Questions and answers on DTG use in women of childbearing age
21 May 2018


1. What are the new findings?
   A preliminary analysis of an independent observational study in Botswana has identified a potential safety issue with dolutegravir (DTG) -- a commonly used antiretroviral (ARV) drug for HIV. The preliminary findings identified 4 cases of neural tube defects out of 426 women who became pregnant while taking DTG. This rate of 0.9% compares to a rate of 0.05% seen among women treated with EFV-based ARV and 0.09% among HIV-negative women. These findings are statistically significant. However, given that this is an interim analysis of an observational study from only a single country, these findings will need to be followed with a complete analysis as well as other studies.

   The manufacturer, regulatory authorities and WHO are taking this potential risk seriously. WHO is working with all stakeholders to gather information about women who have become pregnant while taking DTG worldwide to determine if this risk is confirmed.

2. Given these observations, what is WHO’s advice?
   Until we have more evidence, WHO advises that:
   - Women who are already taking DTG should not stop their ARV therapy and should speak with their health provider for additional guidance. (Note: The same observational study found no neural tube defects among women who had started DTG after conception.)
   - Women who plan to get pregnant (or who are not using consistent contraception) should avoid the use of DTG.
   - ARV therapy for women and adolescents of childbearing age, including those who are pregnant, should be based on drugs for which adequate efficacy and safety data are available; an efavirenz (EFV)-based regimen is a safe and effective first-line regimen.
• If other first-line ARVs cannot be used in women and adolescents of childbearing age, for example due to drug resistance to EFV, DTG may be considered in cases where consistent contraception can be assured. Women who take DTG should be fully informed about the potential risk of NTDs so that they can make the decision with their health care provider.
• Programmes should continue strengthening pharmacovigilance including monitoring of birth outcomes.

3. What are the benefits of DTG for treatment of HIV?
Dolutegravir (DTG) has established efficacy, tolerability and a high genetic barrier to resistance. It is an effective first- and possibly second-line HIV treatment. It is now available as a fixed dose combination of tenofovir (TDF) + lamivudine (3TC) + dolutegravir (DTG), known as TLD.

4. What is a neural tube defect?
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, i.e. before most women have received confirmation that they are pregnant. 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, but it is not clear whether taking folic acid while taking DTG will reduce the risk of neural tube defects.

5. When does WHO issue safety statements and why was a statement issued in this case?
WHO issues alerts about quality and safety of products when it receives reports of suspected substandard and falsified products, when there are new important safety signals or when products are withdrawn from the market. These alerts are generally issued after collaboration and consultation with regulatory authorities as appropriate. All the alerts are listed on this page:

In this case, the alert was issued because of the potential safety signal and public health importance of the information. The manufacturer also will be sending out a "dear doctor" letter to alert doctors worldwide about the matter.

6. Have similar observations been made in other countries?
Current post-market reporting systems have not identified the same signal of potential risk of neural tube defect in other countries. The strength of the Botswana study was that the team established a prospective surveillance system with trained health care workers in the maternity services. It is possible that the absence of such observations in
other countries could be due to smaller numbers (as fewer pregnancies have occurred among women taking DTG than other ARVs), cases not being reported, or because the safety signal seen in Botswana is a chance finding.

7. When are we going to have more information on the potential risk?
   The ongoing observational study shared preliminary findings of 4 cases of NTD out of 426 births from women taking DTG prior to pregnancy. There are approximately 600 more pregnant women who started DTG prior to conception who are being followed in a well-established surveillance programme. WHO has also been working with many stakeholders worldwide to follow all pregnant women with DTG exposure prior to pregnancy.

   We believe we will know within the next 9-12 months if this observation is confirmed or if it is a chance finding. It may take longer to be absolutely certain, given the low rate of occurrence of neural tube defects in the background population.

8. When will the new WHO guidance be published?
   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 ARVs, including the recent findings on DTG, and will release updated guidance on the role of DTG in first- and second-line HIV treatment in July 2018.

9. Should countries change their policies now? Or wait for more information?
   WHO advises national HIV programme managers to become familiar with all the information being shared about this signal of potential risk. They should inform their stakeholders and share the same information in an effort to be as transparent as possible.

   Many countries have started to transition to DTG-based regimens and will have to review their policies based on this new information. Though each country may decide on its own approach, the most conservative approach would be to avoid using DTG in women of childbearing age.

10. What are PEPFAR and other partners’ views on the new finding?
    PEPFAR is a major funder of antiretroviral therapy in many countries and a key player in the rollout of DTG-based ARV. It has been actively promoting the transition to TLD (the fixed dose combination of tenofovir + lamivudine + dolutegravir). At this time, PEPFAR encourages countries to continue with their transition to DTG through the implementation of its 2018 Country Operational Plans.
PEPFAR has agreed with WHO that HIV-infected women who desire to become pregnant should take EFV-based regimens as a safe and effective first-line regimen, until further data become available.

WHO country staff should continue to closely monitor the situation with in-country UNAIDS, PEPFAR, CDC, USAID, Global Fund and implementing partner colleagues to support discussions around policies. UNAIDS also supports the advice in this Q&A document.

11. How will this affect procurement for both DTG- and EFV-based regimens?

Large donors and the Global ARV Procurement Working Group (APWG) have already begun to discuss these new findings to address potential shifts in procurements to meet the needs of all low- and middle-income countries. Currently there is enough stock and availability for both DTG-based and EFV-based first-line treatments. More work will be needed over the next weeks to understand each country’s drug stocks and procurement plans for these medications. Since many countries have already started to transition to greater use of DTG, the situation in each country with regard to procurement and stock will need to be taken into account before decisions are made.

In case you need additional information, approach your regional office, or the HIV Department (Gottfried Hirnschall, hirnschallg@who.int) and EMP Department (Suzanne Hill, hills@who.int)

Links for more information:

4. **PEPFAR:** [https://www.pepfar.gov/press/releases/282221.htm](https://www.pepfar.gov/press/releases/282221.htm)