Title: Pain Inflammation and Cannabis in HIV

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1) Background and Significance

1. A. Specific Aims

There is an explosive increase in medical cannabis use in the United States (US).[1] Medical cannabis is legal in 37 states, and severe pain and HIV are qualifying conditions in most states.[1] In New York (NY), all medical cannabis products have precise dosing of its two main active components, THC and CBD.[2,3] Medical cannabis products in NY are oil-based (e.g., soft-gel capsules), making dosing and titration easily measurable. Thus, NY offers a unique opportunity to conduct studies to study how medical cannabis use affects pain in PLWH.

PLWH have a high burden of pain,[4-11] and most commonly experience neuropathic pain.[12,13] The etiology of neuropathic pain in PLWH is complex. It is related to persistent systemic inflammation from HIV infection regardless of VL suppression,[14] with increased pro-inflammatory cytokines (TNFα, IL-6) and decreased anti-inflammatory cytokines (IL-4, IL10).[15] These same cytokines are related to psychological symptoms in PLWH, which are deeply interrelated with neuropathic pain.[16-21] Neuropathic pain is associated with poor HIV outcomes, including poor antiretroviral (ARV) adherence,[22] virologic failure,[23] and poor retention in care.[10,23] Despite this, little is known about its optimal management.[12] Current treatment modalities for neuropathic pain in PLWH carry many associated risks, prompting investigations into novel therapies, such as medical cannabis.[12]

In two randomized trials of PLWH, cannabis reduced neuropathic pain more than placebo.[24,25] While existing studies are informative,[24,25] **critical gaps remain in our understanding of how cannabis alleviates neuropathic pain in PLWH.** Studies have not evaluated how different THC/CBD content impacts pain and have not used products comparable to available medical cannabis products.[26] Additionally, studies in PLWH had short follow up time (5-12 days) and no longitudinal outcomes. The mechanism of cannabis's analgesia in PLWH with neuropathic pain remains unknown. No studies have examined how cannabis interacts with the complex relationship of psychological symptoms, inflammation, and neuropathic pain in PLWH.

The benefits of cannabis may be offset by its adverse events.[27] Cannabis is linked to psychological symptoms including anxiety, depression,[28] and psychotic symptoms.[29] In some studies, cannabis use is associated with poor ARV adherence and virologic failure;[30] in others, this is not the case.[31] No studies have examined how THC/CBD content contributes to adverse events (psychological symptoms, poor ARV adherence, and virologic failure).

Our overarching goal is to test how medical cannabis use affects neuropathic pain, with particular attention to THC/CBD content and adverse events. We propose an observational cohort study of 100 PLWH with (a) neuropathic pain, (b) active certification for medical cannabis, and (c) intent of being dispensed soft-gel capsule products at a medical cannabis dispensary (including high THC: low CBD product and high CBD:low THC product). Over 14 weeks, participants will have 2 in-person visits and 15 phone-based questionnaires (one at baseline, and every week for 14 weeks). Data sources will be blood and urine samples, questionnaires, and medical and pharmacy records. The primary independent variable will be the type of soft-gel capsule product. The secondary independent variable will be reported cumulative THC and CBD dose. The primary outcome will be self-reported pain severity.[32] Secondary outcomes will be pro-inflammatory cytokines (TNFα, IL-6), anti-inflammatory cytokines (IL-4, IL-10),[15] psychological symptoms (symptoms of depression,[33] anxiety,[34] and psychosis[35]), ARV adherence, and VL. Among PLWH with neuropathic pain, we will:

Aim 1: Examine how medical cannabis use affects self-reported pain. *H1:* The effect of medical cannabis use on self-reported pain-severity will differ by THC/CBD content.

Aim 2: Examine how medical cannabis use affects pro- and anti-inflammatory cytokines. *H2:* Medical cannabis that has higher THC content will have greater reduction in pro-inflammatory cytokines (TNFα, IL-6). *H3:* Medical cannabis that has higher CBD content will have greater increase in anti-inflammatory cytokines (IL-4, IL-10).

Aim 3: Examine how medical cannabis use affects adverse events. *H4:* Participants who use high THC (vs. high CBD) cannabis products will have more psychological symptoms, poorer ARV adherence, and less suppressed VL.
Aim 4: Explore mechanisms by which medical cannabis promotes analgesia. Using a pooled analysis of reported cumulative THC and CBD dose we will explore how THC/CBD content, inflammatory cytokines and psychological symptoms relate to cannabis and analgesia. *H5:* Different doses of THC and CBD will have differing effects on inflammatory cytokines, psychological symptoms, and ultimately analgesia.
Findings will provide key data that will be integral to the care of PLWH.

1.B. Significance

PLWH have a high burden of pain, especially neuropathic pain. Pain is prevalent in 39 to 85% of PLWH.[1-8] It is often due to neuropathy,[9,10] which is a common complication of HIV infection and its treatment. Neuropathic pain occurs in up to 57% of ambulatory PLWH, of which the vast majority (40-90%) experience painful neuropathy.[11-13] It is associated with significant disability and poor HIV outcomes, including functional impairment, reduced quality of life, poor ARV adherence, virologic failure, and poor retention in care.[14-18]

The etiology of neuropathic pain in PLWH is complex. Neuropathic pain in PLWH was traditionally thought to be related to direct toxic effects from early ARV regimens.[19] However, neuropathic pain remains prevalent despite phasing out of these ARVs.[13,20] It is now understood that peripheral neurons experience inflammation indirectly through HIV-infected monocyte-macrophage lineage cells.[19] Infected cells excrete pro-inflammatory cytokines (TNFα, IL-6)[21] and down-regulate anti-inflammatory cytokines (IL-4 and IL-10), leading to astrocyte activation in the spinal dorsal horn.[22-24] This pro-inflammatory state persists despite VL suppression, resulting in neuronal injury, peripheral nerve cell apoptosis, neurodegeneration, and pain.[19,25]

Neuropathic pain, psychological symptoms and HIV are tightly interrelated. Psychological symptoms, including depression and anxiety, are commonly experienced by PLWH and are associated with neuropathic pain.[26] Further, symptoms of depression and anxiety are associated with increased pro-inflammatory (TNFα, IL-6) and decreased anti-inflammatory (IL-4,IL-10) cytokines.[27] Dr. Jessica Merlin (Advisor) described the complex relationship of the biological, psychological, and social factors that lead to chronic pain in PLWH in the adapted Biopsychosocial framework (BPS) (Figure 1).[26]

Neuropathic pain is difficult to manage in PLWH. Studies of serotonin reuptake inhibitors, anti-epileptics, topical analgesics, HIV entry inhibitors, and anti-arrhythmics for the relief of neuropathic pain in PLWH show no efficacy.[28-35] Subsequently, neuropathic pain is frequently managed with opioids, despite a high potential for misuse and use disorder.[36] PLWH are more likely to receive opioids for pain than those without HIV.[37-41] With the opioid epidemic and lack of evidence for chronic opioids for pain management, national guidelines for the treatment of pain in PLWH recommend medical cannabis and other non-opioid therapies.[9] *PLWH are seeking medical cannabis, yet little evidence is available to guide clinical decision-making. Studies are needed to examine mechanisms, risks, and benefits of medical cannabis in PLWH.*

Medical cannabis legalization is rapidly expanding. Medical cannabis is legal in 37 states and recreational cannabis in 18 states.[42] Acceptance of the therapeutic use of cannabis continues to grow, with increasing state and local legislative action.[43] Despite this, cannabis remains heavily restricted at the federal level. Federally, cannabis is classified as a Schedule 1 substance with "no currently accepted medical use and a high potential for abuse."[44] This classification, which includes substances like heroin, has important research

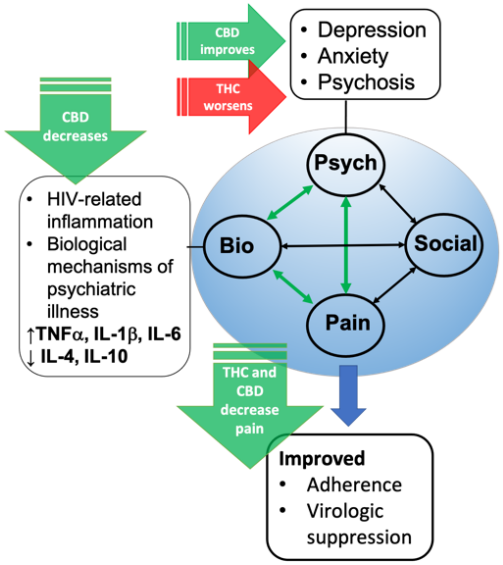

Figure 1. Adapted Biopsychosocial framework for neuropathic pain in HIV and how it can be interrupted by THC and CBD

implications. Currently, only two entities can produce and supply cannabis to US researchers.[45] Cannabis products available for research are limited in scope and not comparable to products available in dispensaries.[46] Along with barriers to obtaining medical cannabis, *federal regulations require directly observed use of research cannabis products in settings such as human labs. Thus, clinical trials of medical cannabis for chronic pain with research cannabis provided by the federal government are infeasible.* Consequently, in the US, over the past 30 years, only two short term (5-12 days) RCTs in human labs have tested the effect of cannabis on neuropathic pain in PLWH.[47,48]

Medical cannabis policy in New York. In 2016, NY's Medical Marijuana Program (NYMMP) was implemented.[49] To be certified for medical cannabis, individuals must meet qualifying conditions, which include neuropathy, severe or chronic pain, and HIV. Medical cannabis products must be purchased from a state-licensed dispensary, which reports dispensed products, including milligrams of THC and CBD content and route of administration, to the NY Prescription Monitoring Program (PMP).[49] All products are oil extracts and are tested by the NY State Department of Health's lab to confirm content. *Because the precise THC/CBD content is reliable and known in NY's medical cannabis products, we have a unique opportunity to rigorously examine how medical cannabis affects neuropathic pain in PLWH*.

As of December 2020, over 3000 physicians and 130,000 patients are registered with the NYMMP.[50] Of patients, 75% have chronic or severe pain.[49] In the Montefiore Medical Cannabis Program (in which I am a provider), approximately 25% certified for medical cannabis are PLWH.

The mechanism of cannabis' analgesia in PLWH is complex. Cannabis acts at several different points of the BPS framework of neuropathic pain (Figure 1). THC and CBD act through two main receptors: CB1 and CB2. CB1 is primarily in the brain and spinal cord, and CB2 is mainly on macrophages and macrophage-derived cells that are part of the immune system and inflammatory response. Both THC and CBD act on these receptors but in different ways.[51]

THC achieves analgesic, anti-inflammatory, and muscle-relaxant effects through partial agonist action at CB1 and CB2.[52] Psychoactive symptoms (anxiety, memory suppression) occur though THC's binding to CB1.[53] CBD weakly binds to CB1 and CB2, and has anti-inflammatory, anti-spasmodic, and analgesic effects in animal models.[53-56] When CBD is used with THC, other receptors are activated to regulate pain perception.[53]

CBD may reduce pain by reducing psychological symptoms. Neuropathic pain is associated with anxiety and depression.[57] Preclinical and clinical studies report reduced anxiety with CBD.[58-61] However, it is not known if anxiety improves or worsens when CBD is taken with THC. In cohort studies of street cannabis use, cannabis caused increased depression, but it is unknown how THC and CBD contribute to this.[62,63]

Clinical studies evaluating how cannabis affects inflammatory cytokines in PLWH are limited. In one study heavy THC consumption decreased TNFα and IL-6 and increased anti-inflammatory cytokines.[64] In another study, high THC cannabis use was associated with reduced pro-inflammatory cytokines.[65] In mouse models, CBD leads to less TNFα and IL-6 and more IL-4;[66] THC reduces TNFα and IL-6.[67] These findings have not been replicated in humans. It is not clear yet how these changes in inflammatory cytokines differ between THC and CBD, and how they are related to the experience of pain.

Only two RCTs have studied cannabis's effect on neuropathic pain in PLWH.[47,48] In both, high THC products administered in human labs over 5-12 days had greater pain reduction than placebo.[47,48] In an ongoing qualitative study that I am leading (G.1.), pain relief from medical cannabis fell into one of two categories: 1) improved tolerability of pain, and 2) elimination of pain and other symptoms (e.g. swelling). These preliminary findings suggest differing mechanisms of pain relief. We will examine how pain defers in PLWH using high THC vs high CBD medical cannabis and the mechanism by which it does so.

Medical cannabis may cause adverse effects in PLWH. Though cannabis relieves neuropathic pain, this benefit may be offset by its potential adverse events. Cannabis may affect psychological symptoms such as anxiety, depression, and psychosis. Studies evaluating the impact of cannabis on psychological symptoms in PLWH are limited. Most studies were in adolescents and young adults using street cannabis.[46,62] In these, cannabis use was associated with depression, anxiety, and early onset psychosis.[62,63] It is likely that these findings are representative of the effects of high THC cannabis because street cannabis is generally high THC.[46] Pre-clinical and clinical trials evaluating CBD for the management of anxiety report reduced anxiety.[58-61] Psychosis from CBD has not been extensively studied; it has not been implicated in psychotic symptoms.[68] In two RCTs, THC and CBD together led to reduced psychotic symptoms compared with THC alone.[69,70]

Cannabis use may lead to worse HIV outcomes, but findings are mixed. Cannabis use is associated with improved, worsened, and no change in VL suppression. [71-73] Cannabis use is associated with improved, worsened, and no change in ARV adherence.[72,74-81] In all of these studies, street cannabis use was examined rather than medical cannabis. *To our knowledge, no studies have examined how medical cannabis affects HIV outcomes. In the setting of rapidly increasing medical cannabis acceptance, it is critical to understand how cannabis affects HIV outcomes and psychological symptoms in PLWH.*

Summary: Neuropathic pain in PLWH is common and difficult to manage. Medical cannabis is an emerging new treatment, but gaps remain in our knowledge about its efficacy, mechanism, and effect on adverse events. To better understand how medical cannabis affects neuropathic pain in PLWH, we propose an observational cohort study to examine how medical cannabis affects pain, inflammation, and adverse events.

2) Study Design

2. A. Overview of study design: Our goal is to understand how medical cannabis affects self-reported pain, with attention to THC/CBD content, markers of inflammation, and adverse events. We will conduct an observational cohort study of 100 PLWH with neuropathic pain, active medical cannabis certification, and intent to use newly dispensed soft-gel capsule product from a medical cannabis dispensary. At baseline and over the following 14 weeks, participants will have 2 in-person visits and 14 web-based weekly questionnaires. Data sources will include questionnaires, medical

Table 4. Eligibility Criteria

Criterion	Source
Inclusion Criteria	
≥18 years old	SQ
Diagnosis of HIV	MR
Fluency in English	SQ
Active certification for medical cannabis	MR
No medical cannabis dispensed in 60 days or used within the previous 30 days	PR SQ
Intends to have new soft-gel capsule product dispensed at Vireo	MR PR
ICD-10 diagnosis code for neuropathic pain, OR Neuropathic pain in problem list of electronic medical record, OR Neuropathic pain per medical cannabis certification form, OR Neuropathic Pain Questionnaire- Short Form >0	MR MR MR SQ
Exclusion Criteria	
Inability to provide informed consent	SQ
Inability to complete 14 wks of study visits	SQ
Medical cannabis use within 30 days prior to enrollment	PR
Unique pain symptoms (e.g., multiple sclerosis, rheumatoid arthritis)	MR
Terminal illness	MR
Current or prior psychotic disorder	SQ
Unregulated cannabis, opioid, cocaine, or benzodiazepine use in the past 30 d	SQ, U

Dispensed opioids or benzodiazepines within 60 d	PR
Non-steroidal anti-inflammatory use within 7 d prior to enrollment	SQ, PR
Steroid use within the past 14 d with duration of therapy ≥21 d	SQ, MR
COVID vaccination or booster within 14 days of screening	SQ, MR
SQ=screening questionnaire, MR= medical record, PR=pharmacy records or PMP, TQ=telephone questionnaire; U=urine sample	

records, pharmacy records, and blood and urine samples (see Table 8). Our primary independent variable will be the initial soft-gel product obtained from the medical cannabis dispensary, and our primary outcome will be self-reported pain severity using the Brief Pain Inventory severity subscale.

2.A. Settings: *Montefiore Health System (Montefiore)* is the largest healthcare system in the Bronx, NY with 11 hospitals and over 200 community clinics. Directed by Dr. Arnsten (Primary Mentor), the Montefiore Medical Cannabis Program includes 2500 patients certified by 25 physicians; approximately 25% of patients are PLWH. *Vireo* is a medical cannabis company with dispensaries in 11 states; two dispensaries are located in the NYC area. As of August 2020, in NY, Vireo served over 30,000 unique patients. Vireo staff will refer potential participants to the study and facilitate study retention; recruitment will occur at dispensaries.

2.C. Research visits and data collection.

Eligibility criteria. *Inclusion criteria* are: 1) ≥18 years old; 2) diagnosis of HIV 3) fluency in English; 4) actively certified for medical cannabis (medical records); 5) no medical cannabis dispensed in 60 days or used within the previous 30 days; 6) intent to have new soft-gel capsule product dispensed at Vireo (PMP or medical record); 7) ICD-10 diagnosis code for neuropathic pain, OR neuropathic pain in problem list of electronic medical record, OR neuropathic pain per medical cannabis certification form, OR Neuropathic Pain Questionnaire Short Form >0. *Exclusion criteria* are:1) inability to provide informed consent; 2) inability to complete 14 weeks of study visit; 3) medical cannabis use within 30 days prior to enrollment; 4) unique pain symptoms (e.g. multiple sclerosis, rheumatoid arthritis); 5) terminal illness; 6) current or prior psychotic disorder; 7) unregulated cannabis, opioid, cocaine, or benzodiazepine use in the past 30 days (self-report and urine drug screen); 8) dispensed opioids or benzodiazepines within 60 days of enrollment; 9) non-steroidal anti-inflammatory (NSAID) use within 7 days prior to enrollment; 10) steroid use within the past 14 days with duration of therapy >21 days; 11) COVID vaccination within 14 days of screening.

Individuals who do not qualify for the study due to exclusion criteria #3, 7, or 9, can choose to cease medical cannabis for a 30-day wash-out period (confirm with self-report, PMP and urine drug screen); cease unregulated cannabis, cocaine, opioid, or benzodiazepine use for 30 days (confirmed with self-report and urine drug screen); and/or cease NSAID use for 7 days (self-report). Once they have done this, they can screen for the study again and may be eligible.

Recruitment will occur via Vireo and Montefiore staff referrals. Letters can also be mailed to potential participants in which information will be provided about the study. Flyers will be posted at Vireo dispensary facilities as well as online. We will recruit 3-4 participants per month for 36 months (total sample size of 100). Recruitment will be feasible, as Vireo has over 100 new patients per month. Also, we will utilize the CFAR database to assist with recruitment for this study.

Screening will occur by phone after obtaining oral informed consent. The screening questionnaire will include some questions related to eligibility criteria and others unrelated to eligibility criteria. We will obtain oral consent to review patient's PMP at the same time that we conduct the screening questionnaire. We will schedule eligible participants for a baseline visit and written informed consent will be obtained. In-person screening will occur at Montefiore and Einstein.

Participant tracking. My mentors have extensive experience following populations in studies with follow-up rates of 84%-86% over 6-12 months. At all visits, we will record: 1) participants' address and phone numbers; 2) contact information of family or friends; and 3) locations where participants work or "hang out."

Aim	Construct	Measure	Source
Main independent variable			
Aims 1-4	Medical cannabis use	Initial soft-gel capsule dispensed at Vireo Certification for medical cannabis (date, doctor, conditions) All medical cannabis products dispensed (date, product, dose, amount dispensed) Self-reported medical and unregulated cannabis use (product, # of days used, route, dollar amount of unregulated cannabis purchased, ASI)	PR MR PR TQ
Primary outcome variables			
Aims 1, 4	Pain Severity	Brief Pain Inventory (BPI) Severity subscale[90]	TQ
Secondary outcome variable			
Aims 2, 4	Inflammatory cytokines	Pro-inflammatory cytokines (TNFα, IL-6) Anti-inflammatory cytokines (IL-4, IL-10)	B B
Aims 3, 4	Adverse events	VL, CD4 count AIDS Clinical Trial Group (ACTG Adherence)[93], Visual Analog Scale (VAS)[94] ARVs dispensed Depression (Center for Epidemiological Studies-Depression Scale [CES-D])), Generalized Anxiety Disorder (GAD-7)[96]	B IQ PR IQ
Other measures			
Aims 1-4	Sociodemographics	Age, race/ethnicity, education, insurance, sex, gender	IQ
Aims 1-4	Pain characteristics	Brief Pain Inventory (BPI) Interference subscale[90] Pain catastrophizing scale[98], Pain DETECT questionnaire[84]	IQ IQ
Aims 1-4	Pain treatment	Pain treatment (SSRIs, gabapentin, injections, physical therapy)	IQ/MR/PR
Aim 3	Substance use/disorder	Smoking (Fagerstrom test for nicotine dependence)[99], Alcohol Use Disorders Identification Test (AUDIT)[100], ASI[97]	IQ
Aim 3	HIV Risk Behaviors	HIV risk behaviors (HIV Risk-taking Behavior Scale[101-103])	IQ
Aims 3, 4	Psychiatric symptoms	PTSD Checklist (PCL),[104] Insomnia severity index,[105]	IQ
Aims 1, 3, 4	Quality of Life	Roland Morris Disability Questionnaire[106], Patient Reported Outcomes Quality of Life-HIV (PROQOL-HIV)[107]	IQ
Aims 1-4	Medical comorbidities	Comorbidities (obesity, cardiovascular disease, diabetes)	MR
Aims 1-4	Side effect vs benefit	Treatment Satisfaction Questionnaire for Medication (TSQM-9)[91]	TQ
Aims 1-4	Urine cannabinoid	Urine GCMS for cannabinoids	

B=blood test; MR=Medical records; PR=Pharmacy records or Prescription Monitoring Program; IQ= in-person questionnaire; TQ=phone questionnaire; SSRI=selective serotonin reuptake inhibitor; TQ measures occur every week; IQ occurs at 0 and 14 weeks. B occurs at 0 at 14 weeks.

In-person visits: Participant's 2 in-person visits will occur in private rooms at the Montefiore/Einstein ICTR Clinical Research Center. At the baseline visit, study staff will describe the study and obtain written informed consent. Tracking forms as well as agreements to release medical, pharmacy, and PMP records will be completed. Participants will receive a refillable debit card for compensation. At all in-person visits, we will administer questionnaires, and collect blood and urine samples. Participants will receive $27.50 for each in-person visit.

Phone or web visits will occur weekly over 14 weeks and include brief (5-7 minute) questionnaires administered by study staff over the phone or completed on-line. A total of 15 visits will occur, the first at baseline, when participants can be trained on how to complete it, and then one at the end of each week of the follow-up period. Participants will receive $3 on debit cards after completing each phone or web-based questionnaire.

Blood draws will occur at week 0 and 14 in-person visits. They will measure VL, CD4 count, pro- and anti-inflammatory cytokines. Participants will be compensated an additional $15 for each visit in which there is a blood draw.

Main independent variable will be the soft gel capsule product dispensed at Vireo, including a 1) high THC capsule, or 2) high CBD capsule. Other key independent variables will be cumulative THC and CBD taken (weeks 3-14, continuous measures).

Main outcome variables: Our primary outcome is pain severity, measured via the BPI severity scale (ordinal variable), as recommended by a committee of international pain experts.[92] It is an 11-point (0-10) numerical rating scale of pain intensity, where 0 is 'No pain' and 10 is 'Pain as

bad as you can imagine'. Participants will complete the BPI severity scale in each phone visit (baseline and at each weekly visit).

Pro- (TNFα, IL-1β, IL-6) and *anti- (*IL-4, IL-10) *inflammatory cytokines (secondary outcomes; 0, 14 week blood draws)* will be measured with Luminex assay and reported as picograms per mm^3 (continuous measure).

Adverse events (secondary outcomes) will be ARV adherence (AIDS Clinical Trial Group [ACTG] Adherence Interview,[93,108] Adherence Visual Analog Scale [VAS; weekly]);[94] VL suppression (blood draws at 0, 14 weeks; copies/mL); and psychological symptoms—depression (CES-D; 0 and 14 weeks),[95] anxiety (GAD-7; 0 and 14 weeks),[9694,97,109]

Other key outcome variables will be alternative pain measures (painDETECT,[84] pain catastrophizing[98]).

Other measures that have strong associations with medical cannabis use or neurologic pain will be measured, including biological sex, substance use, quality of life, HIV risk behaviors, symptoms of post-traumatic stress disorder (PTSD), insomnia and medical comorbidities (Table 8).

3) Study Population

3.A. Sample size and power determination. For our primary analysis (Aim 1), we based our power analysis on proportion of participants with clinically significant change in BPI pain severity scale (30% reduction) in each condition.[8,48] We will recruit 100 participants in total; we anticipate that approximately 50 will use high THC soft gel capsules and 50 will use high CBD soft gel capsules. Conservatively assuming 15% attrition in each arm, 42 participants will be in each arm. Because the individual-level intra-class correlation coefficient (ICC) associated with change in pain severity over time is unknown, we conducted simulation studies with varying ICC values, i.e., 0.2, 0.3, and 0.4. We present power calculations for pain severity in Table 9. Based on prior studies,[47,48] we predict that 40% of those using high THC capsules will experience clinically significant reduction in pain and 20% of those using high CBD capsules will experience clinically significant reduction in pain.[110] We will have 84% power at a significance level of 5% (two-tailed test) to detect a 20% difference in proportion of participants who achieve clinically significant reduction in pain during the follow-up period between high THC soft-gel capsules (40%) and high CBD (20%) soft gel capsules. We will have greater power to detect a larger difference or when ICC is lower.

Table 9. Power calculation for Aim 1

	High THC capsules	High CBD capsules	Power
ICC=0.2	40%	15%	>0.99
ICC=0.3	40%	15%	0.99
ICC=0.4	40%	15%	0.96
ICC=0.2	40%	20%	0.97
ICC=0.3	40%	20%	0.91
ICC=0.4	40%	20%	0.84

For analyses with continuous dependent variables (Aim 2-3), a sample size of 42 participants/arm will allow us to have >90% power to detect a moderate effect size (i.e., Cohen's d=0.5) under a more stringent condition (ICC=0.4). We will have greater power when the effect size is larger or when ICC is lower.

3.B. Eligibility criteria are described in Table 4. There are no eligibility restrictions based on gender, race or ethnicity. The study population is expected to reflect the racial and ethnic composition of PLWH receiving medical cannabis in the Bronx, NY. We estimate participants' characteristics based on the characteristics of patients receiving care in the collaborating medical cannabis dispensaries and having been certified at Montefiore. Taken together, characteristics from these sites are approximately: 60% men, 15% Hispanic, 40% non-Hispanic white, 30% non-Hispanic black, 13% non-Hispanic Asian, and 2% non-Hispanic other race. Thus, we expect to enroll the following participants: 40 women, 60 men; 15 Hispanic, 85 non-Hispanic; 40 non-Hispanic white, 30 non-Hispanic black, 13 non-Hispanic Asian, 2 non-Hispanic other race (see Targeted/Planned Enrollment Table).

Justification for the exclusion of minors.

We will not include children under the age of 18 in our study population because: a) neuropathic pain in PLWH is much more common among adults, and b) the vast majority of providers at Montefiore who certify patients for medical cannabis use provide care only for adult patients. We expect that the age range of participants will be similar to that of patients certified for medical cannabis at Montefiore. Taken together, the median age of patients seen for medical cannabis visits was 51 years, and ranges from 19 years to 94 years. This correlates well with the population of PLWH in the US, in which more than 40% are 50 years old or over[1]

3.C. Data sources: *Questionnaires:* At in-person research visits, research staff will administer questionnaires using Audio Computer-Assisted Self Interview (ACASI) technology; participants will enter responses directly onto computers. During phone visits, study staff will administer questionnaires and enter answers directly into the computer. Questionnaires will focus on pain, dose of THC and CBD in medical cannabis taken, psychological symptoms, and ARV adherence (Table 3).

Medical record data will be extracted 6 months prior to enrollment through 14 weeks after enrollment, including medical cannabis certification forms, prescriptions, and notes regarding pain treatment (nerve blocks, physical therapy, occupational therapy).

Pharmacy and PMP records will be extracted for medications dispensed 6 months prior to enrollment to 14 weeks after enrollment. Data will include ARVs, controlled substances (e.g., dispensed medical cannabis products, THC and CBD content in milligrams, doses dispensed) and pain medications (i.e., anticonvulsant, selective serotonin reuptake inhibitor, topical lidocaine).

Blood draws: Approximately 15 ml of blood will be drawn to assess VL, CD4 count, pro-inflammatory and anti-inflammatory cytokines. *VL and CD4 count* will be processed through Montefiore's central lab. VL will be quantified using the Abbott RealTime HIV-1 Viral Load assay (Abbott Park, Illinois), and CD4 count will be measured by the BD Multitest (BD Biosciences, San Jose). *Pro-* (TNFα, IL-6) and *anti-* (IL-4, IL-10) *inflammatory cytokines* will be analyzed using the Olink cytokine assay (Thermo Fisher Scientific, Waltham, MA) at Mount Sinai's Human Immune Monitoring Center.

Urine samples: We will check urine drug screens to confirm that patients are taking medical cannabis and to confirm that they abstain from opioid use during the course of the study.

4) Recruitment

4.A. Recruitment will occur from Montefiore's Medical Cannabis Program in which 25 patients are certified per month. Of those, approximately 6 are PLWH. In June 2020, Dr. Slawek expanded the program to include Montefiore's HIV clinic, where 2500 PLWH receive care. With this expansion, at least 20 PLWH per month are certified for medical cannabis, and an overwhelming majority have pain. We will also leverage the clinical core of the ERC-CFAR to identify and recruit PLWH with neuropathic pain. Through these targeted clinical activities, we anticipate that enrolling 100 PLWH over 36 months (3-4/month) will be feasible.

Participant tracking**:** To facilitate tracking participants over 14-weeks, we will record: 1) participants' address and phone numbers; 2) contact information of family or friends; and 3) locations where participants work. This method allowed for 85% retention over 6 months of follow up in previous research studies.[85-87]

4.B. Participant retention

We will use previously established methods by my mentors to maximize retention in clinical trials.

Subject tracking and appointment reminders. At all visits, we will record: 1) participants' address and phone numbers; 2) contact information of family or friends; and 3) locations where participants work. Locator forms will be updated at all visits.

Screening process. After obtaining oral informed consent, a standardized screening process will occur by phone or in-person. Eligible participants will be scheduled for a baseline visit and written informed consent will be obtained.

Loss to follow up. We conservatively estimate a 15% loss to follow up. Dr. Cunningham has achieved 85% retention over 6-month follow-up in difficult to reach populations.

5) Informed Consent

Informed consent will be obtained from participants by the research assistant. Potential participants will first complete an oral consent prior to completing a screening questionnaire by phone. Included in this consent is verbal consent to reviewing the PMP. If they are eligible for the study, they will be scheduled for an enrollment visit, as which time a written informed consent will be completed.

Participant Compensation. Participant reimbursement will be given to compensate for time and inconvenience. Participants will be compensated $27.50 for each in-person visit (of which there will be 2) and an additional $15 for each visit in which there is sample collection (blood draw, urine collection; of which there will be 2). Participants will complete 15 total weekly phone visits. They will be compensated $3 for each completed phone visit (total $45/participant for phone-based surveys). Thus, if participants remain in the study for the full 14-week study period, they will receive a total compensation of $130.

6) Risk Benefit

6.A. Potential Risks. We identified four potential risks to participants: (1) breach of confidentiality regarding HIV or certification for medical cannabis, (2) Discomfort with participation, (3) fear that refusal to participate will affect care or services, and (4) inconvenience and discomfort associated with phlebotomy.

1. *Confidentiality issues:* We will collect personal information from participants to follow-up if they are interested in participating in subsequent parts of the study. We have outlined our procedures to address maintaining confidentiality below
2. *Discomfort with participation:* Because participants will be queried about sensitive issues, including HIV status, antiretroviral adherence, opioid use, and substance use, interviews may produce anxiety. Participants will be told that they may stop the interview or withdraw from the study if they find the questions troubling. Additionally, all participants will be receiving treatment by medical providers who can address additional medical and mental health problems.
3. *Fear that refusal to participate will affect care or services:* In the informed consent process, participants will be clearly instructed that refusal to participate will in no way affect their care at the affiliated health center.
4. *Inconvenience and discomfort associated with phlebotomy:* Participants will have blood drawn at enrollment and 14 weeks. Withdrawing blood from a vein is quite safe. Sometimes a bruise will occur at the puncture site, and very rarely a blood clot or infection may form in the vein. If this occurs, appropriate treatment will be instituted. During research visits in which phlebotomy will occur, the amount of blood withdrawn for these lab tests is approximately 15 ml, or 3 teaspoons, which is not dangerous.

6.B. Protections Against Risks.

Confidentiality. We will institute the following processes to ensure confidentiality is maintained:

1. We will create a system that prevents linking sensitive material to participants' personal identifiers. We will have a "name-based" system and "ID-based" system that will remain separate. In the name-based system, all documents that have patient identifiers will be filed together. Some of these documents will have participants' signatures (e.g. consent forms) and others will have personal information (e.g. tracking forms). In the ID-based system, all documents that do not include identifying information or signatures will use

participants' IDs (rather than names) and will be filed together. All forms will contain study ID's or participant names, but not both. There will only be one electronic document that links participants' names to their study IDs. Only the PI will have access to this document, which will be password protected.

2. We will obtain a Certificate of Confidentiality to protect participants' sensitive information.
3. Letters and/or phone messages that are left for participants will not include any personal identifying information and will not mention HIV or substance use.
4. Study records will be kept in locked files and/or within limited access, code-protected computer files, available only to the investigators and study personnel.
5. Publication or presentation of study results will not identify subjects by name.

In addition to addressing issues of confidentiality, it is crucial that we protect participants from emotional distress that may occur during research visits. All visits will occur in medical facilities. If emotional distress occurs during research visits an on-site physician will assess the patient. Per clinical judgment, the participant will either be referred to the Emergency Room or to their treating physicians the following day.

6.C. Potential benefits.

Neuropathic pain in PLWH is associated with poor HIV outcomes, including poor ARV adherence,[32] virologic failure,[33] and poor retention in care.[19,33] PLWH experience a high burden of pain,[4-11] and most commonly experience neuropathic pain.[12,13] Medical cannabis has known analgesic properties in PLWH with neuropathic pain.[24,25] Participants in our study will have been evaluated by their own physicians and deemed to be appropriate to receive medical cannabis based on those standards already. By participating in this study, they may experience benefit from medical cannabis use by experiencing improved pain. They may experience increased attention from research staff during the study period, resulting in improved pain, psychological, and HIV outcomes.

7) Data Analysis

7.A Data Analyses: *Intention-to-treat principle* will be used in primary analyses. If key variables (age, sex, medical comorbidities) are unequal among arms, we will conduct adjusted analyses. We will also conduct per-protocol analyses; medical cannabis use for at least 3 months of products will represent sufficient study participation.

Missing data: We will conduct multiple imputations using Markov Chain Monte Carlo imputation methods. Results from multiple imputed data sets will be pooled into a single dataset. We will compare statistical results using datasets with imputed values and the dataset that drops missing values.

Aim 1: Examine how medical cannabis use affects self-reported pain. *H1: The effect of medical cannabis use on self-reported pain-severity will differ by THC/CBD content.* The primary outcome will be change in BPI pain severity scale (ordinal variable, 0-10; measured at baseline and weekly for 14 weeks). A clinically significant change is 30% reduction in BPI pain severity scale.[92] Secondary measures will include BPI pain interference scale and neuropathic pain (painDETECT). We will compare the proportion of participants who achieve clinically significant change in pain at 14 weeks between those who use high THC soft gel capsules and those who use high CBD soft gel capsules. BPI pain interference scale and painDETECT will be compared between those using high THC vs high CBD as well. We will use mixed-effects logistic regression to test the effect of study arm on pain relief across the course of the study. Results will be adjusted for covariates associated with the outcomes of interest on bivariate testing. We will repeat this model using alternative measures of medical cannabis (cumulative dose of THC and CBD).

Aim 2: Examine how medical cannabis use affects pro- and anti-inflammatory cytokines. *H2: Medical cannabis that has higher THC content will have greater reduction in pro-inflammatory*

cytokines (TNFα, IL-6). H3: Medical cannabis that has higher CBD content) will have greater increase in anti-inflammatory cytokines (IL-4, IL-10). We will examine how pro- and anti-inflammatory cytokines measured at 0 and 14 weeks change in participants using high THC products versus high CBD products. We will use mixed-effects linear regression analyses to examine intervention and time effects as well as intervention-by-time interactions. This approach is appropriate in the event that the pro- and anti-inflammatory cytokine data show a non-normal distribution. We will repeat this model using alternative measures of medical cannabis (cumulative dose of THC and CBD). We will adjust for other chronic conditions that may lead to change in inflammatory cytokines, such as obesity, cardiovascular disease, and diabetes.

Aim 3: Examine how medical cannabis use affects adverse events. *H4: Participants who use high THC (vs. high CBD) cannabis products will have more psychological symptoms, poorer ARV adherence, and less suppressed VL.* We will examine whether participants using high THC products vs high CBD products have a greater chance of adverse events, including psychological symptoms, ARV adherence, and VL. We will use mixed-effects linear regression analysis for continuous measures (VL, ARV adherence, and psychological symptoms). Each adverse event (Table 8) will be included in a separate model. We will repeat this model using alternative measures of medical cannabis (cumulative dose of THC and CBD).

Aim 4: Explore mechanisms by which medical cannabis promotes analgesia. *H5: Different doses of THC and CBD will have differing effects on inflammatory cytokines, psychological symptoms, and ultimately analgesia.*

We will use a pooled analysis of THC and CBD, using weekly questionnaires and PMP records. We will examine these relationships longitudinally in a stepwise process. First, we will conduct a mixed-effects model to examine how potential mediators lead to analgesia (reduction in BPI severity score). We will repeat analyses for possible mediators, including inflammatory cytokines and psychological symptoms. We will also determine if exposures influence changes in these variables over time, which in turn, influence change in analgesia (e.g., using time-lagged mediators and outcomes). Mediators found to be significant will be included in the final model.[92] We will calculate the standardized total effect from the exposures to analgesia as well as the standardized mediational (i.e., indirect) effects via mediators. The mediational effect is calculated as the product of the effect from the exposures to the mediators, and the effect from the mediators to the outcome.

8) Data quality control and database management

Data management: Questionnaire, medical records, and PMP data will be de-identified and entered by study staff into a password-protected computer and database. Paper records will be stored in a locked filing cabinet that only research staff can access. Medical and PMP record data will be de-identified and entered in a secure HIPAA compliant web-based system. To protect confidentiality, we will use separate processes for ID- and name-based files and seek a certificate of confidentiality.

Responsibility for Monitoring. The PI will retain responsibility for overall study monitoring in conjunction with the Einstein IRB. Responsibility or data safety and monitoring for this study will reside with the Data Safety Monitoring Board (DSMB). The DSMB for PITCH will be made up of the following members:

- Susanna Curtis, MD, PhD, Assistant Professor of Medicine and Assistant Director of the Adult Sickle Cell Program at Mount Sinai Hospital. She conducts research on pain and inflammation in patients with sickle cell disease using cannabis and cannabinoids. Dr. Curtis has experience with clinical research and is an expert in measuring pain outcomes. She will have no direct role in the study. Potential conflicts: none.

- Devan Kansagara, MD, MS, Professor of Medicine. Dr. Kansagara is an internist with expertise in medical cannabis and evidence-based practices. He will have no direct role in the study. Potential conflicts: none.
- Rebecca Ashare, PhD, Associate Professor of Psychology. Dr Ashare is a psychologist and researcher with research interests in substance use in medical and psychiatric comorbidities, cannabis use for symptom management and serious illness communication. She will have no direct role in the study. Potential conflicts: none.

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