An analysis of congenital anomalies in pregnant women living with HIV in Canada: no signal for neural tube defects in women exposed to dolutegravir

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Introduction

Background:

- National Institute of Health's birth surveillance study in Botswana found 0.94% (4/426) of babies born to mothers taking dolutegravir at conception had a neural tube defect (NTD), compared to 0.12% (14/11,300) of women on other antiretroviral therapy (ART) combinations.[1]
- With increasing rates of dolutegravir use internationally, limited pregnancy safety data, and recent evidence raising a safety concern of NTDs, it is crucial to further explore any association between dolutegravir and NTDs, or other congenital anomalies.

Objectives:

1. To examine the rates of congenital anomalies in infants born to women living with HIV (WLWH) and their potential associations with dolutegravir and other ART combinations
2. To determine the rates of NTDs and other congenital anomalies in dolutegravir-exposed pregnancies using the Canadian Perinatal HIV Surveillance Program (CPSHP)

Methods

Study Population:

- Data extracted from Canadian Perinatal HIV Surveillance Program's (CPHSP) dataset (2007-2017)
  - 22 sites, 19 HIV referral health centres, 3 health departments from all Canadian provinces and territories
- From 2007 – 2017, there were 2,591 live infants born to WLWH, of which 2,423 had data available on congenital anomalies and antiretroviral therapy in pregnancy.

Study Design:

- Descriptive analyses were conducted to determine demographics of pregnant WLWH, and the incidence of congenital anomalies, including NTDs, among those women exposed to dolutegravir, and other antiretrovirals, during pregnancy

Results

Demographics

- Majority of deliveries were at term (81.9%); mean gestational age of 38.1 weeks
- No difference in congenital anomaly frequency by maternal ethnic background (p=0.683)

	No Anomalies	Anomaly Present	All
Maternal region of birth, n (%)			
Canada	944 (40.6)	31 (31.6)	975 (40.2)
Africa	1041 (44.8)	47 (48.0)	1088 (44.9)
Other	285 (12.3)	18 (18.4)	303 (12.5)
Unknown	55 (2.4)	2 (2.0)	57 (2.4)
Ethnicity, n (%)			
Black	1227 (52.8)	58 (59.2)	1285 (53)
Indigenous	463 (19.9)	18 (18.4)	481 (19.8)
White	440 (18.9)	16 (16.3)	456 (18.8)
Asian	71 (3.1)	4 (4.1)	75 (3.1)
Hispanic	32 (1.4)	0 (0)	32 (1.3)
Other	55 (2.4)	1 (1.0)	56 (2.3)
Unknown	37 (1.6)	1 (1.0)	38 (1.6)

Results

Congenital Anomalies by Timing of ART Exposure

	Congenital Anomalies	Total
ART timing unknown	2 (2%)	100
No ART exposure in pregnancy	6 (5.1%)	118
ARTs at conception	55 (4.2%)	1,311
ARTs started in 1st trimester	8 (3.9%)	204
Any ART exposure in 1st trimester	63 (4.1%)	1,511
ARTs started from 14 weeks onwards	27 (3.9%)	690

- The prevalence of congenital anomalies was not significantly different according to timing of exposure by gestational age groups (p=0.915)

Frequency of Congenital Anomalies by System

Type of Anomaly by System	Frequency	Rate
Chromosomal	12	0.50%
Cardiac	17	0.70%
Isolated polydactyly	15	0.61%
Urinary	13	0.53%
Musculoskeletal (other than polydactyly)	9	0.37%
Vascular	9	0.37%
Respiratory	7	0.28%
Nervous System (other than NTD)	5	0.20%
Isolated Neural tube defect	3	0.12%
Eye, Ear, Face and Neck	2	0.08%
Digestive	1	0.04%
Genital	1	0.04%
Multisystem anomalies (non-chromosomal)	4	0.16%
TOTAL	98	4.00%

Congenital Anomalies by ART Type

ART in 1st Trimester	No Anomalies	Chromosomal	Non-Chromosomal	Total
Unknown	112	0	2	114
No ART	770 (95.9)	2 (0.25)	31 (3.9)	803
Regimen including NRTI's + NNRTI	214 (96.8)	0 (0.0)	7 (3.2)	221
Efavirenz	43 (93.5)	0 (0.0)	3 (6.5)	46
Nevirapine	120 (96.8)	0 (0.0)	4 (3.2)	124
Rilpivirine or etravirine	51 (100.0)	0 (0.0)	0 (0.0)	51
Regimen including NRTI's + PI	932 (95.7)	8 (0.8)	34 (3.5)	974
Regimen including NRTIs + INSTI	170 (94.4)	1 (0.6)	9 (5.0)	180
Dolutegravir	76 (95.0)	0 (0.0)	4 (5.0)	80
Elvitegravir	25 (89.3)	0 (0.0)	3 (10.7)	28
Raltegravir	72 (94.7)	1 (1.3)	3 (4.0)	76
Other*	127 (97.0)	1 (0.8)	3 (2.3)	131
TOTAL	**2325**	**12**	**86**	

- Rate of NTDs of those exposed to ART at conception was 2/1311 (0.15%)
- Rate of NTDs of those unexposed to ART in first trimester 1/690 (0.14%)
- **No NTDs associated with dolutegravir in the 80 infants born to women with first trimester exposure, including 69 who were on dolutegravir at time of conception**
- 10.7% rate of congenital anomalies in 28 women on elvitegravir

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References

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Conclusions

- **Canadian data demonstrates no NTDs among neonates exposed to dolutegravir**
- No difference in the rate of congenital anomalies in neonates exposed to dolutegravir during pregnancy
- However, 3-fold higher rate of congenital anomalies in neonates with elvitegravir exposure in the first trimester (10.7%)