Effect of Dolutegravir on Glucose Homeostasis in Female Mice

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BACKGROUND

- Dolutegravir (DTG) has a favourable safety and tolerability profile but has been associated with a small increased risk of neural tube defects (NTDs) as well as weight gain and hyperglycemia.
- Maternal hyperglycemia has been associated with increased risk for fetal defects.
- We evaluated the impact of DTG on glucose homeostasis using a mouse model.

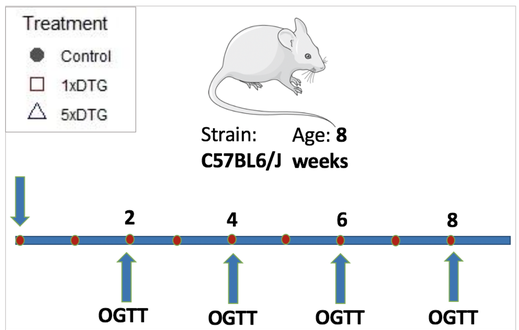
HYPOTHESIS

- We hypothesize that DTG alters glucose homeostasis and that these changes may be transient.

METHODS

- Euglycemic female mice were assigned to daily gavage treatments for 8 weeks of either control (water, N=15), 1xDTG (N=13), yielding therapeutic levels of DTG, or 5xDTG (N=15).

Regimen	Dosage
1xDTG+E/T (therapeutic)	2.5mg/kg DTG+33.3/50mg/kg emtricitabine (E)/tenofovir disoproxil fumarate (T)
5xDTG+E/T (supratherapeutic)	12.5mg/kg+33.3/50mg/kg E/T



- Overnight fasted glucose, body weight, and oral glucose tolerance test (OGTT) were measured at 2, 4, 6 and 8 weeks.
- Fasting hyperglycemia was defined as fasting glucose >10.5 mmol/L (>2 S.D. from control mean)
- Secondary outcomes included severe fasting hyperglycemia defined as >13.3 mmol/L and area under the curve (AUC) glucose concentrations through the OGTT.

RESULTS

DTG is associated with a transient increase in overnight fasted blood glucose

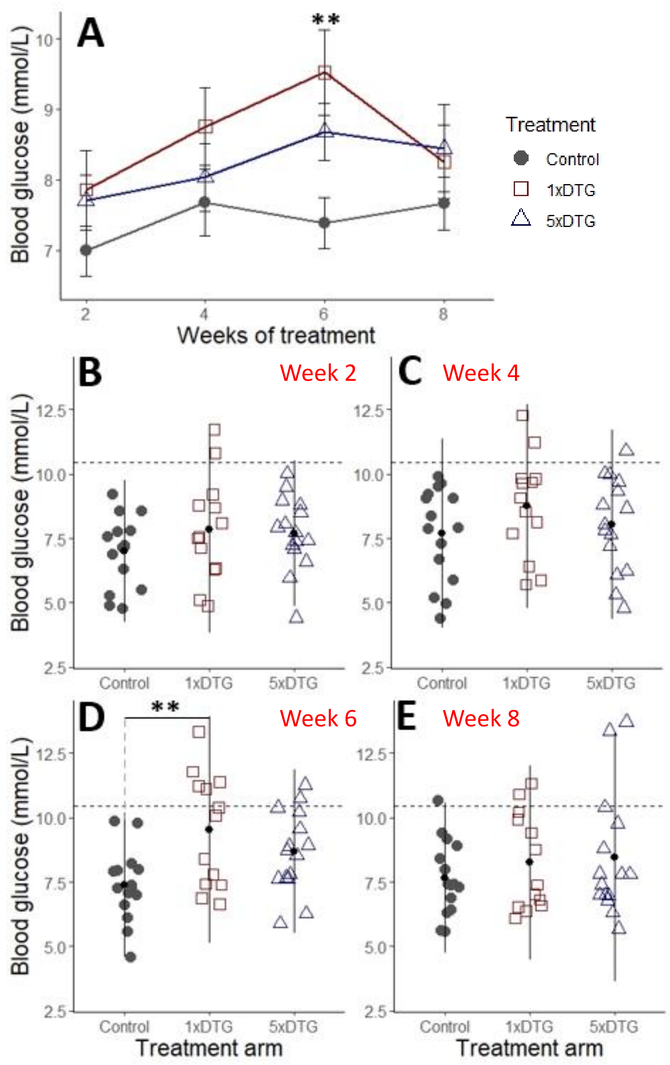


Fig. 1. Fasted blood glucose compared between treatment arms. Biweekly mean ± SE glucose measure across treatment arms is shown (A), where control, 1xDTG, and 5xDTG are represented as grey circles, red squares, and blue triangles respectively. Week 2 (B), week 4 (C), week 6 (D), and week 8 (E) fasted blood glucose across treatment arms are shown, where dotted line indicates mean+2SD fasted blood glucose over the 8 week period of the control arm. All statistical analysis was performed by one-way ANOVA and Tukey post-hoc test. ** p<0.01 compared to control

RESULTS

AUC for oral glucose tolerance test is transiently higher in 1xDTG-treated mice

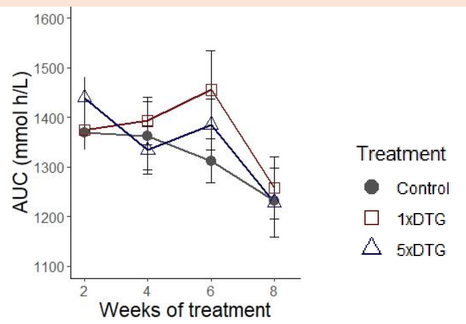


Fig 2. OGTT AUC compared between treatment arms over time is shown. Control, 1xDTG, and 5xDTG are represented as grey circles, red squares, and blue triangles respectively. Mean ± SE is shown. All statistical analysis was performed by one-way ANOVA and Tukey post-hoc test.

No weight change difference was observed between treatment arms

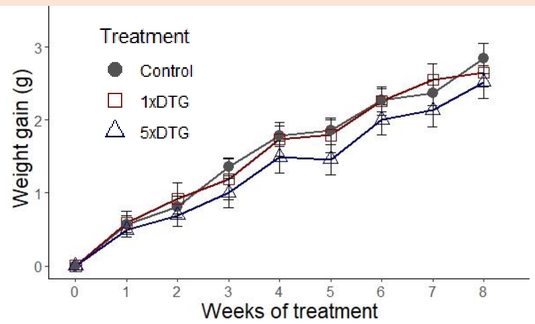


Fig 3. Weekly body weight gain was compared between treatment arms, where control, 1xDTG, and 5xDTG are represented as grey circles, red squares, and blue triangles respectively. Data presented are treatment group means ± SE. All statistical analysis was performed by one-way ANOVA and Tukey post-hoc test.

CONCLUSIONS

- DTG treatment was associated with transient elevation in blood glucose and fasting hyperglycemia
- No significant change to body weight was observed.
- If further research shows DTG is associated with transient hyperglycemia in humans, this may partially explain the increase in NTDs seen after the rollout of DTG in Botswana, as hyperglycemia is a known risk factor for NTDs.

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