Dolutegravir (DTG) Use During Pregnancy and Birth Outcomes: Data from the Antiretroviral Pregnancy Registry (APR)

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- I am an employee of ViiV Healthcare & own company (GSK) stock
- The views are those of the authors and do not reflect the opinions of the U.S. Department of State or the U.S. government

Introduction

- In May 2018 an unscheduled interim analysis of the Tsepamo study data suggested a potential signal for neural tube defects (NTD) with use of DTG based ART at conception[1]
  - 4 NTDs in 426 **(0.94%)** women receiving DTG at conception

- In July 2019 updated, planned analysis with expanded sites covering 72% of all births in Botswana from August 2014 through March 2019 reported a decrease in NTD prevalence[2] compared to initial report

- However, the prevalence difference is significantly higher with DTG ART at conception than with non-DTG ART at conception or in HIV-uninfected women:
  - **5 NTDs among 1,683 deliveries (0.30%, 95% CI 0.13-0.69) in women receiving DTG at conception**
  - 15 NTDs among 14,792 deliveries (0.10% 95% CI 0.06-0.17) in women receiving non-DTG ART at conception
  - 70 NTDs among 89,372 deliveries (0.08%, 95% CI 0.06-0.10) in HIV-uninfected women
  - **Prevalence difference of 0.20 (95% CI 0.01-0.59) DTG at conception vs. Non-DTG at conception**

[1]Zash et al, NEJM 2018; [2]Zash et al, NEJM 2019

Introduction

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

- Data are updated through July 2019 (and differ from abstract)

The Antiretroviral Pregnancy Registry

- The APR is a voluntary, international, prospective exposure-registration cohort study
  - Started as zidovudine in Pregnancy Registry in 1989; became APR in 1993
  - Currently 29 sponsoring ARV manufacturers
  - Overseen by an independent Advisory Committee
  - As of July 2019, include >21,120 prospective reports of ARV exposed pregnancies
- Designed to assist clinicians and patients in weighing potential risks and benefits of ARVs during pregnancy
  - Monitors prenatal exposures to ARVs to detect a potential increase in the risk of birth defects
  - 150 ARV drugs: 57 brand-name single-entity drugs or fixed-dose combinations; 93 generic versions
- APR Objectives:
  - Provide early warning signals of major teratogenicity
  - Estimate prevalence of major birth defects and compare to the general population
  - Supplement animal toxicology, clinical, and epidemiological study data

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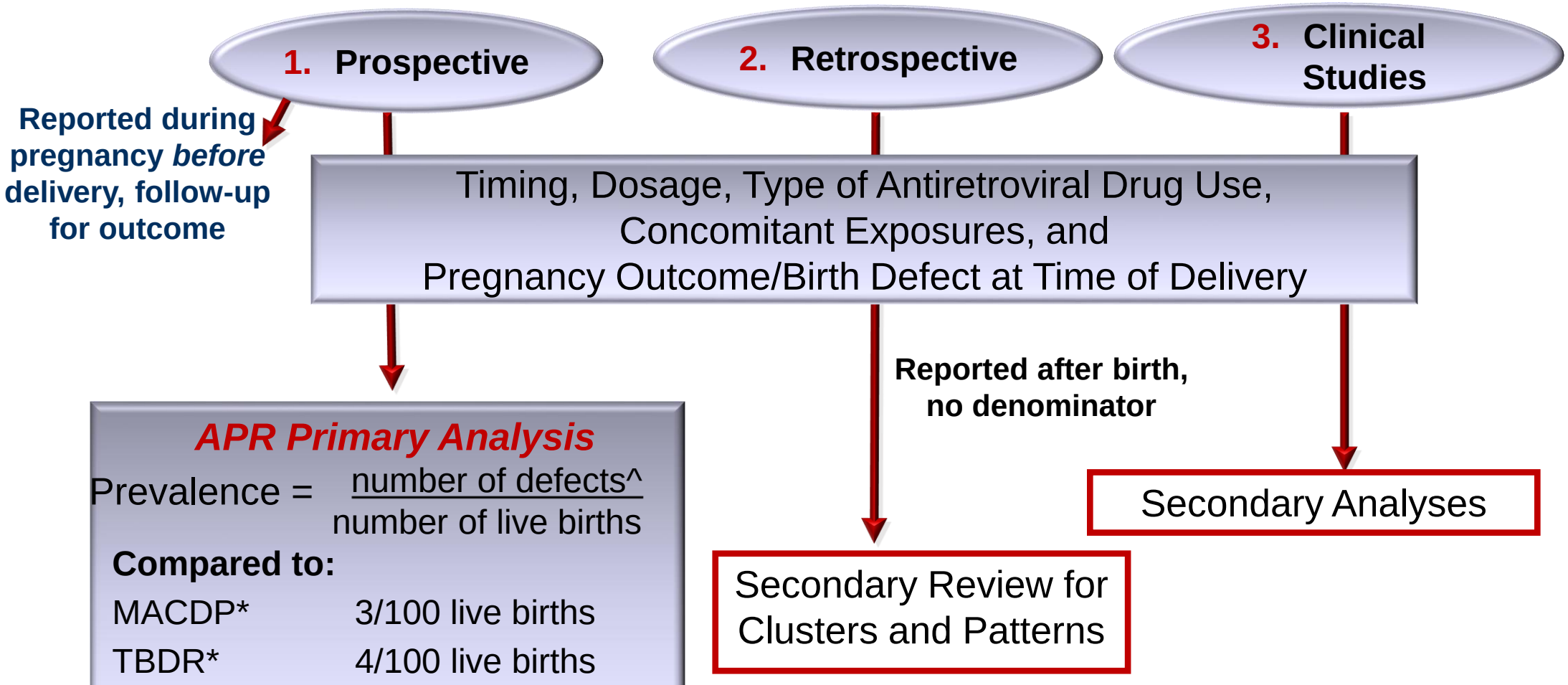
Methods: APR Primary Prospective cohort

- Clinicians 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 & confidential; patient data is 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 birth defects, defined as ≥1 major birth defect or ≥2 minor defects.

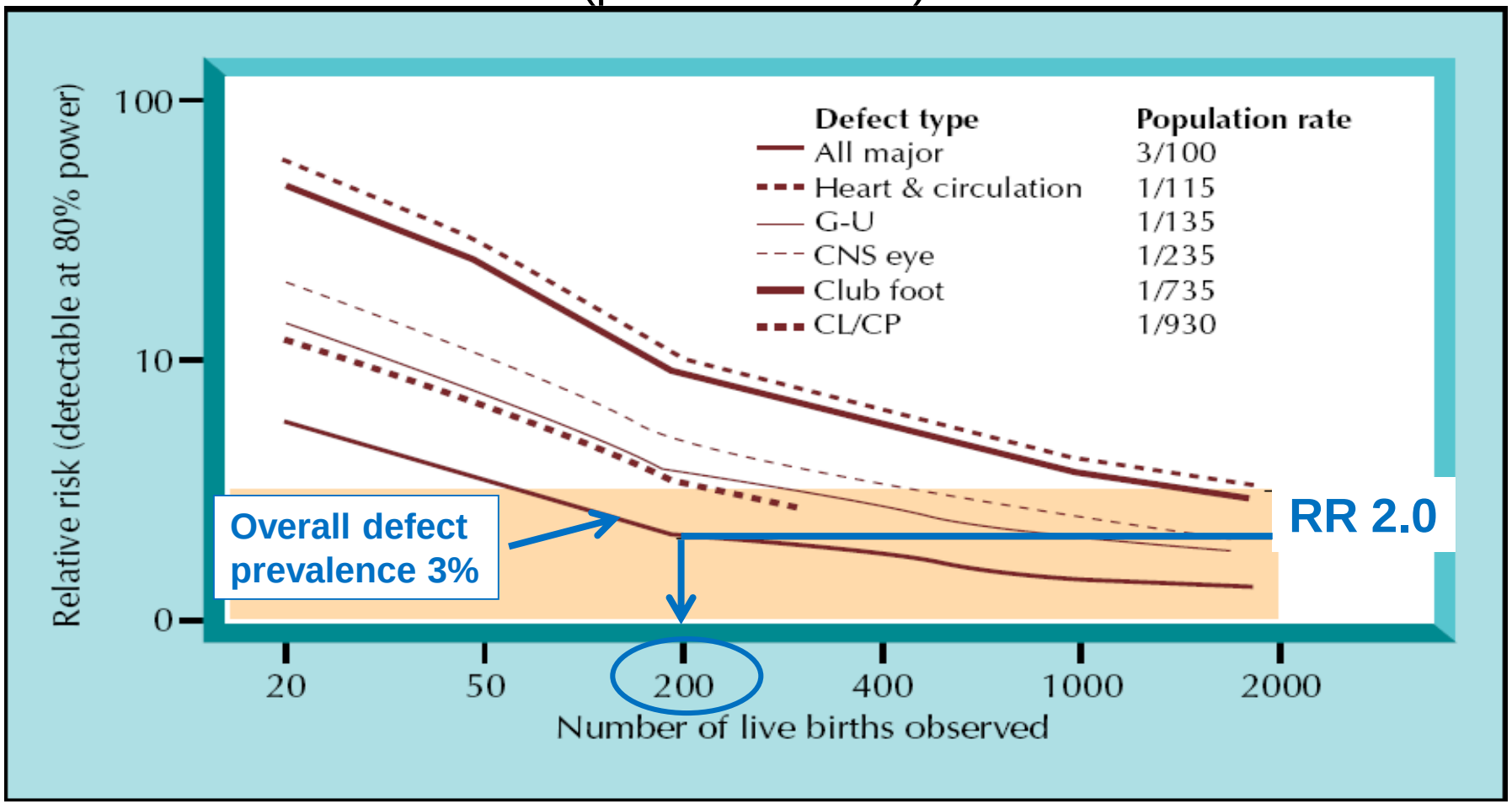
Antiretroviral Pregnancy Registry Analysis



^ defects counted among all outcomes >20 wks gestation including stillbirth, induced abortion & live births
** MACDP = Metropolitan Atlanta Congenital Defects Program; TBDR = Texas Birth Defects Registry*

Ability to Rule-Out An Increase in Birth Defects With Drug Exposure is Related to Defect Prevalence and Number of Observed Exposures

200 first trimester exposures are needed to rule out a 2-fold ↑ in overall birth defects (prevalence 3%)

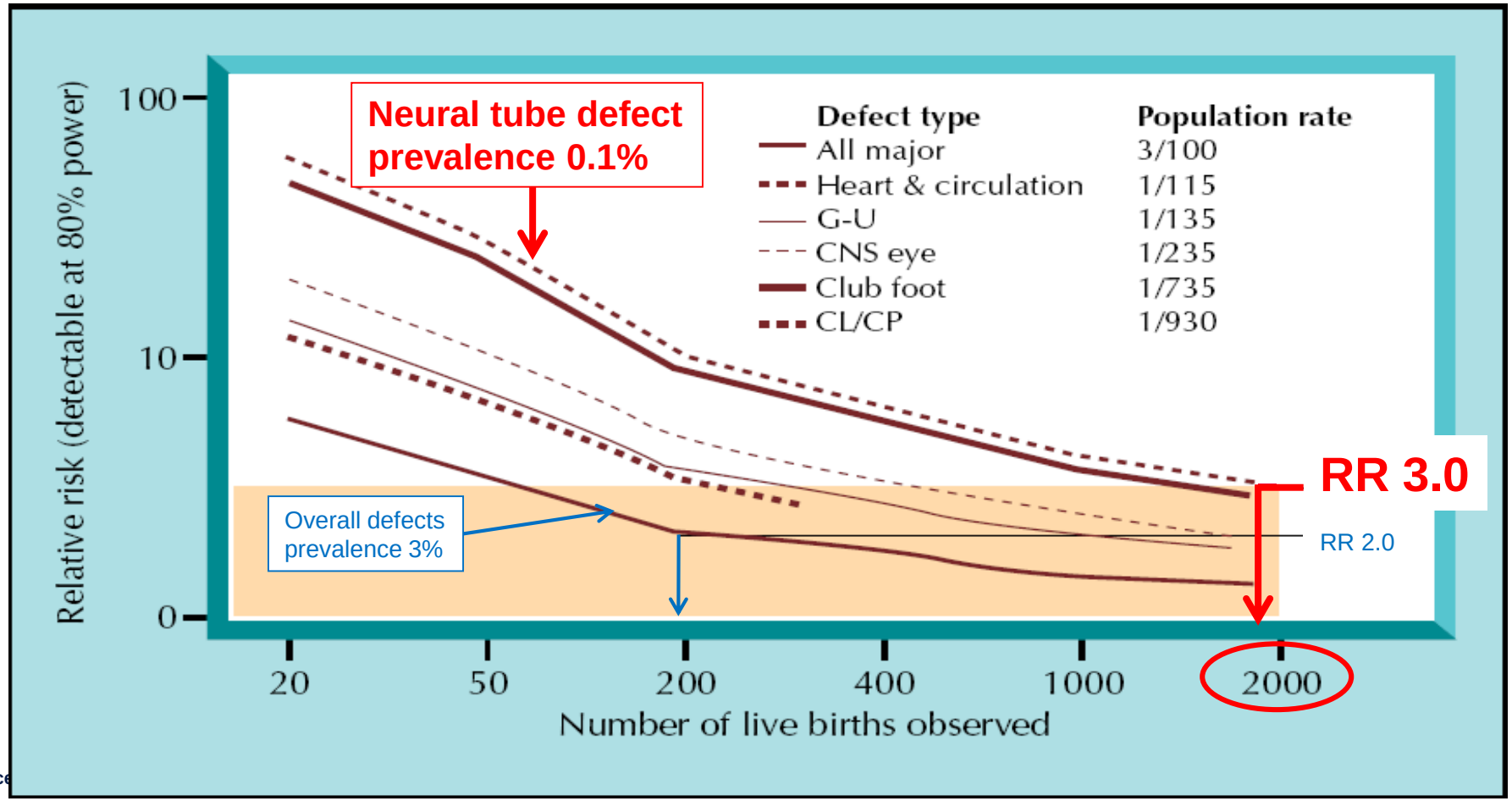


Watts DH. Curr HIV/AIDS Rep 2007;4:135-140

Ability to Rule-Out An Increase in Birth Defects With Drug Exposure is Related to Defect Prevalence and Number of Observed Exposures

2,000 periconception exposures are needed to rule-out a 3-fold increase in a rare event like NTD (prevalence 0.1%)

Watts DH. Curr HIV/AIDS Rep 2007;4:135-140



Methods

- Data on prospectively enrolled pregnancies through July 2019 with birth outcomes are summarized for dolutegravir:
  - Earliest timing of exposure was assigned to each pregnancy:
    - *Periconception* – ARV exposure from 2 weeks before 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 & encephalocele (reported separately from NTD).

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

Total pregnancies, N	650
Maternal age at conception, y	
Mean	29.7
Median	29.0
Range, min-max	14-54
CD4+ T-cell categories at time of reporting, n (%)	
≥500 cells/µL	302 (46.5%)
200-499 cells/µL	213 (32.8%)
<200 cells/µL	87 (13.4%)
Missing	48 (7.4%)
Race/Ethnicity, n (%)	
Black	400 (61.5%)
White	89 (13.7%)
Asian	15 (2.3%)
Hispanic	82 (12.6%)
Other	50 (7.7%)
Missing	14 (2.2%)

Demographic and Clinical Characteristics of Pregnant Women Exposed to DTG

HIV status, n (%)	
Positive	645 (99.2%)
Negative	5 (0.8%)
Country of origin, n (%)	
USA	518 (79.7%)
UK	51 (7.8%)
Other	81 (12.5%)
Timing of earliest exposure to DTG, n (%)	
Periconception	347 (53.4%)
Later 1st trimester	67 (10.3%)
2nd trimester	158 (24.3%)
3rd trimester	78 (12.0%)

Vannappagari et al. IAS 2017; Paris, France. Poster MOPEB0283.

Pregnancy Outcomes by Timing of Exposure to DTG

	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	667*	357	67	243
Live births	614 (92.1%)	312 (87.4%)	63 (94.0%)	239 (98.4%)
Stillbirths	9 (1.3%)	5 (1.4%)	1 (1.5%)	3 (1.2%)
Spontaneous abortions	26 (3.9%)	24 (6.7%)	2 (3.0%)	0
Induced abortions	18 (2.7%)	16 (4.5%)	1 (1.5%)	1 (0.4%)

*include 17 twin births

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Neonatal Outcomes by Timing of Exposure to DTG: Among Singleton, Live Births Without Defect

	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	562	285	61	216
Gestational age				
≥37 weeks	502 (89.3%)	251 (88.1%)	52 (85.2%)	199 (92.1%)
<37 weeks (preterm)	59 (10.5%)	34 (11.9%)	9 (14.8%)	16 (7.4%)
Missing	1 (0.2%)	0	0	1 (0.5%)
Birth weight				
≥2500 grams	483 (85.9%)	238 (83.5%)	53 (86.9%)	192 (88.9%)
<2500 grams (LBW)	65 (11.6%)	37 (13.0%)	8 (13.1%)	20 (9.3%)
<1500 grams (VLBW)	13 (2.3%)	8 (2.8%)	2 (3.3%)	3 (1.4%)
Missing	14 (2.5%)	10 (3.5%)	0	4 (1.9%)

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Overall Birth Defect Rate Among Live Births Exposed to DTG

Timing of Exposure:	Defect per Live Births	Prevalence	95% CI
Any Trimester	21/614	(3.4%)	(95% CI: 2.1–5.2)
Periconception	10*/312	(3.2%)	(95% CI: 1.6-5.8)
Later First Trimester	2/63	(3.2%)	(95%CI: 0.4-11.0)
Second/Third Trimester	9/239	(3.8%)	(95% CI: 1.7–7.0)

** Includes One Neural Tube Defect*

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Drug-Specific Overall Birth Defect Rates*

Prevalence of Birth Defects (95% CI) with 1st Trimester Exposure: 1 January 1989 – 31 July 2019

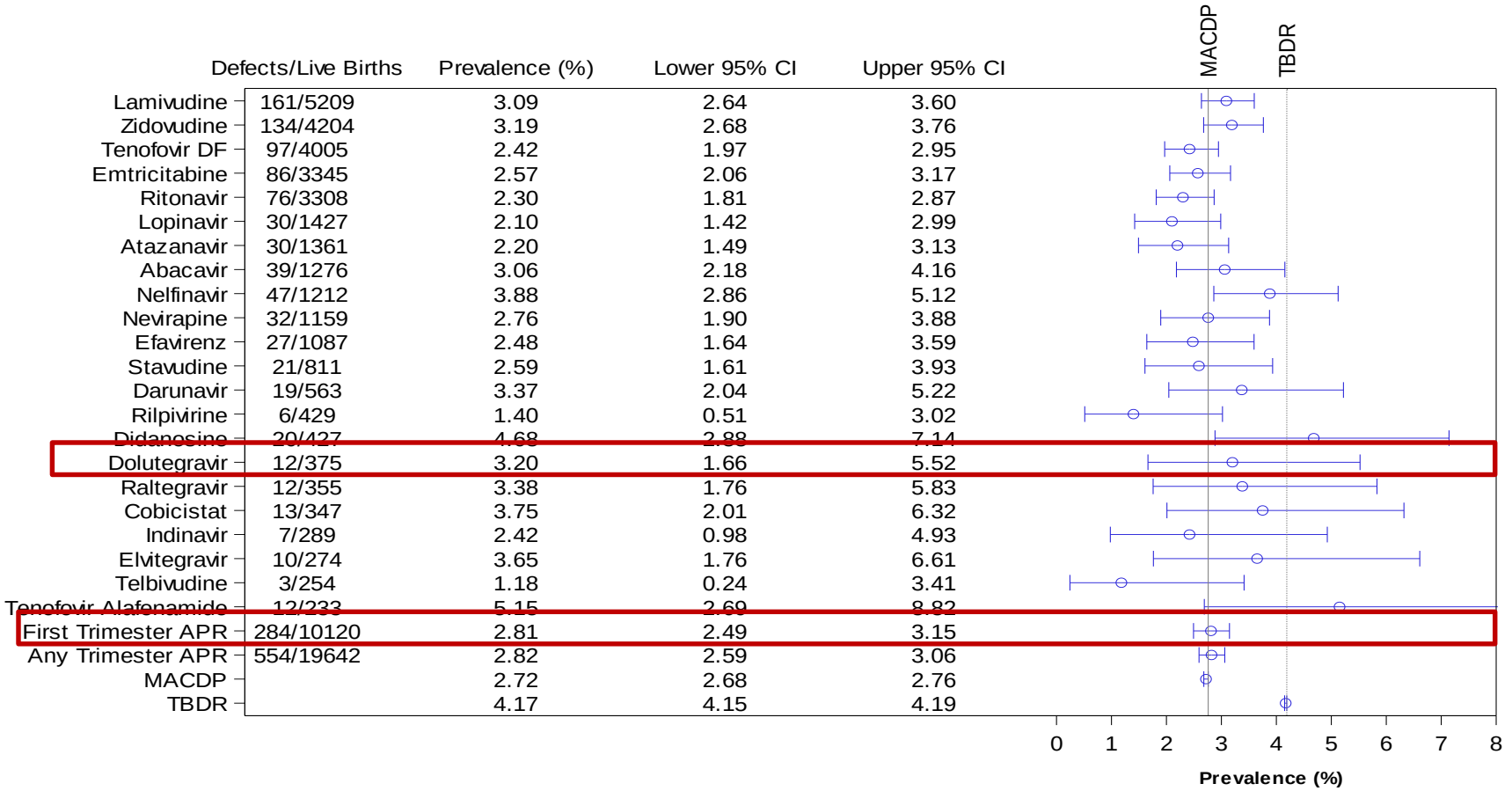
***For drug to be included for comparison with population rates, must meet threshold of having ≥200 1st trimester exposed pregnancies**

Metropolitan Atlanta Congenital Defects Program (2.76%)

Texas Birth Defects Registry (4.19%)

22 ARVs have ≥200 exposures

	Defects/Live Births	Prevalence (%)	Lower 95% CI	Upper 95% CI
Lamivudine	161/5209	3.09	2.64	3.60
Zidovudine	134/4204	3.19	2.68	3.76
Tenofovir DF	97/4005	2.42	1.97	2.95
Emtricitabine	86/3345	2.57	2.06	3.17
Ritonavir	76/3308	2.30	1.81	2.87
Lopinavir	30/1427	2.10	1.42	2.99
Atazanavir	30/1361	2.20	1.49	3.13
Abacavir	39/1276	3.06	2.18	4.16
Nelfinavir	47/1212	3.88	2.86	5.12
Nevirapine	32/1159	2.76	1.90	3.88
Efavirenz	27/1087	2.48	1.64	3.59
Stavudine	21/811	2.59	1.61	3.93
Darunavir	19/563	3.37	2.04	5.22
Rilpivirine	6/429	1.40	0.51	3.02
Didanosine	20/427	4.68	2.88	7.14
Dolutegravir	12/375	3.20	1.66	5.52
Raltegravir	12/355	3.38	1.76	5.83
Cobicistat	13/347	3.75	2.01	6.32
Indinavir	7/289	2.42	0.98	4.93
Elvitegravir	10/274	3.65	1.76	6.61
Telbivudine	3/254	1.18	0.24	3.41
Tenofovir Alafenamide	12/233	5.15	2.69	8.82
First Trimester APR	284/10120	2.81	2.49	3.15
Any Trimester APR	554/19642	2.82	2.59	3.06
MACDP		2.72	2.68	2.76
TBDR		4.17	4.15	4.19



Conclusions

- APR data through 31 July 2019 do not demonstrate an increased risk of overall birth defects with DTG use (3.4%) above the population expected rate of defects (2.7% and 4.2% from Metropolitan Atlanta Congenital Defects Program and Texas Birth Defects Registry, respectively).

- In the updated APR data, there is one NTD with 312 periconception DTG exposures, giving an NTD prevalence of 0.30%.

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.
- APR continues to closely monitor birth defects in pregnancies exposed to DTG and other integrase inhibitors, including NTDs with periconception exposure.
- Healthcare providers are encouraged to continue to report pregnancies with prospective antiretroviral exposures to the APR, especially those involving newer ARVs [www.APRegistry.com]

ADVISORY COMMITTEE CONSENSUS Statement (Précis)

The Antiretroviral Pregnancy Registry finds no apparent increases in frequency of defects with first trimester exposures to ARVs 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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