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Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception

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TO THE EDITOR:

Since August 2014, the Botswana Harvard AIDS Institute Partnership has conducted birth outcome surveillance at eight government hospitals throughout Botswana. A primary on-going aim of the surveillance is to evaluate the prevalence of neural-tube defects associated with exposure to antiretroviral drugs from the time of conception (the risk period for neural-tube defects ends approximately 28 days after conception). At each site, trained government midwives perform surface examinations of consecutive live-born and stillborn infants who are born in the hospital to women infected with human immunodeficiency virus (HIV) and to women without HIV infection. As part of an institutional review board-approved research protocol, research assistants photograph major abnormalities after obtaining written informed consent from the mother; a medical geneticist reviews photos quarterly, without knowledge of mothers' HIV infection status or exposure to antiretroviral drugs. In May 2016, Botswana changed its first-line antiretroviral therapy from tenofovir-emtricitabine-efavirenz to tenofovir-emtricitabine-dolutegravir for all adults, a change that allowed for the inclusion of dolutegravir in surveillance.

We recently reported that the risk of adverse birth outcomes or congenital abnormalities among women who started dolutegravir-based antiretroviral therapy after conception (including therapy initiated during the first trimester of pregnancy) was not higher than the risk among women who started efavirenz-based therapy after conception.[1] However, in April 2018, we detected a higher-than-expected number of neural-tube defects among infants born to women who started treatment with dolutegravir before conception. We performed an unplanned interim analysis to compare the prevalence of neural-tube defects among infants born to women who had been receiving dolutegravir-based antiretroviral therapy from the time of conception with the prevalence in other exposure groups. For each exposure group, we calculated the prevalence of neural-tube defects (and 95% confidence interval, calculated

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with the Wilson method) and the difference in prevalence relative to the group with dolutegravir-based therapy from the time of conception (and 95% confidence interval, calculated with the Newcombe method).[2]

As of May 1, 2018, a total of 89,064 births had been included in our surveillance; 88,755 births (99.7%) had an infant surface examination that could be evaluated, with 86 neural-tube defects identified (0.10% of births; 95% confidence interval [CI], 0.08 to 0.12) (57% identified with a photograph, 43% identified by description). The defects included 42 instances of meningocele or myelomeningocele, 30 of anencephaly, 13 of encephalocele, and 1 of iniencephaly. Among the 426 infants born to HIV-positive women who had been taking dolutegravir-based antiretroviral therapy from the time of conception, 4 (0.94%) had a neural-tube defect. The defects in these 4 infants were encephalocele, myelomeningocele (along with undescended testes), and iniencephaly (along with major limb defect), all three of which were identified with photos, and anencephaly, which was identified by description. The 4 mothers delivered in three geographically separated hospitals over a 6-month period; none had epilepsy or diabetes or received folate supplementation at conception. In comparison, neural-tube defects occurred in 14 (0.12%) of 11,300 infants born to women who had been exposed to any non-dolutegravir antiretroviral therapy from the time of conception, 0 (0.00%) of 2812 infants born to women who had been exposed to dolutegravir treatment that was started in pregnancy, and 61 (0.09%) of 66,057 infants born to HIV-uninfected women (Fig. 1). Seven neural-tube defects occurred in other exposure groups. In the analysis of the prevalence of neural-tube defects associated with exposure to antiretroviral therapy from the time of conception, the difference between non-dolutegravir-based antiretroviral therapy (prevalence, 0.12%) and dolutegravir-based antiretroviral therapy (0.94%) was –0.82 percentage points (95% CI, –0.24 to –2.3).

In conclusion, we found a potential early signal for an increased prevalence of neural-tube defects in association with dolutegravir-based antiretroviral therapy from the time of conception. Our study is ongoing, and more data are needed to confirm or refute this signal, given the small number of events and the small difference in prevalence.

Acknowledgments

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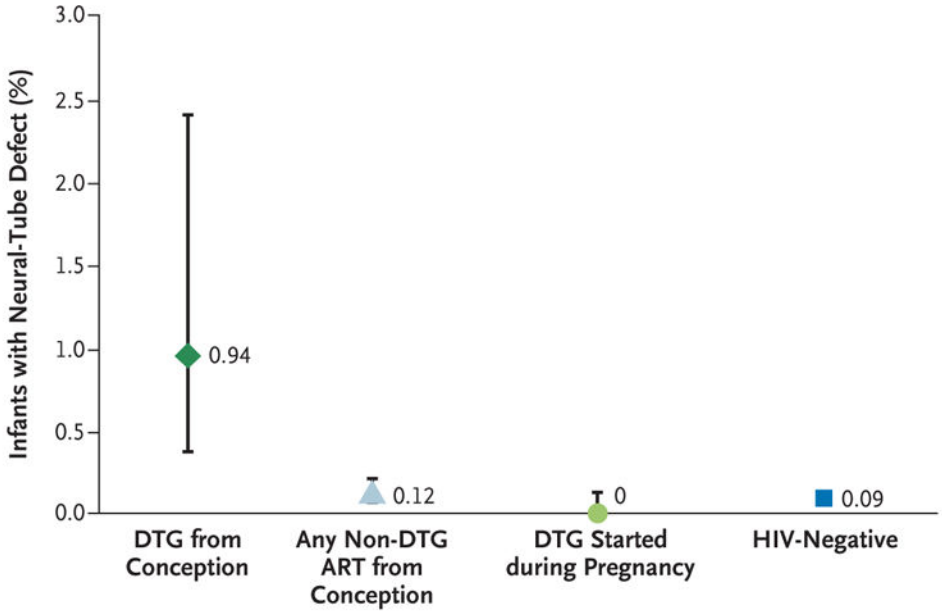
THIS WEEK'S LETTERS



No. of infants with defect	4	14	0	61
No. of exposures	426	11,300	2812	66,057
Percent with defect (95% CI)	0.94 (0.37 to 2.4)	0.12 (0.07 to 0.21)	0.0 (0.0 to 0.13)	0.09 (0.07 to 0.12)
Difference in prevalence (95% CI) — percentage points	Reference	–0.82 (–0.24 to –2.3)	–0.94 (–0.35 to –2.4)	–0.85 (–0.27 to –2.3)

Figure 1. Neural-Tube Defects in Infants According to Maternal ART Exposure Group and HIV Infection Status.

There were 7 additional infants with neural-tube defects in the full cohort: 3 born to women who started non-dolutegravir (DTG) antiretroviral therapy (ART) during pregnancy, 3 to human immunodeficiency virus (HIV)-infected women who did not receive ART during pregnancy, and 1 to a woman of unknown HIV infection status who did not receive ART. Among the women who had been receiving any non-DTG ART at conception, 5675 were receiving tenofovir-emtricitabine-efavirenz, 1446 tenofovir-emtricitabine-nevirapine, 2439 zidovudine-lamivudine-nevirapine, 452 tenofovir-emtricitabine-lopinavir-ritonavir, 312 zidovudine-lamivudine-lopinavir-ritonavir, 242 other specified ART regimens, and 734 unspecified non-DTG regimens. Among the women receiving DTG treatment that was started during pregnancy, the median gestational age at the initiation of ART was 19 weeks (interquartile range, 14 to 25), and there were 75 women who started ART at a gestational age of less than 6 weeks.