Dolutegravir Use at Conception Not Tied to Neural Tube Defects After All

A 2018 report had suggested that HIV-positive women's use of the drug at conception increased the risk of the rare birth defects.

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The multiyear study known as Tsepamo, which previously suggested that HIV-positive women's use of the antiretroviral dolutegravir around the time of conception was tied to a higher risk of neural tube defects among their babies, has finally concluded that this interim finding amounted to a false alarm.

With greater follow-up time, the study of new mothers in Botswana found no significant difference in the rate of neural tube defects among infants based on whether their mothers were taking a regimen that contained dolutegravir at conception.

A neural tube defect, including spina bifida and anencephaly, occurs when an infant experiences incomplete development of the brain or spinal cord. Such defects typically arise during the first several weeks of gestation.

The interim finding that dolutegravir was associated with these birth defects, reported in 2018, led the World Health Organization (WHO) to delay its recommendation of the highly potent integrase inhibitor for pregnant women and those of childbearing potential. In July 2019, after further data showed that the risk was low, the WHO went ahead and recommended the antiretroviral (ARV) as a preferred first-line treatment option for all populations with HIV, including such women.

Rebecca Zash, MD, of Beth Israel Deaconess Medical Center in Boston, presented updated findings from the Tsepamo study on Tuesday at the International AIDS Conference, held virtually this year due to the COVID-19 pandemic.

During a teleconference with reporters last week, Monica Gandhi, MD, PhD, of the University of California, San Francisco, said the updated Tsepamo findings "completely lay to rest" concerns about the safety of dolutegravir with regard to neural tube defects and "should give us even more comfort to recommend dolutegravir" to women who are pregnant or may become pregnant.

The Tsepamo study, launched in Botswana in August 2014, was originally designed to evaluate the risk of neural tube defects related to HIV-positive women's exposure to efavirenz.

Efavirenz is sold under the brand name Sustiva and is included in Atripla (efavirenz/tenofovir disoproxil fumarate/emtricitabine). The ARV is no longer widely used in the United States due to its neuropsychiatric side effects but is included at different doses in Mylan's cut-price single-tablet regimens Symfi (efavirenz 600 milligram/lamivudine/tenofovir disoproxil fumarate) and Symfi Lo (efavirenz 400 mg/lamivudine/tenofovir disoproxil fumarate), which were approved in 2018.

After dolutegravir was rolled out in Botswana in mid-2016, the study adjusted to include the new ARV in its comparative analyses.

Dolutegravir is sold as an individual tablet under the brand name Tivicay and is included in the single-tablet regimens Dovato (dolutegravir/lamivudine), Juluca (dolutegravir/rilpivirine) and Triumeq (dolutegravir/abacavir/lamivudine).

In Tsepamo, trained midwives alert the study's research assistants if they find an abnormality after examining a newborn. A medical geneticist then reviews photos of the abnormality.

Between August 2014 and July 2018, the study included eight sites that between them cared for about 45% of all women giving birth in Botswana. By September 2018, the study expanded to include 18 sites, covering about 72% of all births in the sub-Saharan African nation. Since September 2019, the study has maintained surveillance at 16 sites, covering about 70% of all births.

In April 2018, the WHO asked Tsepamo's investigators to share any preliminary data from the study as the global agency prepared for an upcoming committee meeting pertaining women's use of dolutegravir around the time of conception.

Zash and her colleagues reported at the International AIDS Conference in Amsterdam in July 2018 and in a paper in The New England Journal of Medicine two months later that there were four cases of neural tube defects among babies born to 426 women in Tsepamo who had taken dolutegravir at conception, for a rate of 0.94%.

By comparison, the neural tube defect rate among women with HIV who took any other ARVs at conception was 0.12% (14 such defects among babies born to 11,300 women). The rate was 0.05% (3 of 5,787) among women with HIV who took efavirenz at conception, zero percent (0 of 2,812) among women who started dolutegravir during pregnancy and 0.09% (61 of 66,057) among HIV-negative women.

Because the sample size of women who had taken dolutegravir at conception remained relatively small at the time of the interim analysis, the study authors could not determine with great confidence whether the apparent increased risk of neural tube defects associated with the integrase inhibitor had been driven by chance.

The investigators would need longer follow-up time to allow for any statistical noise to settle—and settle it did, in favor of the safety of dolutegravir use at conception.

Subsequent results from the study through March 2019, which Zash presented in August 2019 at the 10th International AIDS Society Conference on HIV Science in Mexico City, indicated that, in fact, the risk of neural tube defects among babies born to women who took dolutegravir was much lower than seen in the 2018 analysis.

Between May 2018 and March 2019, the study had seen only one additional case of a neural tube defect among infants born to the women who took dolutegravir at conception, an overall group that had grown fourfold since the first analysis.

At that time, the neural tube defect rate fell to 0.3% (5 of 1,683) among women exposed to dolutegravir at conception. The rate was 0.10% (15 of 14,792) among women exposed to any other ARV at conception, 0.04% (3 of 7,959) among women exposed to efavirenz at conception, 0.03% (1 of 3,840) among women exposed to dolutegravir during pregnancy and 0.08% (70 of 89,372) among HIV-negative women.

Today, Zash reported results from the study running through April 30 of this year. Since the 2019 report, there have been only two additional cases of neural tube defects—among babies born to 1,908 women exposed to dolutegravir at conception.

So now, the neural tube defect rate is just 0.19% (7 of 3,591) among women exposed to dolutegravir at conception. Otherwise, the rate is 0.11% (21 of 19,361) among women exposed to any other ARV at conception, 0.07% (8 of 10,958) among women exposed to efavirenz at conception, 0.04% (2 of 4,581) among women exposed to dolutegravir starting during pregnancy and 0.07% (87 of 119,630) among HIV-negative women.

Zash and her colleagues concluded that with additional follow-up time since the 2018 report, the neural tube defect rate among babies born to women exposed to dolutegravir during conception was leveling off at about 2 per 1,000 births. They concluded that there was no statistically significant difference in this rate compared with the rate seen among women taking non-dolutegravir ARV regimens around the time of conception.

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