

*Statement on DTG – Geneva 18 May 2018*

**Potential safety issue affecting women living with HIV using dolutegravir at the time of conception**

The investigator of an independent NIH-funded study has identified a potential safety issue with the HIV antiretroviral medicine dolutegravir (DTG), and reported it to the World Health Organization (WHO) and ViiV Healthcare. The potential safety issue is related to neural tube defects in infants born to women who were taking DTG at the time of conception.

The issue has been identified from a preliminary unscheduled analysis of an ongoing observational study in Botswana, which has found 4 cases of neural tube defects out of 426 women who became pregnant while taking DTG. This rate of approximately 0.9% compares to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception.

**Information on Neural Tube Defects**

The neural tube is the foundation of the spinal cord, brain and the bone and tissues that surround it. Neural tube defects occur when the neural tube fails to completely form; this formation takes place between 0 and 28 days after conception. Neural tube defects may be related to folate deficiency, other medications or family history.

WHO recommends that women take daily supplements of folic acid before conception and during pregnancy to help prevent neural tube defects.

**Details on preliminary findings concerning the potential safety issue**

Preliminary data from the aforementioned study in Botswana so far seem to suggest that the potential safety issue arises from a woman's exposure to DTG at the time of conception, rather than during pregnancy. From the same study, there is currently no evidence of any infant born with a neural tube defect to a woman who started DTG during her pregnancy.

Surveillance is ongoing for additional pregnant women in Botswana who were exposed to DTG at time of conception. Their deliveries will be monitored closely over the next 9 months (May 2018 – February 2019), and results are expected to be known soon thereafter. These data will provide more information about the safety of DTG for women of childbearing age.

According to manufacturer ViiV Healthcare, DTG was tested in a complete package of reproductive toxicology studies, including embryofetal development studies in rats and rabbits, where dosing occurred during the sensitive window for neural tube defects in these species. There was no evidence of adverse developmental outcomes in these studies.

## **WHO's Response**

WHO recognizes that dolutegravir (DTG) has established efficacy, tolerability and a high genetic barrier to resistance.

Current WHO Guidelines released in 2016 cautioned that there were insufficient data for using DTG during pregnancy or breastfeeding and recommended efavirenz (EFV) in combination with tenofovir (TDF) + lamivudine (3TC) or emtricitabine (FTC) as the preferred option in pregnancy.

WHO convened an expert guideline development group meeting on 16-18 May 2018 to review all available data on the efficacy and safety data of dolutegravir, including the Botswana data, and will release updated guidance on the role of DTG in first- and second-line HIV treatment in the coming months.

In the interim, WHO advises that countries and ministries follow the existing 2016 WHO Consolidated ARV Guidelines, and consider the following:

- Pregnant women who are taking DTG should not stop their ARV therapy and should speak with their health provider for additional guidance.
- Antiretroviral (ARV) therapy for women of childbearing age, including pregnant women should be based on drugs for which adequate efficacy and safety data are available; an efavirenz-based regimen is a safe and effective first-line regimen.
- If other first-line ARVs cannot be used in women of childbearing age, DTG may be considered in cases where consistent contraception can be assured.
- Programmes should continue strengthening pharmacovigilance including monitoring of birth outcomes.

## **Next steps**

WHO is taking this potential safety issue very seriously and is working closely with all relevant stakeholders including ministries of health, the study investigators, the manufacturer and partner organizations to investigate these preliminary findings. Regulatory authorities are also reviewing this matter.

WHO will update this data and information at a later date as more information becomes available.

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