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Pregnancy and Neonatal Outcomes Following Prenatal Exposure to Dolutegravir

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Abstract

Background: Birth outcomes data with dolutegravir exposure during pregnancy, particularly in the first trimester, are needed.

Setting: Data were prospectively collected from the Antiretroviral Pregnancy Registry and European Pregnancy and Paediatric HIV Cohort Collaboration.

Methods: We reviewed 2 large, independent antiretroviral pregnancy registries to assess birth outcomes associated with maternal dolutegravir treatment during pregnancy.

Results: Of 265 pregnancies reported to the Antiretroviral Pregnancy Registry, initial exposure to dolutegravir occurred at conception or first trimester in 173 pregnancies and during the second or third trimester in 92 pregnancies. There were 246 (92.8%) live births resulting in 255 neonates (9 twins), 6 (2.3%) induced abortions, 11 (4.2%) spontaneous abortions, and 2 (0.8%) stillbirths. Birth defects occurred in 7 (2.7%) of 255 live-born neonates, 5 (3.1%) of 162 (includes 6 twins) with conception/first-trimester exposure. Of 101 pregnancies reported to the European Pregnancy and Paediatric HIV Cohort Collaboration, outcomes were available for 84 pregnancies (16 continuing to term and 1 lost to follow-up). There were 81 live births (80 with

known initial dolutegravir exposure at conception or first, second, and third trimesters in 42, 21, and 17 live births, respectively), 1 stillbirth (second-trimester exposure), 1 induced abortion (first-trimester exposure), and 1 spontaneous abortion (first-trimester exposure), respectively. Birth defects occurred in 4 live births (4.9%; 95% confidence interval, 1.4-12.2), 3 of 42 (7.1%) with exposure at conception or first trimester.

Conclusions: Our findings are reassuring regarding dolutegravir treatment of HIV infection during pregnancy but remain inconclusive due to small sample sizes.

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Keywords (3-6 words/phrases): dolutegravir, pregnancy, birth defect, preterm, low birth weight

INTRODUCTION

Dolutegravir is an integrase strand transfer inhibitor approved for the treatment of HIV-1 infection in adults and children aged >6 years or weighing >30 kg as part of combination antiretroviral (ARV) therapy.[1,2] Safety and efficacy of dolutegravir exposure during pregnancy have not been studied in randomized controlled trials because pregnancy was an exclusion criterion in all phase III dolutegravir trials.[3-7]

The Tsepamo birth study in Botswana compared birth outcomes of 4593 pregnant women starting efavirenz/tenofovir disoproxil fumarate/emtricitabine during pregnancy between August 2014 and August 2016 with those of 1729 pregnant women starting dolutegravir/tenofovir disoproxil fumarate/emtricitabine during pregnancy between November 2016 and September 2017.[8] In adjusted analyses, the dolutegravir-based regimen had a similar safety-risk profile for adverse birth outcomes when compared with efavirenz-based regimens. In addition, among 280 women starting dolutegravir-based ART and 395 starting efavirenz-based ART during

pregnancy, only one major congenital abnormality occurred: skeletal dysplasia in an efavirenz-exposed infant. However, the study only reported data on exposure to dolutegravir after conception. In May 2018, following an interim analysis of Tsepamo study data conducted to inform the World Health Organization guidelines development group, a potential safety signal was identified with 4 cases of neural tube defects reported among infants born to 426 women who conceived while on dolutegravir-based regimens.[9]

The present study assessed fetal and neonatal outcomes following maternal dolutegravir use during pregnancy by using prospective data from the Antiretroviral Pregnancy Registry (APR) and pregnancy cohorts participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC).

METHODS

Two separate analyses of prospectively collected data on prenatal exposure to dolutegravir were performed using data from the APR and EPPICC. Data from EPPICC were supplemented with patient data collected during the same time frame in the European Treatment Network for HIV, Hepatitis and Global Infectious Diseases and obstetric sites participating in the Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-Infected Pregnant Women network.[10] These analyses included pregnant women who received dolutegravir-containing regimens, prospectively enrolled into the studies before any knowledge of pregnancy outcome. In addition to data on dolutegravir exposure, we also assessed sociodemographic and clinical characteristics, delivery details, frequency of birth defects, birth weight, gestational age, and other neonatal outcomes.

APR receives annual institutional review board (IRB) approval from Western IRB, including waivers of informed consent and authorization for use and disclosure of protected health information. No patient identifiers were collected, ensuring the confidentiality of APR registrants.

Participating studies in EPPICC obtained ethical approval from national, local, or both levels, as well as informed consent where required, within these approvals.

Data Sources

APR

APR is an international, voluntary, prospective exposure registry that contains case reports from 70 countries, with women from the United States and its territories comprising 77.3% of those reports. The methods and analyses from APR have been previously published.[11] Pregnant women with prenatal exposure to ARV medication were registered by their healthcare providers, who reported the women's exposure to ARVs during pregnancy and the pregnancy and birth outcome data. All data were semiannually reviewed by an independent advisory committee. Exposures to ARV were classified and analyzed by the earliest trimester of exposure to each ARV medication. The proportion of birth defects was compared with internal and external comparator groups. External comparators were 2 population-based surveillance systems, Metropolitan Atlanta Congenital Defects Program (MACDP) of the Centers for Disease Control and Prevention and the Texas Birth Defects Registry. Internal comparators included exposures to other drugs and exposures in the second or third trimester of pregnancy relative to exposures during the first trimester (when organogenesis occurs). Only singleton births without defects were analyzed for spontaneous and induced abortions, stillbirths, and premature birth (<37 weeks

of gestation, low birth weight [LBW], and very low birth weight [VLBW]). Multiple births were excluded due to the increased risk of adverse outcomes associated with multiple births. The reporting period for APR data in this analysis began on January 1, 1989, and ended on January 31, 2018.

EPPICC

EPPICC is an international network of cohort studies conducting epidemiologic research on pregnant women and children infected with HIV and children exposed to HIV during pregnancy.[12,13] Participating studies collect prospective data on pregnant women and their infants, with exposure data collected before the pregnancy outcome is known, and pregnancies with birth defects were not excluded. All pregnant women reporting exposure to dolutegravir during their pregnancy to participating European studies by August 2016 were included in this analysis (see Appendix, Supplemental Digital Content 1, http://links.lww.com/QAI/B304 which lists these cohorts/studies/networks).

Anonymous, individual-level data were merged at University College London Great Ormond Street Institute of Child Health using a standard operating procedure for data formatting according to a modified HIV Cohorts Data Exchange Protocol data specification using study-specific unique identifiers. In addition to standard pregnancy and neonatal outcomes, mode of HIV acquisition, including vertical transmission, was reported.

The merged database underwent a comprehensive set of data-quality checks to prevent duplication and ensure accuracy and completeness.

Definitions

In both studies, LBW was defined as <2500 g and VLBW was defined as <1500 g. Preterm delivery was defined as birth occurring at <37 completed gestational weeks. Birth defect prevalence was calculated by dividing the number of birth defects by the number of live births.

In the APR analysis, birth defects were reported based on the MACDP classification. The first and second trimester cutoffs were 14 and 28 weeks of gestation, respectively. Preterm delivery was defined as birth before 37 weeks of gestation by the health care provider's best obstetric estimate. Spontaneous abortion was defined as death of a fetus or expulsion of the products of conception before 20 weeks of gestation. Stillbirth was defined as the death of a fetus at ≥20 weeks of gestation or a fetus weighing ≥500 g (in cases for which the gestational age was unavailable).

In the EPPICC analysis, birth defects were classified according to the World Health Organization's International Classification of Diseases, 10th Revision, and European Surveillance of Congenital Anomalies (EUROCAT) classification. The first, second, and third trimesters were defined as <13, 13 to 24, and ≥25 completed gestational weeks, respectively. Small for gestational age (SGA) was defined according to sex-specific US standards.[14] Induced abortion was defined as voluntary termination of pregnancy at <22 weeks of gestation. Spontaneous abortion was defined as the death of a fetus or expulsion of the products of conception at <22 weeks of gestation. Stillbirth was defined as death of a fetus occurring at ≥22 weeks of gestation.

Statistical Analysis

Separate analyses were conducted for data from the EPPICC and APR cohorts. Data were not combined due to differences in data collection and methods used for analysis. For the EPPICC and APR data sets, standard descriptive statistics were used to summarize the data using STATA v12.0 (StatCorp, College Station, TX) and SAS v9.3 (Cary, NC), respectively. For the APR, statistical inference was based on exact methods for binomial proportions, with 80% power and a type 1 error rate of 5% for detecting a doubling of overall risk of birth defects. For specific defects, the power varied with the frequency of the defect and the size of the exposed group.

RESULTS

Maternal Characteristics and Pregnancy Outcomes

APR

APR received 265 prospective reports of dolutegravir exposure during pregnancy; 86% of the participants were from the United States, 62% were black, and the median (range) age at conception was 29.0 (16-43) years (Table 1). A majority (77%) had CD4+ cell counts ≥200 cells/μL at the time of reporting. Initial exposure to dolutegravir occurred before or during the first trimester in 173 pregnancies (65%), with 130 exposures occurring preconception and after the first trimester in 92 pregnancies (35%).

Of these 265 pregnancies, 246 (92.8%) resulted in live births that included 9 twins for a total of 255 neonates; 6 (2.3%) pregnancies reported induced abortions, 11 (4.2%) reported spontaneous abortions, and 2 reported stillbirths (Table 2). Of the 231 singleton live births without defects, 24 (10.4%) were preterm (<37 weeks of gestation) and 24 (10.4%) had LBW of 1500 to <2500 g (Table 3). Very low birth weight (<1500 g) was reported for 5 (2.2%) of the live

births, and 18 births were both preterm and LBW/VLBW. The percentages of neonates born preterm were 10.9% and 9.5% for those with the earliest dolutegravir exposure in the first and second/third trimesters, respectively.

EPPICC

One hundred women, representing 101 pregnancies, were included in the analysis of EPPICC data (84 known pregnancy outcomes, 16 pregnancies ongoing, and 1 lost to follow-up); 67% (n=62/93) were from Sub-Saharan Africa, 46% were aged 25 to 34 years at conception, and 71% were black (Table 4). There were 51 (57%) women with CD4+ cell counts >350 cells/µL. One pregnancy was missing data regarding maternal dolutegravir initiation. Of those with data of dolutegravir initiation, the majority had earliest exposure to dolutegravir in the first trimester (58%; 37 of 58 pregnancies were conceived while the mothers were on dolutegravir), with 24% in the second trimester and 18% in the third trimester. Of the 84 pregnancies with outcomes data, 81 resulted in live births (resulting in 83 neonates), 1 resulted in spontaneous abortion, 1 in induced abortion, and 1 in stillbirth. Overall, 11 of the 80 singleton neonates (13.8%) were delivered preterm; 9 were born between 34 and 36 weeks of gestation, and 2 were born before 34 weeks of gestation (31 weeks, n=1; 23 weeks, n=1; Table 5).

The median birth weight was 3120 g (interquartile range, 2750-3470). A total of 16.9% (n=2 missing birth weights) of neonates had LBW and 18.7% were SGA (Table 5). The proportions of neonates born preterm were 7.5%, 27.3%, and 11.8% for those whose earliest dolutegravir exposures started in the first, second, and third trimesters, respectively.

Congenital Abnormalities

APR

In the APR cohort, among the 255 live born neonates (including 9 sets of twins) with prenatal exposure to dolutegravir, birth defects occurred in 7 (2.7%) neonates. Of the 121 neonates first exposed to dolutegravir at conception, 3 (2.5%) were reported to have abnormalities: a male with bilateral polydactyly postaxial to both hands who was also exposed to darunavir/ritonavir; a female with an ectopic right kidney who was also exposed to emtricitabine, lamivudine, raltegravir, and tenofovir disoproxil fumarate at conception, darunavir/ritonavir during the second trimester, and zidovudine during the third trimester; and a male with endocardial fibroelastosis who was also exposed to abacavir and lamivudine. Ages of the mothers (ethnicity) at delivery were 26 years (black), 26 years (black), and 19 years (Hispanic), respectively. Of the 40 neonates with first exposure after conception and during the first trimester, 2 (5.0%) were reported to have abnormalities: a male with polydactyly on the ulnar side and syndactyly on the second, third, and fourth fingers who was also exposed to tenofovir disoproxil fumarate and emtricitabine and a male with Talipes equinovarus also exposed to abacavir, lamivudine, and raltegravir. Ages of the mothers (ethnicity) at delivery were 22 (black) and 24 (Asian), respectively. Of the 94 neonates with first exposure during the second or third trimester, 2 (2.1%) were reported to have abnormalities: a female with hypoglossia–hypodactylia syndrome with dolutegravir exposure during the third trimester who was also exposed to darunavir/ritonavir, tenofovir disoproxil fumarate, and emtricitabine during the second trimester as well as zidovudine in the third trimester; and a female with Down syndrome who was exposed to dolutegravir, abacavir, and lamivudine during the second trimester. Ages of the mothers

(ethnicity) at delivery were 31 (black) and 38 (Hispanic), respectively. No neural tube defects or central nervous system defects were reported.

EPPICC

Data on congenital abnormalities in the EPPICC studies were available for 81 of 84 live and stillborn neonates (twin/singleton pregnancies). Overall, abnormalities were recorded in 4 neonates (4.9%; 95% confidence interval [CI], 1.4-12.2): 3 from the Italian cohort and 1 from the Swiss cohort. Of the 42 neonates first exposed to dolutegravir during the first trimester, 3 males (7.1%) were reported to have abnormalities: 1 neonate with a patent foramen ovale with small left-to-right interatrial shunting, who was first exposed to dolutegravir from conception and also exposed to lamivudine and abacavir; 1 neonate with bilateral hexadactyly and hypospadias, who was first exposed to dolutegravir at Week 3 and also exposed to lamivudine/abacavir and emtricitabine/tenofovir disoproxil fumarate; and 1 neonate with ankyloglossia (tongue-tie), who first exposed to dolutegravir at Week 12 was also exposed to darunavir/ritonavir, emtricitabine/tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, and raltegravir. Ages of the mothers (ethnicity) at delivery were 38 years (black African), 40 years (white), and 31 years (white), respectively. Of the 24 neonates first exposed to dolutegravir during the second trimester (Week 14), 1 (4.2%) male neonate was also exposed to lamivudine and abacavir and presented with hyperpigmentation on his back. His mother was of black African ethnicity and was 34 years of age. No central nervous system defects were reported.

DISCUSSIONS

The 2 separate analyses using data from APR and EPPICC account for many of the prospectively collected, prenatal exposures of dolutegravir to date. For most pregnancies included in these analyses (APR, 65%; EPPICC, 58%), dolutegravir was initiated during or before the first trimester (including 158 outcomes after dolutegravir exposure at conception), thus providing important safety information for use of dolutegravir-based regimens during early pregnancy. More than 90% of pregnancies from both data sets resulted in live births. Induced and spontaneous abortions primarily were reported in women exposed to dolutegravir during their first trimester of pregnancy (as expected, because most abortions occur in the first trimester).[15,16] Rates of both induced and spontaneous abortions among APR (2.3% and 4.2%, respectively) and EPPICC (both 1.2%) cohorts who received dolutegravir are lower than recent estimates among general populations for these outcomes; however, neither study is designed to capture early pregnancy loss or termination prevalence.[17-19]

Of the 231 singleton live births in the APR data set without defects and with prenatal exposure to dolutegravir, 10.4% were delivered at <37 weeks (preterm) and 12.6% had birth weights <2500 g. Of the 79 singleton live births and 1 stillbirth in the EPPICC data set, 13.8% were delivered preterm, 16.9% of neonates had LBW (1500-2499 g; none were <1500 g at birth), and 18.7% were SGA. Congenital abnormalities occurred in 2.7% and 4.9% (95% CI, 1.4-12.2) of live births from APR and EPPICC, respectively, with most anomalies being polydactyly, a common birth defect.[20] Congenital upper-extremity abnormalities comprise approximately 10% of all birth defects[21]; by contrast, the birth prevalence rate of radial polydactyly is approximately 25 per 100,000 births.[22] The risk factors associated with polydactyly include race/ethnicity

(predominance of postaxial polydactyly in people of African descent),[23] male sex,[24] birth order,[25] and maternal smoking.[26]

The preterm delivery rate of 14% of the 79 pregnancies assessed in women exposed to dolutegravir-containing regimens from EPPICC was similar to that reported among women living with HIV infection who delivered during the same time period in the United Kingdom—the country accounting for approximately 60% of the studied women. In a recent analysis of data from the UK and Ireland National Study of HIV in Pregnancy and Childhood regarding pregnant women taking protease inhibitor– or non-nucleoside reverse transcriptase inhibitor–based ARV treatment regimens who delivered neonates between 2007 and 2015, the preterm delivery rate was 11.5% for women taking ARV therapy at conception with CD4+ counts ≤350 cells/μL.[27] The 10.4% preterm delivery rate in the APR cohort is similar to rates reported in overall populations in North America (10.6%; excluding Mexico)[29] and worldwide (11.1%; approximately 14.9 million preterm deliveries).[30] However, a meta-analysis of prospective and retrospective cohort studies conducted across developed and developing countries found that women with HIV infection were at increased risk of preterm delivery (summary odds ratio 1.56; 95% CI, 1.49-1.63) when compared with their uninfected counterparts.[31]

Approximately 10% of the women in the EPPICC cohort were vertically infected themselves, and an additional 9% were coinfected with hepatitis C virus (HCV)/HIV. These proportions are higher than expected considering the larger cohort populations of pregnant women with HIV infection living in western Europe from which they are drawn.[12,28] They most likely reflect the preferential use of dolutegravir in specific groups of women. Factors such as coinfection with HCV/HIV may also be associated with worse pregnancy outcomes.[28]

The observed LBW prevalence among singleton live births without defects in APR (10.6%) was higher than reported US rates in the general population (8.2%) in 2016[32] but lower than expected compared with a recent analysis of APR birth outcomes through 2011 reporting birth weight <2500 g was 15.9%.[33] Although 5 cases were reported, the prevalence of VLBW (<1500 g) following dolutegravir exposure (2.2%) was similar to earlier APR data (2.1%) but higher than the 2016 prevalence of the general US population (1.4%).[32] Overall, a meta-analysis of reports comparing pregnancy outcomes in women with or without HIV found that those living with HIV infection are at increased risk of delivering a neonate with LBW compared with their uninfected counterparts (summary odds ratio 1.73; 95% CI, 1.64-1.82).[31]

Birth defect numbers were comparable across APR (7 of 255) and EPPICC (4 of 81) data sets. Confidence intervals relating to EPPICC data were large, reflecting the small sample size and that considerable heterogeneity was observed across cohorts (eg, age, region, CD4+ count, timing of dolutegravir exposure). When applying the EUROCAT classification of birth defects to EPPICC (which exclude isolated tongue-tie and hyperpigmentation on the back), the rate decreased to 2.5%. Through January 31, 2018, among APR reports with any ARV exposure during pregnancy, 516 birth defects were identified of the 18,660 live births, with a prevalence of 2.8 birth defects per 100 live births (95% CI, 2.5-3.0).[34] This proportion was not substantially higher than the 3.0 and 4.6 per 100 live births reported in other similar US population-based databases, ie, MACDP and the Texas Birth Defects Registry, respectively.[35,36] In the APR, ≥200 first-trimester exposures to any individual drug are needed to estimate the overall prevalence of birth defects, a statistical threshold the present assessment of dolutegravir pregnancy exposure does not meet.

There are multiple limitations with these 2 analyses. It is also possible that birth defects may go unrecognized or be differentially reported. Unlike the APR, data relating to birth defects from participating studies in EPPICC are not reviewed by a teratologist. Conclusions based on the proportions of induced and spontaneous abortions were limited because some cohorts included patients first enrolled in the cohort later in the pregnancy than when most abortions occur. First-trimester exposures in both cohorts are not large enough for definitive conclusions. Conclusions about regional differences in pregnancy outcomes between the 2 studies are limited, because the APR and EPPICC cohorts included 18 (6.8%) and 61 (60.4%) patients from the United Kingdom/Ireland, respectively, and it is possible that the some of the 18 participants may have been included in both cohorts. Similarly, because the EPPICC cohort included participants from 6 cohorts in different countries, differences in study design could affect overall conclusions of pregnancy outcomes in western Europe. Further postmarketing surveillance within EPPICC is ongoing.

HIV-positive women of childbearing potential, pregnant women, and their health care professionals should follow recommendations on dolutegravir use.[9,37,38] In the United Kingdom and Ireland, the percentage of pregnant women exposed to dolutegravir-based regimens has increased >10-fold from 0.3% in 2015 to 3.3% in 2016.[39] Even with this analysis of pregnancies with first-trimester exposure to dolutegravir combined from APR and EPPICC, the expanding use of dolutegravir, together with the potential safety signal of neural tube defects dolutegravir exposure at the time of conception from Botswana[9] highlights the importance for continuing the prospective monitoring of pregnant women and their infants through APR and EPPICC. Following recommendations from global, US, and European agencies,[9,37,38] conceptions on dolutegravir may decline, but continued monitoring is critical. Our assessment of collective 198

birth outcomes following first-trimester dolutegravir exposure from 2 prospective registries (APR, 156 outcomes; EPPICC, 42 outcomes) as well as data cited from 3 other studies with 104 pregnancy outcomes identified no birth defect signal, either in defect prevalence or in defect type clustering.[40-42] In addition, among birth defects reported after dolutegravir exposure during pregnancy or at the time of conception, none involved the neural tube. These findings may provide some reassurance to women whose pregnancies have already been exposed to dolutegravir or who have limited therapeutic options.

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All listed authors meet the criteria for authorship set forth by the International Committee of Medical Journal Editors. Both Vani Vannappagari and Claire Thorne were involved in design of the study, data analysis, manuscript development, and manuscript approval.

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DATA SHARING AND DATA ACCESSIBILITY

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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TABLES

Table 1. Demographic and Clinical Characteristics of Pregnant Women Exposed to Dolutegravir: Prospective Registry Reports From the Antiretroviral Pregnancy Registry

Variable	Total pregnancies (N=265)
Maternal age at conception, y	
Mean	29.2
Median	29.0
Range, min-max	16-43
CD4+ T-cell categories at time of reporting, n (%)	
≥500 cells/µL	127 (47.9)
200-499 cells/µL	78 (29.4)
<200 cells/µL	47 (17.7)
Missing	13 (4.9)
Race/Ethnicity, n (%)	
Black	163 (61.5)
White	42 (15.8)
Asian	9 (3.4)
Hispanic	37 (14.0)
Other	8 (3.0)
Missing	6 (2.3)
Maternal HIV status, n (%)	
Positive	262 (98.9)
Negative	3 (1.1)
Country of origin, n (%)	
United States	228 (86.0)
United Kingdom	18 (6.8)
Other[a]	19 (7.2)
Trimester of earliest exposure to dolutegravir, n (%)	
Prior to conception/first	173 (65.3)
Second/Third	92 (34.7)

[a]1 each from Argentina, Brazil, Ethiopia, France, Puerto Rico, and Switzerland; 2 each from Canada and South Africa; 3 each from Australia, Israel, and Russia.

Table 2. Pregnancy Outcomes: Prospective Registry Reports From the Antiretroviral Pregnancy Registry (Among Pregnancies With Prenatal Dolutegravir Exposure)

Pregnancy outcome, n (%)	Overall (N=265)	Earliest exposure to dolutegravir		
		Prior to conception (n=130)	First trimester (n=43)[a]	Second/Third trimester (n=92)
Pregnancy with live birth	246 (92.8)[a]	118 (90.8)[b]	38 (88.4)[c]	90 (97.8)[d]
Stillbirth	2 (0.8)	0	0	2 (2.2)
Spontaneous abortion	11 (4.2)	7 (5.4)	4 (9.3)	0
Induced abortion	6 (2.3)	5 (3.8)	1 (2.3)	0

[a]9 pregnancies resulted in twin births for a total of 255 live neonates. [b]3 pregnancies resulted in twin births for a total of 121 live neonates. [c]2 pregnancies resulted in twin births for a total of 40 live neonates. [d]4 pregnancies resulted in twin births for a total of 94 live neonates.

Table 3. Neonatal Outcomes With Prenatal Exposure to Dolutegravir: Reports From the Antiretroviral Pregnancy Registry (Among Singleton, Live Births Without Defect)

Neonatal outcome, n (%)	Total (N=231)	Earliest exposure to dolutegravir		
		Prior to conception (n=112)	First trimester (n=35)	Second/Third trimester (n=84)
Gestational age				
≥37 wk	207 (89.6)	102 (91.1)	29 (82.9)	76 (90.5)
<37 wk (preterm)	24 (10.4)	10 (8.9)	6 (17.1)	8 (9.5)
Birth weight				
≥2500 g	198 (85.7)	96 (85.7)	30 (85.7)	72 (85.7)
1500-2499 g (LBW)	24 (10.4)	14 (12.5)	5 (14.3)	8 (9.5)
<1500 g (VLBW)	5 (2.2)	0	3 (8.6)	2 (2.4)
Missing data	4 (1.7)	2 (1.8)	0	2 (2.4)

LBW, low birth weight; VLBW, very low birth weight.

Table 4. Maternal Characteristics: Reports From the European Pregnancy and Paediatric HIV Cohort Collaboration

Variable	Total pregnancies (N=101)
Race/Ethnicity, n (%)[a]	
Black	71 (71)
White	22 (22)
Other	7 (7)
Region of origin, n (%)[b]	
Sub-Saharan Africa	62 (67)
Europe	22 (24)
Other	9 (10)
Maternal age at conception, n (%)	
<25 y	16 (16)
25-34 y	46 (46)
≥35 y	39 (39)
Mode of HIV acquisition, n (%)[c]	
Heterosexual	81 (86)
Injecting drug use	3 (3)
Vertical	9 (10)
Other	1 (1)
Timing of HIV diagnosis, n (%)	
Pre-pregnancy	86 (85)
Current pregnancy	15 (15)
Has a history of AIDS, n (%)[d]	10 (11)
Does not have a history of AIDS, n (%)[d]	79 (89)
Hepatitis C virus status, n (%)[e]	
Seropositive	8 (9)
Seronegative	83 (91)
Positive HBsAg, n (%)[e]	4 (4)
Negative HBsAg, n (%)[e]	87 (96)
CD4+ T-cell count (first in pregnancy), n (%)[d]	
≤350 cells/μL	38 (43)
>350 cells/μL	51 (57)
Antiretroviral therapy at conception, n (%)[f]	
Yes	55 (60)
No	37 (40)
Country of delivery (cohort), n (%)	
UK and Ireland (NSHPC)	61 (60)
Germany (NEAT-ID)	19 (19)
Spain/Catalonia (NENEXP, PANNA)	9 (9)
Italy (Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy)	5 (5)
Switzerland (Swiss MoCHiV)	3 (3)
Belgium (European Collaborative Study)	2 (2)
The Netherlands (PANNA)	2 (2)

[a]n=100. [b]n=93. [c]n=94. [d]n=89. [e]n=91. [f]n=92. HBsAg, hepatitis B surface antigen.

Table 5. Gestational Age, Birth Weight, and SGA by Earliest Dolutegravir Exposure From EPPICC

Pregnancy outcomes, n (%)	Earliest dolutegravir exposure			Total[a]
	First trimester	Second trimester	Third trimester	
All pregnancies	58 (58.0)[b]	24 (24.0)[c]	18 (18.0)	100
Pregnancies ending in live births	42 (52.5)	21 (26.2)	17 (21.2)	80
Gestational age[d]				
n	40	22	17	79
≥37 wk	37 (92.5)	16 (72.7)	15 (88.2)	68 (86.1)
34-36 wk	2 (5.0)	5 (22.7)	2 (11.8)	9 (11.4)
<34 wk	1 (2.5)	1 (4.6)	0 (0)	2 (2.5)
Birth weight[d,e]				
n	39	21	17	77
≥2500 g	35 (89.7)	15 (71.4)	14 (82.3)	64 (83.1)
1500–2499 g	4 (10.3)	6 (28.6)	3 (17.7)	13 (16.9)
SGA[d]				
n	39	20	16	75
No	34 (87.1)	13 (65.0)	14 (87.5)	62 (81.3)
Yes	5 (12.8)	7 (35.0)	2 (12.5)	14 (18.7)

EPPICC, European Pregnancy and Paediatric HIV Cohort Collaboration; SGA, small for gestational age. [a]1 pregnancy was excluded because the dolutegravir start date was unavailable. This pregnancy ended in live birth. [b]Earliest exposure to dolutegravir occurred prior to conception in 37 pregnancies and during the first trimester in 21 pregnancies; 2 pregnancies terminated in abortions (spontaneous, n=1; induced, n=1). No fetal abnormalities were associated with the induced abortion. [c]1 pregnancy ended in a stillbirth. [d]Birth outcomes included the singleton-live neonates and the 1 stillbirth. [e]None of the live neonates weighed <1500 g.