Dolutegravir Impedes Cerebral Organoid Maturation

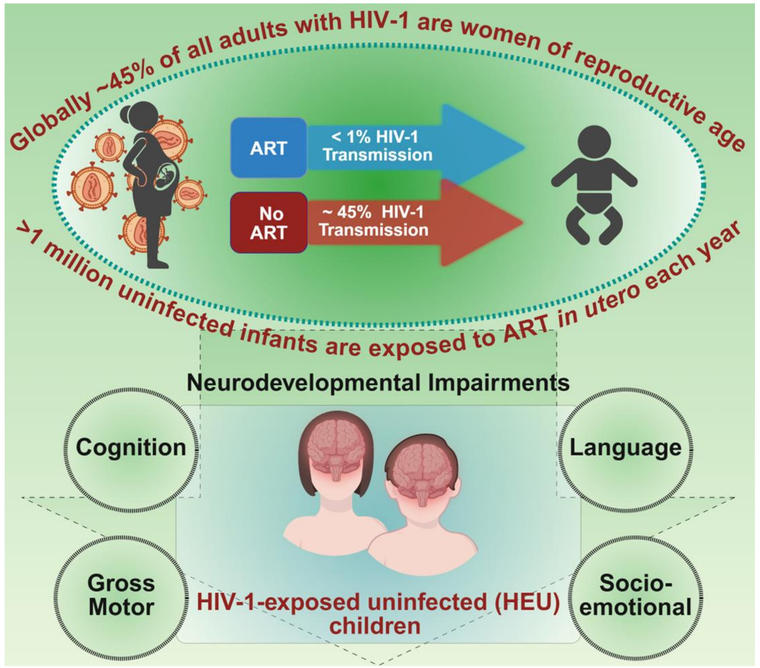
Manjeet Kumar[1], Jhyama Gurung[1], Micah Summerlin[1], Christine Adalikwu[1], Emma G. Foster[1], Baojin Yao[1], Sandip Godse[1], Yutong Liu[2], Aditya N. Bade[1]

[1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198
[2]Department of Radiology, University of Nebraska Medical Center, Omaha, NE, 68198

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Introduction



Knowledge gap

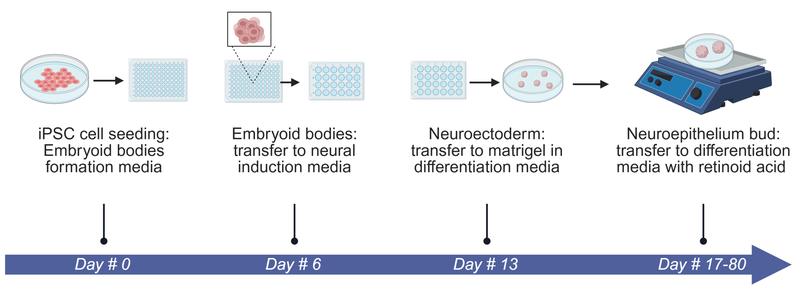
Effects of Gestational-ARV Exposure on Neurodevelopment

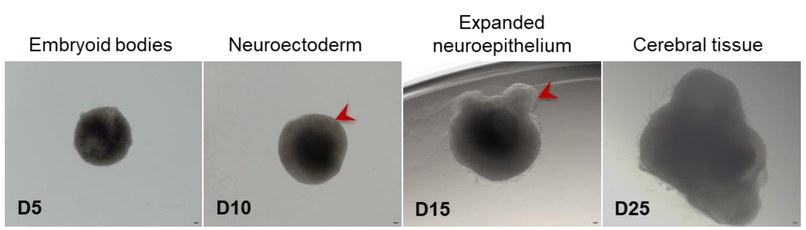
Hypothesis

We posit that novel cerebral organoids can reflect Dolutegravir's (DTG) effects on fetal neurodevelopment.

Methods

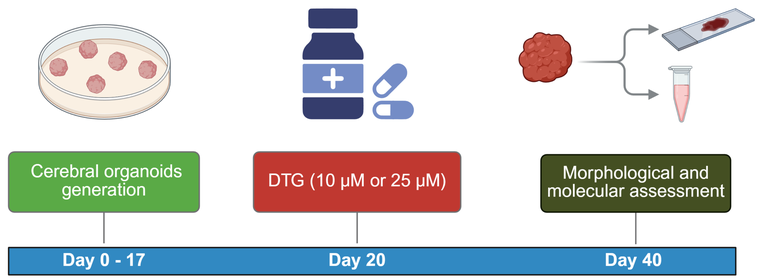
Cerebral Organoid Generation





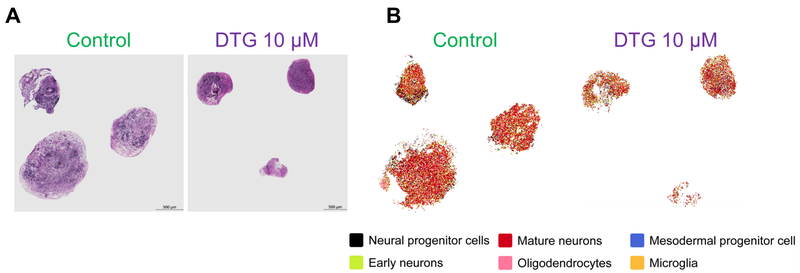
Results

Study Outline

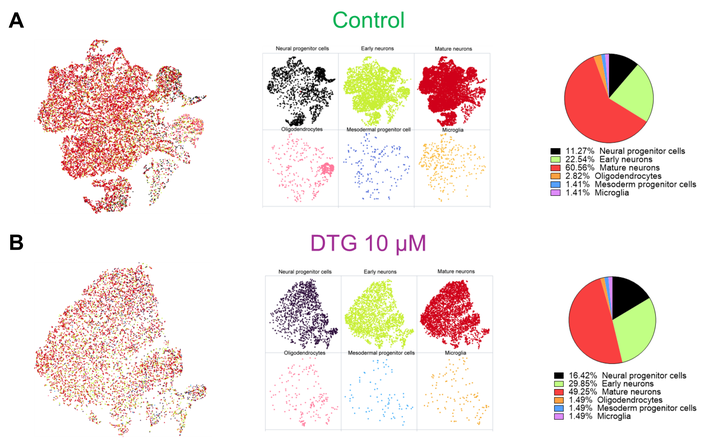


Dolutegravir Impaired Cerebral Organoid Maturation

Spatial Transcriptomic Profiling of Cerebral Organoids

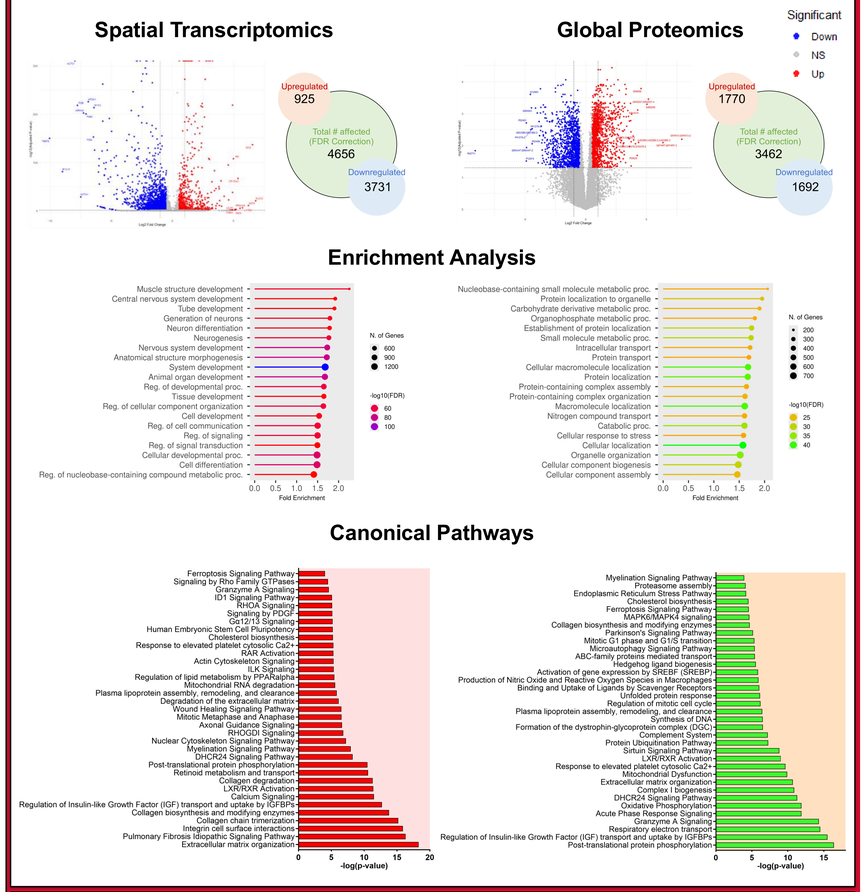


Dolutegravir Restricted Development of Mature Neurons



Transcriptomic and Proteomic Profiling Confirmed Dolutegravir-Associated Impairment in Neuronal Development

DTG Vs Control



Conclusions

- Dolutegravir (DTG) exposure at clinically relevant concentration impaired cerebral organoid maturation.
- DTG exposure caused reduction in mature neurons.
- Spatial transcriptomic and global proteomic profiling confirmed disturbances in gene enriched and canonical pathways critical for neuronal development.
- These proof-of-concept data demonstrate that *in utero* DTG exposure may limit neuronal differentiation and maturation.
- Novel cerebral organoids would enable studying complex co-morbid effects of HIV-1, ARVs, and substance use on fetal neurodevelopmental processes.

References

- Mohan H et al., eBioMedicine, 2023, PMID: 37586112 PMCID: PMC10450420
- Bade AN et al., Mol Neurobiol., 2021, PMID: 34390469 PMCID: PMC8599359
- Ormel, et al. Nature Communications. 2018, PMID: 30301888, PMCID: PMC6177485

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