HIV integrase inhibitor bictegravir inhibits proliferation, increases apoptosis and mitochondrial damage in PBMCs

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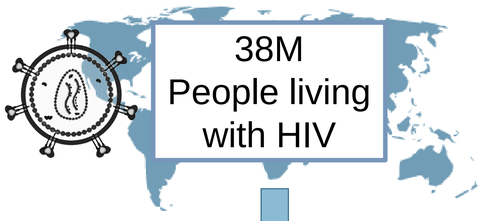
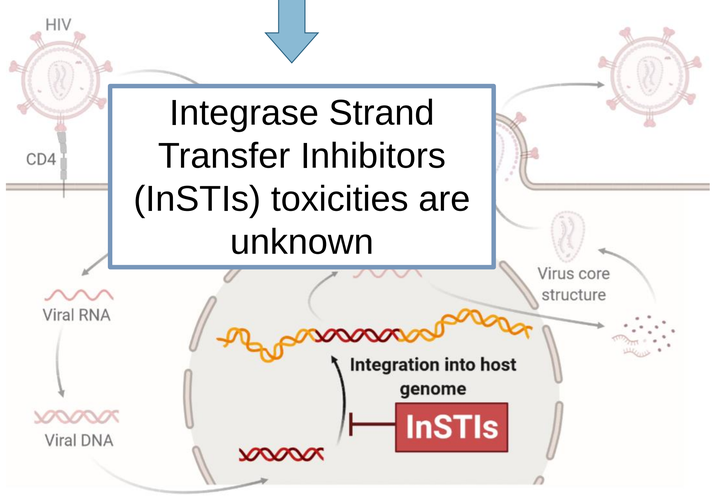
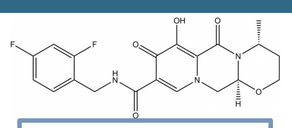
Introduction

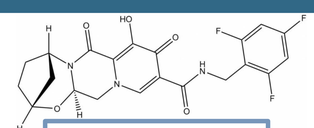


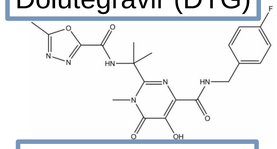
HIV requires lifelong antiretroviral treatment

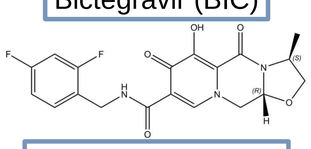


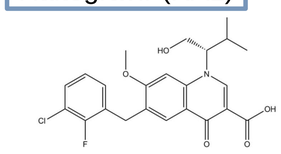
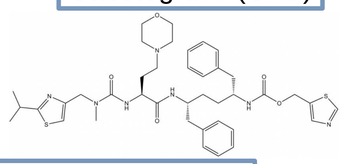
Integrase Strand Transfer Inhibitors (InSTIs) toxicities are unknown


Dolutegravir (DTG)


Bictegravir (BIC)


Raltegravir (RAL)


Cabotegravir (CAB)



Elvitegravir+Cobicistat (EVG/COBI)

? ? ?

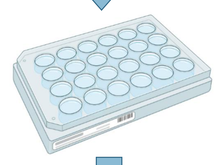

Proliferation | Apoptosis | Mitochondrial health

Aim

Using peripheral mononucleated cells (PBMCs) from healthy donors, characterize the effect of InSTI exposure *ex vivo* on immune cell mitochondrial health, activation, and proliferation

Methods


Isolate PBMCs from healthy volunteers


Drug exposure at pharmacological concentration ($1xC_{max}$) in 0.1% DMSO

6 days


Flow cytometry

1. Mitochondrial mass
2. Mitochondrial intermembrane potential (mt potential)
3. Mitochondrial reactive oxygen species (mt ROS)

4. Apoptosis
5. Proliferation
6. Cell activation
7. Cell differentiation

Results

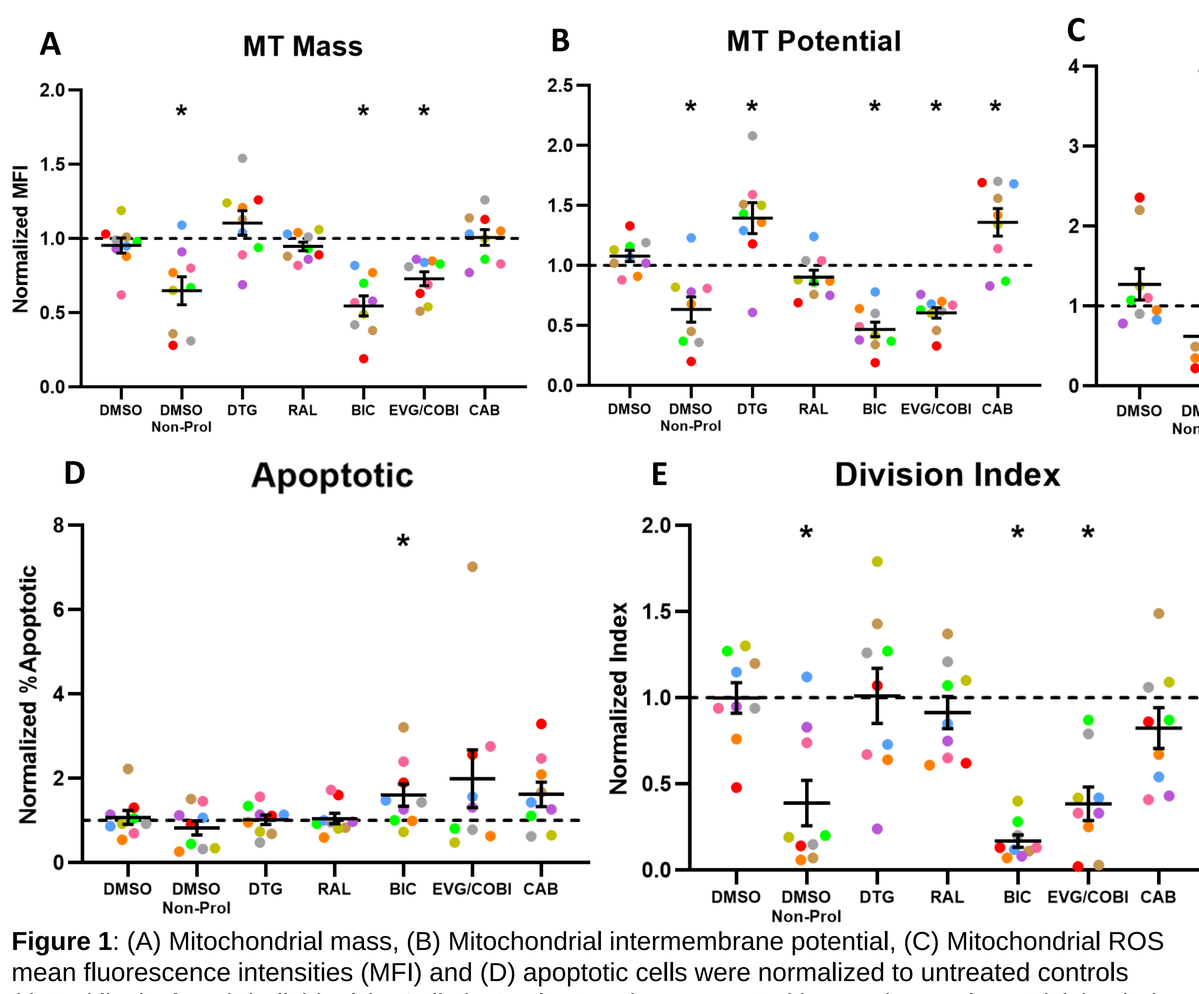


Figure 1: (A) Mitochondrial mass, (B) Mitochondrial intermembrane potential, (C) Mitochondrial ROS mean fluorescence intensities (MFI) and (D) apoptotic cells were normalized to untreated controls (dotted line) of each individual (n=9 distinct volunteers), represented by a unique colour. Division index measured as total divisions/number of cells at day 0. Stars indicate significant difference vs. DMSO using paired t-test.

BIC decreases mt mass, potential and ROS, **increases** apoptosis, and **inhibits** proliferation

CAB and **DTG** **increase** mt potential

EVG/COBI decreases mt potential and proliferation

RAL has **no effect** on any parameters

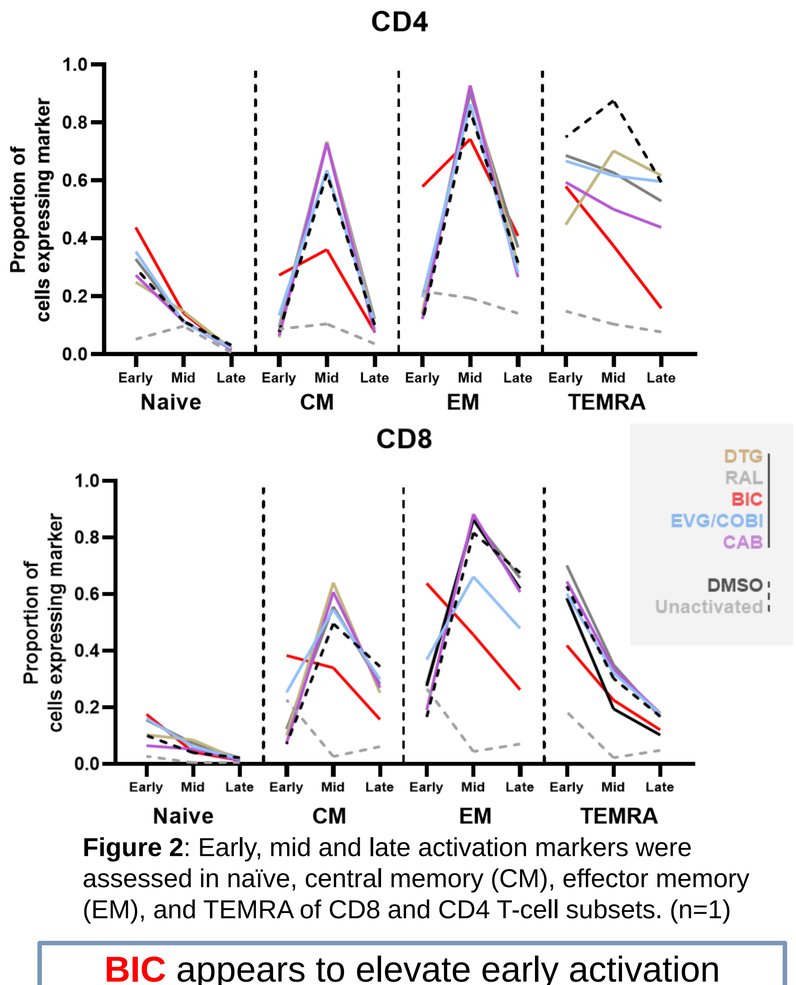


Figure 2: Early, mid and late activation markers were assessed in naïve, central memory (CM), effector memory (EM), and TEMRA of CD8 and CD4 T-cell subsets. (n=1)

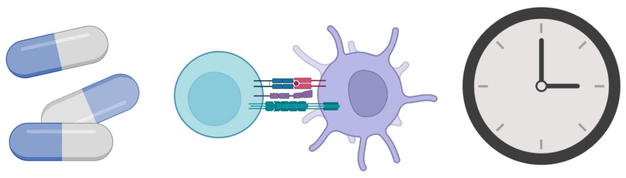
BIC appears to elevate early activation marker and decrease mid and late activation markers in CM and EM compartments

Significance

- HIV treatment is lifelong, and these data clearly show that InSTIs can affect PBMC mitochondria
- The effects of **BIC** *ex vivo* suggest a potential underlying metabolic mechanism which could hinder immune responses
- This highlights the importance of further investigation of InSTIs as they may exert long-term immunological consequences that may not be detected in trials

Future Directions

- Repeat immune activation experiment
- We will perform a 12-day experiment exploring the temporal effects of InSTIs on T-cell activation



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