Antiretroviral Drugs Affect the Placental Vasculature

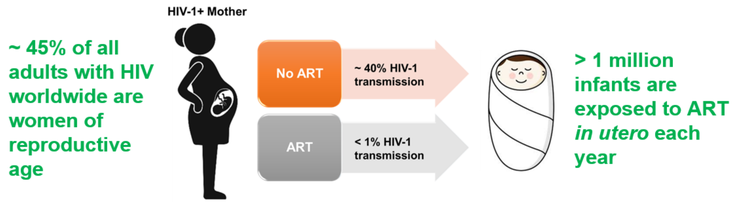
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Introduction

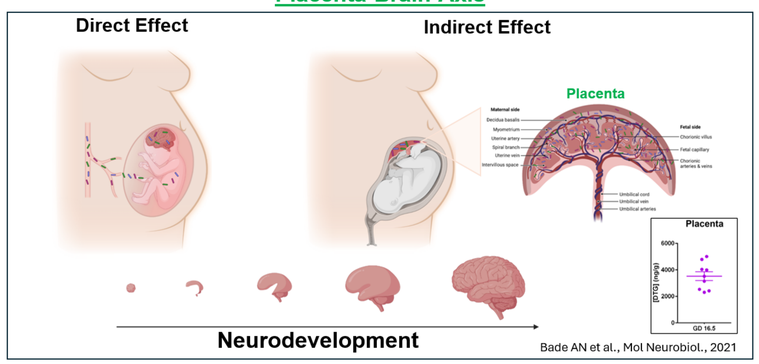
Objective: ***Safety of dolutegravir (DTG) in pregnancy***



- 84% of pregnant women living with HIV-1 had access to ART in 2023 (UNAIDS 2024).
- More than 15 million people living with HIV-1 worldwide are being treated with DTG-based regimen. These include pregnant women or those of child-bearing age.
- DTG poses potential risks of fetal neurodevelopmental toxicities.

Knowledge Gap: ***Effects of DTG on placental development***

Placenta-Brain-Axis



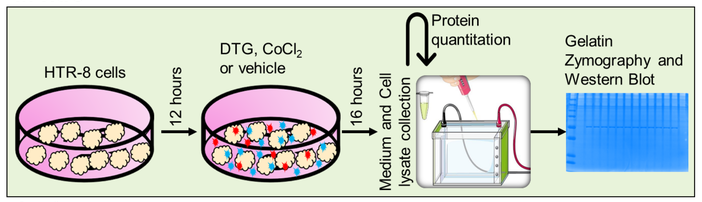
Bade AN et al., Mol Neurobiol., 2021

Hypothesis

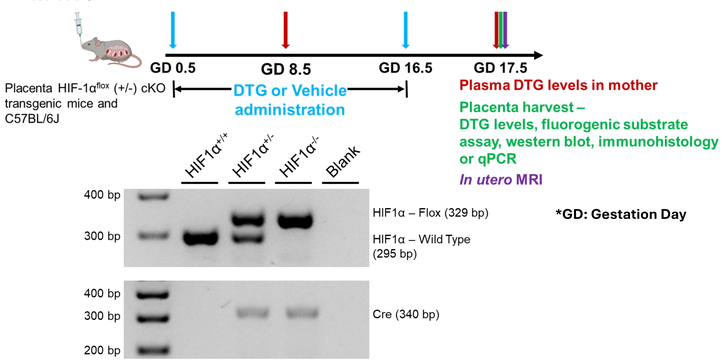
Genetic deficits in HIF-1α could influence DTG-linked placental vascular abnormalities.

Methods

In vitro

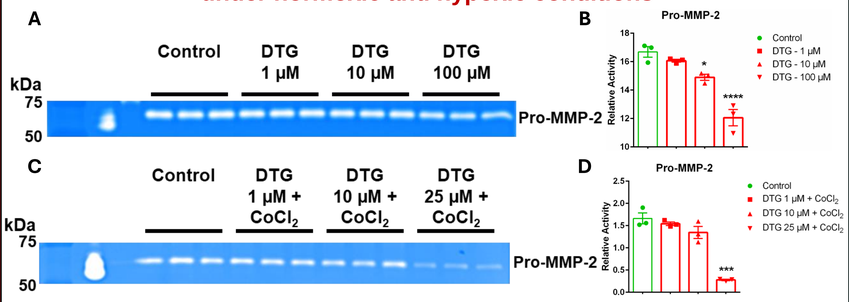


In vivo

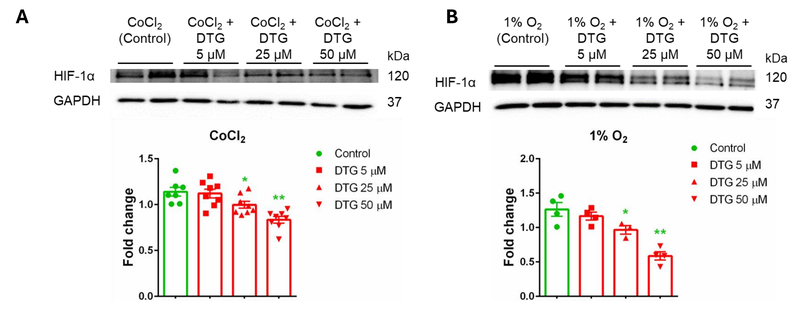


Results

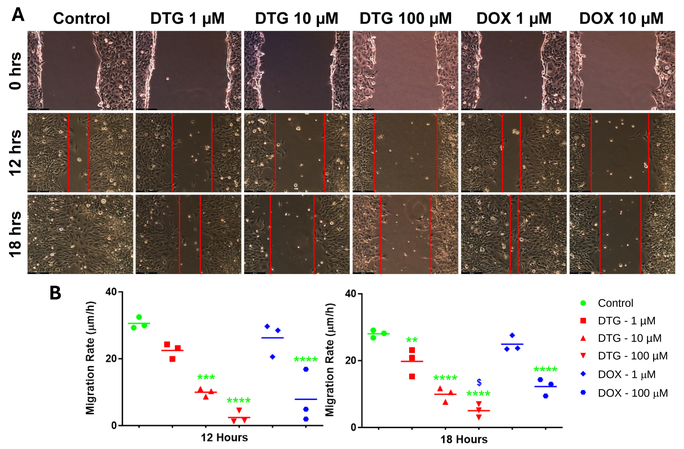
DTG inhibits matrix metalloproteinases (MMPs) activities in HTR-8 cells under normoxic and hypoxic conditions



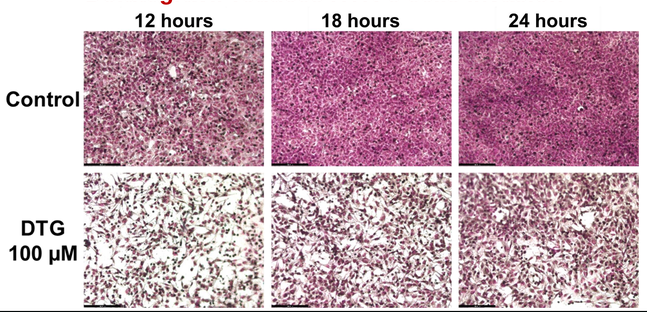
DTG decreases HIF-1α expression



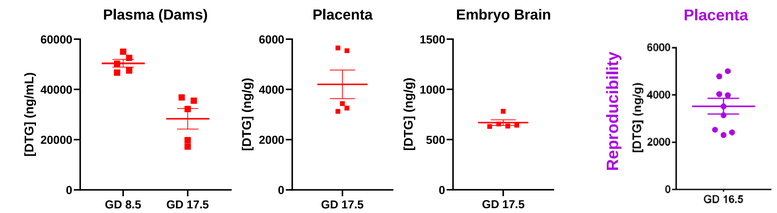
DTG reduces HTR-8 cells migration



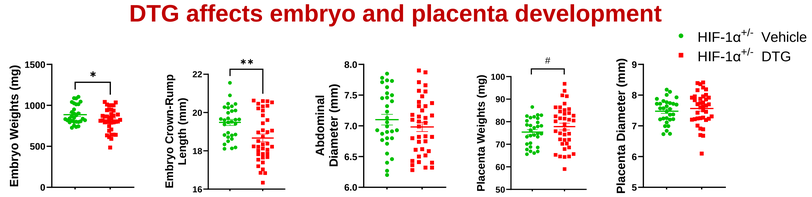
Dolutegravir reduces HTR-8 cells invasion



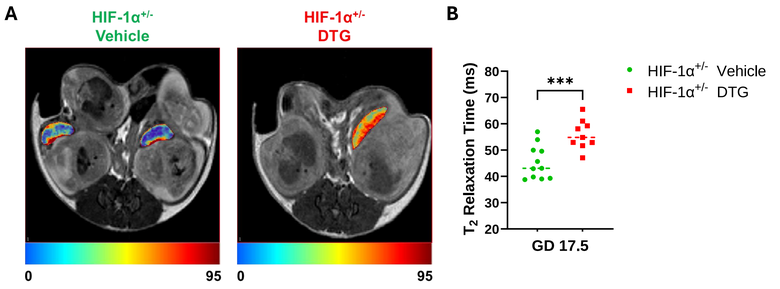
High levels of DTG accumulate in the placenta



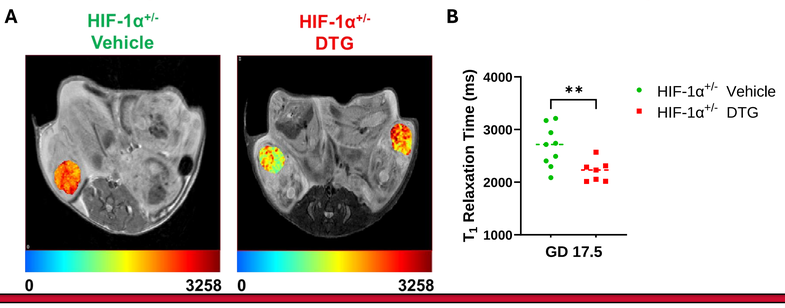
DTG affects embryo and placenta development



DTG exposure alters the labyrinth vasculature



DTG exposure induces oxidative stress in the embryo brain



Conclusions

- DTG inhibits MMP-2 activity and decreases HIF-1α expression under normoxic and hypoxic conditions in HTR-8 trophoblastic cells.
- DTG reduces HTR-8 cells migration and invasion.
- MRI data indicate potential increase in labyrinth vasculature and decrease in junctional zone following gestational DTG exposure.
- DTG-linked oxidative stress was detected in the embryo brain.
- Preliminary observations indicate compensatory mechanisms in placenta at GD 17.5 to support fetal development following placental injury during early duration of pregnancy.
- Our work concludes that DTG can potentially impair placental development by affecting HIF-1α expression and MMPs activities early in pregnancy.

References

- Bade AN et al., Mol Neurobiol., 2021, PMID: 34390469 PMCID: PMC8599359
- Mohan H et al., eBioMedicine, 2023, PMID: 37586112 PMCID: PMC10450420

Acknowledgements: 1R01HD115482-01 (NICHD); R21HD106842-01 (NICHD); Nebraska Center for Women's Health Research Pilot Project Award; University of Nebraska Collaboration Initiative Grant (NRI)