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Dolutegravir Use at Conception — Additional Surveillance Data from Botswana

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To the editor: In May 2018, an unscheduled analysis from the Botswana-Harvard AIDS Institute Partnership Tsepamo birth-outcomes surveillance study showed a higher prevalence of neural-tube defects among infants born to women who were using dolutegravir-based antiretroviral treatment (ART) regimens at the time of conception relative to infants born to women taking other types of ART.¹ In response to this safety signal, the Botswana Ministry

of Health and Wellness expanded surveillance for neural-tube defects in selected non-Tsepamo health facilities.

The Ministry of Health and Wellness surveillance system followed a protocol that had been approved by the institutional review boards of the Botswana Health Research Development Committee, the Centers for Disease Control and Prevention, and the University of Maryland, Baltimore, and included all pregnancies in which live-born or stillborn infants were delivered at more than 24 weeks of gestation at 22 non-Tsepamo facilities from October 2018 through March 2019. The end date of March 31, 2019, was chosen in light of the anticipated change in practice associated with the 2018 data release from the Tsepamo study, which was expected to result in a decrease in the number of pregnancies with periconceptional exposure to dolutegravir.

Midwives conducted systematic surface examinations of all live-born and stillborn infants. Information regarding maternal human immunodeficiency virus (HIV) infection status, ART exposure at conception, and infant examination findings was collected. Data on the use of folate supplements and other medications, including antiepileptic medications, were abstracted only in cases in which a neural-tube defect was found. Data on folate use before pregnancy were not available. A clinical geneticist who was unaware of maternal HIV infection and ART exposure status reviewed and classified suspected neural-tube defects. We estimated the prevalence of neural-tube defects according to maternal HIV infection and ART status and differences in prevalence relative to pregnancies in which mothers had been taking dolutegravir at conception, with 95% confidence intervals calculated by the exact binomial² and the Newcombe–Wilson hybrid score³ methods, respectively.

During the study period, the surveillance system captured 3076 deliveries (3064 singleton and 12 twin); 2328 (76%) were among HIV-negative women, 742 (24%) were among HIV-positive women, and 6 (<1%) were among women with an unknown HIV status. At the time of conception, the majority (544 [73%]) of HIV-positive mothers were taking ART; of these, 152 (28%) were taking dolutegravir. Six suspected neural-tube defects were initially identified among all the infants; one was confirmed as a neural-tube defect by surgical records (a case of spina bifida), two were classified as probable neural-tube defects on the basis of clinical description and surgical referral (one case of spina bifida and one case of spina bifida plus frontal encephalocele), and two were excluded on the basis of records consistent with a sacral dimple. The final suspected neural-tube defect (a lesion on the side of the head) was classified as “possible” because the available information was insufficient to either confirm it or rule it out. Single-gene causes of isolated neural-tube defects are unlikely, and genetic testing was not performed for the three confirmed or probable cases in this analysis.

The final analyses included only the three confirmed or probable neural-tube defects (Table 1). One neural-tube defect was found among the 152 deliveries in which the mother had been taking dolutegravir at conception (prevalence, 0.66%; 95% confidence interval [CI], 0.02 to 3.69), and two neural-tube defects were found among the 2326 deliveries in which the mother was HIV-negative (prevalence, 0.09%; 95% CI, 0.01 to 0.31). The difference in the prevalence of neural-tube defects between deliveries in which the mothers had been

taking non-dolutegravir-based ART at conception and those among mothers who had been taking dolutegravir-based ART at conception was 0.66 percentage points (95% CI, -0.48 to 3.63). We conducted a sensitivity analysis to assess how inclusion of the possible neural-tube defect, which occurred in an infant born to an HIV-negative woman, would affect the estimate of the difference in prevalence and found no meaningful change.

Our findings suggest a slightly higher prevalence of neural-tube defects among deliveries in which the mothers were HIV-positive and had been taking dolutegravir at the time of conception than among deliveries in which the mothers were HIV-negative. However, because of the short duration of our study and the infrequent occurrence of neural-tube defects in the general population, the number of cases identified was small, the prevalence estimates were unstable, and the resultant differences in prevalence had confidence intervals that included the null value. These data suggest that the magnitude of the risk of neural-tube defects associated with dolutegravir exposure at the time of conception remains less than 1%, which is consistent with findings from the Tsepamo study (now published in the *Journal*)⁴ and important in individual decision making regarding ART options. Although our findings are independent from those of the Tsepamo study, together they represent coverage of more than 90% of all births in Botswana. These findings should be considered in an assessment of global data to further examine ART exposure and adverse birth outcomes.

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Table 1.

Prevalence of Neural-Tube Defects According to Maternal ART Exposure at Conception.*

Finding	Dolutegravir at Conception (N = 152)	Non-Dolutegravir ART at Conception (N = 381)	Efavirenz at Conception (N = 261)	HIV-Negative (N = 2328)
No. of neural-tube defects	1	0	0	2
Percent of deliveries with neural-tube defect (95% CI) [†]	0.66 (0.02 to 3.69)	0 (0 to 0.79)	0 (0 to 1.15)	0.09 (0.1 to 0.31)
Difference in prevalence (95% CI) — percentage points [‡]	Reference	0.66 (−0.48 to 3.63)	0.66 (−0.89 to 3.63)	0.57 (−0.02 to 3.55)

* Information on the type of antiretroviral treatment (ART) was unavailable for 11 women. HIV denotes human immunodeficiency virus.

[†] Exact confidence intervals (CIs) are shown.[‡] Newcombe-Wilson hybrid score confidence intervals are shown. The difference in prevalence between deliveries among HIV-negative mothers and deliveries among mothers who had been taking dolutegravir at conception from our sensitivity analysis, which included the “possible” neural-tube defect, was 0.53 percentage points (95% CI, −0.07 to 3.50).