More Specifics Emerge About Tivicay's Link to Neural Tube Birth Defects

A large ongoing study in Botswana has found that about 1 in 150 babies exposed to Tivicay at conception developed such birth defects.

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Researchers have presented more detailed results from the African study that recently prompted the Food and Drug Administration to warn women with HIV that taking Tivicay (dolutegravir) at conception or during the first trimester may increase their risk of giving birth to infants with severe birth defects.

The ongoing Tsepamo study, conducted in Botswana and begun in August 2014, has thus far seen just four cases of neural tube birth defects, or about 1 in 150 babies born to mothers exposed to Tivicay at conception. More data are needed to properly ascertain whether the antiretroviral (ARV) is indeed associated with a statistically significant increase in such risk, meaning the excess birth defect rate seen in the study was not driven by chance.

Tivicay, an integrase inhibitor, is included in Triumeq (dolutegravir/abacavir/lamivudine) and Juluca (dolutegravir/rilpivirine).

Researchers presented preliminary findings from the study today at the International AIDS Conference in Amsterdam (AIDS 2018). The research endeavor's overall goal is to compare adverse birth outcomes based on women's HIV status and their ARV regimens.

Initially, the study authors planned to conduct a four-year analysis in August 2018 to look at the prevalence of neural tube defects (birth defects of the brain and spinal cord) in the combined group of live-born and stillbirth infants among HIV-positive women taking Sustiva at conception compared with women in other groups. However, in 2016, Botswana changed its guidelines from recommending that all adults (including pregnant women) starting HIV treatment for the first time take the Sustiva-inclusive Atripla (efavirenz/tenofovir disoproxil fumarate/emtricitabine) to recommending the same regimen but replacing Sustiva with Tivicay—in other words, dolutegravir/tenofovir disoproxil fumarate/emtricitabine. Consequently, the study conducted an unplanned analysis on Tivicay's association with birth defects, specifically among women who started the ARV before getting pregnant.

A recently published study found that compared with starting Sustiva during pregnancy (not

before conception), starting Tivicay during pregnancy (1,729 women did so in the study) was not associated with a greater risk of adverse birth outcomes, including stillbirth, preterm birth, infants born small for their gestational age or death after birth. Additionally, there was no increased risk of major congenital abnormalities among the small number of pregnant women, 280, who started Tivicay during their first trimester.

Tsepamo is taking place at eight of the largest maternity wards in Botswana, which account for 45 percent of the nation's live births.

Botswana has an HIV prevalence of 25 percent. More than 90 percent of pregnant women with HIV in the nation take ARVs, 52 percent of them before conception. Various ARV regimens are used in the country.

As of May 1, 2018, the study has amassed data on 89,064 births. Excluding 309 births without proper exam-based information, these births occurred among 21,955 HIV-positive mothers, 66,057 HIV-negative mothers and 743 mothers of an unknown HIV status. Of the HIV-positive mothers, 11,726 had taken ARVs since conception, 2,812 started Tivicay after conception and during their pregnancy, and 5,624 started non-Tivicay-inclusive ARV regimens during pregnancy. Of the mothers who took ARVs since conception, 426 (3.3 percent) took Tivicay since conception and 11,300 (96.7 percent) took a non-Tivicay-inclusive regimen since conception. Out of that latter group, 5,787 took Sustiva since conception and 5,513 took a non-Sustiva-inclusive regimen since conception.

Out of 88,755 live births included in the analysis that was presented at the conference in Amsterdam, 86 (0.1 percent) of the babies had neural tube defects. Of 88 stillbirths, 22 (25 percent) had such birth defects. Among the babies born alive but with neural tube defects, 25 (39 percent) died within four weeks.

Of the 426 babies born to mothers who took Tivicay at conception, four (0.94 percent) had neural tube defects. By comparison, such birth defects occurred among 14 of the 11,300 babies (0.12 percent, or 0.82 percentage points less than the rate for the Tivicay-at-conception group) born to mothers who took non-Tivicay-inclusive ARV regimens at conception; three of the 5,787 babies (0.05 percent, or 0.89 percentage points less than babies born to mothers who took Sustiva at conception); none of the 2,812 (zero percent, or 0.94 percentage points less) born to mothers who started Tivicay after conception and during pregnancy; and 61 of the 66,057 babies (0.09 percent, or 0.85 percentage points less) born to the HIV-negative mothers.

None of the women in the study reported that they took folate supplementation—which can lower the risk of neural tube birth defects—prior to pregnancy. Botswana does not fortify its grains with folate.

The study authors could find no other risk factors for neural tube defects among the women.

At the AIDS 2018 conference, the researchers further reported that between May 1 and July 15,

the study saw two additional neural tube defects, including one in an infant exposed to Tivicay about eight weeks into pregnancy (not prior to conception) and one in an HIV-negative woman. So the updated proportion of babies born to mothers who started Tivicay during pregnancy was 0.03 percent (1 of 3,104).

Additionally, with an additional month and a half of follow-up data, the updated proportion of babies born with neural tube defects to mothers who started Tivicay by conception was a bit lower than seen in the analysis of data through May 1, 2018, at 0.67 percent (4 of 596). Nevertheless, this birth-defect rate was statistically significantly higher than that seen in any of the other groups included in the analysis.

The study's next formal analysis will take place after March 31, 2019. By then, the investigators hope to expand the study from including eight maternity wards to 18, increasing the coverage of live births in the nation to 72 percent.

The final analysis, expected next year, will include data on neural tube defects and all major congenital malformations as well as other adverse birth outcomes, including stillbirth, preterm birth, small for gestational age birth and death after birth.
