

DOLUTEGRAVIR USE IN PREGNANCY  
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Revised RECOMMENDATIONS for BC prescribers

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Data from an unplanned interim analysis of an observational study conducted in Botswana that was released on May 18, 2018, reported **a possible increased risk of NTD in women taking dolutegravir preconception (0.9% vs 0.1% among non-DTG ART from conception).**

Based on that information, the Oak Tree Clinic, BC Women's Hospital, in collaboration with the BC Centre for Excellence in HIV (BCCFE) made recommendations regarding dolutegravir prescribing. Since that time there has been new data published and also presented at the International AIDS Society meeting in July 2019, **reporting the prevalence of NTDs in women taking DTG at conception was 0.3% compared with 0.1% among women taking non-DTG ART at conception.** Based on this new data, revised, updated recommendations follow:

1. Women who are taking dolutegravir and become pregnant should have their antiretroviral regimen reviewed by their HIV and pregnancy care providers and, if the pregnancy is at less than 10-12 weeks of gestation, should consider switching their regimen changed to a non-dolutegravir containing regimen if possible.
2. Women who are pregnant and have had dolutegravir exposure at conception and/or through the first trimester, should have their pregnancy management reviewed by experts at or affiliated with the Oak Tree Clinic and ensure that prenatal screening for neural tube defects are completed. Because the likelihood of a neural tube defect remains small (less than 0.5%), they should be reassured and recommendation for termination of pregnancy on the basis of dolutegravir exposure alone is **not** appropriate.
3. Women who are pregnant and on dolutegravir beyond the first trimester should NOT stop their antiretroviral regimen, but their providers can discuss this with Oak Tree Clinic associated care providers.
4. Reproductive aged women who are not on highly reliable methods of birth control (e.g. intrauterine device) should be counseled on the risks associated with being on a dolutegravir containing regimen if they become pregnant and the safety of alternative regimens which do not carry the same NTD risk. Decisions to switch should be based on

patient values and a clear understanding of the increased risk of NTD associated with dolutegravir containing regimens.

5. Non-pregnant, reproductive aged women being considered for, or on, dolutegravir containing regimens, should have their pregnancy intentions and contraceptive use reviewed in each HIV visit. If pregnancy is a possibility, switching to non-dolutegravir containing regimen should be considered. Perform a pregnancy test prior to starting a woman of reproductive potential on dolutegravir and counsel on the risks of neural tube defects in the setting of dolutegravir use. Encourage the use of highly reliable forms of contraception (e.g. IUDs) prior to or at the time of initiating Dolutegravir based regimens.
6. Given the lack of safety information on **any** new antiretroviral formulations, including but not limited to elvitegravir, bictegravir, TAF and cobisistat containing regimens, caution should be used in prescribing these in non-pregnant, reproductive aged women and they should be avoided in the first trimester of pregnancy when possible.

#### **Information on dolutegravir in pregnancy to date:**

Data was released on May 18, 2018 based on an interim analysis of an NIH funded birth surveillance study, the Tsepamo study, based in Botswana. At that time, they found that in 11,558 women living with HIV in Botswana who became pregnant, 0.9% of babies (4 of 426) whose mothers became pregnant while taking dolutegravir had a neural tube defect, compared with 0.1% of babies (14 of 11,173) whose mothers took other antiretroviral combinations (1,2).

Since that time, further study data from the Tsepamo has been released and was presented at the International AIDS Society (IAS) conference on July 22, 2019. The new data reported that the prevalence of neural tube defects associated with dolutegravir use in the first trimester was 0.30% (5 of 1683) compared to 0.1% (15 of 14,792) in non-dolutegravir exposed pregnancies (10).

This reported decline in the risk of neural tube defects has downgraded the 'safety signal' of concern for use of dolutegravir however the risk remains higher than other antiretroviral drug exposure groups. Moreover, data recently reported, from 22 sites in Botswana not included in the Tsepamo study, between 2014-2019, showed a rate of neural tube defects of dolutegravir exposed pregnancies of 0.65% compared to 0.08% in non-dolutegravir exposed pregnancies (11). Canadian surveillance data on congenital anomalies in pregnancies exposed to dolutegravir pre-conception and in the first trimester did not show a significant difference in overall rate of congenital anomalies between women on antiretroviral therapy compared with those not exposed; 3.9% vs 3.0%. Of the 4 of the 80 neonates born to women on dolutegravir during the first trimester who had congenital anomalies, none had neural tube defects (12). (In Canada, folic acid is recommended prior and during pregnancy, which has been shown to reduce the rates of NTD). Our data from the BC provincial perinatal HIV surveillance data was reviewed for any safety signals regarding NTDs on May 24, 2018. We have data on 678 pregnancies (between 1994 and January 30, 2018) that involved exposure to antiretroviral medications. Of these, 562 were live births. Of 562 live births, 4 women took dolutegravir in

pregnancy (0.7%). There have not been any neural tube defects in any infants of women living with HIV treated with antiretrovirals in BC. There was one neural tube defect diagnosed in the fetus of a woman living with HIV who had not taken antiretrovirals in her first trimester.

A systematic review of safety of dolutegravir in pregnancy (4) reported information on congenital anomalies in 442 women exposed to dolutegravir. This review, included data from six main studies including, an ongoing observational study in Botswana with 845 women on dolutegravir compared to 4,593 women on efavirenz; 142 women reported to be taking dolutegravir during pregnancy (88 exposed in first trimester) from the antiretroviral pregnancy registry; 81 pregnancies from EPPICC, PANNA, NEAT-ID; dolutegravir phase 3 trials; dolutegravir post marketing surveillance; and 15 women enrolled in IMPAACT P1026s. Of the total of 442 women exposed to dolutegravir in pregnancy 16 had congenital anomalies (3.6%), which is in keeping with the global rate of congenital anomalies of 3-5%. Of the congenital anomalies, most were polydactyly, which is a common anomaly in children of African descent (1%), and there were two renal cysts. None were documented to be neural tube defects. In a single center retrospective cohort analysis from Sweden (5), 36 pregnant women seen at the Karolinska University Hospital were treated with dolutegravir; 14 before pregnancy and 22 started during pregnancy. There were 4 early spontaneous abortions, one late termination and no congenital malformations.

Overall, the data reported to date appears to reaffirm that there is a small increased risk of neural tube defects, in the Botswana setting, in dolutegravir exposed pregnancies, however, that the absolute risk is very low. As a result, the WHO has recommended dolutegravir based regimens for first line therapy in all adults due to their risk/benefit analysis for population-based treatment recommendations in sub-Saharan Africa. (WHO press release regarding dolutegravir in pregnancy (10)

<https://www.who.int/news-room/detail/22-07-2019-who-recommends-dolutegravir-as-preferred-hiv-treatment-option-in-all-populations>)

### **General background on congenital anomalies and neural tube defects:**

It is important to note that at a population level approximately 4-5% of infants have major congenital anomalies. Therefore, any increased risk associated with prescribing Dolutegravir can be taken into account, with the background risk in mind. With the advent of modern prenatal screening capabilities, prenatal genetic testing, maternal serum screening for alpha fetoprotein (AFP) and detailed ultrasound examinations for fetal anomalies, the majority of these anomalies can be recognized. Neural tube defects occur at variable rates in different populations and in different countries. The incidence of neural tube defects in Canada and in British Columbia (BC) is approximately 0.04%. This has decreased from 0.076%. (6) following folate supplementation in grain products, which started in 1998. Given this, there are approximately 16 cases of neural tube defects per year in BC.

In Canada, although there is folate supplementation in food, additional folate supplementation is recommended 12 weeks prior to conception and through at least the first 12 weeks of the pregnancy. In low risk women (without a prior or family history), the supplementation in multivitamins of 0.4-0.6mg of folic acid is sufficient or prenatal vitamins which contain 1mg (7).

Studies globally have shown variability in rates of neural tube defects from 5.2/10,000 live births to 75.4/10,000 live births in African countries (8). Of note, the highest rate is less than 0.1% which is the rate noted in women living with HIV on non-dolutegravir containing regimens in the above-referenced report from the Botswana surveillance study.

In summary, this information on dolutegravir is less concerning than the initial data from May 2018, but it highlights the importance of careful consideration when prescribing ART for women of reproductive potential or during pre-conception. In countries where individualized, patient specific prescribing can be conducted, choosing regimens that have long track records of safety in pregnancy is the wisest option. It takes many years of post-marketing surveillance to reveal if there are concerns regarding low event rate complications including teratogenicity. Few pre-licensure studies include women and very few include pregnant women so new drugs on the market need to be assumed to have unknown risks in pregnancy and caution should be exerted in prescribing to women in reproductive age (13).

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