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Delta-9-Tetrahydrocannabinol:Cannabidiol combination counteracts colonic epithelial and blood-brain barrier dysfunction in SIV-infected rhesus macaques on combination anti-retroviral therapy

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Background: Despite viral suppression by combination anti-retroviral therapy (cART), intestinal and blood-brain barrier (BBB) dysfunction persists, which drives chronic inflammation and HIV/SIV comorbidities. Nevertheless, the specific cell types and the epigenetic mechanisms that drive barrier dysfunction in the cART setting are unclear. Accordingly, we hypothesized that dysregulation of tight junction (TJP) and associated protein expression in the colonic epithelium (CE) and the BBB (striatum) drives barrier dysfunction and supplementation of cART with low-dose delta-9-Tetrahydrocannabinol:Cannabidiol [THC:CBD (1:3)] may reverse barrier dysfunction by reducing inflammation and modulating TJP expression. **Methods:** As a first step, we profiled mRNA (bulk RNA-seq) expression in the striatum and CE of SIV-infected rhesus macaques (RMs) administered vehicle (SIV/cART/VEH; n=7) or delta-9-THC:CBD (SIV/cART/THC:CBD; n=7) compared to control (striatum) RMs or pre-infection (CE) samples. **Results:** Key barrier-associated genes (*Jam3*, *TJP1*, and *TJP2*, in striatum and *IL-18*, *FoxO1*, *FoxO3*, *CLDN23*, *OCLN*, and *TJP1*, in CE) were significantly downregulated in SIV/cART/VEH relative to control RMs. While SIV/cART/THC:CBD RMs upregulated *TGFB1* in both tissues, and *CRYM* in the striatum relative to controls, they showed signficant upregulation of *IL-18*, *FoxO1*, *FoxO3*, *CLDN1*, *CLDN23*, and *TJP1*, in CE relative to SIV/cART/VEH RMs. We are currently performing immunofluorescence, snRNA-seq and snATAC-seq to identify specific cell types in the striatum and CE involved in barrier dysfunction and epigenetic regulation including quantitation of BBB disruption markers. **Conclusions:** Our data suggests that intestinal epithelial and blood-brain barrier dysfunction persists despite effective cART, and low-dose THC:CBD as an adjunct to cART may restore barrier integrity and prevent HIV-associated comorbidities.