Long-acting Antiretroviral Formulations Restore the Fetal Neurodevelopment

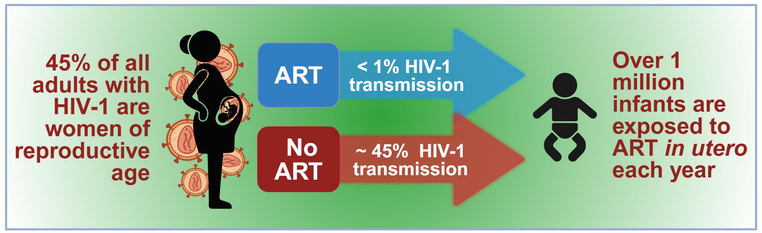
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Introduction

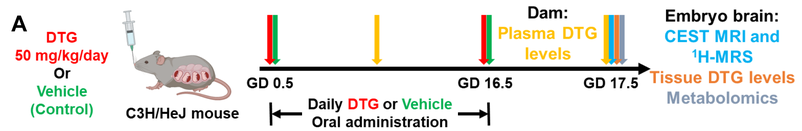
Objective: ***Safety and Benefits of long-acting ARV-formulations in pregnancy***



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

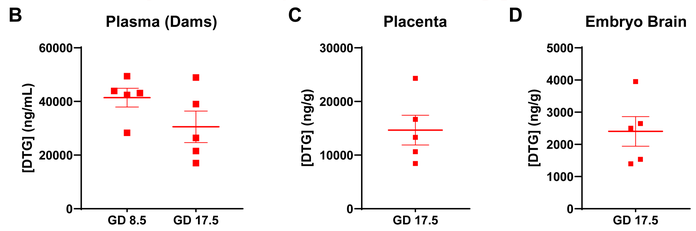
Hypothesis: Injectable long-acting (LA) formulations elicit improved ARVs safety profiles during pregnancy

Methods

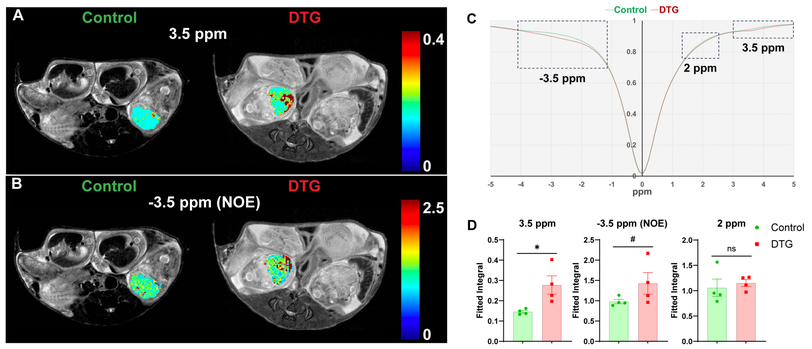


Results

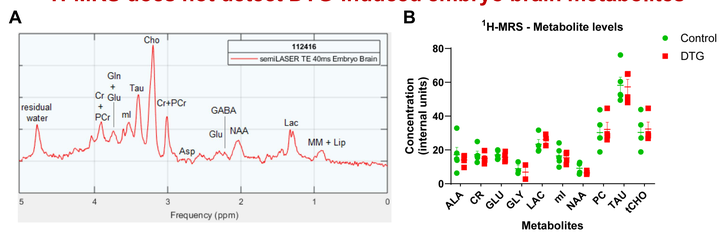
Embryo brain is exposed to DTG during gestation



CEST MRI measures DTG-induced embryo brain metabolic changes

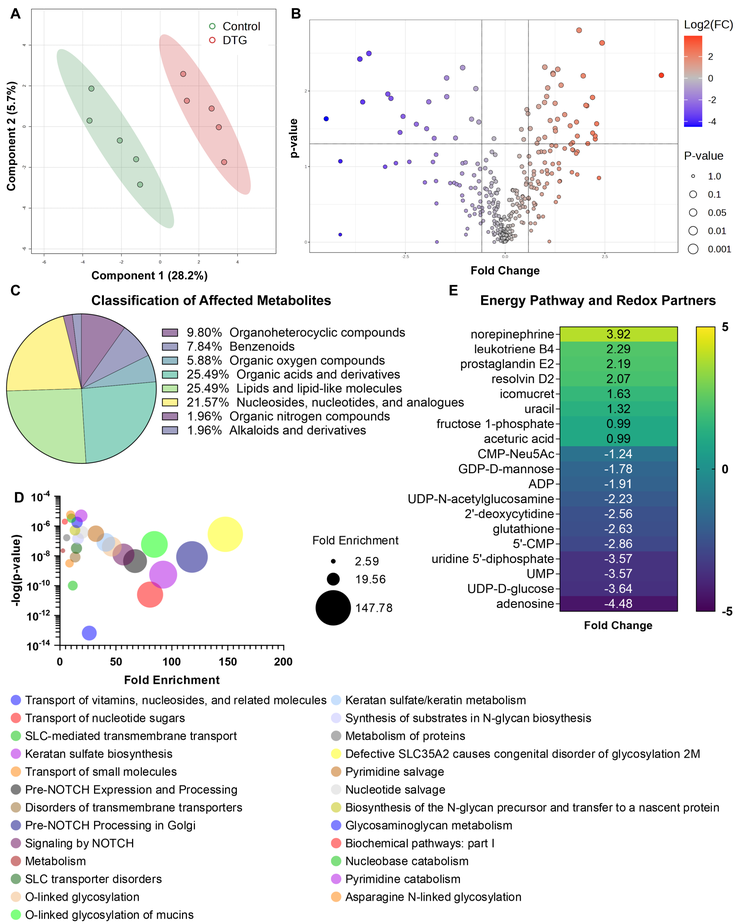


¹H-MRS does not detect DTG-induced embryo brain metabolites



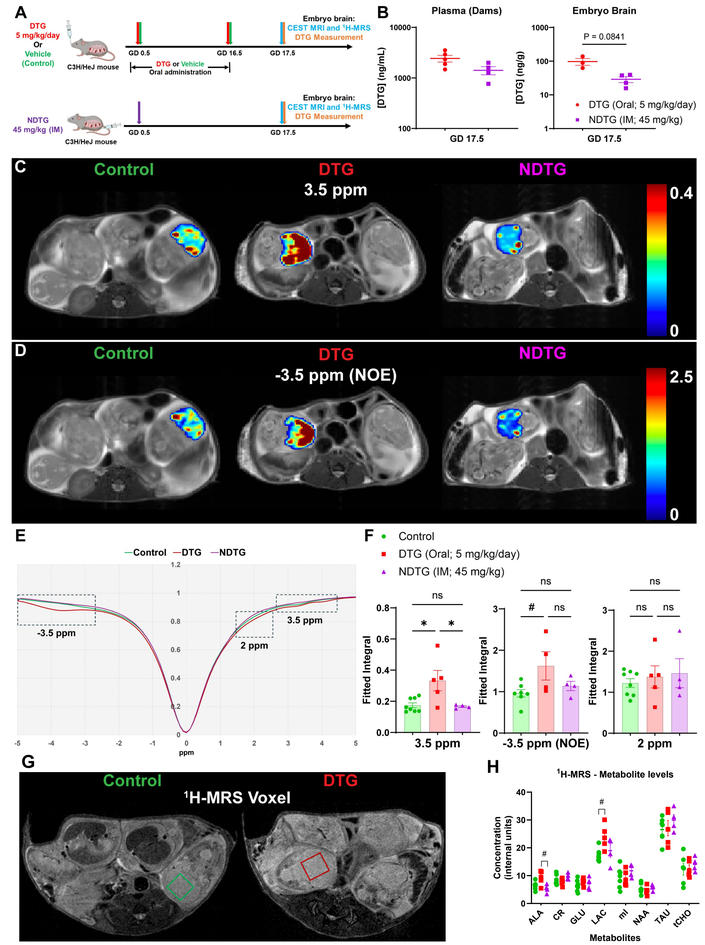
No significant differences were observed for any of measured metabolites by ¹H-MRS between control and DTG-exposed groups. These data signify that CEST MRI is more sensitive than ¹H-MRS in detecting metabolite alterations in a rodent embryo brain.

DTG-linked embryo brain metabolomic dysfunction



Differentially expressed metabolites and affected pathways in the embryo brains of DTG-exposed group indicated impairments in cellular processes such as neurogenesis, neuronal growth, dendrite and synapse formation.

CEST MRI detects formulation safety profile



Conclusions

- CEST hyperintensities at -3.5 ppm (nuclear Overhauser effect) and 3.5 ppm (amide/amine protons) are measured in brains of mouse embryos exposed to dolutegravir (DTG), indicating impairments in cellular membrane lipids, mobile proteins or peptides, and glutamate levels.
- Non-targeted metabolomics found altered energy and membrane-linked metabolites in DTG-exposed embryos brains validating CEST data.
- CEST MRI demonstrated prevention of DTG-induced metabolomic changes in embryo brains when delivered as long-acting nanoformulated DTG (NDTG).
- Therapeutic benefits of long-acting injectable delivery of ARVs in mitigating neurodevelopmental impairments were observed, potentially, due to limited drug exposure to the embryo brain.

References

Mohan H et al., eBioMedicine, 2023, PMID: 37586112 PMCID: PMC10450420
Summerlin M et al., Front Pharmacol., 2025, PMID: 41235110; PMCID: PMC12605090

Funding: 1R01HD115482 (NICHD); R21HD117691 (NICHD); R21HD106842 (NICHD)