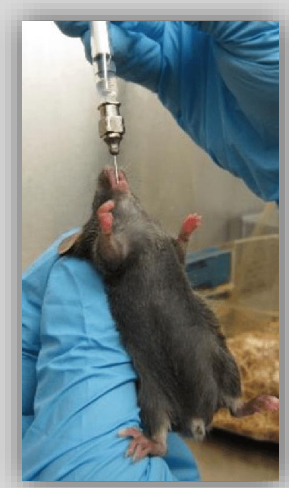


CONFERENCE CAHR 2022

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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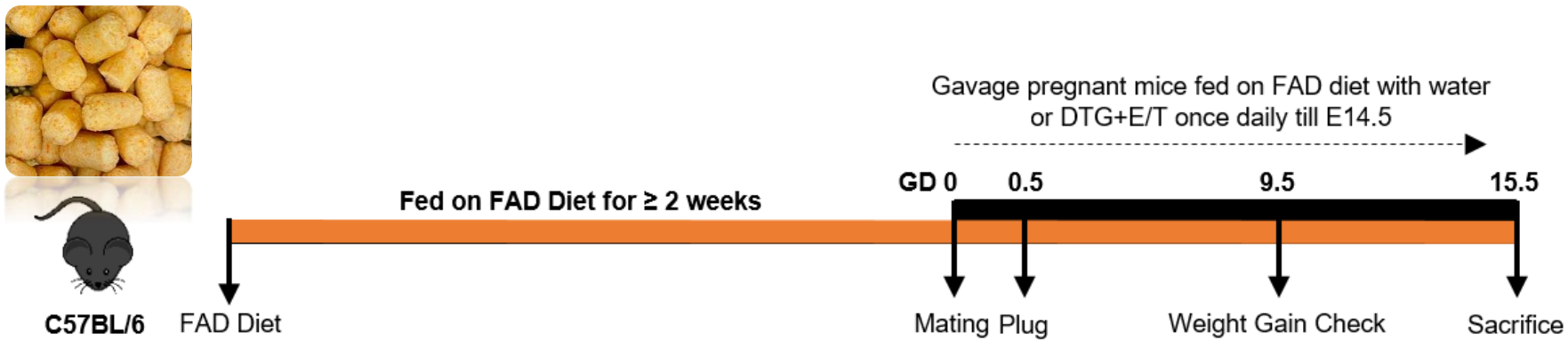
Introduction

- In 2016, Dolutegravir (DTG), a highly efficacious, well-tolerated drug, became the World Health Organization preferred first-line regimen for all people living with HIV
- In 2018 and later in 2019, the Tsepamo study conducted in Botswana reported a higher than expected number of neural-tube defects (NTD) among infants born to women who started treatment with DTG.
- Surveillance is on-going but many published studies have limitations
- Studies have implicated that folate's biological role and its metabolism could be in part altered by dolutegravir use in pregnancy and therefore we performed DTG fetotoxicity assessment on C57BL/6 mice fed a folic acid deficient diet (FAD)

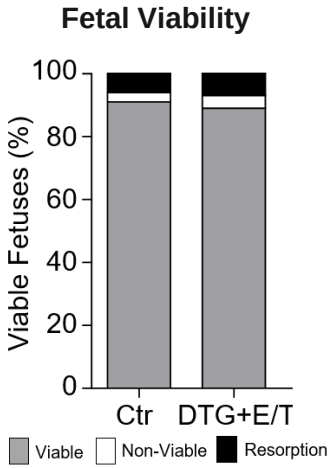
We ***hypothesize*** that in the context of maternal folate deficiency, DTG+E/T exposure at a clinically relevant dose from conception may alter fetal development, increasing the incidence rate of NTD and other congenital abnormalities.

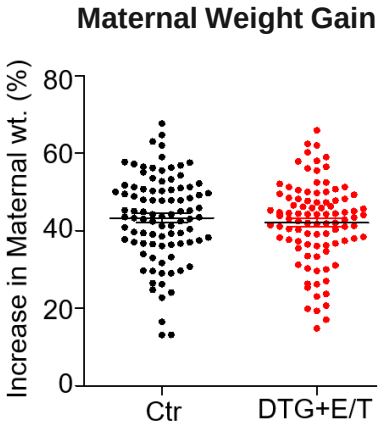
Treatment Schematic Methodology

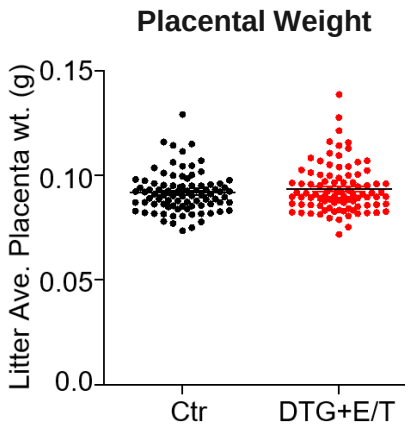


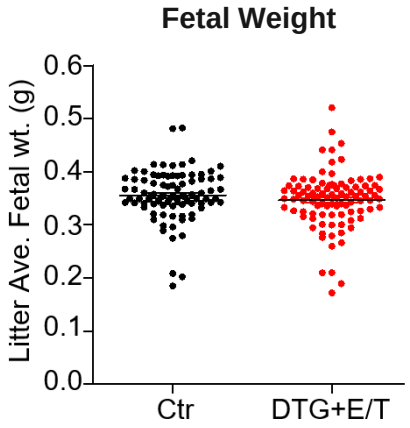
Treatment	Litters	Fetuses
Con-Water – FAD	103	756
DTG+E/T – FAD	106	777

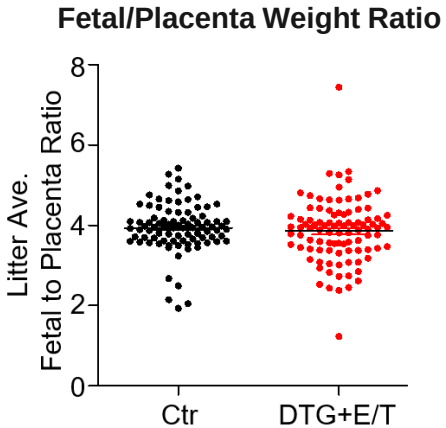
Maternal and Fetal Outcome

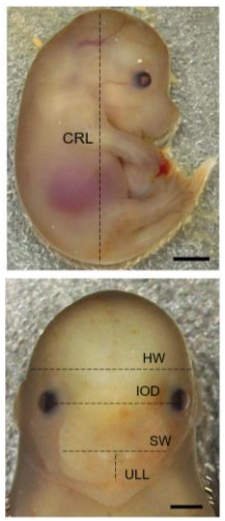


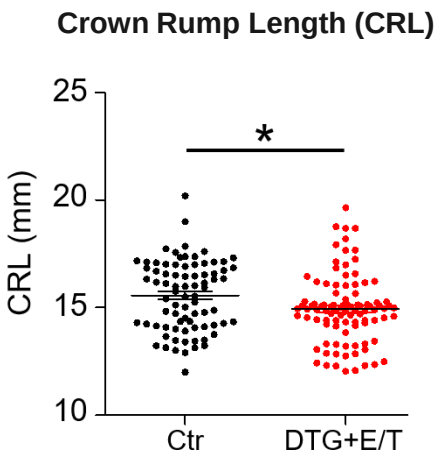


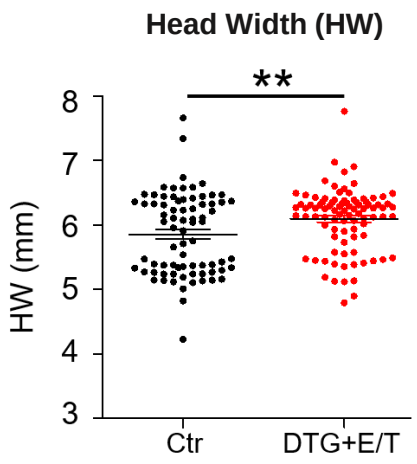


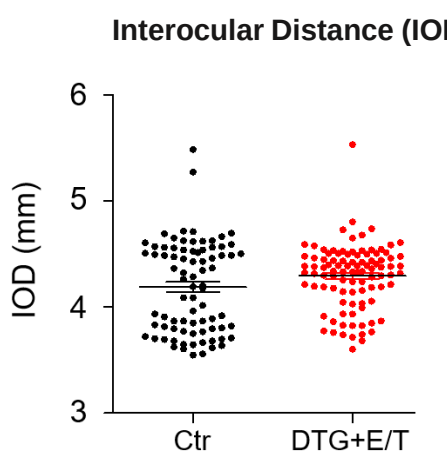


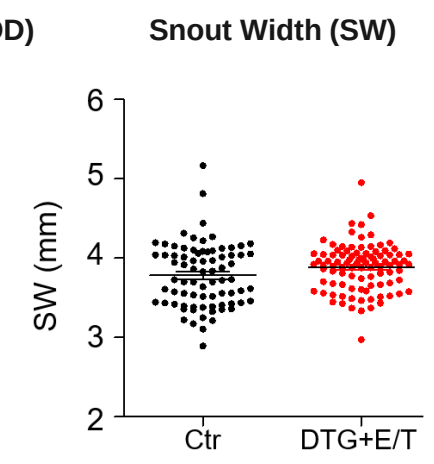


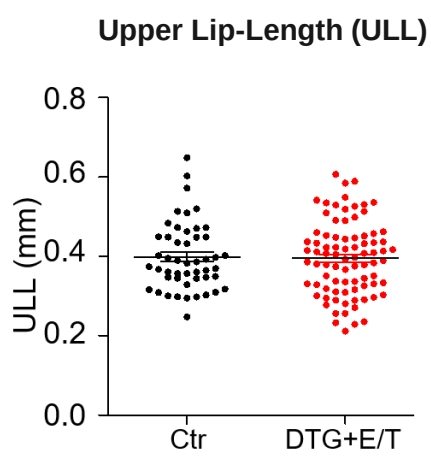




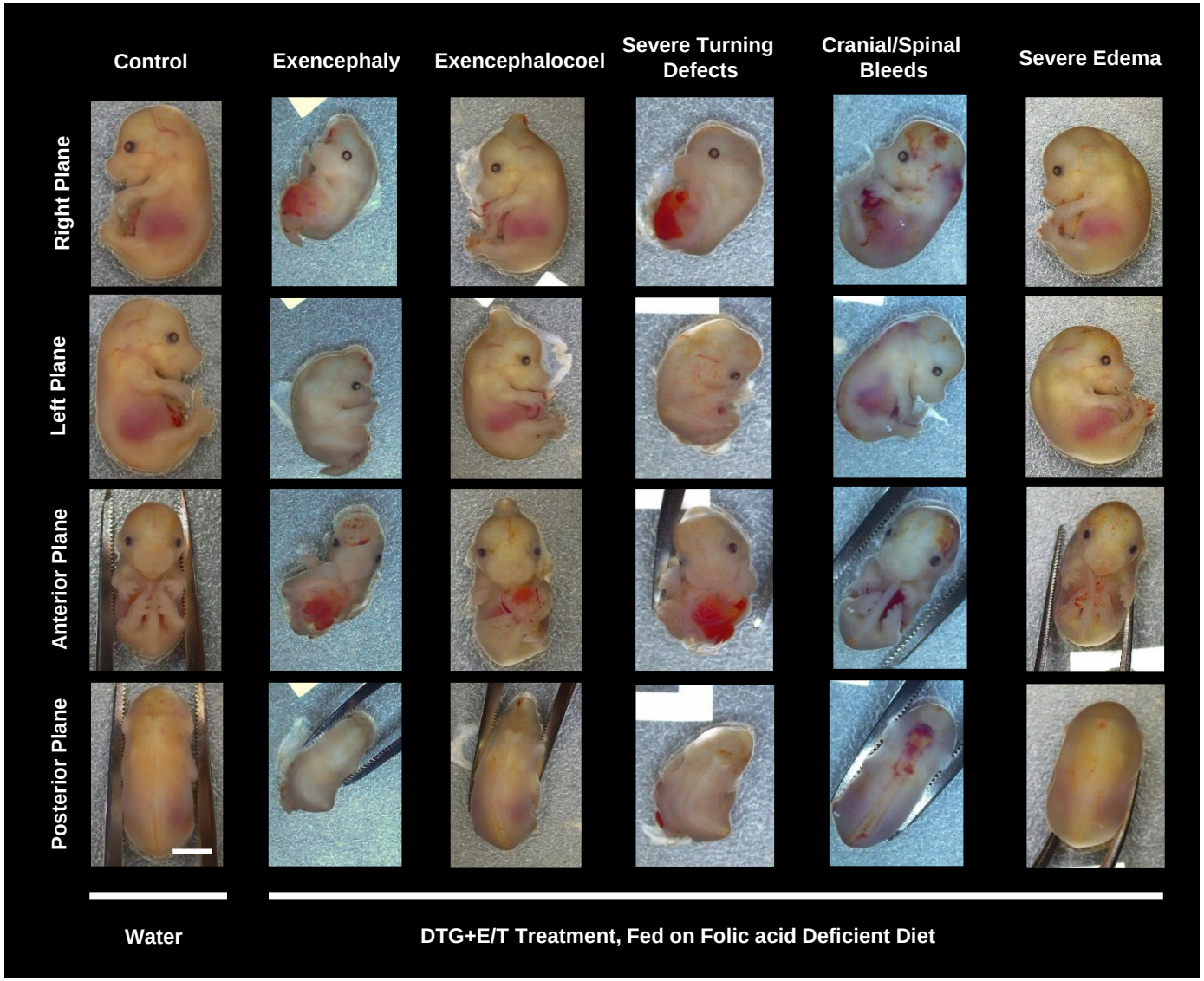








Congenital Anomalies



	Control N (Litter) = 103 N (Fetuses) = 756	1xDTG+E/T N (Litter) = 106 N (Fetuses) = 777	p value
	Fetuses Affected n (%)	Fetuses Affected n (%)	
Neural Tubes Defects Exencephaly, Encephalocele, Spinal bifida	**0 (0%)**	**7 (0.90%)**	
Severe Turning Defects	**3 (0.40%)**	**17 (2.19%)**	**0.04**
Abdominal Wall Defects	**3 (0.40%)**	**27 (3.47%)**	**0.04**
Limb Defects	**4 (0.53%)**	**30 (3.86%)**	**0.001**
Cranial/Spinal Bleeds	**41 (5.42%)**	**122 (15.70%)**	**<0.001**
Severe Edema	**10 (1.32%)**	**54 (6.95%)**	**<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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