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Reproductive Feto-toxicity Studies to Evaluate Dolutegravir in Combination with Emtricitabine and Tenofovir in Pregnant Mice on a Folate Deficient Diet

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Background and Rationale

Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), is a WHO preferred regimen. Initial findings from an observational study in Botswana showed an elevated incidence of neural tube defects (NTDs) with peri-conceptional exposure to DTG. We have previously shown that pregnant mice treated with therapeutic levels of DTG-based ART from conception had higher rates of fetal congenital defects including NTD. Folate deficiency increases the risk for congenital defects and therefore we performed a DTG fetotoxicity assessment on C57BL/6 mice fed a folic acid deficient diet (FAD).

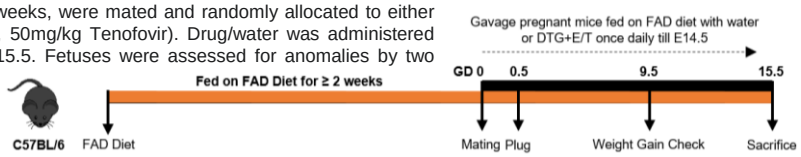
Hypothesis

We ***hypothesize*** that in the context of maternal folate deficiency, DTG+E/T exposure at a clinically relevant dose from conception may alter fetal development, increasing the incidence rate of NTD and other congenital abnormalities.

Methods

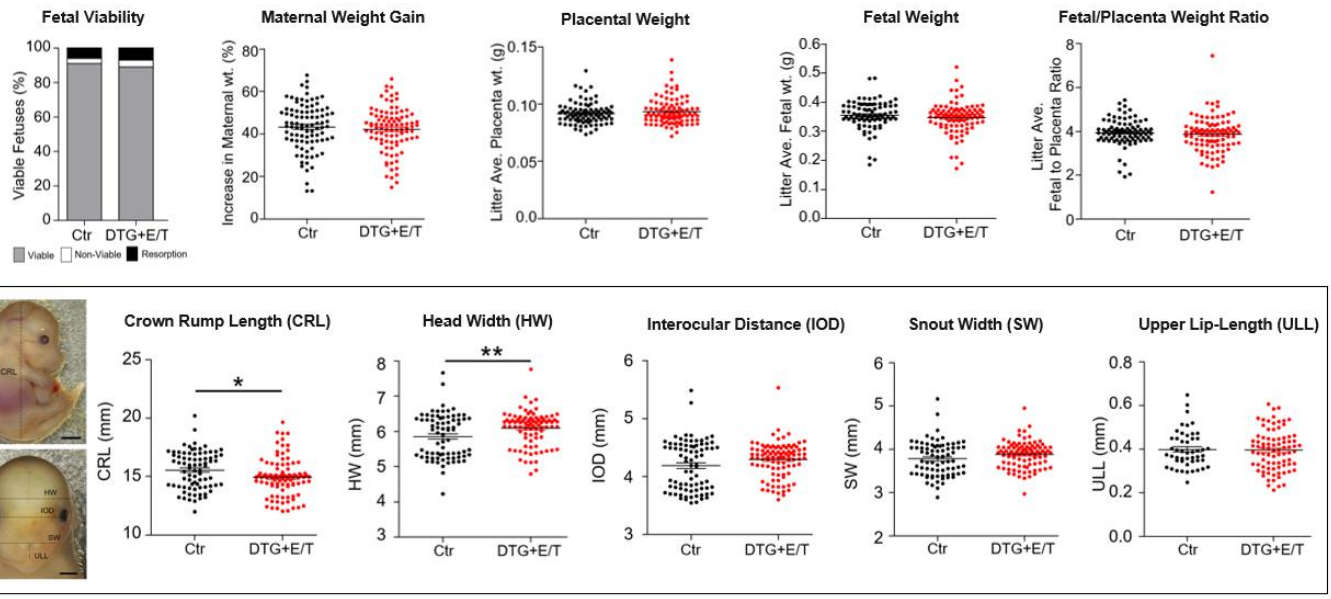
Female C57BL/6 mice fed a folic acid deficient diet for a minimum of 2 weeks, were mated and randomly allocated to either control (water) or DTG+E/T (2.5mg/kg DTG + 33.3mg/kg Emtricitabine, 50mg/kg Tenofovir). Drug/water was administered once daily by oral gavage from day of plug detection to sacrifice at E15.5. Fetuses were assessed for anomalies by two independent reviewers who were blinded to treatment allocation.

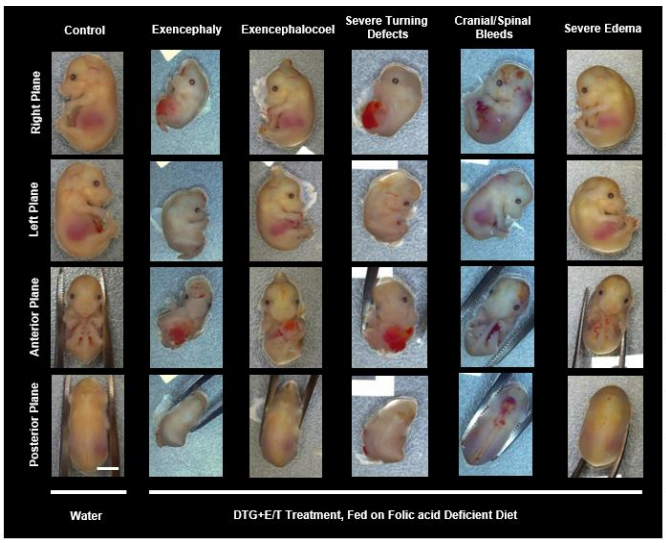
Mixed effects logistic regression was used to assess differences between treatment groups accounting for litter effects. A total of 1533 fetuses from 209 litters were assessed (control n=103 litters, 756 fetuses; DTG+E/T n=106 litters, 777 fetuses).



Results

Percent viability, maternal weight gain, placental weight, fetal weight, and fetal/placenta weight ratio, did not differ between groups. Crown-rump length was lower and head width was higher in the DTG+E/T vs. control groups. Interocular distance, snout width and upper lip-length did not differ between groups





Seven NTDs (exencephaly, n=2; encephalocele, n=3; spinal bifida, n=2) were observed in the DTG+E/T group (7/777=0.9%), with no NTDs in controls. Fetuses exposed to DTG+E/T also had higher rates of severe turning defects (2.2% vs. 0.4%, p=0.04), abdominal wall defects (3.5% vs. 0.4%, p=0.04), limb defects (3.9% vs. 0.5%, p=0.001), cranial/spinal bleeds (15.7% vs. 5.4%, p<0.001), and severe edema (7.0% vs. 1.3%, p<0.001).

Conclusion

Exposure to therapeutic levels of DTG+E/T from conception in the context of maternal folate deficiency is associated with higher rates of NTD and other congenital abnormalities compared to folate-deficient controls

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