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CATIE-News

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Agencies issue caution about use of dolutegravir by pregnant HIV-positive women

24 May 2018

- **The HIV drug dolutegravir was associated with a birth defect in a Botswana study**
- **Regulators are issuing precautionary advice to HIV-positive women**
- **Findings are preliminary and the study has not proven the cause of the defect**

Dolutegravir is an anti-HIV drug widely used as part of combination therapy for HIV. Dolutegravir is sold in Canada and other high-income countries and regions under the brand name Tivicay and in a pill called Triumeq (dolutegravir + 3TC + abacavir). Dolutegravir belongs to a class of anti-HIV drugs called integrase inhibitors. It was first approved in Canada and the U.S. in 2013 and in the EU since 2014 and is widely used.

The European Union's drug regulatory agency, the European Medicines Agency (EMA), was the first agency to issue a press release announcing that it is evaluating the preliminary results from an observational study of 11,558 pregnant HIV-positive women in Botswana. Researchers in Botswana assessed the health of infants born to women in that study and found a signal of concern: There is a possibility that women who were taking dolutegravir at the time they became pregnant had an increased risk of giving birth to an infant with a type of birth defect called a neural tube defect. Such defects affect the brain and spinal cord. The specific figures that the EMA made available were as follows:

- 426 women who took dolutegravir at the time they became pregnant – four babies were born with neural tube defects (rate: 0.9)
- 11,173 women who took other anti-HIV drugs at the time they became pregnant – 14 babies were born with neural tube defects (rate: 0.1)

Readers can see from the figures above that the rate of neural tube defects in babies born to women who took dolutegravir is almost 10-fold greater than in babies born to women who took other anti-HIV drugs at the time they were pregnant. There have not been any cases of neural tube defects in babies born to women who took dolutegravir later in pregnancy. The study in Botswana is observational in design; such studies can only find associations between a drug and an issue. That is, the Botswana study cannot prove that dolutegravir caused birth defects (or any other problems). However, as a precaution, health agencies have issued preliminary information from the Botswana study.

Why are the findings preliminary?

These findings from Botswana are considered preliminary because the study is ongoing and regulatory authorities such as Health Canada, EMA, U.S. Food and Drug Administration (FDA) and the World Health Organization (WHO) plan to conduct further investigation and, in some cases, meet with medical and scientific advisors to better assess the data. The manufacturer of dolutegravir, ViiV Healthcare, has analysed data from more than 2,000 HIV-positive women, 648 who used dolutegravir at conception, and found only one case of neural tube defect in an infant. The cause of the neural tube defect in this particular case is unclear.

In the ongoing Botswana study, there are still data from several hundred women who took dolutegravir-based therapy during pregnancy and have yet to give birth. There are factors known to increase the risk of neural tube defects during pregnancy (mentioned later in this bulletin). The EMA and the Botswana researchers need to take such risk factors into account when trying to discern the cause of such birth defects in women who used

dolutegravir at the time of conception.

According to the WHO, ViiV tested dolutegravir during pregnancy in rats and rabbits and there was no evidence of birth defects.

Additional steps

Dolutegravir is an integrase inhibitor and, like all integrase inhibitors, it was designed to interfere with an enzyme called integrase that is needed by HIV-infected cells. Working independently of ViiV, researchers in the U.S. and the UK have scoured six publicly available datasets containing information from 1,200 HIV-positive women and their infants and did not find any association between dolutegravir and birth defects.

Health Canada will shortly alert healthcare professionals about the EMA's findings.

Many low- and middle-income countries rely on guidance from WHO about which medicines to use during pregnancy. Here is WHO's advice concerning dolutegravir: http://www.who.int/hiv/en/

Until a final analysis of the data from Botswana is complete, here is some advice from the FDA:

FDA advice for HIV-positive women

If you are already taking dolutegravir, do "not stop taking dolutegravir without first talking to your healthcare professional because stopping your medicine can cause HIV infection to worsen."

"If you are already pregnant, stopping your dolutegravir-containing regimen without switching to alternative HIV medicines could cause the amount of HIV [in your body] to increase and spread to your baby."

"If you take a dolutegravir-containing regimen at the time of becoming pregnant and during the first trimester of pregnancy, there is a risk that your baby may develop neural tube defects. Neural tube defects happen early in pregnancy, before many women even know they are pregnant. For this reason, women of childbearing age should talk to their healthcare professional about other non-dolutegravir-containing anti-HIV medicines."

"You should tell your healthcare professional if you are pregnant or are planning to become pregnant before you start a dolutegravir-containing regimen. Your healthcare professional may discuss other treatment options with you. "

"Women of childbearing age who decide to take a dolutegravir-containing regimen should consistently use effective birth control (contraception) while on HIV treatment. Women should talk to their healthcare professional(s) about an effective birth control method to use while taking a dolutegravir-containing regimen."

"Before you start a dolutegravir-containing regimen you will need a pregnancy test to determine if you are already pregnant."

FDA advice for healthcare professionals

"Healthcare professionals should inform women of childbearing age about the potential risk of neural tube defects when a dolutegravir-containing regimen is used at the time of conception and early in pregnancy. "

"Healthcare professionals should weigh the benefits and risks of dolutegravir when prescribing antiretroviral medicines to women of childbearing age. Alternative antiretroviral medicines should be considered. Discuss the relative risks and benefits of approximate alternative antiretroviral therapies."

"If the decision is made to use dolutegravir in women of childbearing age, healthcare professionals should reinforce the [importance of] consistent use of effective birth control."

"Perform pregnancy testing before initiating a dolutegravir-containing regimen in women of childbearing age to exclude pregnancy."

General information about neural tube defects

Neural tube defects are birth defects that affect the brain and spinal cord. They tend to occur early in the course of pregnancy, typically in the first month; this would be a time when most women are not aware yet that they are pregnant. Here are some types of neural tube defects:

- spina bifida – the spinal column in the fetus does not completely close. In some cases, this can result in injured nerves causing paralysis of the legs and other problems. Note that there are subtypes of spina bifida.
- anencephaly – most of the brain and skull fail to develop; this usually ends in stillbirth
- encephalocele – there is a hole in the skull through which the brain and the membranes that cover it protrude

All of the risks factors for neural tube defects are not known, but here are some that are known:

- having a family history of birth defects
- certain anti-seizure medicines (women should check with their pharmacist and doctor about which anti-seizure medicines are safe to take during pregnancy)
- obesity
- low levels of the B-vitamin folic acid (this is why healthcare providers and WHO recommend that women who want to have a baby or who are pregnant take a supplement of folic acid)

Neural tube defects can be diagnosed prior to birth with blood tests and ultrasound scans.

Reporting potential drug side effects

Prior to approval, most medicines are tested in clinical trials consisting of hundreds or even thousands of people. Such clinical trials tend to include generally healthy and young people. As a result, some side effects that are uncommon may not be noticed or side effects in people who are sick are not captured.

It is important to report side effects. Here are some websites where that can be done:

Canada

Reporting by Consumers and Health Professionals

Reporting for Health Products (except medical devices)

- Complete a report online.
- Call a Canada Vigilance Regional Office at **1.866.234.2345** (toll-free).
- Download and print the Side Effect Reporting Form (read the instructions before completing the form):
  - mail it to a Canada Vigilance Regional Office, using the postage paid label, or
  - send it by fax at **1.866.678.6789**

United States

Patients - https://www.fda.gov/Safety/MedWatch/HowToReport/ucm053074.htm

Healthcare providers - https://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm

European Union

http://www.adrreports.eu/en/national.html

—Sean R. Hosein

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