METABOLIC PERTURBATIONS BY INTEGRASE INHIBITORS IN DIFFERENTIATED HUMAN ADIPOCYTES

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Background

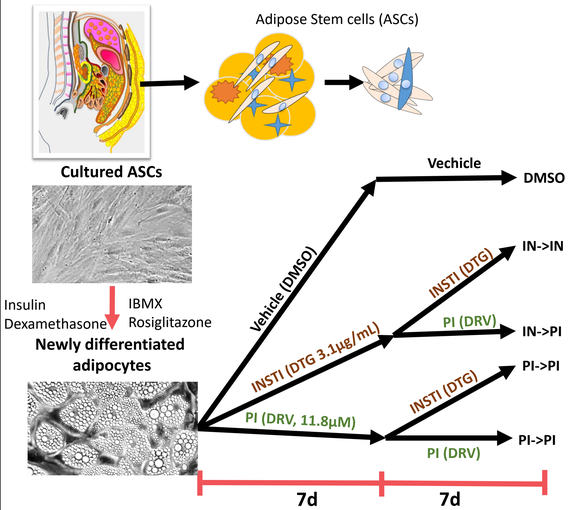
- Both HIV and antiretroviral (ARV) medications have dramatic effects on adipose tissue biology
- Integrase-Strand Transfer Inhibitors (INSTIs) have been implicated in excess weight gain among people living with HIV
- The effects of INSTIs on adipose tissue remain unclear

Objectives

- Examine the effects of INSTIs on aspects of adipose biology related to weight gain
- Determine if switching off INSTIs to other ARVs (protease inhibitors, PI) can reverse these effects

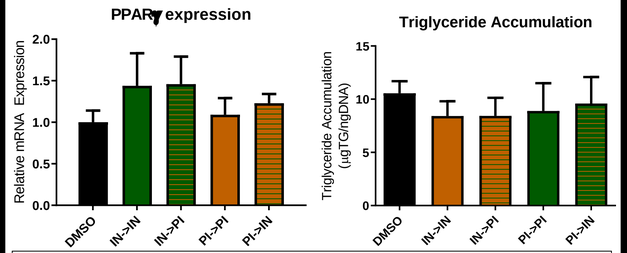
Methods

Culture and treatment of newly differentiated human adipocytes



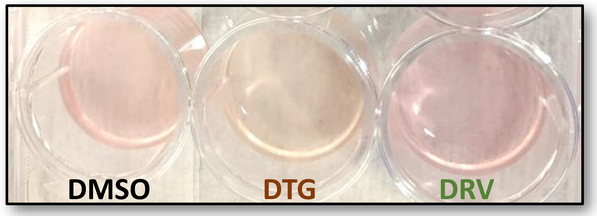
Results

Treatment of newly differentiated adipocytes with ART does not alter markers of adipogenesis

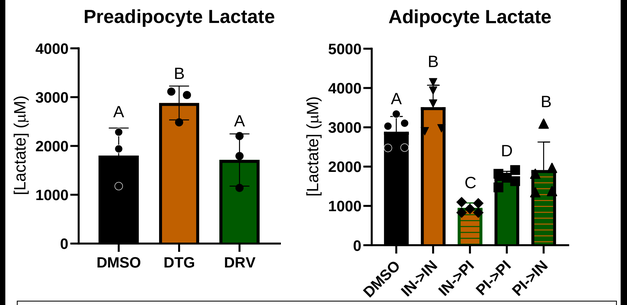


mRNA Expression was determined using qRTPCR and normalized to DMSO; Triglyceride content was determined via enzymatic assay and normalized to DNA content. Data are derived from abdominal subcutaneous ASCs. n=10

Treatment of differentiated adipocytes with Dolutegravir resulted in media acidification



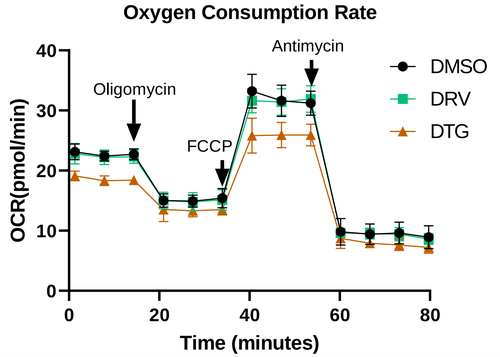
Dolutegravir increases lactate production in both preadipocytes and adipocytes



Lactate was measured using an enzymatic assay from 24 hour media incubations. Different letters indicate significant differences between conditions as determined by repeated measures ANOVA, p<0.05. n=5

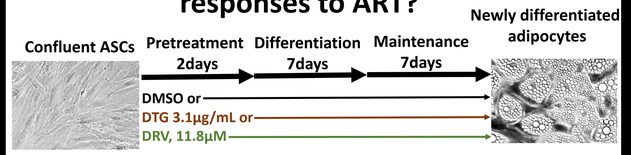
Results

Dolutegravir suppresses basal and maximal respiration rates in preadipocytes

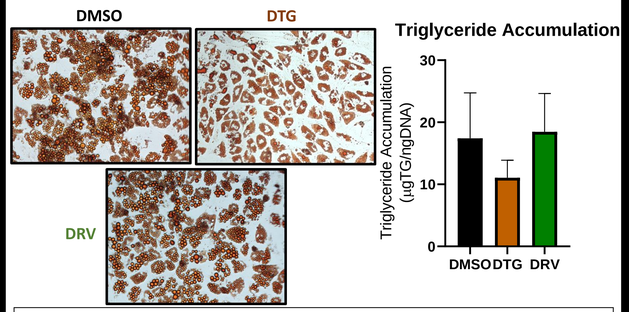


Preadipocytes were cultured in the presence of DMSO, Dolutegravir (DTG), or Darunavir (DRV) for 2 days prior to a Seahorse mitochondrial stress test, n=3

Does exposure during adipogenesis alter responses to ART?



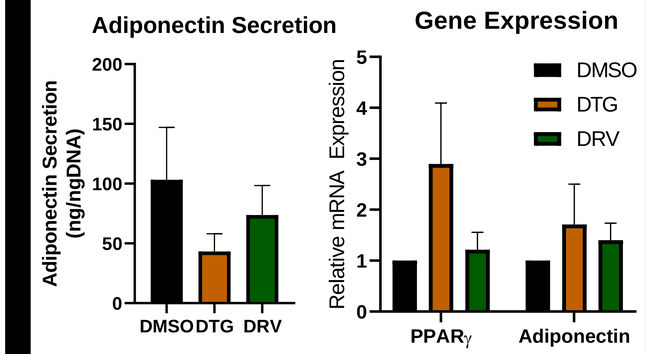
Exposure to Dolutegravir suppresses triglyceride accumulation in newly differentiated adipocytes



Newly differentiated adipocytes were stained with oil red O following long term exposure to vehicle, dolutegravir or darunavir. Triglyceride content was determined via enzymatic assay and normalized to DNA content. n=3

Results

Dolutegravir decreases adiponectin secretion despite changes in gene expression



Adiponectin secretion was determined using ELISAs and normalized to DNA content. mRNA Expression was determined using qRTPCR and normalized to DMSO, n=3

Summary/Conclusions

- INSTI exposure increased lactate production in both preadipocytes and mature adipocytes
- Dolutegravir decreased oxygen consumption of preadipocytes, indicating mitochondrial impairment
- INSTI exposure during differentiation reduced triglyceride accumulation and adiponectin secretion

Alterations in adipocyte metabolism and adipokine secretion may contribute to excess weight gain observed in people living with HIV taking integrase-strand transfer inhibitors

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