ORIGINAL ARTICLE

Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana

Rebecca Zash, M.D., Lewis Holmes, M.D., Modiegi Diseko, B.P.H.,
Denise L. Jacobson, Ph.D., M.P.H., Sean Brummel, Ph.D., Gloria Mayondi, B.Sc.,
Arielle Isaacson, B.A., Sonya Davey, M.Phil., Judith Mabuta, Mompati Mmalane, M.D.,
Tendani Gaolathe, M.D., M. Essex, D.V.M., Ph.D., Shahin Lockman, M.D.,
Joseph Makhema, M.B., B.S., and Roger L. Shapiro, M.D., M.P.H.

ABSTRACT

BACKGROUND

A preliminary safety signal for neural-tube defects was previously reported in association with dolutegravir exposure from the time of conception, which has affected choices of antiretroviral treatment (ART) for human immunodeficiency virus (HIV)–infected women of reproductive potential. The signal can now be evaluated with data from follow-up of additional pregnancies.

METHODS

We conducted birth-outcomes surveillance at hospitals throughout Botswana, expanding from 8 to 18 sites in 2018. Trained midwives performed surface examinations of all liveborn and stillborn infants. Research assistants photographed abnormalities after maternal consent was obtained. The prevalence of neural-tube defects and major external structural defects according to maternal HIV infection and ART exposure status was determined. In the primary analyses, we used the Newcombe method to evaluate differences in prevalence with 95% confidence intervals.

RESULTS

From August 2014 through March 2019, surveillance captured 119,477 deliveries; 119,033 (99.6%) had an infant surface examination that could be evaluated, and 98 neural-tube defects were identified (0.08% of deliveries). Among 1683 deliveries in which the mother was taking dolutegravir at conception, 5 neural-tube defects were found (0.30% of deliveries); the defects included two instances of myelomeningocele, one of anencephaly, one of encephalocele, and one of iniencephaly. In comparison, 15 neural-tube defects were found among 14,792 deliveries (0.10%) in which the mother was taking any non-dolutegravir ART at conception, 3 among 7959 (0.04%) in which the mother was taking efavirenz at conception, 1 among 3840 (0.03%) in which the mother started dolutegravir treatment during pregnancy, and 70 among 89,372 (0.08%) in HIV-uninfected mothers. The prevalence of neural-tube defects was higher in association with dolutegravir treatment at conception than with non-dolutegravir ART at conception (difference, 0.20 percentage points; 95% confidence interval [CI], 0.01 to 0.59) or with other types of ART exposure. Major external structural defects were found in 0.95% of deliveries among women exposed to dolutegravir at conception and 0.68% of those among women exposed to non-dolutegravir ART at conception (difference, 0.27 percentage points; 95% CI, –0.13 to 0.87).

CONCLUSIONS

The prevalence of neural-tube defects was slightly higher in association with dolutegravir exposure at conception than with other types of ART exposure at conception (3 per 1000 deliveries vs. 1 per 1000 deliveries). (Funded by the National Institutes of Health.)

From the Division of Infectious Diseases, Beth Israel Deaconess Medical Center (R.Z., R.L.S.), the Department of Immunology and Infectious Diseases (R.Z., M.E., S.L., J. Makhema, R.L.S.) and the Center for Biostatistics in AIDS Research (D.L.J., S.B.), Harvard T.H. Chan School of Public Health, MassGeneral Hospital for Children, Massachusetts General Hospital (L.H.), and the Division of Infectious Diseases, Brigham and Women's Hospital (S.L.) — all in Boston; the Botswana–Harvard AIDS Institute Partnership (R.Z., M.D., G.M., A.I., S.D., J. Mabuta, M.M., T.G., M.E., S.L., J. Makhema, R.L.S.) and the University of Botswana Faculty of Medicine (T.G.), Gaborone, Botswana; and the University of Pennsylvania Perelman School of Medicine, Philadelphia (S.D.). Address reprint requests to Dr. Zash at the Division of Infectious Diseases, Beth Israel Deaconess Medical Center, LMOB, Suite GB, 110 Francis St., Boston, MA 02215, or at rzash@bidmc.harvard.edu.

1

NEURAL-TUBE DEFECTS OCCUR BY THE end of the sixth week of pregnancy (i.e., the fourth week after fertilization) and have been associated with exposure to specific drugs early in pregnancy.[1] Concerns about neural-tube defects among children exposed to efavirenz at the time of conception were raised by an early study in nonhuman primates[2] and from case reports in patients,[3-5] but no subsequent clinical association was detected.[6] Dolutegravir is a newer antiretroviral agent with a higher barrier to resistance, fewer side effects, and more effective viral suppression than efavirenz,[7] but data on congenital abnormalities and other potential adverse birth outcomes associated with exposure at the time of conception have been lacking. In 2016, Botswana became the first African country to shift from efavirenz-based antiretroviral treatment (ART) to dolutegravir-based ART as first-line therapy for all adults with human immunodeficiency virus (HIV) infection.[8]

In 2014, to confirm the safety of efavirenz exposure at conception, surface examination surveillance to detect neural-tube defects was initiated at eight large government maternity wards in Botswana as part of the Tsepamo Study. This surveillance system captures all antiretroviral exposure, including dolutegravir exposure since the introduction of the drug in 2016. In May 2018, a review of data to inform the development of World Health Organization (WHO) HIV guidelines revealed a potential early signal for neural-tube defects associated with dolutegravir exposure at conception, with 4 such defects found among 426 exposures.[9] Since that time, advisory statements from regulatory agencies have recommended more-limited use of dolutegravir among women planning pregnancy.[10,11] In the present study, we evaluated the signal for neural-tube defects with follow-up of additional births.

METHODS

STUDY SITES

The Tsepamo Study is a nationally representative birth-outcomes surveillance study in Botswana, described previously.[12] The study was originally designed to evaluate birth outcomes (including neural-tube defects) associated with exposure to efavirenz from conception. We recorded obstetrical outcomes at 8 public hospital maternity wards from August 2014 to June 2018 (approximately 45% of all births in the country), adding 10 additional sites between July 2018 and March 2019 (increasing coverage to approximately 72% of all births).[13] The maternity sites that were originally included were 2 tertiary referral hospitals, 5 district hospitals, and 1 primary-level hospital; 4 district and 6 primary-level hospitals were added in 2018. At each site, research assistants abstracted data from the obstetrical record for all consecutive in-hospital deliveries. Abstracted data included information on maternal demographic characteristics, medical history, routine laboratory measurements in pregnancy, pregnancy complications, medications reported to have been taken at the time of conception and medications prescribed during pregnancy, HIV infection and ART history, and delivery and infant outcomes before hospital discharge.

ETHICS APPROVAL

Ethics approval for this study was granted by the Health Research and Development Committee in Botswana and by the Office of Human Research Administration at the Harvard T.H. Chan School of Public Health. Women provided written informed consent for photographs to be taken of infants with abnormalities. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol, available with the full text of this article at NEJM.org.

SURVEILLANCE FOR CONGENITAL ABNORMALITIES AND OTHER ADVERSE BIRTH OUTCOMES

Government midwives received training from the study team to standardize infant surface examinations and to assess congenital abnormalities. Midwives described all visible abnormalities observed during the infant examination in the obstetrical record and alerted the study research assistants, who sought maternal consent to photograph the abnormality. Photographs of major abnormalities, as well as any unclear descriptions, were reviewed by a medical geneticist (the second author) at MassGeneral Hospital for Children in Boston who was not aware of any exposure information.

Abnormalities identified by routine surface examination before discharge from the hospital were classified as major external structural malformations if they had clinical, surgical, or cos-

metic importance. Surface examinations did not routinely include examination inside the mouth, auscultation of the heart, or testing for inguinal hernias, undescended testes, or hip dysplasia. Imaging, chromosomal testing, mutation analysis, and autopsy data were not available. Chromosomal trisomies identified on the basis of physical appearance were not included. Neural-tube defects were defined as definite (confirmed by photograph) or probable (diagnosed on the basis of a description but with no photograph) myelomeningocele, meningocele, encephalocele, anencephaly with or without craniorachischisis, or iniencephaly. Other adverse birth outcomes were extracted from obstetrical records, including stillbirth, preterm birth (<37 weeks of gestation), very preterm birth (<32 weeks of gestation), small for gestational age (body weight <10th percentile for gestational age), very small for gestational age (body weight <3rd percentile for gestational age),[14,15] and neonatal death at less than 28 days among infants who never left the hospital.

HIV INFECTION AND ART EXPOSURE GROUPS

Women were considered to be HIV-uninfected if the last HIV test recorded during pregnancy was negative. Women were considered to be HIV-infected if they had been documented as such in the obstetrical or medical record. Information on ART regimen, ART start date, and changes in or terminations of ART was extracted from the obstetrical or medical record. The ART regimen and start date were confirmed with the mother at the time of delivery and with the outpatient HIV records, when available, for all cases of head or spine abnormalities throughout the study and for all HIV-infected women since January 2018. ART at conception was defined as maternal ART that started before the calculated date of the last menstrual period, and ART that started during pregnancy was defined as maternal ART that started after that date. Deliveries were classified according to ART exposure at conception for the analyses of congenital malformations and were excluded if the timing of ART or the type of ART regimen was not known.

ANTIRETROVIRAL REGIMENS

The Botswana HIV Program provides free ART to citizens. In 2012, tenofovir–emtricitabine–efavirenz (coformulated) became the first-line treatment for all HIV-infected women who had not previously received ART and had a CD4 cell count of less than 350 per cubic millimeter, a shift from nevirapine-based or lopinavir–ritonavir–based ART. In May 2016, Botswana updated its national HIV guidelines to designate tenofovir–emtricitabine with dolutegravir (not coformulated) as treatment for all HIV-infected adults who had not previously received ART, regardless of CD4 cell count (this regimen was replaced by coformulated tenofovir–lamivudine–dolutegravir in September 2018). Patients with viral suppression without side effects while taking their ART regimens were not switched to newer regimens (with the exception of tenofovir–emtricitabine being replaced with tenofovir–lamivudine plus dolutegravir).

STATISTICAL ANALYSIS

After the initial safety signal associated with dolutegravir was reported in May 2018, we specified that the next analysis would occur after March 31, 2019, to detect neural-tube defects in infants conceived before the June 2018 guidance in Botswana that advised avoidance of dolutegravir-based ART if pregnancy was desired.[16] The aim of the prespecified primary evaluation was to determine whether the prevalence of neural-tube defects and the total prevalence of external structural malformations were higher in association with dolutegravir treatment at conception than with other types of exposure during the entire study period. Prevalence was calculated as the number of events divided by the total number of births (including live births and stillbirths). The 95% confidence intervals around the prevalence of abnormalities in each exposure group were calculated with the Wilson method.[17] Differences in prevalence between the group with exposure to dolutegravir at conception and the other exposure groups were determined and 95% confidence intervals calculated with the Newcombe method.[18]

The risk of other adverse birth outcomes associated with continuous exposure to dolutegravir with a tenofovir–emtricitabine or tenofovir–lamivudine backbone from the time of conception was compared with the risk associated with continuous exposure to efavirenz with the same ART backbones from the time of conception. These comparisons were performed among singleton pregnancies and were restricted to the eight original sites after the dolutegravir rollout

to reduce potential confounding by geographic or historical differences in these outcomes. An increased risk of adverse birth outcomes in association with other antiretroviral regimens has been reported previously.[12,19] Unadjusted and adjusted (for age, gravida, and education) relative risks for adverse birth outcomes were determined with the use of a log binomial model.[20]

RESULTS

STUDY POPULATION

From August 15, 2014, to March 31, 2019, there were 119,477 total deliveries (117,594 singleton, 1859 twin, 23 triplet, and 1 quadruplet) at the surveillance maternity sites. Among all deliveries, 444 (0.4%) lacked at least one surface examination that could be evaluated or a sufficient description to evaluate for neural-tube defects (including 5 among women with dolutegravir exposure at conception) and were excluded from the analysis, which left 119,033 available for analysis. Figure 1 summarizes the exposure groups according to HIV infection status, maternal ART regimen, and the timing of ART initiation.

The baseline characteristics of the women in the study are shown in Table 1. The differences among the ART exposure groups were small or negligible with regard to delivery site, history of epilepsy or diabetes, and proportion of women with high body weight (>90 kg) during pregnancy. Prescription of folate supplementation with folate alone, folate combined with iron, or multivitamin supplements was similar across groups, and 99.8% of the women for whom folate was prescribed started taking folate during, not before, pregnancy. Personal histories of a previous birth with a congenital abnormality and family histories of neural-tube defects were not available.

NEURAL-TUBE DEFECTS

The total number of neural-tube defects identified in the population was 98 (0.08% of deliveries; 95% confidence interval [CI], 0.07 to 0.10), including 49 instances of meningocele or myelomeningocele, 33 of anencephaly, 15 of encephalocele, and 1 of iniencephaly (Table 2). Photographs supported the diagnosis in 60 cases, and 38 cases were diagnosed on the basis of descriptions only. There were 26 (0.92%) neural-tube defects among stillbirths and 72 (0.06%) among live births. Among the live-born infants in whom neural-tube defects were found, 25 (35%) died within 28 days, and 1 had an unknown vital status.

Neural-tube defects according to exposure group are shown in Figure 2. Among the 1683 deliveries in which the mother was taking dolutegravir-based ART at conception, 5 neural-tube defects were found (0.30% of deliveries; 95% CI, 0.13 to 0.69), as compared with 15 defects among 14,792 deliveries (0.10%; 95% CI, 0.06 to 0.17) in which the mother was taking any non-dolutegravir ART at conception. The absolute difference in prevalence between dolutegravir-based and non–dolutegravir-based ART exposure from conception was 0.20 percentage points (95% CI, 0.01 to 0.59). Among the 7959 deliveries in which the mother was taking efavirenz at conception, 3 neural-tube defects were found (0.04%; 95% CI, 0.01 to 0.11). Among the 3840 deliveries in which the mother had started dolutegravir treatment during pregnancy, 1 neural-tube defect was found (0.03%; 95% CI, 0.00 to 0.15); in this case, the mother had started dolutegravir treatment at 8 weeks of gestation. Among the 89,372 deliveries in which the mothers were HIV-uninfected, 70 neural-tube defects were found (0.08%; 95% CI, 0.06 to 0.10). The 5 neural-tube defects in deliveries among women who were taking dolutegravir-based ART at conception included 2 instances of myelomeningocele, 1 of encephalocele, and 1 of iniencephaly (all diagnosed with photographs), as well as 1 of anencephaly (diagnosed with a description only). These events are described in Table S1 in the Supplementary Appendix, available at NEJM.org.

From May 1, 2018, when the signal regarding neural-tube defects was first reported, until March 31, 2019, one additional neural-tube defect was identified in a delivery in which the mother was taking dolutegravir-based ART at conception (1 of 1257, 0.08%), as compared with one neural-tube defect in all other groups with any ART exposure at conception (1 of 3492, 0.03%), none in the group with efavirenz exposure at conception (0 of 2172), one in the group with dolutegravir treatment started during pregnancy (1 of 1028, 0.10%), and nine in the group of HIV-uninfected women (9 of 23,315; 0.04%). To address potential temporal fluctuations in the prevalence of neural-tube defects, we also re-
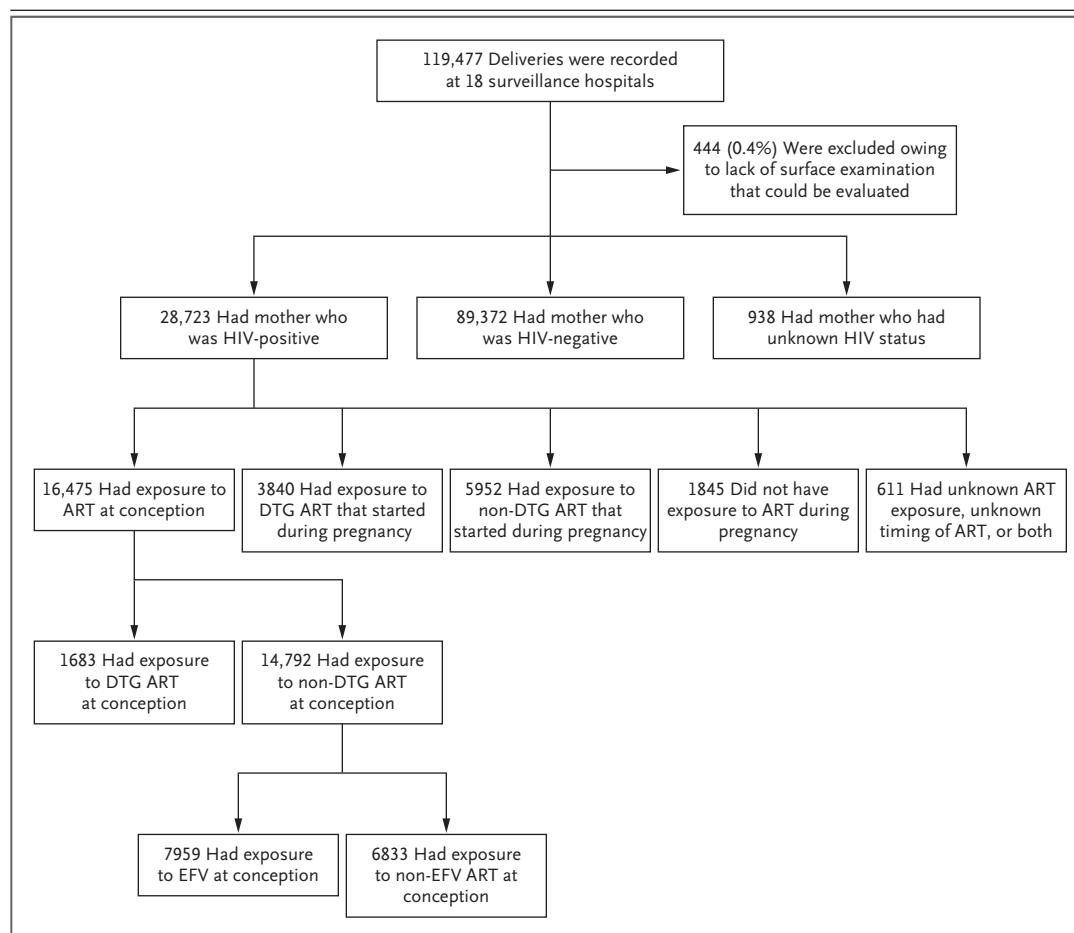
Figure 1. Deliveries at the Surveillance Sites According to Maternal ART and HIV Infection Status, August 2014–March 2019.

In the case of 72 (4%) of the 1683 deliveries in which the mother had been taking dolutegravir (DTG) at conception, the mother switched to a different regimen during pregnancy, and in 6 (0.4%) the mother switched during the first 6 weeks of pregnancy (no neural-tube defects or major malformations were identified in the infants in these 6 deliveries). Tenofovir–emtricitabine or tenofovir–lamivudine was the nucleoside reverse-transcriptase inhibitor backbone in the regimen taken by 1653 (98.2%) of the mothers who took DTG-based antiretroviral treatment (ART) and by 7792 (97.9%) of the mothers who took efavirenz (EFV)–based ART. In addition to 7959 deliveries in which the infants were exposed to EFV at the time of conception, deliveries in which the infants had non-EFV ART exposure from conception included 1848 with exposure to nevirapine–tenofovir plus either emtricitabine or lamivudine, 2966 to nevirapine–zidovudine–lamivudine, 579 to lopinavir–ritonavir–tenofovir plus either emtricitabine or lamivudine, 385 to lopinavir–ritonavir–zidovudine–lamivudine, 884 to unspecified (non-DTG) regimens, and 171 to other regimens.

stricted analyses to deliveries that occurred after the dolutegravir rollout in 2016 and found no notable differences in the magnitude or direction of any findings (Table S2 in the Supplementary Appendix). During this period, the difference in the prevalence of neural-tube defects between the group with exposure to dolutegravir at conception and the group with exposure to any other type of ART at conception was 0.22 percentage points (95% CI, 0.03 to 0.62).

OTHER MAJOR EXTERNAL STRUCTURAL ABNORMALITIES AND ADVERSE BIRTH OUTCOMES

All major external structural malformations, including neural-tube defects, are listed in Table 2. Of the reported defects, 23 lacked sufficient description for categorization. There were 719 major external structural malformations found (0.60% of deliveries; 95% CI, 0.56 to 0.65), with neural-tube defects accounting for 14%. A total of 16 major external structural malformations

Table 1. Characteristics of Women According to Maternal ART and HIV Infection Status, August 2014–March 2019.*

Maternal Characteristic	DTG at Conception (N=1683)	Non-DTG ART at Conception (N=14,792)	EFV at Conception (N=7959)	DTG Started in Pregnancy (N=3840)	HIV-Negative (N=89,372)
Demographic characteristics					
Median age (IQR) — yr†	29 (25–34)	33 (29–37)	32 (27–36)	28 (23–33)	25 (21–30)
Married — no./total no. (%)	115/1631 (7)	1,636/14,382 (11)	743/7750 (10)	232/3736 (6)	9,713/86,808 (11)
Education — no./total no. (%)					
None or primary school	165/1647 (10)	2,116/14,456 (15)	1048/7788 (13)	306/3795 (8)	5,176/87,465 (6)
Secondary or tertiary	1482/1647 (90)	12,340/14,456 (85)	6740/7788 (87)	3489/3795 (92)	82,280/87,465 (94)
Occupation — no./total no. (%)					
Housewife or no occupation	1036/1620 (64)	8,367/14,167 (59)	4683/7620 (61)	2243/3726 (60)	49,275/85,731 (57)
Student	39/1620 (2)	206/14,167 (1)	121/7620 (2)	152/3726 (4)	7,220/85,731 (8)
Salaried	545/1620 (34)	5,594/14,167 (39)	2816/7620 (37)	1331/3726 (36)	29,236/85,731 (34)
Noncitizen	16/1632 (1)	250/14,750 (2)	180/7936 (2)	26/3828 (1)	2,839/89,128 (3)
Medical and obstetrical history					
Preconception diagnosis of epilepsy — no./total no. (%)	3/1610 (0.2)	35/14,348 (0.2)	19/7677 (0.2)	11/3773 (0.3)	193/86,760 (0.2)
Preconception diagnosis of diabetes — no./total no. (%)	6/1610 (0.4)	38/14,348 (0.3)	23/7677 (0.3)	13/3773 (0.3)	230/86,760 (0.3)
High body weight in pregnancy — no./total no. (%)‡	218/1555 (14.0)	1,717/14,043 (12)	904/7494 (12)	506/3691 (14)	11,669/84,924 (14)
Trimethoprim–sulfamethoxazole exposure at conception — no./total no. (%)	1/1625 (0.1)	0/14,370	0/7685	0/3795	0/86,897
Folate prescribed before conception — no./total no. (%)	1/1618 (0.1)	28/14,319 (0.2)	13/7651 (0.2)	4/3781 (0.1)	132/86,565 (0.2)
Folate prescribed during pregnancy — no./total no. (%)§	1110/1618 (69)	7,416/14,319 (52)	4032/7651 (53)	2087/3781 (55)	42,637/86,565 (49)
Iron prescribed during pregnancy — no./total no. (%)¶	1526/1618 (94)	13,164/14,319 (92)	7125/7651 (93)	3554/3781 (94)	78,746/86,565 (91)
Gravida — no./total no. (%)					
No previous pregnancies	277/1678 (17)	1,106/14,768 (7)	598/7954 (8)	1041/3834 (27)	38,163/89,126 (43)
1–4 Previous pregnancies	1104/1678 (66)	9,491/14,768 (64)	5317/7954 (67)	2378/3834 (62)	44,510/89,126 (50)
≥5 Previous pregnancies	297/1678 (18)	4,171/14,768 (28)	2030/7954 (26)	415/3834 (11)	6,453/89,126 (7)
Median gestational age at presentation for ANC (IQR) — wk‖	16 (12–22)	17 (12–21)	17 (13–22)	17 (13–22)	17 (12–22)
No prenatal care received — no./total no. (%)	52/1675 (3)	357/14,697 (2)	257/7923 (3)	40/3827 (1)	2,073/88,780 (2)
Alcohol or smoking in pregnancy — no./total no. (%)	171/1508 (11)	1,042/13,543 (8)	586/7229 (8)	466/3549 (13)	7,987/82,492 (10)
Delivery at a tertiary hospital — no./total no. (%)	762/1683 (45)	6,454/14,792 (44)	3380/7959 (42)	1901/3840 (50)	39,944/89,371 (45)
Birth by cesarean section — no./total no. (%)	392/1680 (23)	3,450/14,779 (23)	1750/7953 (22)	942/3838 (25)	19,927/89,255 (22)

HIV infection history			
Time from HIV diagnosis to conception			
Median (IQR) — wk	97 (47–317)	319 (180–494)	221 (130–367)	—
<2 yr — no./total no. (%)	850/1607 (53)	1,343/13,261 (10)	1212/7166 (17)	—
2–5 yr — no./total no. (%)	349/1607 (22)	5,131/13,261 (39)	3661/7166 (51)	—
>5 yr — no./total no. (%)	408/1607 (25)	6,787/13,261 (51)	2293/7166 (32)	—
Duration of ART before conception			
Median (IQR) — wk	45 (20–69)	240 (131–392)	156 (93–242)	—
<2 yr — no./total no. (%)	1477/1602 (92)	2,569/14,234 (18)	2256/7647 (30)	—
2–5 yr — no./total no. (%)	106/1602 (7)	6,478/14,234 (46)	4441/7647 (58)	—
>5 yr — no./total no. (%)	0/1602	5,187/14,234 (36)	950/7647 (12)	—
CD4 cell count in pregnancy			
Median (IQR) — cells/mm^3	566 (410–713)	532 (408–686)	525 (399–679)	426 (291–588)
<200 cells/mm^3 — no./total no. (%)	18/472 (4)	91/3,134 (3)	60/1672 (4)	98/777 (13)
200–349 cells/mm^3 — no./total no. (%)	63/472 (13)	377/3,134 (12)	225/1672 (13)	192/777 (25)
350–499 cells/mm^3 — no./total no. (%)	96/472 (20)	873/3,134 (28)	456/1672 (27)	204/777 (26)
≥500 cells/mm^3 — no./total no. (%)	295/472 (62)	1,793/3,134 (57)	931/1672 (56)	283/777 (36)

* Percentages may not total 100 because of rounding. ART denotes antiretroviral treatment, DTG dolutegravir, EFV efavirenz, HIV human immunodeficiency virus, and IQR interquartile range.

† Data on age were missing for 53 women (6 who received non-DTG ART at conception, 4 who received EFV at conception, 1 who started DTG treatment during pregnancy, and 46 who were HIV-negative).

‡ High body weight during pregnancy was defined as a weight greater than 90 kg.

§ The median gestational age at the time of the first folate prescription during pregnancy was 22 weeks (IQR, 16 to 29).

¶ Data on the date of prescription of iron supplementation during pregnancy were not collected.

‖ Data on the gestational age at presentation for antenatal care (ANC) were missing for 5214 women (89 who received DTG at conception, 730 who received non-DTG ART at conception, 450 who received EFV at conception, 118 who started DTG during pregnancy, and 4277 who were HIV-negative).

Table 2. Major External Structural Abnormalities According to ART Exposure and HIV Infection Status, August 2014–March 2019.*

Structural Abnormality	Total Population (N=119,033)	DTG at Conception (N=1683)	Non-DTG ART at Conception (N=14,792)	EFV at Conception (N=7959)	DTG Started in Pregnancy (N=3840)	HIV-Negative (N=89,372)
	number (percent)†			number†		
Major external structural malformations‡						
No. of defects	719	16	101	55	17	528
Percent (95% CI)	0.60 (0.56–0.65)	0.95 (0.59–1.54)	0.68 (0.56–0.83)	0.69 (0.53–0.90)	0.44 (0.28–0.71)	0.59 (0.54–0.64)
Neural-tube defects						
Myelomeningocele or meningocele	49 (0.04)	2	8	2	1	34
Anencephaly	33 (0.03)	1	6	1	0	24
Encephalocele	15 (0.01)	1	1	0	0	12
Iniencephaly	1 (0.001)	1	0	0	0	0
Other nervous system defects						
Hydrocephalus, presumed§	102 (0.09)	0	11	5	1	83
Holoprosencephaly, presumed	13 (0.01)	1	2	2	1	8
Defects of face, eye, ear, and neck						
Cleft lip	44 (0.04)	0	4	2	1	34
Anophthalmia or micro-phthalmia	5 (0.004)	1	1	0	0	2
Congenital cataract	3 (0.003)	0	1	0	0	2
Cystic hygroma	3 (0.003)	0	0	0	0	3
Microtia	5 (0.004)	0	0	0	0	2
Gastrointestinal defects						
Omphalocele	19 (0.02)	2	3	2	0	14
Gastroschisis	19 (0.02)	2	0	0	0	15
Imperforate anus	10 (0.01)	0	2	0	0	7
Genitourinary defects						
Hypospadias, severe¶	12 (0.01)	0	2	1	0	8
Ambiguous genitalia	11 (0.009)	0	6	4	0	4
Posterior urethral valves, presumed	3 (0.003)	0	1	0	0	2
Limb defects						
Club-foot deformity‖	209 (0.18)	1	30	18	4	155
Amniotic band syndrome	18 (0.02)	0	1	1	1	10
Limb–body wall defect	3 (0.003)	0	0	0	0	3
Split-foot or split-hand deformity	13 (0.01)	0	2	1	0	9
Polydactyly**						
Postaxial, type A	21 (0.02)	0	4	3	1	16
Preaxial or bifid digit	26 (0.02)	0	3	2	1	20
Terminal transverse limb defect	3 (0.003)	0	0	0	0	3

Table 2. (Continued.)

Structural Abnormality	Total Population (N=119,033)	DTG at Conception (N=1683)	Non-DTG ART at Conception (N=14,792)	EFV at Conception (N=7959)	DTG Started in Pregnancy (N=3840)	HIV-Negative (N=89,372)
	number (percent)†			number†		
Absent or hypoplastic radius	3 (0.003)	0	0	0	1	2
Syndactyly and polysyndactyly	23 (0.02)	1	4	3	2	15
Major limb defect not further classified††	27 (0.02)	2	4	1	2	18
Other major defects						
Skeletal dysplasia	27 (0.02)	1	5	3	0	20
Arthrogryposis, presumed	3 (0.003)	0	1	0	0	2
Skin pedicles, removed surgically	3 (0.003)	0	0	0	0	3
Multiple abnormalities not further classified‡‡	31 (0.03)	0	6	3	1	24
Other abnormalities§§	35 (0.03)	0	6	3	1	25

* The sums of the major external structural malformations and total neural-tube defects in each exposure group do not equal the category totals listed because EFV from conception is a subset of non-DTG ART from conception. There were also additional major external structural malformations and neural-tube defects in other groups with exposures that are not of interest.

† The number of defects (percent of deliveries) or the number of defects is given, except as indicated.

‡ The total includes all deliveries in the entire study population in which at least one major external structural malformation was found. The numbers of specific defects total more than 719 because of 75 deliveries in which more than one major defect was found.

§ Hydrocephalus was defined on the basis of the appearance of the head in a photograph or a description of hydrocephalus from the person who performed the surface examination and not on the basis of head circumference measurements.

¶ Severe hypospadias included penile, scrotal, and perineal hypospadias and epispadias. Glanular hypospadias was not considered to be a major external structural malformation.

‖ Club-foot deformity included unilateral and bilateral talipes equinovarus and talipes calcaneovalgus.

** Postaxial polydactyly type B, a common abnormality, was not considered to be a major abnormality because the extra digit was resolved when tied off with a string or twine by a nurse after birth.
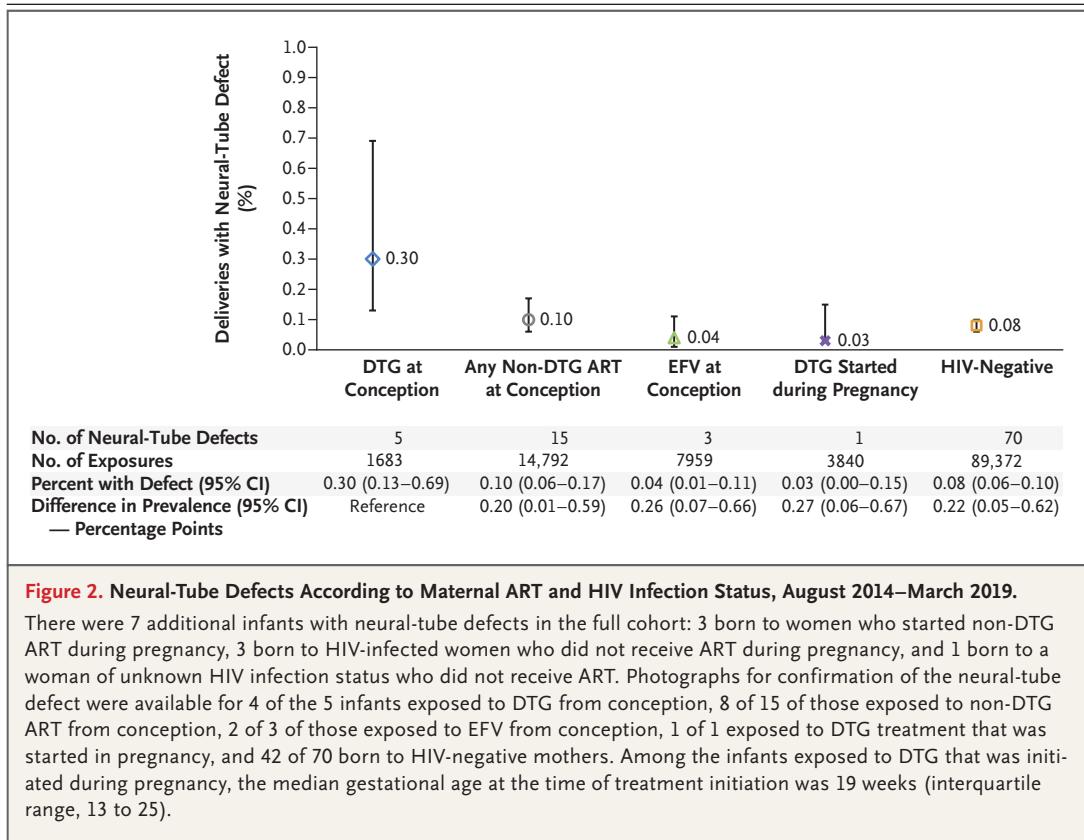
†† Major limb abnormalities that could not be further classified included abnormalities of the limb that could not be diagnosed without further imaging or testing but were clearly of clinical, surgical, or cosmetic significance.

‡‡ Abnormalities were considered multiple abnormalities that could not be further classified when the photo or description showed abnormalities in multiple areas of the body that were clearly of clinical or cosmetic significance, but without further diagnostic testing, no specific diagnosis was possible.

§§ Other abnormalities were found in 28 deliveries with no more than two specific defects (the numbers of deliveries and the exposure groups are given in parentheses): upper-limb reduction and monodactyly (1 HIV-negative), triphalangeal thumb and wide index finger (1 HIV-negative), total absence of chest and abdominal wall (1 HIV-negative), thumb hypoplasia (1 HIV-negative), hypoplastic fingers (1 HIV-negative), amelia (1 HIV-negative), severely small head (1 HIV-negative), central digit hypoplasia (1 non-DTG ART at conception [not EFV]), rugae over brain with microcephaly suggesting underlying brain defect (1 HIV-negative), hypodactyly (1 HIV-negative), premalignant sebaceous nevus, presumed (1 HIV-negative), hemifacial microsomia (1 HIV-negative), major penis deformity (1 HIV-negative), missing thumb (1 HIV-negative), Pierre Robin sequence, presumed (1 HIV-negative), very large cyst inside the mouth (1 non-DTG ART at conception), large cystic protrusion about the symphysis pubis (1 DTG started in pregnancy), large cyst below the tongue (1 HIV-negative), inguinal hernia (1 EFV at conception), craniofacial abnormalities not able to be classified further (1 HIV-negative), absence of tibia (1 EFV at conception), absence of forearm (1 EFV at conception), bilateral adactyly or hypodactyly (1 HIV-negative), facial cleft (1 HIV-negative), midface deformity (1 HIV-negative), large cystic lesion on upper back (possibly lipoma, but with an odd appearance and probable cosmetic significance) (1 HIV-negative), brachial cleft cyst (presumed) (1 HIV-negative), isolated bowed tibia (2 HIV-negative), gigantism of fingers (2 HIV-negative), severe arteriovenous malformation (1 HIV-negative and 1 non-DTG ART at conception), and sacrococcygeal teratoma (2 HIV-negative).

were found among 1683 deliveries (0.95%) in which the mother was taking dolutegravir at conception and included presumed holoprosencephaly (1 delivery), omphalocele (2), gastroschisis (2), club foot (2), upper-limb defects (2), anophthalmia (1), skeletal dysplasia (1), and neural-tube defects (5) (Table S1 in the Supplementary Appendix). The prevalence of major external structural malformations did not differ substantially in other exposure groups (Table 2): 0.68% of deliveries among women who were taking any non-dolutegravir ART at conception,

Figure 2. Neural-Tube Defects According to Maternal ART and HIV Infection Status, August 2014–March 2019.

There were 7 additional infants with neural-tube defects in the full cohort: 3 born to women who started non-DTG ART during pregnancy, 3 born to HIV-infected women who did not receive ART during pregnancy, and 1 born to a woman of unknown HIV infection status who did not receive ART. Photographs for confirmation of the neural-tube defect were available for 4 of the 5 infants exposed to DTG from conception, 8 of 15 of those exposed to non-DTG ART from conception, 2 of 3 of those exposed to EFV from conception, 1 of 1 exposed to DTG treatment that was started in pregnancy, and 42 of 70 born to HIV-negative mothers. Among the infants exposed to DTG that was initiated during pregnancy, the median gestational age at the time of treatment initiation was 19 weeks (interquartile range, 13 to 25).

0.69% of those among women who were taking efavirenz at conception, 0.44% of those among women who started dolutegravir treatment during pregnancy, and 0.59% among deliveries to HIV-uninfected women. Major external structural defects were found in 0.95% of deliveries among women with exposure to dolutegravir at conception and 0.68% of those among women with exposure to non-dolutegravir ART at conception (difference, 0.27 percentage points; 95% CI, −0.13 to 0.87).

Table 3 shows other adverse birth outcomes among deliveries in which infants were exposed to continuous treatment with dolutegravir or efavirenz from the time of conception. The prevalence of any adverse birth outcome associated with continuous dolutegravir exposure was 33.2%, and that associated with continuous efavirenz exposure was 35.0% (adjusted relative risk, 0.94; 95% CI, 0.86 to 1.02). There were no substantial differences between these groups in the prevalence of total or severe adverse birth outcomes.

DISCUSSION

We performed nationwide birth surveillance in Botswana and found evidence of a potential association between neural-tube defects and dolutegravir exposure at the time of conception. Since our initial 2018 report, the estimated prevalence has diminished in magnitude to approximately 3 per 1000 births but remains greater than for all other types of antiretroviral exposure at conception.

The potential association between dolutegravir and neural-tube defects was unexpected. Preclinical studies in animals did not identify a risk for birth defects associated with this compound.[21] As of January 31, 2019, the Antiretroviral Pregnancy Registry (APR) has reported 1 instance of neural-tube defect (anencephaly) among 247 periconception exposures to dolutegravir that were identified prospectively[22]; outside the APR, no other neural-tube defects have been reported in association with dolutegravir treatment from conception in eight observational studies with a

Table 3. Adverse Birth Outcomes in Deliveries among Women with Exposure to Dolutegravir or Efavirenz from Conception, October 2016–March 2019.*

Adverse Birth Outcome	DTG from Conception (N = 1271)	EFV from Conception (N = 4430)	Adjusted Relative Risk (95% CI)†
	number/total number (percent)		
Any adverse birth outcome	422/1271 (33.2)	1550/4430 (35.0)	0.94 (0.86–1.02)
Any severe birth outcome	151/1271 (11.9)	568/4430 (12.8)	0.89 (0.74–1.05)
Preterm birth‡	237/1254 (18.9)	841/4369 (19.2)	1.01 (0.89–1.15)
Very preterm birth§	58/1254 (4.6)	215/4369 (4.9)	0.91 (0.68–1.23)
Small for gestational age¶	211/1244 (17.0)	787/4328 (18.2)	0.87 (0.75–1.00)
Very small for gestational age‖	81/1244 (6.5)	315/4328 (7.3)	0.82 (0.64–1.04)
Stillbirth	33/1271 (2.6)	89/4429 (2.0)	1.36 (0.91–2.04)
Neonatal death in hospital	14/1232 (1.1)	71/4334 (1.6)	0.71 (0.39–1.28)

* Comparisons included singleton pregnancies with continuous exposure to dolutegravir-based or efavirenz-based ART from the time of conception and in which infants were born at one of the eight original sites since October 1, 2016, when the first exposure to dolutegravir from conception occurred.
† All models were adjusted for maternal age, gravida, and educational attainment. These variables were chosen a priori and added to the model simultaneously.
‡ Preterm birth was defined as birth before 37 weeks of gestation.
§ Very preterm birth was defined as birth before 32 weeks of gestation.
¶ Small for gestational age was defined as a body weight lower than the 10th percentile for gestational age.
‖ Very small for gestational age was defined as a body weight lower than the 3rd percentile for gestational age.

total of 245 exposures.[23-31] However, a lack of such reports is not surprising, given the small number of preconception exposures outside Botswana to date. Because neural-tube defects could be affected by low folate levels (Botswana does not mandate folate-fortified grains) or by a genetic predisposition specific to Botswana, systematically collected data from other regions in which dolutegravir is being used are needed.

Folate deficiency is a well-known risk factor for neural-tube defects,[32] and folate antagonism by dolutegravir has been investigated as a potential mechanism to explain our clinical data. Findings in in vitro studies performed by Cabrera et al. included partial antagonism between dolutegravir and folate at high concentrations and a link between dolutegravir and developmental toxic effects in a folate-reversible zebra fish model.[33] An industry study showed high-dose folate antagonism in cell-culture experiments, which the authors of that study did not consider to be clinically relevant, although the cutoff values used in cell-culture experiments to determine clinical relevance to humans are of uncertain accuracy.[34] At this time, no firm conclusions can be drawn as to whether a folate pathway should be implicated, but folic acid fortification of grains can decrease the population prevalence of neural-tube defects by half,[32] and preconception folate supplementation is an existing WHO recommendation.[35] Further research is critical to determine whether dietary or vitamin supplementation of folate in women of childbearing age who are receiving dolutegravir might mitigate the excess risk that was estimated in our study.

Our data show no signal concerning the use of efavirenz at conception and the risk of neural-tube defects. Several additional findings deserve further study. We identified more major external structural abnormalities associated with dolutegravir treatment at conception (9 per 1000 births) than after dolutegravir treatment that was started during pregnancy (4 per 1000 births), with two cases of gastroschisis and two cases of omphalocele associated with dolutegravir exposure from conception that are notable. More surveillance is required to interpret these findings. In our study, we also observed that dolutegravir treatment from conception was associated with fewer adverse birth outcomes than efavirenz treatment from conception, with the exception of stillbirths, although the differences were not sub-

stantial. Continued surveillance to further evaluate birth outcomes is important, because small increases in the risk of common adverse birth outcomes have a proportionally large effect on overall infant morbidity and mortality.[36-38]

Our study was observational by necessity, and therefore it could have been susceptible to confounding. Because of the very low prevalence of neural-tube defects, we could not reliably adjust for potential measured confounders. However, no measured confounders (obesity, diabetes, or exposure to antiepileptic agents or to trimethoprim–sulfamethoxazole at conception) were present in the five cases of neural-tube defects associated with dolutegravir treatment at conception, so bias from measured confounding cannot explain our results. Maternal age was lower among women who were taking dolutegravir at conception than among those who were taking other types of ART at conception, and this could have biased our estimated effect toward zero. Differences in preconception folate levels or genetic predisposition could have led to unmeasured confounding, but the distribution of these differences would not be expected to differ between exposure groups. Misclassification of exposure among cases of neural-tube defects associated with dolutegravir exposure at conception could also lead to bias for this rare outcome. However, in all five cases, the start date of ART occurred when dolutegravir was being used as the first-line drug nationally, the ART regimen and start date reported by the mother at delivery matched what was recorded in the obstetrical record, and all these women started dolutegravir more than 3 months before the estimated date of conception. We did not have a direct assessment of ART adherence; however, the incidence of in utero mother-to-child transmission among women taking ART in Botswana is 0.4%, which includes women who started ART late in pregnancy.[39] Therefore, we infer that the level of ART adherence was high among the women in our study. Although increased numbers of pregnancy terminations among women taking dolutegravir after the signal report could have biased results toward the null, the number of deliveries among women who were taking dolutegravir at conception continued to rise after May 2018 (Table S3 in the Supplementary Appendix), which suggests that terminations were not increasing.

Additional limitations of our study include the inability to evaluate defects that require more than a routine surface examination to detect, including heart defects, which are the most common type of major birth defect worldwide and can be associated with folate deficiency.[1] We also could not evaluate pregnancy loss before 24 weeks, which could have resulted in bias.[40-42] The strengths available with our study design included a large sample size that made it possible to ascertain the outcomes of most pregnancies (>95% of deliveries occur in hospitals, and termination of pregnancy is not legal in Botswana except in extreme circumstances), nearly complete reporting of a surface examination for all live births and stillbirths, photographic confirmation of trained midwife examinations for a majority of neural-tube defects, and nearly complete information on HIV infection status and ART regimen. Although our sample was large, neural-tube defects are a rare outcome, and additional surveillance is warranted. Future surveillance trends are particularly important given the decline in overall neural-tube defects that has been observed since May 2018.

The data from nationwide birth surveillance in Botswana examined in our study suggest a potential association between dolutegravir exposure at conception and the development of neural-tube defects. Although the prevalence of neural-tube defects was 3 times as high with dolutegravir as with non-dolutegravir antiretrovirals, this represented only approximately 2 excess defects per 1000 exposures. Clinical and policy recommendations based on these findings should consider the lack of similar data for most other modern antiretrovirals (with the exception of efavirenz), the lack of data on malformations that could not be evaluated in our study, unstudied long-term childhood effects of in utero ART exposure, the magnitude of the risk of other adverse birth outcomes, and the benefits of dolutegravir for maternal health.[43-45] Our findings highlight the need to address global disparities in access to effective contraception and preconception folate repletion, which would benefit the health of all women. Finally, given that women of reproductive age make up close to half the global population living with HIV infection, the inclusion of pregnant women in clinical safety trials and strengthened requirements mandating postmar-

keting surveillance for rare outcomes are needed for new agents that treat or prevent HIV infection.[46-49]

REFERENCES

1. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural-tube defects. N Engl J Med 1999;341:1509-19.
2. Cadman J. Efavirenz pregnancy warning. GMHC Treat Issues 1998;12(3):12.
3. De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. Arch Intern Med 2002;162:355.
4. Fundarò C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. AIDS 2002;16:299-300.
5. Saitoh A, Hull AD, Franklin P, Spector SA. Myelomeningocele in an infant with intrauterine exposure to efavirenz. J Perinatol 2005;25:555-6.
6. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS 2014;28:Suppl 2: S123-S131.
7. Vitoria M, Hill A, Ford N, et al. The transition to dolutegravir and other new antiretrovirals in low-income and middle-income countries: what are the issues? AIDS 2018;32:1551-61.
8. Handbook of the Botswana 2016 integrated HIV clinical care guidelines. Gaborone: Botswana Ministry of Health, 2016 (https://aidsfree.usaid.gov/sites/default/files/botswana_art_2016.pdf).
9. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. N Engl J Med 2018;379:979-81.
10. New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir. Amsterdam: European Medicines Agency, May 18, 2018 (https://www.ema.europa.eu/en/news/new-study-suggests-risk-birth-defects-babies-born-women-hiv-medicine-dolutegravir).
11. FDA drug safety communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolu-tegravir (Juluca, Tivicay, Triumeq). Silver Spring, MD: Food and Drug Administration, September 2018 (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-evaluate-potential-risk-neural-tube-birth-defects-hiv-medicine).
12. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of antiretroviral treatment regimens in pregnancy. JAMA Pediatr 2017;171(10):e172222.
13. Health statistics report 2010. Gaborone: Statistics Botswana, November 2017 (www.statsbots.org.bw/sites/default/files/publications/Health%20Statistics%20Report%202010.pdf).
14. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 2014;384:857-68.
15. Villar J, Giuliani F, Fenton TR, Ohuma EO, Ismail LC, Kennedy SH. INTER-GROWTH-21st very preterm size at birth reference charts. Lancet 2016;387:844-5.
16. Safety issues affecting women living with HIV using dolutegravir at the time of conception: advice for healthcare workers. Gaborone: Botswana Ministry of Health and Wellness, May 24, 2018.
17. Agresti A, Coull B. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 1998; 52:119-26.
18. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873-90.
19. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health 2018;6(7):e804-e810.
20. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol 2005; 162:199-200.
21. Tivicay: dolutegravir (DTG): New Drug Application (NDA) 204790. Drugs@FDA: FDA approved drug products. Silver Spring, MD: Food and Drug Administration, August 6, 2013 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204790Orig1S000SumR.pdf).
22. Antiretroviral Pregnancy Registry Steering Committee. The Antiretroviral Pregnancy Registry interim report for 1 January 1989 through 31 January 2019. Wilmington, NC: Registry Coordinating Center, June 2019 (http://www.apregistry.com/forms/interim_report.pdf).
23. Chandiwana N, Hill A, Chersich M, et al. Serum folate and birth outcomes: DTG vs EFV trial evidence in South Africa. Presented at the Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, March 4–7, 2019.
24. Grayhack C, Sheth A, Kirby O, et al. Evaluating outcomes of mother-infant pairs using dolutegravir for HIV treatment during pregnancy. AIDS 2018;32:2017-21.
25. Kowalska J, Gökengin D, Aho I, et al. Exposure to dolutegravir in pregnant HIV-positive women in Central and Eastern Europe and neighbouring countries: data from the ECEE Network Group. Presented at HIV Glasgow, Glasgow, United Kingdom, October 28–31, 2018. J Int AIDS Soc 2018;21:Suppl 8:e25187.
26. Money D, Lee T, Farjou G, et al. An analysis of congenital abnormalities in pregnant women living with HIV in Canada: no signal for neural tube defects in women exposed to dolutegravir. J Int AIDS Soc 2018;21:Suppl 8:e25187.
27. Sibiude J, Le Chenadec J, Mandelbrot L, et al. No increase in birth defects in infants exposed to integrase inhibitors at conception. Presented at the Conference on Retroviruses and Opportunistic

Infections, Seattle (CROI), March 4–7, 2019.

28. Weissmann D, De Leuw P, Gute P, et al. Use of integrase inhibitors in HIV-positive pregnant women: data from the Frankfurt HIV Cohort. J Int AIDS Soc 2018;21:Suppl 8:e25187.

29. Bornhede R, Soeria-Atmadja S, Westling K, Pettersson K, Navér L. Dolutegravir in pregnancy — effects on HIV-positive women and their infants. Eur J Clin Microbiol Infect Dis 2018;37:495-500.

30. Chouchana L, Beeker N, Treluyer JM. Is there a safety signal for dolutegravir and integrase inhibitors during pregnancy? J Acquir Immune Defic Syndr 2019;81: 481-6.

31. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet HIV 2017;4(12): e536-e546.

32. Williams LJ, Rasmussen SA, Flores A, Kirby RS, Edmonds LD. Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. Pediatrics 2005;116:580-6.

33. Cabrera RM, Souder JP, Steele JW, et al. The antagonism of folate receptor by dolutegravir: developmental toxicity reduction by supplemental folic acid. AIDS 2019 June 26 (Epub ahead of print).

34. Zamek-Gliszczynski MJ, Zhang X, Mudunuru J, et al. Clinical extrapolation of the effects of dolutegravir and other HIV integrase inhibitors on folate transport pathways. Drug Metab Dispos 2019 June 5 (Epub ahead of print).

35. Periconceptional folic acid supplementation to prevent neural tube defects. Geneva: World Health Organization, February 11, 2019 (https://www.who.int/elena/titles/folate_periconceptional/en/).

36. Behrman R, Butler A, eds. Preterm birth: causes, consequences, and prevention. Washington, DC: National Academies Press, 2007.

37. Chen J, Chen P, Bo T, Luo K. Cognitive and behavioral outcomes of intrauterine growth restriction school-age children. Pediatrics 2016;137(4):e20153868.

38. Schieve LA, Tian LH, Rankin K, et al. Population impact of preterm birth and low birth weight on developmental disabilities in US children. Ann Epidemiol 2016;26:267-74.

39. Davey S, Ajibola G, Sakoi M, et al. In utero mother-to-child transmission (MTCT) in Botswana does not differ between efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) and dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC). Presented at the 10th IAS Conference on HIV Science, Mexico City, July 21–24, 2019.

40. Howards PP, Hertz-Picciotto I, Poole C. Conditions for bias from differential left truncation. Am J Epidemiol 2007;165:444-52.

41. Lisonkova S, Joseph KS. Left truncation bias as a potential explanation for the protective effect of smoking on preeclampsia. Epidemiology 2015;26:436-40.

42. Schisterman EF, Cole SR, Ye A, Platt RW. Accuracy loss due to selection bias in cohort studies with left truncation. Paediatr Perinat Epidemiol 2013;27:491-502.

43. Dugdale CM, Ciaranello AL, Bekker LG, et al. Risks and benefits of dolutegravir- and efavirenz-based strategies for South African women with HIV of childbearing potential: a modeling study. Ann Intern Med 2019 April 2 (Epub ahead of print).

44. Phillips AN, Venter F, Havlir D, et al. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. Lancet HIV 2019;6(2):e116-e127.

45. Hoffman RM, Mofenson LM. Decision-making in a time of uncertainty: dolutegravir for reproductive-age women. Ann Intern Med 2019 April 2 (Epub ahead of print).

46. Krubiner CB, Faden RR, Cadigan RJ, et al. Advancing HIV research with pregnant women: navigating challenges and opportunities. AIDS 2016;30:2261-5.

47. Wickremsinhe MN, Little MO, Carter AS, Sullivan KA, Lyerly AD. Beyond "vessels and vectors": a global review of registered HIV-related clinical trials with pregnant women. J Womens Health (Larchmt) 2019; 28:93-9.

48. Zash RM, Williams PL, Sibiude J, Lyall H, Kakkar F. Surveillance monitoring for safety of in utero antiretroviral therapy exposures: current strategies and challenges. Expert Opin Drug Saf 2016;15:1501-13.

49. Mofenson LM. In-utero ART exposure and the need for pharmacovigilance. Lancet Glob Health 2018;6(7):e716-e717.

Copyright © 2019 Massachusetts Medical Society.