DOLUTEGRAVIR USE IN PREGNANCY
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INTERIM RECOMMENDATIONS

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Based on new information from an unplanned interim analysis of an observational study conducted in Botswana that was released on May 18, 2018, the Oak Tree Clinic in collaboration with the BC Centre for Excellence in HIV (BCCFE) is making the following new recommendations:

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 have 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 1%), 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 should 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 not be prescribed dolutegravir containing regimens if there are other reasonable treatment options.
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 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, raltegravir and elvitegravir 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:

New data was released on May 18, 2018 on an interim analysis of an NIH funded birth surveillance study based in Botswana. 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). Final results are expected in about a year. Our analysis of this difference is that it is statistically significantly different, (p-value = 0.003). This information is considered a 'safety signal', which is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation.

Prior information on dolutegravir in pregnancy had been reassuring until this time. However, dolutegravir is part of a relatively new class of antiretrovirals (i.e., integrase inhibitors) with a short time span in clinical use and very limited data in pregnancy. Based on manufacturer data, the use of dolutegravir has not demonstrated evidence of teratogenicity or developmental toxicity in animal studies or in early clinical trials where women had unplanned pregnancies while on dolutegravir. However, dolutegravir does cross the placenta and no systematic studies in pregnancy have been completed to date (3).

A recent 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.

General background on congenital anomalies and neural tube defects:

At a population level approximately 4-5% of infants have major congenital anomalies. With the advent of modern prenatal screening capabilities, prenatal genetic testing, maternal serum

screening for alpha feto-protein (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.

Our data from 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.

In summary, given the information presented from WHO of the Botswana study observation of 0.9% neural tube defects in first trimester dolutegravir exposed pregnancies compared to 0.1% in the infants of women on other antiretroviral combinations, it is important to consider this a safety signal until further information is available. This has prompted WHO, FDA, CDC, United States DHHS and the European Medicines Agency to release cautionary recommendations around the use of dolutegravir in pregnancy. Our recommendations presented above are in line with those of the international agencies. Further recommendations will be forthcoming once additional information is available.

References:

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