Characterization of the Effects of Chronic Marijuana Use and its Routes of Administration on the Brain, Inflammation, Immune Function and Pain in People with HIV Infection

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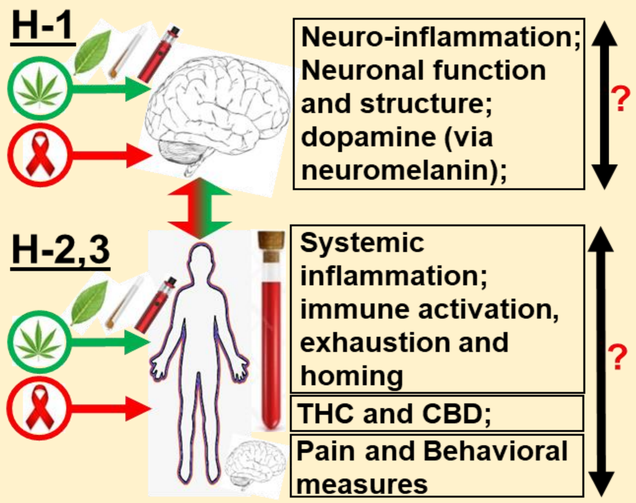
Introduction

Despite the success of antiretroviral therapy (ART) in suppressing HIV and achieving virological control, **chronic-inflammation and immune-activation persist in people living with HIV (PLWH)**. This plays a major role in causing HIV disease progression and **developing non-AIDS comorbidities such as neuropathic pain, anxiety, depression, and cognitive dysfunction**. Varying proportions of **PLWH use medicinal or recreational marijuana (MJ) to alleviate these symptoms**. The effects of MJ and its different routes of administration on the immune system, and brain structure and metabolism have not been investigated fully in PLWH.

Specific Aim

This cross-sectional study aims **to characterize the effects of marijuana (MJ) and its routes of administration** on:

1. The metabolism, morphology, and neural circuits of the whole-brain.
2. Systemic inflammation, and immune-cell phenotypes associated with activation, exhaustion and homing.
3. Pain and behavioral measures in HIV+/HIV- chronic MJ users (MJ+), compared to MJ-non-users (MJ-).



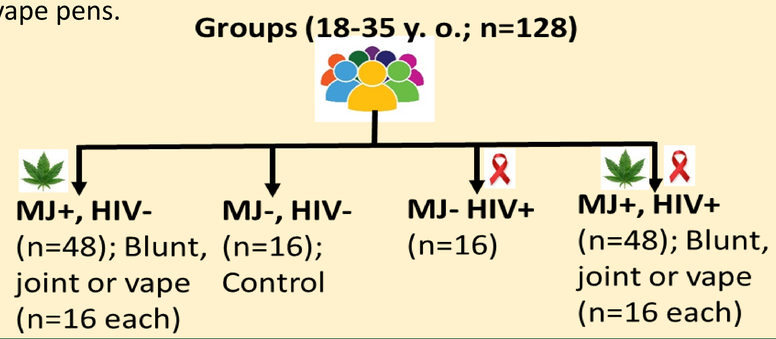
Hypothesis-1: *Chronic MJ use and its routes of administration will alter levels of neuro-inflammation, neuronal function and structure, and dopamine (via neuromelanin MRI as a proxy) in the brain of HIV+/HIV- MJ+ groups.*

Hypothesis-2: *The immunomodulatory effects of MJ+ and its routes of administration will alter the systemic inflammation, and immune-activation, -exhaustion and -homing in HIV+/HIV- MJ+ groups.*

Hypothesis-3: *The extent of alterations in brain imaging markers will associate with blood-based markers, including THC and CBD, pain and behavioral measures in HIV+/HIV- MJ+ groups.*

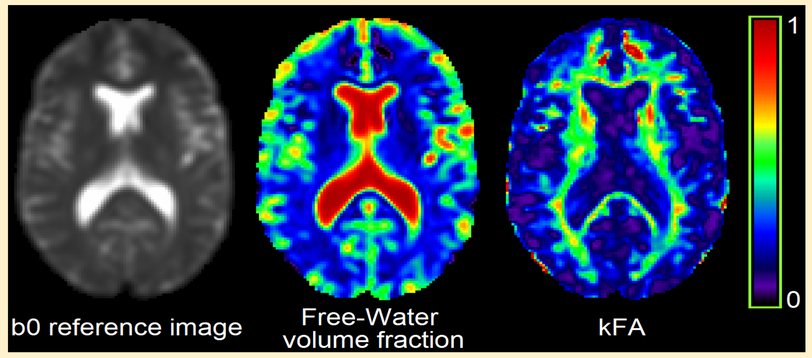
Study Design

A total of 128 subjects will be enrolled into four groups: MJ+HIV+ (n=48), MJ+HIV- (n=48), MJ-HIV+ (n=16) and MJ-HIV- (n=16). MJ users will be equally divided into those who smoke blunts, joints or vape pens.

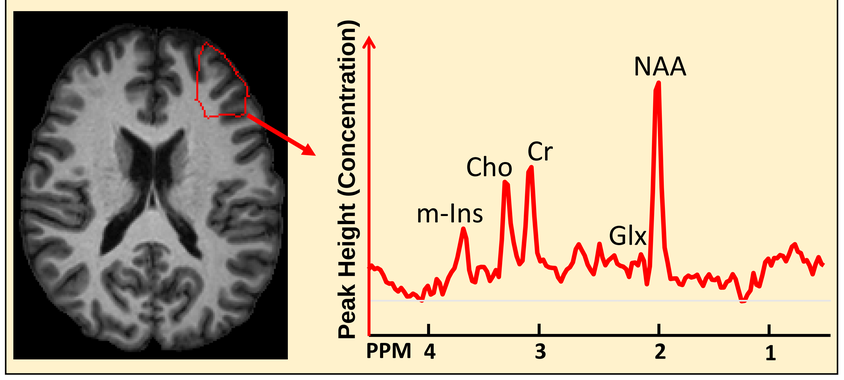


H-1: Neuroimaging

Whole-brain Diffusion Kurtosis Imaging (DKI) with Free-Water Elimination (FWE):[1,2] Unlike diffusion tensor imaging (DTI), DKI metrics have the sensitivity to detect microstructural changes even in gray matter regions within the brain. We propose to use our own FWE-DKI method on 3T MRI data for mapping **neuro-inflammation** (free-water volume fraction, FW) and **neuronal structural integrity** (kurtosis fractional anisotropy, kFA) at the whole-brain.



Whole-brain Short-TE MR Spectroscopic Imaging (MRSI):[3] Our unique whole-brain MRSI method will permit us to find anatomical distributions of markers of **neuro-inflammation** (myo-inositol, m-Ins; primarily due to gliosis of microglia, the primary CNS immune cells) and **neuronal functional viability** (N-acetyl aspartate, NAA).



Neuromelanin-MRI (NM-MRI): Neuromelanin, a product of dopamine oxidization, accumulates in dopaminergic neurons in the substantia nigra (SN), and can be detected using NM-MRI.

H-2: Blood-based Measures

Plasma biomarkers: will be assayed using ELISA or magnetic bead based multiplex platform using FLEXMAP 3D for markers of immune activation, microbial translocation, monocyte activation, vascular adhesion molecules and markers of lung epithelial injury and inflammation. **Biomarkers** include **monocyte activation** (sCD14), **inflammatory cytokines** (IL-6, IL-8, TNF), **neurofilament light** (NFL), **vascular adhesion** molecules (sVCAM, sICAM), soluble **immune activation markers** (TNFRI, TNFRII, CRP, neopterin).[5]

T cell and monocyte phenotypes, immune activation and exhaustion: will be performed using a validated 30 color flow cytometric panel using Cytek aurora. **T cell markers** include the **immune activation** (CD38, HLA-DR) and **checkpoint inhibitory** molecules (PD1, TIGIT, TIM3, LAG3, CTLA4) molecules associated with **lung and tissue homing** (CD49a, CD103, CCR4, CCR5, CCR6, CCR9, CXCR3, CXCR4, CX3CR1), and **brain homing** (CD69, ICAM1, VCAM 1, LFA1, PSGL1) on CD4, CD8 T cells. **Monocyte subsets** include CD14+ (Total monocytes), CD14+CD16- (Classical monocytes), CD14+CD16+CCR2+ (Inflammatory monocytes), CD14+CD16+CCR2- (Nonclassical monocytes).[5,6]

H-3: Pain and Behavioral Measures

Pain Questionnaires: Participants will complete (1) **A Pain History** interview modified from the **International SCI Basic Pain Dataset - v2.0** for descriptive purposes; (2) The **Short-Form McGill Pain Questionnaire-version 2** to assess somatosensory, affective, and evaluative aspects of pain; and (3) The **Neuropathic Pain Symptom Inventory** specifically designed to evaluate neuropathic pain symptom severity to assess severity of common neuropathic pain characteristics.[7]

Behavioral and Other Tests: include **Beck anxiety inventory**, **Beck depression inventory**, **Adverse Childhood Events Perceived Stress Scale-10**, Coping Orientation to Problems Experienced Inventory – Brief, Interpersonal Support Evaluation List Intimate Partner Violence, and Abbreviated Profile of Mood States.

Quantification of Components of Cannabis in Blood (THC and CBD): The primary compounds within cannabis (cannabinoids) that will be measured via blood are THC and metabolites, and CBD.

Current Status

We are waiting to get an IRB approval for starting the study.

Acknowledgement

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