth year, maternal age at delivery, pre-pregnancy BMI, pregestational diabetes, and first-trimester alcohol use, and accounted for correlation among siblings and/or multifetal births.
- Sensitivity analyses were conducted adjusting for NRTI backbones and excluding chromosomal anomalies.

Table 1. Demographic Characteristics by Anomaly Status

Demographic Characteristics	Total (n=2034)	No Major Congenital Anomaly (n=1899)	At Least One Major Congenital Anomaly (n=135)
Infant Birth Year			
2012-2015	979 (48%)	895 (47%)	84 (62%)
2016-2019	808 (40%)	769 (40%)	39 (29%)
2020-2022	247 (12%)	235 (12%)	12 (9%)
Age at delivery (median, IQR)	29.7 (25.5, 34.4)	29.7 (25.5, 34.4)	29.4 (25.6, 34.6)
Pregestational Diabetes	60 (3%)	55 (3%)	5 (4%)
First Trimester Alcohol Use	154 (8%)	144 (8%)	10 (7%)
Pre-Pregnancy BMI (kg/m^2)			
Underweight/Normal (<25)	468 (23%)	438 (23%)	30 (22%)
Overweight (25-29.9)	363 (18%)	336 (18%)	27 (20%)
Obese (30+)	604 (30%)	557 (29%)	47 (35%)
Unknown	599 (29%)	568 (30%)	31 (23%)

In a U.S. cohort of infants born to pregnant persons with HIV, exposure to newer ARVs in the first trimester did not significantly elevate the odds of major congenital anomalies.

— RESULTS —

Summary of Results

- Of 2034 eligible infants, at least one major congenital anomaly occurred in 135 (6.6%; 95%CI: 5.6%-7.8%).
- Cardiovascular (n=43) and musculoskeletal (n=37) anomalies were most common.
- The adjusted odds ratios (95% CI) for at least one congenital anomaly are shown in **Figure 1**.
- Findings were similar after adjustment for nucleoside backbones in the ARV regimen, and when excluding 10 infants with chromosomal anomalies.

Figure 1: Adjusted ORs for 1st Trimester Exposure to Newer ARVs and ≥1 Major Congenital Anomaly

1st Trimester ARV Exposure	# Infants Exposed in 1st Trimester N=2034	Congenital Anomaly Prevalence in Exposed % (95% CI)	Congenital Anomaly Prevalence in Unexposed % (95% CI)
Rilpivirine (RPV)-exposed vs RPV-unexposed	291	19/291 6.5% (4.0%-10.0%)	116/1743 6.7% (5.5%-8.0%)
Darunavir (DRV)-exposed vs DRV unexposed	268	18/268 6.7% (4.0%-10.4%)	117/1766 6.6% (5.5%-7.9%)
Elvitegravir (EVG)-exposed vs EVG-unexposed	193	13/193 6.7% (3.6%-11.2%)	122/1841 6.6% (5.5%-7.8%)
Dolutegravir (DTG)-exposed vs DTG-unexposed	186	8/186 4.3% (1.9%-8.3%)	127/1848 6.9% (5.8%-8.1%)
Raltegravir (RAL)-exposed vs RAL-unexposed	152	9/152 5.9% (2.7%-10.9%)	126/1882 6.7% (5.6%-7.9%)
Bictegravir (BIC)-exposed vs BIC-unexposed	52	1/52 1.9% (0.05%-10.3%)	134/1982 6.8% (5.7%-8.0%)

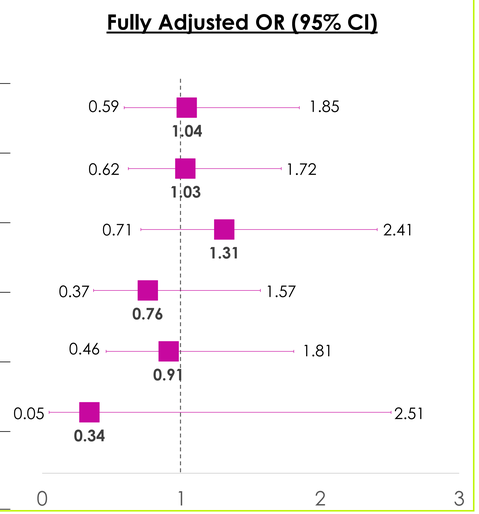

Table 2. Types of Major Congenital Anomalies

Congenital Anomaly	Number of Children with At Least One Anomaly (% out of those with anomalies, n=135)
Cardiovascular	43 (31.9%)
Musculoskeletal	37 (27.4%)
Central Nervous System	24 (17.8%)
Genital	16 (11.9%)
Renal/Ureteral	11 (8.2%)
Chromosomal	10 (7.4%)
Lower Gastrointestinal	5 (3.7%)
Diaphragm/Abdominal Wall	4 (3.0%)
Respiratory	2 (1.5%)
Facial	3 (2.2%)
Skin	1 (0.8%)

| CONCLUSIONS |

- The odds of congenital anomalies among infants with first trimester exposure to newer ARVs did not differ substantially from that among infants unexposed to these specific ARVs.
- However, modest effects cannot be ruled out, highlighting the need for continued evaluation of these associations in larger populations.

— CONTACT INFORMATION —

Paige L. Williams, PhD
Department of Biostatistics
Harvard T. H. Chan School of Public Health
665 Huntington Ave, 443 Building II
Boston, MA 02115-6017
Email: paige@hsph.harvard.edu

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