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Session: **CS1**: Friday May 1 – 11:00:12:30 – HIV in Women and Children

Track:	Clinical Sciences
Subject:	HIV in Women and in Pregnancy
Presentation Type:	Oral
Title of Abstract:	**Reproductive Toxicity Studies to Evaluate Potential Neural Tube and Other Abnormalities Associated with Dolutegravir Exposure in Pregnancy**
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Abstract

The benefits of antiretroviral therapy in improving maternal health and preventing vertical HIV transmission are indisputable. However, exposure to any potent drug during pregnancy carries the risk of embryo-fetal toxicities. Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), is a WHO-alternative first-line regimen, because of its efficacy, tolerability, and a higher genetic barrier to resistance. However, initial findings from an observational study in Botswana showed an increased incidence of neural tube defects (NTDs) with peri-conceptional exposure to DTG. Here we explore potential DTG reproductive toxicities in a mouse model. Wild-type female C57BL/6 mice, were mated and randomly allocated to control (water) and 1x-DTG (2.5mg/kg DTG+50mg/kg TDF+33.3mg/kg FTC-yielding DTG peak plasma concentration of ~3,000ng/ml) administered once daily by oral gavage from the day of plug detection to sacrifice at embryonic day (E)15.5. Mice were on a folate-sufficient diet. Fetuses were assessed blinded to treatment allocation by two independent reviewers. 241 litters and 1921 fetuses were assessed (control n=91 litters, 747 fetuses; 1x-DTG n=150 litters, 1174 fetuses). Resorption rates, viability, and fetal/placental weight ratio did not differ between groups. Lower placenta weight, lower fetal weight and lower maternal weight gain were observed in the 1x-DTG vs. control groups. Five NTDs (Exencephaly, n=2; Anencephaly, n =1; Spinal Bifida, n=2) were observed in the 1x-DTG group (5/1174=0.43%), with no NTDs in controls (odds ratio (OR) 1x-DTG vs. control=6.92, 95%CI 0.38-127, p=0.16). Fetuses exposed to 1x-DTG also had higher rates of anophthalmia/microphthalmia (OR(95%CI): 2.0 (1.18-3.45), p=0.011), severe edema (OR(95%CI): 2.76 (1.33-5.73), p=0.007), vascular/cranial/spinal bleeding issues (OR(95%CI): 3.32 (1.63-6.74), p=0.001), and enlarged liver (OR(95%CI): 1.61 (0.99-2.62), p=0.057) compared to control. Contrary to expectations, several fetal abnormalities are evident when dams are exposed to a clinical dose of DTG supporting the link between DTG in pregnancy and the risk of NTD and other adverse fetal outcomes.