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MATERNAL DOLUTEGRAVIR (DTG) USE, AND PREGNANCY AND BIRTH OUTCOMES: THE ANTIRETROVIRAL PREGNANCY REGISTRY (APR)

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Introduction

- In 2018, preliminary findings from Tsepamo Study, a birth outcomes surveillance study conducted in Botswana, showed a higher-than-expected number of neural tube defects (NTD) among newborn infants whose mothers were exposed to DTG-based antiretroviral therapy (ART) at the time of conception
  - 4 NTDs in 426 (0.94%) infants born to women receiving DTG at conception compared to 14/11,300 (0.12%) among infants born to women on non-DTG ART at conception[1]
  - NTD prevalence difference between DTG and non-DTG ART at conception was −0.82% (95% CI: −0.24%, −2.3%)

- The latest analysis with data through March 2021 shows a lower prevalence rate
  - 9 NTDs in 5,860 (0.15%) infants born to women receiving DTG at conception compared to 22 NTDs among 22,475 (0.10%) infants born to women on non-DTG ART at conception[2]
  - NTD prevalence difference between DTG and non-DTG ART at conception is 0.06% (95% CI: −0.03, 0.20)

1. Zash et al. IAS 2018; Amsterdam, the Netherlands. Presentation TUSY15. **2.** Zash et al. IAS 2021; Virtual. Presentation OAXLB0102.

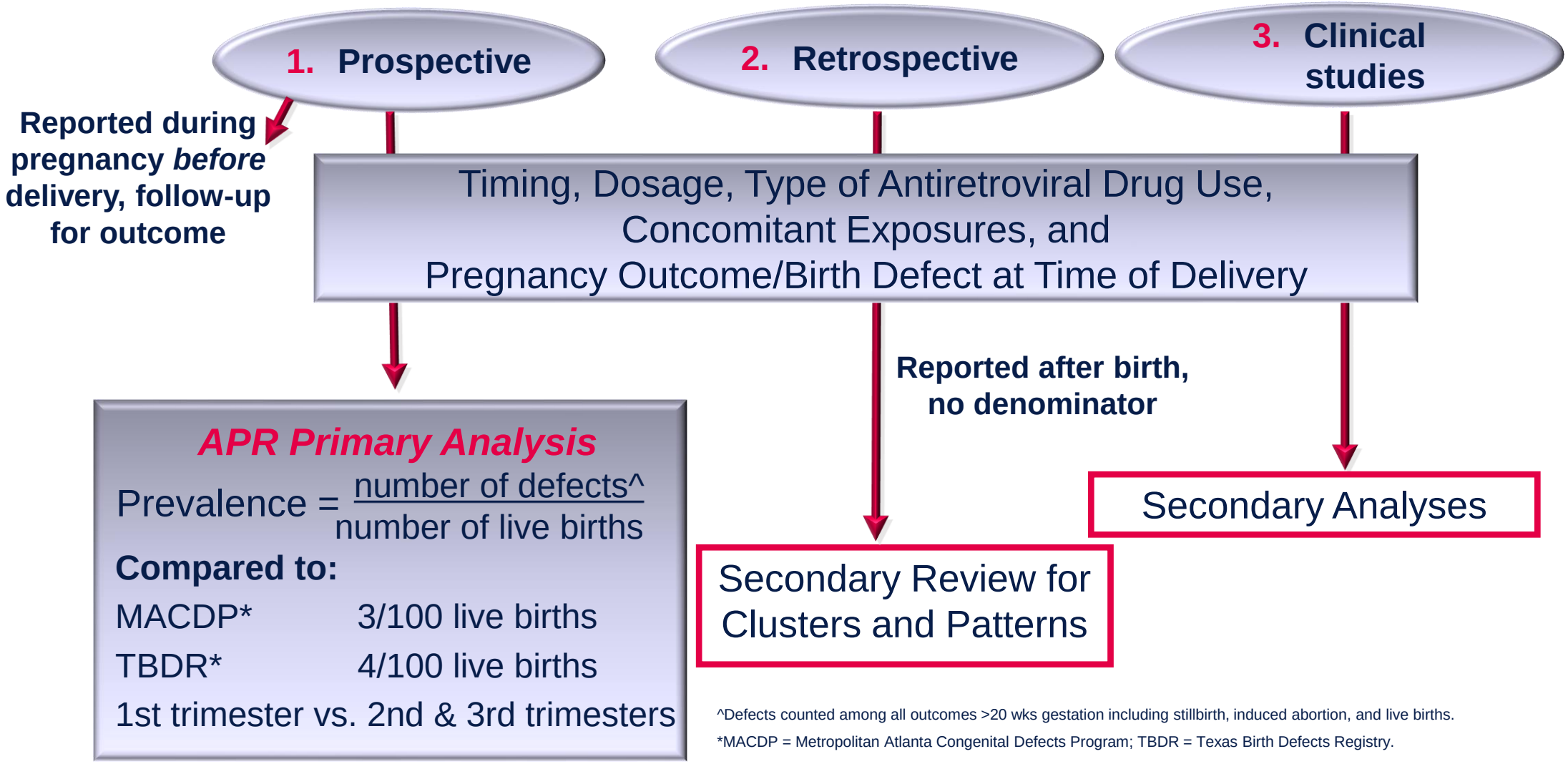
The Antiretroviral Pregnancy Registry (APR)

- The APR is an international, prospective exposure–registration cohort study
  - Overseen by an independent Advisory Committee
  - Currently 27 funding sponsors
  - Includes 170 ARV drugs: 59 brand-name single-entity drugs or fixed-dose combinations plus 111 generic versions
  - As of January 2021, has accumulated data on 21,861 prospectively reported pregnancies with ARV exposure
- Designed to provide early warning signals of major teratogenicity to assist clinicians and women of child-bearing potential (WCBP) in assessing potential risks and benefits of ARV use during pregnancy
- Primary objectives of the APR are to:
  - Monitor prenatal exposures to ARVs to detect a potential increase in the risk of birth defects
  - Estimate prevalence of major birth defects and compare to the general population
  - Supplement animal toxicology, clinical, and epidemiological study data

Methods: APR Primary Prospective Cohort

- Healthcare providers register pregnant women with prenatal ARV exposures before pregnancy outcome is known, report data on exposure throughout pregnancy, and provide birth outcome data
- Registration is voluntary and confidential; patient data are anonymized
- Birth defects are reviewed by a dysmorphologist, coded according to modified Metropolitan Atlanta Congenital Defects Program (MACDP) criteria, and classified by organ system
- Analysis includes estimating prevalence of birth defects, defined as ≥1 major birth defect or ≥2 minor defects

Antiretroviral Pregnancy Registry Analyses



^Defects counted among all outcomes >20 wks gestation including stillbirth, induced abortion, and live births.

*MACDP = Metropolitan Atlanta Congenital Defects Program; TBDR = Texas Birth Defects Registry.

Study Objective

- We evaluated pregnancy and neonatal outcomes among infants with periconception and prenatal exposure to dolutegravir using data from the Antiretroviral Pregnancy Registry (APR)

- Only prospectively reported pregnancies reported through January 2021 are included in this analysis

Methods

- Data on prospectively enrolled pregnancies through January 2021 with birth outcomes are summarized for dolutegravir:
  - Earliest timing of exposure was assigned to each pregnancy:
    - *Periconception* – Exposure from 2 weeks prior to conception through ≤28 days after conception (6 weeks estimated gestational age)
    - *Later 1st trimester* – Initial exposure started later in the 1st trimester (after 6 weeks estimated gestational age)
    - *2nd/3rd trimester* – Exposure started after the 1st trimester ended (>12 weeks estimated gestational age)
- Birth defects in the central nervous system (CNS) include both NTDs and encephalocele (reported separately from NTD)

Results: Demographic and Clinical Characteristics of Pregnant Women Exposed to DTG

Total pregnancies, N	1010
Maternal age at conception (years)	
Mean	29.8
Median	30.0
Range, min-max	14-54
CD4+ T-cell categories at time of reporting, n (%)	
≥500 cells/μL	471 (46.6%)
200-499 cells/μL	321 (31.8%)
<200 cells/μL	126 (12.5%)
Missing	92 (9.1%)
Race/Ethnicity, n (%)	
Black	624 (61.8%)
White	124 (12.3%)
Asian	18 (1.8%)
Hispanic	119 (11.8%)
Other	100 (9.9%)
Missing	25 (2.5%)

Results: Demographic and Clinical Characteristics of Pregnant Women Exposed to DTG (cont)

HIV status, n (%)	
Positive	995 (98.5%)
Negative (e.g., PrEP, PEP)	15 (1.5%)
Country of origin, n (%)	
USA	778 (77.0%)
UK	69 (6.8%)
Other	163 (16.1%)
Timing of earliest exposure to DTG, n (%)	
Periconception	526 (52.1%)
Later 1st trimester	105 (10.4%)
2nd trimester	260 (25.7%)
3rd trimester	119 (11.8%)

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Pregnancy Outcomes of Enrolled Women Exposed to DTG – Prospective Registry Reports

Pregnancies = 1010	Overall DTG exposed	Earliest exposure to DTG – Periconception	Earliest exposure to DTG – Later 1st trimester	Earliest exposure to DTG – 2nd/3rd trimester
Total outcomes, N	1036*	539	107	390
Live births	956 (92.3%)	475 (88.1%)	101 (94.4%)	380 (97.4%)
Stillbirths	12 (1.2%)	5 (0.9%)	2 (1.9%)	5 (1.3%)
Spontaneous abortions	38 (3.7%)	34 (6.3%)	3 (2.8%)	1 (0.3%)
Induced abortions	28 (2.7%)	24 (4.5%)	1 (0.9%)	3 (0.8%)
Missing	2 (0.2%)	1 (0.2%)	0	1 (0.3%)

*Including 26 twin births.

Neonatal Outcomes With Prenatal Exposure to DTG (Among Singleton, Live Births Without Defect, N=873)

	Overall DTG exposed	Earliest exposure to DTG – Periconception	Earliest exposure to DTG – Later 1st trimester	Earliest exposure to DTG – 2nd/3rd trimester
Total outcomes, N	873	436	94	343
Gestational age				
≥37 weeks	778 (89.1%)	387 (88.8%)	80 (85.1%)	311 (90.7%)
<37 weeks (preterm)	92 (10.5%)	48 (11.0%)	14 (14.9%)	30 (8.7%)
Missing	3 (0.3%)	1 (0.2%)	0	2 (0.6%)
Birth weight				
≥2500 grams	750 (85.9%)	368 (84.4%)	83 (88.3%)	299 (87.2%)
<2500 grams (LBW)	103 (11.8%)	55 (12.6%)	11 (11.7%)	37 (10.8%)
<1500 grams (VLBW)	22 (2.5%)	14 (3.2%)	3 (3.2%)	5 (1.5%)
Missing	20 (2.3%)	13 (3.0%)	0	7 (2.0%)

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Prevalence of Birth Defects – DTG Exposed Pregnancies

Prevalence and 95% Confidence Intervals for Birth Defects

Number of live births	956
Number of live births with at least one defect	39 (39/956 = 4.1%, 95% CI: 2.92-5.53)

Timing of Exposure	Birth Defects/Live Births	Prevalence % (95% CI)**
First trimester	19/576	3.3 (95% CI: 2.00-5.10)
Periconception	16*/475	3.4 (95% CI: 1.94-5.41)
Later first trimester	3/101	3.0 (95% CI: 0.62-8.44)
Second/Third trimester	20/380	5.3 (95% CI: 3.24-8.01)

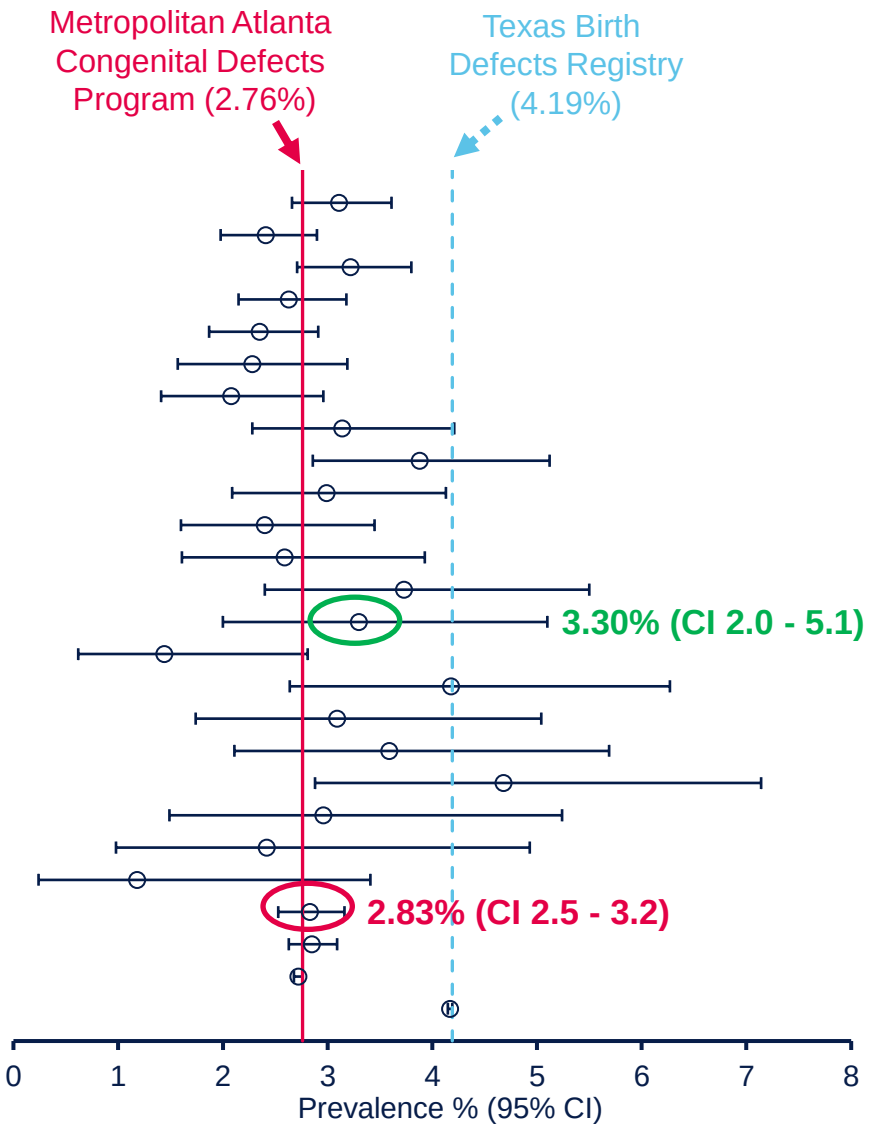
*Includes one neural tube defect.

**Based on Clopper-Pearson exact method.

Drug-Specific Overall Birth Defect Rates

- **Prevalence of birth defects (95% CI) with 1st trimester exposure: 1 January 1989 to 31 January 2021**
  - For drug to be included for comparison with population rates, must meet threshold of having ≥200 1st trimester exposed pregnancies
  - 22 ARVs have ≥200 first trimester exposures

	Defects/Live births	Prevalence (95% CI), %
Lamivudine	169/5433	3.11 (2.66-3.61)
Tenofovir DF	108/4483	2.41 (1.98-2.90)
Zidovudine	136/4225	3.22 (2.71-3.80)
Emtricitabine	104/3952	2.63 (2.15-3.18)
Ritonavir	81/3453	2.35 (1.87-2.91)
Atazanavir	33/1447	2.28 (1.57-3.19)
Lopinavir	30/1439	2.08 (1.41-2.96)
Abacavir	43/1368	3.14 (2.28-4.21)
Nelfinavir	47/1212	3.88 (2.86-5.12)
Nevirapine	35/1171	2.99 (2.09-4.13)
Efavirenz	28/1166	2.40 (1.60-3.45)
Stavudine	21/811	2.59 (1.61-3.93)
Darunavir	24/643	3.73 (2.40-5.50)
Dolutegravir	**19/576**	3.30 (2.00-5.10)
Rilpivirine	8/557	1.44 (0.62-2.81)
Tenofovir alafenamide	22/526	4.18 (2.64-6.27)
Raltegravir	15/486	3.09 (1.74-5.04)
Cobicistat	17/473	3.59 (2.11-5.69)
Didanosine	20/427	4.68 (2.88-7.14)
Elvitegravir	11/371	2.96 (1.49-5.24)
Indinavir	7/289	2.42 (0.98-4.93)
Telbivudine	3/254	1.18 (0.24-3.41)
First Trimester APR	**310/10950**	2.83 (2.53-3.16)
Any Trimester APR	590/20686	2.85 (2.63-3.09)
MACDP		2.72 (2.68-2.76)
TBDR		4.17 (4.15-4.19)



MACDP = Metropolitan Atlanta Congenital Defects Program.

TBDR = Texas Birth Defects Registry.

95% CIs are calculated using the Clopper-Pearson exact binomial method.

Conclusions

- APR data through 31 January 2021 show that the prevalence rate for overall birth defects with DTG use (4.1%) is no different than the population expected rate of defects (2.7% and 4.1% from Metropolitan Atlanta Congenital Defects Program and Texas Birth Defects Registry, respectively)

- In the updated APR data, there is one NTD with 475 periconception DTG exposures, giving an NTD prevalence of 0.21%

Conclusions (cont)

- The number of pregnancies enrolled in the APR with DTG periconception exposure are currently insufficient to rule out or confirm any potential association of DTG with NTD
- The Registry continues to closely monitor birth defects, including NTDs with periconception exposure, in pregnancies exposed to DTG and other integrase inhibitors
- Healthcare providers are encouraged to continue to report pregnancies with antiretroviral exposures prospectively to the APR, especially those involving newer ARVs [www.APRegistry.com]

Advisory Committee Consensus Statement (Precis)

- The Antiretroviral Pregnancy Registry finds no apparent increases in frequency of defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause; however, potential limitations of registries should be recognized

- Providers are strongly encouraged to report eligible patients to **SM_APR@APRegistry.com** or visit **www.APRegistry.com**

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