Dolutegravir Associated With Low Risk of Neural Tube Birth Defects

The World Health Organization recommends this highly effective antiretroviral for all population groups, including young women.

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The risk of neural tube defects in infants exposed to dolutegravir during early pregnancy is very small, and this concern should not keep HIV-positive women of childbearing age from using this effective and well-tolerated medication, according to a set of studies presented at the recent 10th International AIDS Society Conference on HIV Science (IAS 2019) in Mexico City.

Taking these findings into account, the World Health Organization (WHO) issued updated guidelines recommending dolutegravir as the preferred option for first-line antiretroviral therapy for adults and adolescents, including pregnant women and those who could become pregnant. Although the supporting evidence is less clear, WHO also recommends weight-based dolutegravir for infants and children. People with unsuppressed HIV who are not currently using dolutegravir in their initial regimen should switch to a second-line regimen that includes it.

While there is still a need to monitor the risk, “dolutegravir should be accessible for women of childbearing age due to the overwhelming benefits it offers,” Meg Doherty, MD, MPH, of WHO’s Department of HIV/Hepatitis and STIs, said at a press briefing. “What treatment options to pursue is a decision that a woman should make in consultation with her health care provider.”

Dolutegravir is available as a single agent with the brand name Tivicay and is a component of the Triumeq (dolutegravir/abacavir/lamivudine), Juluca (dolutegravir/rilpivirine) and Dovato (dolutegravir/lamivudine) combination pills.

Concern about the use of dolutegravir during early pregnancy arose in the spring of 2018, when early results from the Tsepamo surveillance study in Botswana revealed an increase in the risk of neural tube defects among infants exposed to the drug. These birth defects, including spina bifida and anencephaly, involve incomplete development of the brain or spinal cord. They typically arise during the first several weeks of gestation, often before a woman realizes she’s pregnant.

Rebecca Zash, MD, of Beth Israel Deaconess Medical Center in Boston, and colleagues reported findings from this interim analysis in The New England Journal of Medicine, with further follow-up at the International AIDS Conference last summer in Amsterdam, showing that four cases of neural

tube defects had been observed among 426 mothers taking dolutegravir around the time of conception, for a rate of 0.94%, compared with a rate of 0.12% among HIV-positive women taking other antiretrovirals and 0.09% among HIV-negative women.

These interim findings led the U.S. Food and Drug Administration and European Medicines Agency to issue safety warnings, and WHO released guidelines recommending that women of childbearing potential should not take dolutegravir unless they had consistent access to reliable contraception. This recommendation was controversial, and women living with HIV in low- and middle-income countries protested efforts to limit their use of one of the safest and most effective treatment options.

Zash presented updated findings last week in Mexico City, showing that the risk of neural tube defects was smaller than previously suggested in the Botswana study. These results were also published simultaneously in The New England Journal of Medicine.

Zash et al, IAS 2019, abstract MOAX0105LB

Longer-term follow-up from the Tsepamo study—which now has data on nearly 120,000 births at 18 hospitals through March 2019—showed that there were three cases of neural tube defects per 1,000 women exposed to dolutegravir, or about two additional cases per 1,000 women compared with those not exposed.

The researchers identified five such birth defects among 1,683 deliveries to women taking dolutegravir around the time of conception (0.30%), compared with 15 cases among 14,792 women taking any other antiretrovirals (0.10%), three cases among 7,959 women taking efavirenz

(0.04%) and 70 cases among 89,372 HIV-negative women (0.08%). The difference between exposure to dolutegravir and other antiretrovirals was small but statistically significant, meaning it was probably not attributable to chance. However, there was no rise in the rate of neural tube defects among women who started taking dolutegravir once they were already pregnant (0.03%).

There were no significant differences in the rate of other adverse birth outcomes—including premature birth or neonatal death within the first month—between infants exposed to dolutegravir and those exposed to efavirenz (Sustiva or Stocrin, also in the Atripla combination pill). Zash noted that data are lacking for other modern antiretrovirals that would be acceptable alternatives to dolutegravir.

In a related presentation, Fernanda Fernandes Fonseca, MD, of the Brazilian Ministry of Health, reported results from an analysis of data from that country's national antiretroviral therapy distribution system. Between 2015 and 2018, no neural tube defects were identified either among infants born to the 382 HIV-positive women who had used dolutegravir around the time of conception or those of the 1,086 women who had used raltegravir (Isentress) or efavirenz.

"Dolutegravir is superior to efavirenz and should replace efavirenz as the anchor drug in first-line [ARV] regimens for most individuals worldwide," Monica Ghandi, MD, MPH of the University of California at San Francisco told Healio. "[T]his new analysis, along with other data from other cohorts of women of childbearing age from Brazil and other countries, should give us some comfort. Dolutegravir is a good drug. Use it with caution, and let women decide."

Presenters at the conference stressed the importance of folate, or folic acid, a B vitamin that can prevent neural tube defects. In the United States and many other countries, common foods such as bread are fortified with folic acid, and supplements are recommended for pregnant women. A majority of neural tube defects occur in countries that do not fortify food. Folic acid supplementation is uncommon in Botswana, but in Brazil, food is fortified and nearly half of the women in Fonseca's analysis used supplements.

U.S. Global AIDS Coordinator Deborah Birx, MD, noted at the press briefing that women had unnecessarily lost access to dolutegravir for more than a year because of a hasty decision made with little community consultatio and predicted it would take yet another year to reverse the perception that the drug leads to an increased risk of birth defects.

Jacque Wambui of the treatment advocacy network AfroCAB offered a community perspective at the briefing. "It is my body; it is my pregnancy; I am the one to decide," she said. "Let the woman know what the risks are of all the drugs available and what the benefits are and let the woman decide for herself."

Click here to see the study abstracts and slides.

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