"Acute Effects of Cannabis on Cognition and Mobility in Older HIV-Infected and Uninfected Women"

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1. BACKGROUND/SIGNIFICANCE

Cannabis is the most prevalent drug used by adults aged ≥50 in the U.S., after alcohol and tobacco.[1] Recent trends show dramatic increases in both cannabis use among older U.S. adults,[2] and cannabis potency, defined by Δ^9-tetrahydrocannabinol (THC) content.[3] Cannabis acutely alters short-term memory, attention span, verbal fluency, reaction time, and psychomotor control.[4] Heavy long term cannabis use has been associated with lasting impairments in verbal learning, memory, and attention that correlate with duration of use;[5,6] although some studies have find that cognitive deficits from cannabis are reversible and related to recent exposure.[7,8] Studies on cannabis exposure and cognition are limited to only adolescents through middle-aged adults; acute and long-term cannabis effects on cognition among older adults are virtually unknown. **Given the rising potency and increasing frequency of cannabis use among older adults, studies systematically examining the effects of cannabis use in older adults are urgently needed.**

Cannabis use is particularly common in people living with HIV (PLWH), with 12- 56%[9-18] prevalence rates compared to 9.5% in the general U.S. population.[19] HIV has detrimental effects on both mobility and cognition, and similar to normal aging, mobility in patients with HIV may be influenced by cognitive function. Mild-to-moderate neurocognitive impairments (NCI), notably in attention and executive functions, remain highly prevalent and persist despite suppressive antiretroviral therapy,[20,21] affecting almost half of PLWH.[20,22] Little is known about the combined effects of cannabis use and HIV infection on cognition and mobility, particularly among older individuals. **As the population of older PLWH continues to grow, co-occurring aging and HIV related declines in cognition and mobility will coincide; the effects of continued cannabis use on cognition and mobility in this population at risk for cognitive decline are unknown.**

Our cross-sectional study in the Women's Interagency HIV Study (WIHS) found that **current cannabis use was associated with over twice the odds of single fall, and over 2.5 times the odds of multiple falls in 6 months;** past cannabis use was associated with over 1.5 times the odds of both single fall and multiple falls.[23] Our preliminary longitudinal data show that **40% of WIHS women (mean age 48) reported at least one fall over 2 years; current cannabis users had 1.7 times greater fall risk among HIV+ but not HIV-women**. We hypothesize that falls are related to acute effects of cannabis on attention and mobility, and that given subtle, pre-existing deficits associated with HIV infection, these acute cannabis effects may be more pronounced in HIV+ women, placing them at increased risks of falls. Whether this observed fall risk associated with cannabis use represents acute effects, or persistent effects of past cannabis use on cognition, balance, or mobility, or whether adverse effects of cannabis differ by HIV status merits further study in this aging population.

The "Walking While Talking" (WWT) test requires individuals to walk while performing a secondary attention-demanding task, is used to assess the interactions between cognition and gait, and provides a framework for evaluating the effect of divided attention, a facet of executive functions,[24-27] on mobility.[28] The WWT may help unmask subtle and latent cognitive abnormalities before they become clinically apparent by increasing the complexity of the walking condition,[28,29] and predicts falls, frailty, disability, and mortality among older community-residing adults without HIV.[30] **Because both cannabis use and HIV are associated with impairments in attention and executive functions, the WWT may be a quick and simple mobility stress test to identify subtle cognitive and motor effects of acute**

cannabis administration as a function of HIV status.

Cannabis use among older adults is a growing but under recognized public health problem. The Baby boomer generation (born post–World War II, 1946–1964) represents a large and rapidly increasing segment of the aging U.S. population,[31] and differs from preceding generations in terms of attitudes towards recreational and illicit drug use, greater use of psychoactive drugs, and higher prevalence of substance use disorder (SUD).[32-35] Recent trends show a dramatic increase in cannabis use among older U.S. adults, with a 58% increase for those aged 50–64, and a 250% increase for those aged ≥65, from 2006-07 to 2012-13;[2] increases in past year cannabis use are particularly notable among women, Black and Hispanic persons, and those aged 46-65 and older (≥65).[19] Public attitudes about cannabis use have become more accepting, and most Americans now support cannabis legalization.[36,37] Perceptions of risk associated with cannabis are declining,[38] and these declining risk perceptions are associated with increases in cannabis use and frequency of use.[39] Potency of cannabis has also been rising, from average <2% Δ^9-tetrahydrocannabinol (THC) content in 1980 to 12% THC in 2014, posing higher risks of cannabis use.[3,40] **Little is known about how cannabis use impacts medical conditions associated with aging, despite ongoing cannabis use in older adults.**

Cannabis use is highly prevalent in HIV+ populations. Cannabis is often used by HIV+ patients for management of HIV disease or treatment related symptoms such as loss of appetite, nausea, and pain associated with peripheral neuropathy.[9,14,41-43] Prevalence rates of current cannabis use in HIV+ populations range between 12- 56%,[9-18] compared with 9.5% in the general U.S. population.[19] Data on patterns of cannabis use over time in HIV+ populations are limited; however in the Women's Interagency HIV Study (WIHS), among cannabis users, daily use more than tripled over time, from 15% in 1994 to 51% in 2010.[11] Similarly, among HIV+ men in the Multicenter AIDS Cohort Study (MACS), daily use among current users increased from 14% in 1984 to 32% in 2013 among the HIV+ men.[18] Moreover, HIV/AIDS is a qualifying condition for medical cannabis in 27 of 29 states with medical cannabis laws.[44] **Despite its therapeutic benefits, cannabis use may also be associated with adverse health outcomes, particularly among aging HIV+ populations**. Yet little is known about the adverse health effects of acute or long-term cannabis exposure in older PLWH.

As the life expectancy of PLWH receiving effective antiretroviral therapy now approaches that of HIV- persons, the number of PLWH surviving into older age is growing rapidly.[45-47] **PLWH are experiencing an excess burden of comorbid conditions typically associated with advanced age, occurring with greater incidence and earlier onset than in HIV- groups, including osteoporosis, fractures, falls, and functional and neurocognitive impairment.**[48,49] Cross sectional studies of middle-aged (mean age 52 yr), predominantly male HIV+ adults have found the occurrence rates of falls are similar to that of persons aged 65 years and older.[50-52] HIV+ women have a greater risk of falls than HIV+ men.[50,51] In WIHS, we found that over 40% of women sustained one or more falls over a two-year period, despite a median age of only 48 years (see preliminary data); ~40% of women who fell sought medical attention for a fall-related injury, suggesting that these falls are not only frequent and premature, but also severe. Because low bone mineral density is prevalent in HIV+ populations,[53] occurrence of falls in aging HIV+ persons may confer a greater risk of osteoporotic fracture. We previously demonstrated that HIV+ women had higher 10-year fracture incidence rates than did HIV- women in the WIHS.[54] As the population of older PLWH continues to expand, an improved understanding of the overlapping consequences substance use, aging, and HIV is urgently needed, particularly among women, who are at greater risk for osteoporosis, falls, and fracture than men.

Neurocognitive impairment persists in HIV-infected persons despite suppressive HAART. Currently almost half of HIV+ persons in the U.S. are affected by HIV-Associated Neurocognitive Disorders (HAND), despite widespread availability of effective HAART.[20,22] Although the most severe manifestations of HAND such as HIV associated dementia (HAD) are rare in the HAART era, milder neurocognitive deficits remain, most notably in executive functions, including complex attentional tasks[55] and divided attention tasks.[56] The clinical consequences of HAND are substantial, including a detrimental impact on medication adherence,[57,58] employment,[59,60] driving,[61,62] and every day functioning.[63,64] **Both**

HIV infection and cannabis use have adverse effects on cognitive function, particularly in domains of attention and executive function, and their individual or combined effects may become more pronounced with advancing age.

Acute effects of cannabis on cognition in young persons include alterations in short-term memory, sense of time, sensory perception, attention span, problem solving, verbal fluency, reaction time, and psychomotor control.[4] Experimental studies have found a dose-dependent impairment in cognitive, psychomotor, and actual driving performance, including reaction time, information processing, perceptual–motor coordination, motor performance, attention, and tracking behavior.[65] **There are no data on acute effects of cannabis on cognition in HIV+ persons. Data on the non-acute effects of cannabis on cognitive functioning in HIV+ persons are limited and findings are inconsistent.** Frequent cannabis use has been associated with cognitive impairment in the context of advanced, symptomatic HIV disease,[66] yet among asymptomatic HIV+ persons, no additive effects of cannabis and HIV were found on reaction time.[67] Others have found interactive effects, such that HIV+ persons performed worse on global cognition measures than HIV- persons when cannabis use was <1.43g/week, but not with greater use.[68] These investigators found that HIV+ moderate-to-heavy cannabis users performed worse on neurocognitive testing of learning/memory than all other comparison groups (HIV- heavy cannabis users, and HIV+ and HIV- cannabis non-users and light-users), whereas HIV+ light cannabis users performed better on verbal fluency than HIV− light users.[69]

Much less is known about cannabis effects on mobility. Studies in young adults show alterations in balance with acute cannabis use. In a double-blind, randomized, two-way balanced placebo-controlled, cross-over study of inhaled THC (2, 4, 6, and 8 mg) conducted in healthy young men, dose-dependent effects were observed on postural stability, with increased body sway with THC dose.[70] This is consistent with previous reports of increased body sway and impaired equilibrium in young adults after administration of smoked cannabis (3.5% THC).[71] Subtle movement abnormalities have been observed using a motion capture system in a study of 22 young adults with history of cannabis use compared to non-drug using controls; however the magnitude of effect on gait was not clinically detectable, prompting the study authors to note that additional research on whether these subtle gait abnormalities observed in young adults become more apparent with aging and continued cannabis use.[72] There is a paucity of data on acute effects of cannabis use in older adults and older PLWH, despite rapidly expanding numbers of aging persons with or without HIV who continue to use cannabis. Findings from studies conducted in healthy young adults suggest acute impairment in cognition and mobility with cannabis use, but given the population under study, investigators could not evaluate the role of pre-existing age-related or disease- associated impairment, nor potential additive effects of either HIV or age.

Research on aging has shown that mobility and cognition are interrelated. HIV has detrimental effects on both mobility and cognition. Slow gait and poor physical performance are common in cross-sectional studies of HIV+ individuals,[73-76] and while few longitudinal studies exist, accelerated gait speed decline has been reported in older HIV+ men compared with HIV- men;[77] moreover, HIV status and reduced physical performance both independently and jointly predicted increased mortality risk among former and current injection drug users.[73] **To date, mobility disorders among aging HIV+ persons are poorly understood, particularly among women.** As the prevalence of HIV among older age groups continues to rise, co-occurring aging and HIV-related declines in mobility and cognition will likely coincide, yet the extent to which cannabis use contributes to the development of impaired cognition and mobility remains unclear. **While cannabis use acutely impairs both cognitive function and mobility in younger HIV- persons, acute effects of cannabis on balance, gait, and mobility have not been investigated in older persons, nor in PLWH.**

Our objective is to explore the mechanisms that underlie the increased fall risk associated with cannabis use. We will compare the effects of controlled administration of active (7.0% THC) and inactive (0.0%) cannabis in aging HIV+ women on stable HAART as compared to matched HIV- controls enrolled in the

former WIHS, now MACS-WIHS Combined Cohort Study (MWCCS). Endpoints will be balance, mobility, and cognition, including a cognitive-motor divided attention task (WWT).

An improved understanding of the effects of cannabis use on balance, mobility, and cognition and their relation to fall risk may have important implications for developing effective assessments and interventions to reduce the burden of mobility impairments in aging women who use cannabis, with or without HIV.

2. STUDY DESIGN

Specific Aims and Hypotheses

Aim 1. To compare the acute effects of cannabis on balance and mobility among older HIV+ and HIV- women. We will quantify the effects of active and inactive cannabis in HIV+ and HIV- participants. We hypothesize that, following active cannabis administration, HIV+ women will perform worse than HIV- women on tasks measuring balance and mobility, especially under walking conditions that demand attention. HIV+ and HIV- women will not differ in performance under inactive cannabis conditions.

Aim 2. To compare the acute effects of cannabis on cognition among older HIV+ and HIV- women. We will assess effects of active and inactive cannabis on the Sustained Attention to Response Task (SART) in HIV+ and HIV- women. We hypothesize that following active cannabis administration, HIV+ women will perform worse than HIV- women on cognitive testing of attention. The groups will not differ following inactive cannabis administration.

OVERVIEW OF STUDY APPROACH

The WIHS is the largest and longest running cohort of HIV+ women and their matched HIV- controls in the U.S. and has now merged with the Multicenter AIDS Cohort (MACS) to form the MWCCS. We propose to explore potential mechanisms that underlie the increased fall risk associated with cannabis use observed in aging women with HIV infection in the former WIHS/current MWCCS relative to those without HIV. We will compare between-(HIV+ and HIV-) and within- (active vs placebo cannabis) subject effects of cannabis on measures of balance, mobility, and cognition, including a cognitive-motor divided attention task (WWT), under supervised administration of active (7.0% THC) and inactive (0.0% THC) cannabis in older HIV+ women on stable HAART and HIV- controls enrolled in the MWCCS.

STUDY SETTING The WIHS, established in 1994, was a prospective cohort study of HIV disease progression in women from 9 US cities, in which HIV+ and HIV- participants are well-matched by age, race/ethnicity, education, and high-risk sexual and substance use behavior.[86,87] Semi-annual visits included in-depth interviews, physical exam, and collection of blood, oral, gynecologic, and urine specimens. Current visit structure is now annual in MWCCS. Interviews include sociodemographics, medical history (HIV- and non-HIV related), medication use, HAART use and adherence, substance use, and report of falls and fall-related injury, among others. A neurocognitive testing battery is performed every two years.[88,89] MWCCS has a central Data Analysis and Coordination Center (DACC) and an extensive repository of biological specimens. The Cannabis Research Laboratory, Columbia University Medical Center (CUMC), is directed by Dr. Haney. Her laboratory has been conducting federally-funded, placebo-controlled human laboratory studies of cannabis administration for the past 20 years, including studies with HIV+ research volunteers. By collaborating with Dr. Haney, we have the opportunity to directly assess the acute effects of active vs inactive cannabis administration on a range of clinically-relevant outcome measures, thereby dissociating expectancy effects of cannabis from its pharmacological effects.

STUDY PARTICIPANTS.

We will recruit and test 60 women who report cannabis use within the past six months, including 30 HIV+ women and 30 demographically similar HIV- controls from the Bronx and Brooklyn MWCCS sites, and from clinical populations, such as patients receiving care at Einstein/Montefiore Medical Center, other medical facilities, referred by medical providers, or word-of-mouth if eligibility can be confirmed. Median age of Bronx MWCCS participants is 54 years, with 75% between 49 and 59 years. Inclusion Criteria: (1) current cannabis use (within 6 months) based on self-report, (2) able to perform study procedures, including ability to ambulate independently, (3) adequate hearing and vision, (4) for HIV+ women, use of stable HAART for at least 6 months. Participants must be willing to smoke cannabis during both study

visits. Participants who use cannabis by vaping but are willing to smoke cannabis at the study visits will be allowed to enroll. Exclusion criteria: (1) pregnancy, (2) greater than occasional illicit drug use other than cannabis will be excluded; those with weekly or less frequent substance use will be enrolled but will be require to provide a negative urine drug test (other than cannabis) at each of the two study visits, (3) request for substance use treatment, (4) current parole or probation, (5) history of significant violent behavior within 12 months, (6) current uncontrolled major Axis I psychopathology requiring medical intervention (e.g. active psychosis, suicide risk,), or suicide attempt and/or suicidal ideation within 12 months (7) significant uncontrolled medical illness (such as late stage or metastatic cancer or on active treatment for cancer; chronic pulmonary disease on ventilator or continuous oxygen therapy); uncontrolled hypertension BP>160/100), (8) active heart disease within 12 months, (9) history of dementia, (10) severe hand tremor, (11) poor English fluency. All participants will be consented and compensated for their effort as approved by the IRBs of each participating institution (see Human Subjects).

RECRUITMENT. Established MWCCS research infrastructure and clinical populations will be used for study recruitment. In order to meet recruitment targets, electronic health records will be used to prescreen for eligibility in clinical populations. We have obtained a waiver to access records for recruitment purposes. Potential participants will be contacted via phone to provide initial information about the study and screen for eligibility, followed by an in-person screening visit and initial consent. Written informed consent will then be obtained in person prior to study enrollment.

RANDOMIZATION AND BLINDING. Each participant will smoke both inactive (0.0%) and active (7.0%) cannabis; the order in which each cannabis strength is administered will be counterbalanced and double-blind. Participants will be told that the strength of cannabis that they will smoke in each session will vary.

RESEARCH VISITS AND STUDY PROCEDURES

Study Design (Table 1): A within-subject design will be used in which all participants will experience active and inactive cannabis, thereby increasing statistical power. Participants will be instructed to refrain from using any drugs for or tobacco cigarettes beginning at midnight prior to each session and to abstain from drinking alcohol for at least a 24-hour period prior to testing. A urine drug screen, breathalyzer, carbon monoxide (CO), and pregnancy test will be conducted upon arrival at the laboratory to confirm compliance. If there is evidence of illicit drug, alcohol, or cannabis use on the morning of the session based on CO, the session will be rescheduled. At the beginning of each session, a timeline follow-back questionnaire querying cannabis, alcohol, and other drug use will be completed. Participants will be offered a light breakfast (bagel or cereal, juice, coffee). Following breakfast, baseline cardiovascular measures (heart rate and blood pressure measurement), subjective effects questionnaires, and performance tasks will be completed. Tobacco cigarette smokers will be given up to two smoking breaks per session scheduled at the same time for both sessions in order to minimize nicotine withdrawal symptoms. The participant and study staff will be blind to cannabis cigarette content. Cardiovascular and subjective effects measures, mobility and balance testing, and a cognitive task battery will be completed at baseline and at 15–120 min intervals following cannabis administration. At the end of each session, participants will be carefully assessed to ensure they are no longer intoxicated, and may leave after passing field sobriety and balancing tasks. Participants unable to pass field sobriety testing will remain in the Research Laboratory until they are no longer intoxicated, pass repeat field sobriety testing, and can safely be discharged. They will be compensated for this additional time.

Table 1. Time Course of Sessions

Time	Event	Time	Event
−60	Begin session: urine toxicology, CO, breathalyzer, pregnancy testing timeline flow-back questionnaire, breakfast	105	Vitals, subjective effects, MRF, mobility, balance and cognitive batteries
-30	Field sobriety, vitals, subjective effects, mobility, balance and cognitive batteries		
0	Cannabis administration	150	Vitals, subjective effects, MRF, mobility, balance and cognitive batteries
15	Vitals, MRF (Marijuana Rating Form), subjective effects, mobility, balance and cognitive batteries	180	Lunch/snacks

60	Vitals, MRF, subjective effects, mobility, balance and cognitive batteries	210	Field sobriety, end session

a. Behavioral Measurements: (1) Subjective Effects Ratings: A 3-minute series of visual analog scales (VAS) in which participants indicate how they are feeling at that moment will be done 4 times over the course of the study visit. This 44-item scale assesses the effects of cannabis on a range of affective and physical symptoms (e.g., friendly, mellow, sedated, anxious).[90] (2) Marijuana Rating Form: Cannabis-related effects are assessed using a five-item visual analog scale asking participants to rate the strength of the cannabis effect, good effect, bad effect, drug liking, and willingness to smoke the cannabis again. Participants also indicate whether they think cannabis is active or inactive.

b. Mobility testing: Timed gait and Walking While Talking (WWT). Gait speed is measured under normal walking and attention-demanding conditions. There are two single task conditions: 1) Normal Walk (NW): participants are asked to walk 20 ft at their "normal pace" and are timed; and 2) Cognitive (Alpha): participants stand still while reciting alternate letters of the alphabet starting with the letter B for 30-sec out loud. In WWT, participants walk 20 ft at their normal pace while reciting alternate letters of the alphabet starting with the letter 'B' and are instructed to pay equal attention to both tasks.[28,91] The three test conditions are presented in a counterbalanced order using a Latin-square design. Reliability and validity for this walking paradigm have been established.[30,92] The main comparison is between NW and WWT; cognitive performance is also quantified with the number of correct letters and errors generated.[93-95]

c. Balance Testing: (1) One Leg Stand (OLS): participant stands on one foot with the other stretched out ~6″ off the floor for 30 seconds while counting aloud by thousands, and is observed for body sway, use of arms to maintain balance, hopping, or putting raised foot down.[96] (2) Walk and Turn (WAT): participant takes nine heel-to-toe steps along a straight line, counting steps aloud, turns on the planted foot, and returns in the same manner. The participant is observed for losing balance while listening to instructions, starting too soon, stopping while walking, missing heel-to-toe, stepping off the line, using arms to balance, incorrect number of steps, and improper turn. Standardized Field Sobriety Tests (SFST) include the OLS and WAT, along with Horizontal Gaze Nystagmus (HGN).[96-98] (3) Modified Romberg Balance Test (MRB) detects the ability to maintain a steady standing posture with eyes closed, as well as divided attention and time sense impairment.[99] The participant stands with her feet together, head tilted backward, and eyes closed, estimates the passage of 30 seconds, and is observed for body sway and direction, accuracy of 30 second time, and eyelid and body tremors. These balance tests challenge the ability to divide attention between remembering directions while simultaneously performing a physical task, and are thus considered divided attention tests.[100] (4) Functional Reach: this test of dynamic balance measures the distance the subject can reach in front of her from a standing position without losing balance.[101,102]

d. Cognitive Task Battery: A 25-minute battery assessing cannabis effects on attention, processing speed, recognition memory, and Reaction Time/Response Inhibition [103] will be completed 4 times per session.

(1) Sustained Attention to Response Task (SART)
Length of time: 6 minutes
Measures: Attention
Task: Participants are presented with a single digit 1-9 in the middle of the screen in varying font sizes. The digit disappears after a short while and is replaced with a mask (circle with an X). Participants are asked to press the SPACEBAR if any digit other than 3 is presented and to withhold the response if digit 3 presented.
Main outcomes: (1) number of correct suppressions; (2) number of incorrect suppressions; (3) mean reaction time

(2) Digit Symbol Substitution Task (DSST)

Length of time: 3 minutes
Measures: Processing Speed

Task: Participant are presented with an 18 (columns) x 16 (rows) matrix. Odd rows contain symbols, even rows contain empty answer boxes (18x8 = 144). The task is to translate the symbols into digits with the help of a provided key within a 2 min time frame.

Main outcomes: (1) Total number of correct responses; (2) Total number of incorrect responses

(3) Behavioral Pattern Separation Task – Object Version (BPS-O)
Length of time: 12 minutes
Measures: Recognition Memory
Task: Participants participate in a 2-part experiment to assess recognition memory.
The first part of the experiment presents 128 pictures (default) of everyday items and participants have to decide whether the item is an OUTDOOR or an INDOOR item. The second part of the experiment presents 64 of the previously seen pictures (targets), 64 of very similar items (lures), and 64 new items (foils). Participants are asked to categorize the items as old, new, or similar within 2.5s (default).
Main outcome: Percent correct

(4) Stroop Task: Color
Length of time: 3 minutes
Measures: Reaction Time/Response Inhibition
Task: Participants are given color words written in color and are asked to indicate the color of the word (not its meaning) by key press as fast as they can without making too many errors.
Congruent trials: color word and the color it is presented in are the same
Incongruent trials: color word and the color it is presented in are not the same
Control trials: colored rectangles
Main outcomes:
1) overall proportion correct of all trials
2) overall mean latency (in ms) of all correct trials
3) mean latency of all correct congruent trials (in ms)
4) mean latency of all correct incongruent trials (in ms)
5) mean latency of all correct control trials (in ms)
6) proportion correct of congruent trials
7) proportion correct of all incongruent trials
8) proportion correct of all control trials

TABLE 2. Study Timeline (Quarters)

	Year 1				Year 2			
Hire and train staff								
Obtain IRB approvals								
Enrollment (N=60) and session 1								
Session 2 (N=60)								
Data entry & processing								
Analysis								
Presentation/publication of study results								

e. Cannabis Administration: Inactive and active cannabis cigarettes (0.0%, 7.0% Δ^9- THC) provided by the National Institute on Drug Abuse have leaves that differ slightly in color. One cigarette end is placed in a plastic cigarette holder, and the exposed end pinched to cover the leaves. Cannabis is administered using a standardized cued-smoking procedure, which produces reliable increases in heart rate and plasma Δ^9- THC. Participants will be instructed to 'light the cigarette' (30 sec), 'get ready' (5 sec), 'inhale' (5 sec), 'hold smoke in lungs' (10 sec) and 'exhale.' Participants will smoke 1 puff/minute in this manner, with a 40-sec interval between each puff until 50% of the cigarette has been smoked. Cigarettes are stored frozen in an airtight container and humidified at room temperature for 24 hours before use.

PROPOSED TIMELINE. Table 2 depicts the timeline for recruitment and testing. Recruitment in the first quarter of Year 1 will be lower to account for study planning and initiation. Each participant will complete two study visits (minimum 48 hours apart) for a total of 120 visits. In the final 2 quarters, we will complete data collection, final reliability checks and statistical analyses, write manuscripts, and submit an R01 application.

3. STUDY POPULATION

DESCRIPTION OF STUDY POPULATION: Participants enrolled in the Bronx and Brooklyn (former) WIHS (now MWCCS) sites, those who receive medical care from Einstein/Montefiore Medical Center, or other medical facilities will be invited to participate in the proposed research. Participants may also be recruited from provider referrals and word-of-mouth if eligibility can be confirmed. Specifically, 30 HIV-infected women on stable antiretroviral therapy and 30 uninfected women, who currently use cannabis will be recruited to participate in this study. The volunteers in these studies will be between 40 and 65 years old, non- pregnant females, who are medically and psychiatrically stable, competent to provide informed

consent, non-treatment-seeking, and have no/occasional (once weekly or less) substance use other than cannabis. Women will be tested for pregnancy at each visit. An HIV test will also be administered at the in-person screening visit to confirm the HIV status of those without a documented negative HIV test within the prior 12 months, or with unknown HIV status. Pre-test and post test counseling will be provided, and consent for testing will be obtained prior to administering an oral HIV test. Any participant with a new positive HIV test will be immediately linked to confirmation of test results and HIV care. None will have significant uncontrolled current Axis I psychopathology requiring medical intervention, or suicidal ideation or violent behavior within the past year. Participants with stable depression or anxiety on treatment will not be excluded from participation. Interviews in which drug use is probed will be conducted with each volunteer prior to study onset. Prospective volunteers expressing interest in stopping their cannabis use will be given a treatment referral. We expect to enroll approximately 60 volunteers over 2 years.

INCLUSION/EXCLUSION CRITERIA:

Inclusion criteria:

1. Adequate hearing and vision
2. Able to perform study procedures, including ability to ambulate independently
3. For HIV+ women: use of stable HAART for at least 6 months
4. Current cannabis use (within the past 6 months)

Exclusion criteria:

1. Illicit drug use other than cannabis more than once per week. Participants will be required to produce a negative urine drug test (other than cannabis) at each study visit.
2. Presence of significant uncontrolled medical illness: late stage or metastatic cancer or on active treatment for cancer; chronic pulmonary disease on ventilator or continuous oxygen therapy; uncontrolled hypertension (BP>160/100)
3. History of active heart disease within 12 months (e.g. myocardial infarction, unstable angina, heart failure, bypass surgery)
4. Interest in treatment for cannabis
5. Current parole or probation
6. Pregnancy or current lactation
7. Recent history of significant violent behavior (within 12 months)
8. Current uncontrolled Axis I psychopathology requiring medical intervention (e.g. active psychosis, suicide risk), or suicide attempt and/or suicidal ideation within 12 months
9. History of dementia
10. Severe hand tremor
11. Poor English fluency
12. Willingness to consent to HIV testing if status can not be confirmed from medical records

JUSTIFICATION FOR THE INCLUSION OF WOMEN ONLY, AND FOR THE EXCLUSION OF CHILDREN.

The former WIHS population is an ethnically diverse cohort of women with HIV infection as well as demographically and behaviorally similar uninfected controls and is representative of the domestic HIV epidemic in women. Based on characteristics of the MWCCS participants in our study sites, we anticipate that our sample will consist of: 53% Non-Hispanic black, 38% Hispanic, and 8% Non-Hispanic white/other. We have chosen to limit our proposal by sex in an effort to fill a critical gap of knowledge. Women represent a sizeable proportion of the growing number of older HIV-infected persons, yet they are often underrepresented in HIV research. Women represent 50% of all adults living with HIV globally, and account for 19% of all HIV diagnoses among U.S. adults. Because women have longer life spans than men, yet greater rates of geriatric outcomes such as frailty, falls, and disability, this innovative research on the effects of cannabis and HIV on the balance, mobility, and cognition among aging women is of particular importance as the greater numbers of HIV-infected women survive into old age. HIV- infected women have alarmingly high rates of geriatric syndromes such as falls and fractures, occurring at younger than expected age. Yet research incorporating sex-specific analyses is scarce and is limited in terms of the range of risk factors examined. With its robust dataset and specimens and over 20 years of follow-up, MWCCS is a unique and critical platform for investigations of disease in

HIV-infected women as they age, and in critically important studies of pathogenesis of comorbidities that disproportionately affect older women and intersect with substance use and HIV disease that are both broadly applicable and specific to women.

Participants included in this study will be women age 40 years or older, and the majority will be over age 50 years. Individuals under age 18 are specifically excluded, as well as adults below age 40, as the research topic to be studied is not relevant to children, or younger adults. This proposal aims to understand cannabis effects on balance, mobility, and cognition in aging HIV-infected women and uninfected controls, in an effort to understand potential mechanisms of fall risk and mobility impairment associated with HIV and cannabis use.

SOURCES OF RESEARCH MATERIAL. Participants enrolled from MWCCS currently undergo annual research visits as a scheduled part of their MWCCS participation, which include in-depth interviews, physical exam, and collection of blood, oral, gynecologic, and urine specimens. MWCCS Core interviews include detailed evaluation of sociodemographics, medical and health history (HIV- and non-HIV related), medication use, HAART use, dosage and adherence, reproductive/gynecologic history, substance use, sexual behaviors, engagement in care, and brief pain inventory, among others. Medical exam consists of neuropathy exam, height, weight, anthropometry, bioelectric impedance analysis, blood pressure, and skin, oral cavity, breast, and gynecological examinations. A neurocognitive testing battery is performed in all participants every two years. For MWCCS participants who give medical record release, information will also be gathered from medical charts. Volunteers will be informed that data will be obtained specifically for research purposes. We will use as data all self-report information, observer records, and physiological, and behavioral information collected during test sessions, as well as data collected as part of MWCCS study visits. Electronic Health Records (EHR) will be used to screen participants recruited outside of MWCCS, i.e. clinical populations receiving care at Einstein/Montefiore, other medical facilities. Data will be coded with numbers assigned to each participant. Electronic transmission of information regarding a participant will only use an assigned number to identify the participant.
Additionally, computers with participant-related information are password protected, and only study personnel have access to the passwords.

4. PARTICIPANT RECRUITMENT

Participants already enrolled in the Bronx and Brooklyn MWCCS sites and participants recruited from clinical care at Einstein/Montefiore Medical Center, or other medical facilities will be invited to participate in the proposed research. Specifically, 30 HIV-infected women on stable antiretroviral therapy and 30 uninfected women, who currently use cannabis will be recruited to participate in this study. Established MWCCS research infrastructure will be used for study recruitment. Potential participants will be contacted via phone to provide initial information about the study and prescreen for eligibility. Interested and potentially eligible participants will then complete an in-person screening visit at the Bronx MWCCS site, where written informed consent will be obtained prior to study enrollment. Clinical populations who meet eligibility requirements will also be eligible for participation. For Einstein/Montefiore patients, MWCCS personnel or a Center for AIDS Research (CFAR) nurse will utilize Einstein's CFAR clinical database to prescreen the electronic Health record for potential eligibility. Additionally, patients may be referred to the study by medical providers or word-of-mouth. Similar to the procedures for MWCCS participants, potential participants from clinical sources will be contacted via phone to provide initial information about the study, and will be prescreened for eligibility. Health records will be obtained and reviewed for non-MWCCS participants to ensure eligibility criteria are met, including documentation of HIV status. Interested and potentially eligible participants will then complete an initial telephone prescreen and an in-person screening visit at the Bronx MWCCS site, where written informed consent will be obtained and HIV testing will be performed if documentation of HIV status is unavailable.

5. INFORMED CONSENT

Obtaining informed consent is a multi-tiered process.

(1) *Review of WIHS/MWCCS database* The first phase of recruitment involves review of data collected as part of MWCCS core visits, to identify potential participants. For clinical populations, we will review *Electronic Health Record (EHR)* data obtained as part of clinical care to identify potential participants.

(2) *Telephone screening.* Those deemed eligible based on this initial screening will receive phone calls from MWCCS study staff, receive a brief description of the study, and are asked to consent to be more fully screened via telephone. This screening consent form covers all interviews, questionnaires, and collection of medical information.

(3) *In-person medical and psychiatric evaluation and informed consent.* Participants who meet inclusion/exclusion criteria will be scheduled for an in-person screening visit at the Bronx MWCCS site, which will include a physical exam, ECG, and medical and psychiatric history evaluation. Clinicians will determine whether volunteers have current untreated or uncontrolled major Axis I psychopathology requiring medical intervention (e.g., active psychosis, suicide risk,) or suicidal ideation or violent behavior within the past year. Psychiatric illness will be assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.), a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies and to be used as a first step in outcome tracking in non-research clinical settings. The M.I.N.I. was designed as a brief structured interview for the major psychiatric disorders in DSM-5 and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (median 15 minutes) than the above referenced instruments.

Those who pass this screening will have the study described to them in detail, and the study clinician will perform informed consent at that time. An oral HIV test will also be administered at the in-person screening visit to confirm the HIV status of those without a documented negative HIV test within the prior 12 months, those with unknown HIV status, or those without documented HIV positive status (either laboratory results, or medical records). Pre-test and post-test counseling will be provided, and informed consent for testing will be obtained prior to administering an oral HIV test. Any participant with a new positive HIV test will be immediately linked to HIV care. A copy of the signed consent form will be provided to the participant, as well as faxed to CUMC or uploaded into the study database and filed in a locked cabinet on site. A detailed questionnaire will be administered to participants recruited from clinical sources including sociodemographics, substance use history, medical and health history (HIV- and non-HIV related), and medication use including antiretroviral history and adherence.

Review of Study Procedures at Initial Study Visit. When they report to the laboratory for the initial study visit, participants will have additional study procedures described by Dr. Haney.

We find that this multi-consent process provides participants with substantially more information at each decision point. Such a procedure provides fully informed consent.

Subject Renumeration

Compensation: We will pay subjects for their time and effort, $50 for the screening visit and $75 per each of two 4 hour study visit sessions. This modest amount is consistent with the compensation policies and guidelines approved by the institutional IRB.

Study Completion Bonuses: Participants who complete the entire study will be given a study completion bonus of $50.

Participant Meals: Participants will receive a standardized low-fat breakfast (bagel, juice, coffee) at each study visit, and will also be provided with lunches and snacks on study visit days, consisting of frozen meals, snack foods, and beverages ordered in bulk or purchased from local supermarkets.

Transportation: For the screening visit, we will pay for round-trip taxi $100 for Brooklyn participants to travel to the Bronx MWCCS; we will pay $6.00 for one-way cost of public transportation for Bronx MWCCS participants. For study visits, we will pay for round-trip taxi $160 per visit for travel expenses that include the significant costs of crossing NYC bridges to get to the Columbia University Medical

Center from the Brooklyn MWCCS site (N=20 per year). We will pay $60 for one-way taxi for Bronx MWCCS participants, as well as $6.00 for one-way cost of public transportation (N=40 per year). Transportation costs will be paid directly to the taxi service, and MetroCards will be given directly to participants.

6. RISK/BENEFIT

POTENTIAL RISKS. The major risk of research participation is related to drug administration. It is worth noting that we have had vast experience thus far administering a range of abused drugs, including cannabis, cocaine, amphetamines, opioids, and ethanol, and have used oral, intravenous, intranasal, and smoked, routes of administration. We also have experience with the amount of cannabis proposed in the current study with no adverse consequences. Many of the assessments for this study involve minimal physical, psychological, social, or other risks risk to the participants such as answering questionnaires, physical examination of gait, and performance of simple tasks such as balancing with feet in a tandem position. The timed gait assessments do not require attachment to any monitoring devices. Thus the risks are expected to be similar to those risks involved in everyday standing, stair climbing, walking, and activities of daily living. Subjects might tire during the mobility test. Research assistants will closely monitor subjects for tiredness, loss of balance, or any other physical discomfort symptoms, and stop testing or institute rest breaks as needed.

Participation in research may involve a loss of privacy; however every effort is made to insure the confidentiality of the participant. All samples and study information will be coded onto forms that will be kept in locked files at all times. Confidential information is maintained in a locked cabinet that is accessible only to study personnel. Staff has been trained in the procedures necessary to insure confidentiality. No individual identities will be used in any reports or publications resulting from the study.

Possible side effects of smoked cannabis include: sedation, gait disturbance, tiredness, sadness, anxiety, concentration difficulties, increased heart rate, palpitations, dizziness, sleep disturbance, changes in food intake, restlessness, confusion, sleepiness, clumsiness, gastrointestinal upset, headache, nausea, dry mouth, pallor, flushing, sweating, and slurred speech. All participants will be carefully monitored and fully informed of the side effects that they might experience. Because all currently smoke cannabis, these effects should be familiar to them. Inactive and active cannabis cigarettes are provided by NIDA to Dr. Haney's Cannabis Research Laboratory, which has conducted federally funded, placebo controlled human laboratory studies of cannabis administration for the past 20 years, including studies that include HIV-infected volunteers. Dr. Haney has FDA, DEA and NY State Narcotics licenses to conduct federally funded studies testing the behavioral effects of cannabis. Participants will be closely monitored by staff during the balance and walking task to prevent actual falls.

ADEQUACY OF PROTECTION AGAINST RISKS. All participants are fully informed of the side effects that they might experience. Only those judged suitable are invited to participate in the full study. Throughout participation, we will carefully monitor participants for agitation, hostility, depression, or changes in behavior, thinking, or suicidal thoughts or actions, anxiety, panic, aggression, anger, mania, abnormal sensations, hallucinations, paranoia, or confusion.

Emergency medical equipment is available in Dr. Haney's laboratory, which is located adjacent to New York Presbyterian Hospital so a full medical emergency back-up team is available. We anticipate, however, that careful screening, informed consent, cannabis dose selection, and participant monitoring, will obviate the need for such emergency care. Dr. Haney has been conducting inpatient and outpatient clinical pharmacology research for over 20 years.

Confidentiality issues: Participation in research may involve a loss of privacy. We deal with issues of confidentiality by using coded records, store signed consent forms in a locked safe, and trying to the best of our ability to maintain confidentiality. All participants are assigned a study number that is used as identification on all data sheets and laboratory requests. The participants' names are listed on a separate log that is kept with locator information in a locked file in a locked room separate from the data file room. No individual identities will be used in any reports or publications resulting from the study. All key personnel, including anyone who interacts with the participants in the collection of data, have completed training courses on the Protection of Human Research Subjects. The Department of Health and Human Services has issued a Certificate of Confidentiality to MWCCS ensuring that all confidential and personal information provided remains confidential, and cannot be requested or utilized by other official

governmental or local agencies.

NIH Requirements for Education in the Protection of Human Research Participants: All key personnel on this grant have passed the Einstein or Columbia University "Good Clinical Practices" examination, and received certificates indicating they had learned the necessary information covered by that course. The information covered in this comprehensive one-day course includes knowledge of the regulations guiding clinical research as well as ethical issues involved in research with human participants. In addition to this formal examination, all key personnel on this project will participate in two one-hour sessions discussing ethical issues involved in research with human participants that included the Belmont report, the NIAAA and NIDA guidelines for administration of alcohol and drugs of abuse to humans, and a discussion of the regulations promulgated by HHS for carrying out research with human participants.

POTENTIAL BENEFITS OF PROPOSED RESEARCH. There are few direct benefits to research volunteers in the proposed study. Results from this study may eventually benefit women who use cannabis by providing important information about balance, mobility, and cognitive disorders associated with cannabis use and HIV infection. Prior to study acceptance, all volunteers will be screened for medical and psychiatric exclusion criteria. Volunteers understand that they can obtain a referral for drug treatment at any stage of their research participation. We repeat our offer for treatment referral at screening, and at discharge from the study. We will attempt to obtain a placement in a drug abuse clinic for those people who indicate a desire for help, and will inform all volunteers of our ongoing cannabis-treatment studies conducted within the Division of Substance Abuse.

IMPORTANCE OF THE KNOWLEDGE TO BE GAINED. The risk/benefit ratio for these studies appears favorable. The major benefit of this research is scientific. Despite its therapeutic benefits, cannabis use may also be associated with adverse health outcomes, particularly among aging HIV+ populations. An improved understanding of the effects of cannabis use on balance, mobility, and cognition and their relation to fall risk may have important implications for developing effective risk assessments and intervention procedures to reduce the burden of mobility impairments in aging women who use cannabis, with or without HIV. We anticipate that the degree of risk to which individuals are exposed will be small due to the care with which these studies will be carried out. The potential benefits to society in terms of the knowledge gained are substantial because it will lead to a better understanding of the acute effects of cannabis use on gait, balance, and cognition, in aging women with our with HIV infection. Consequently, we believe the conduct of this research is well justified.

7. DATA ANALYSIS

OVERVIEW AND APPROACH: To determine the acute effects of cannabis on balance, mobility, and cognition among older HIV+ and HIV- women.

OUTCOMES: Primary outcomes are functional reach and gait speed (Aim 1) and number of correct suppressions on the Sustained Attention to Response Task (SART) (Aim 2) under active and inactive cannabis

STATISTICAL ANALYSIS: Descriptive data analysis will identify erroneous values, outliers, distributional properties, and insufficient data dispersion for making analytic comparisons. As needed, transformations such as logarithmic or categorization will be applied to skewed continuous variables. The HIV+ and HIV- arms will be compared using t-tests/ANOVA, and/or rank tests for continuous and exact tests for binary baseline covariates to identify potential confounders and generalizability issues. Within our crossover design for the outcomes of both Aims 1 and 2 with each subject getting both active and inactive cannabis (after verifying distributions are not too skewed for normal approximation), we will use linear mixed effects models, which take account of correlations among measurements within the same subjects, to compare functional reach and gait speed (Aim 1) and number of correct suppressions on the Sustained Attention to Response Task (SART) (Aim 2) after inactive vs. active cannabis administration, and to evaluate whether HIV+ women have greater declines in gait speed and functional reach and attention than HIV- women, after administration of active vs. inactive cannabis (i.e. by fitting interaction terms). In these models the 15, 60, 105 and 150 minute measures with baseline from the same visit subtracted will be the outcome(s). Because peak marijuana effect is expected to occur on 15 to 60 minutes, for the

purpose of effect size estimation, averaged 15 and 60 minute results (with baseline subtracted) will be the primary outcome(s) and this analysis reduces to a two way ANOVA or equivalently two sample t-test of differences in differences. Other quantitative and descriptive approaches previously applied to these measures[104] including area under the curve and trajectories will be fit.

POWER CALCULATIONS: Under the standard approach to power estimation of hypothesis testing at a two sided $\alpha=0.05$ with $\beta=0.2$, this study even with only 60 subjects is powered to detect (active vs. inactive cannabis) effect sizes of at least 0.53 for functional reach and 0.63 for walking time, both of which are considered to be medium.[105] The power here is greatly increased by repeated measures being taken pre and post administration with the outcome being the difference of averaged measures that from our normative data have correlations of $\rho=0.82$ an 0.87 for walking time and functional reach which reduces the variances of within subject difference to $0.27\sigma^2$ and $0.195\sigma^2$ respectively. We do not have similar normative data for power estimation of other outcomes. Some authors believe that in pilot studies that will be later confirmed[105-107] a higher $\alpha=0.25$ is appropriate, in which case, the detectable effect sizes drop to 0.32 for reach and 0.38 for walking time which are considered close to small.[105] Other criteria besides hypotheses testing that are satisfied by smaller sample sizes should be considered for pilot studies[107-109] with other authors finding 20-70 subjects adequate for estimating standard deviations[110-112] and effect sizes[112,113] of outcomes and identification of subject exclusion criteria for the main study.[114]

8. DATA QUALITY CONTROL AND DATABASE MANAGEMENT

DATA MANAGEMENT AND QUALITY ASSURANCE

We will prospectively conduct screening telephone interviews, and if interested and eligible, at the scheduled MWCCS core visit we will additionally perform in-person psychiatric assessments (using the M.I.N.I), physical exams, and EKGs. Study visits at Columbia University include assess of cognitive function with a brief computer-based battery, as well behavioral measurements, and testing of mobility and balance as outlined above. We will utilize previously collected MWCCS data for purposes of pre-screening for eligibility of potential subjects prior to the telephone screen, as well as incorporate existing MWCCS into our study database for ongoing analyses. All these data are collected and coded in databases using unique identifiers.

The Bronx MWCCS data management team also ensures site Quality Assurance. The Bronx MWCCS will also implement procedures outlined by DACC in the MWCCS Manual of Operations (MOO). The research team meets weekly to review protocol deviations, study findings/abnormalities, and data edits in real time and corrects any identified discrepancies within 48 hours and addresses problems weekly as part of Continuous Quality Improvement. Our MWCCS data center will provide substantial support for this study, including preliminary queries of the database, help designing forms, and merging and developing datasets.

Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process led by the Bronx MWCCS Project Director and Data Manager.

DATA ENTRY METHODS

All data that is not in electronic form will be double entered into REDCAP databases, which will be maintained in the research offices by our Data Manager. Each database and all computers will be password protected. Data will be backed up daily on a central server managed by Einstein. In all databases, data will be linked only to participant study ID number, and not participant name.

Nearly all MWCCS data are collected via direct data entry (DDE) to a server at its central MWCCS Data Analysis and Coordination Center (DACC) using Montefiore's secure information network, thus updating data to DACC continuously. Rarely, if internet availability is interrupted, we utilize paper forms and enter the data manually once connectivity is restored. We routinely monitor data for both completeness and accuracy.

PROTECTION OF CONFIDENTIALITY:

Confidentiality throughout the study is maintained by assignment of a unique study identifier with linkage to research subject name included in a single roster with limited accessible to authorized study staff. These files are double locked at all times. All computerized study files are password protected with encryption software and again, only include the unique study identifier. Any research records maintained

as source documentation that includes PHI will always be protected with limited access in double locked and/or password/encrypted files. No PHI will be included in the study database. No reports or publications from the study will include any individual's identifying information. No study data, including laptops that include files with PHI, will ever be removed from the study sites.

All study key personnel, including anyone who interacts with the participants in the collection of data, have or will have completed training courses on the Protection of Human Research Subjects. Staff has been trained in the procedures necessary to insure confidentiality.

9. DATA SAFETY MONITORING PLAN

A. TRIAL SAFETY

Potential risks and benefits for participants

Potential Benefits of Proposed Research. There are few direct benefits to research volunteers in the proposed study. Results from this study may eventually benefit women who use cannabis by providing important information about balance, mobility, and cognitive disorders associated with cannabis use and HIV infection. Prior to study acceptance, all volunteers will be screened for medical and psychiatric exclusion criteria. Volunteers understand that they can obtain a referral for drug treatment at any stage of their research participation. We repeat our offer for treatment referral at screening, and at discharge from the study. We will attempt to obtain a placement in a drug abuse clinic for those people who indicate a desire for help, and will inform all volunteers of our ongoing cannabis-treatment studies conducted within the Division of Substance Abuse.

Potential Risks. The major risk of research participation is related to drug administration. It is worth noting that we have had vast experience thus far administering a range of abused drugs, including cannabis, cocaine, amphetamines, opioids, and ethanol, and have used oral, intravenous, intranasal, and smoked, routes of administration. We also have experience with the amount of cannabis proposed in the current study with no adverse consequences.

Many of the assessments for this study involve minimal physical, psychological, social, or other risks risk to the participants such as answering questionnaires, physical examination of gait, and performance of simple tasks such as balancing with feet in a tandem position. The timed gait assessments do not require attachment to any monitoring devices. Thus the risks are expected to be similar to those risks involved in everyday standing, stair climbing, walking, and activities of daily living. Subjects might tire during the mobility test. Research assistants will closely monitor subjects for tiredness, loss of balance, or any other physical discomfort symptoms, and stop testing or institute rest breaks as needed.

Participation in research may involve a loss of privacy; however every effort is made to insure the confidentiality of the participant. All samples and study information will be coded onto forms that will be kept in locked files at all times. Confidential information is maintained in a locked cabinet that is accessible only to study personnel. Staff has been trained in the procedures necessary to insure confidentiality. No individual identities will be used in any reports or publications resulting from the study.

Possible side effects of smoked cannabis include: sedation, gait disturbance, tiredness, sadness, anxiety, concentration difficulties, increased heart rate, palpitations, dizziness, sleep disturbance, changes in food intake, restlessness, confusion, sleepiness, clumsiness, gastrointestinal upset, headache, nausea, dry mouth, pallor, flushing, sweating, and slurred speech. All participants will be carefully monitored and fully informed of the side effects that they might experience. Because all currently smoke cannabis, these effects should be familiar to them. Inactive and active cannabis cigarettes are provided by NIDA to Dr. Haney's Cannabis Research Laboratory, which has conducted federally funded, placebo controlled human laboratory studies of cannabis administration for the past 20 years, including studies that include HIV-infected volunteers. Dr. Haney has FDA, DEA and NY State Narcotics licenses to conduct federally funded studies testing the behavioral effects of cannabis. Participants will be closely monitored by staff during the balance and walking task to prevent actual falls.

Adequacy of protection against risks. All participants are fully informed of the side effects that they might experience. Only those judged suitable are invited to participate in the full study. Throughout participation, we will carefully monitor participants for agitation, hostility, depression, or changes in behavior, thinking, or suicidal thoughts or actions, anxiety, panic, aggression, anger, mania, abnormal sensations, hallucinations, paranoia, or confusion.

Emergency medical equipment is available in Dr. Haney's laboratory, which is located adjacent to New York Presbyterian Hospital so a full medical emergency back-up team is available. We anticipate, however, that careful screening, informed consent, cannabis dose selection, and participant monitoring, will obviate the need for such emergency care. Dr. Haney has been conducting inpatient and outpatient clinical pharmacology research for over 20 years.

Adverse Event and Serious Adverse Event Collection and Reporting
Because the research visits will include urine collection for pregnancy and drug testing, and a single administration each of cannabis as well as placebo prior to computerized cognitive testing and functional assessments of balance and gait), participants are unlikely to incur more than minimal risk of AEs. However, if AEs occur, they are likely to be non-serious and related to time-limited effects of cannabis, including neuropsychiatric/mood effects (tiredness, restlessness, sadness, anxiety, concentration difficulties, dizziness, sedation, sleepiness or sleep disturbance) and physical effects (increased heart rate, palpitations, changes in food intake, gastrointestinal upset, headache, nausea, dry mouth, pallor, flushing, sweating, clumsiness, and gait disturbance). Whether cannabis use is associated with risk of falls is unclear and falls may be a potential adverse effect of cannabis. AEs will be collected by members of the research team as they conduct the research visits, and serious AE will be reported to Dr. Sharma immediately, while non-serious AEs will be reported during regular project meetings conducted every two weeks.

A serious AE includes an event experienced by a participant during the research visit that: (a) causes or has the potential to cause significant impairment of health or death; or (b) that prompts suspension of the research protocol (temporarily or permanently), even if the risk is explicitly identified in the consent form; or (c) occurs with a frequency or degree of severity greater than anticipated. Examples of serious adverse events are: death, disability, or inpatient hospitalization. Dr. Sharma is responsible for reporting adverse events to the DSMB, Einstein IRB, and NIA. All adverse events will be compiled, and reported in summary form every 6 months and at the conclusion of the study to the DSMB, Einstein IRB, and NIA. Additionally, unanticipated, non-serious AEs will be documented on the Einstein IRB Adverse Event Form and reported to the IRB within 30 days. Serious AEs will be reported to the IRB and NIA within 48 hours by phone, email, or fax.

Management of SAEs or other study risks
Dr. Sharma (at Einstein) and Dr. Yin (at CUMC), board-certified internists and infectious diseases specialists with expertise in HIV, will be available in-person or by cell phone during all research activities. If a serious AE occurs, Dr. Sharma will be notified by a member of the research team. Dr. Sharma will then make a clinical assessment of the participants' health and safety. Per clinical judgment, participants will be referred to treatment at their primary care clinic or escorted to the Columbia University Medical Center (CUMC) emergency department if necessary. The main study risk is a breach of confidentiality and we have set into place several precautions to prevent this. These are described above.

B. Interim Analysis

Plans for interim analysis
Because this is a pilot study which is not designed to be fully powered to detect differences by group, we do not plan to conduct interim analyses of the effects of active cannabis on balance and mobility (Aim 1) and cognition (Aim 2). Instead, we will conduct an interim analysis of serious adverse events, which will be used to make decisions about stopping the study. Interim analyses of the data will be conducted when 50% of the sample has accrued. If we find that serious adverse events are significantly more likely in one group (e.g., active cannabis compared to placebo), the study will be stopped. Interim analyses will be conducted by the data manager and biostatistician. Dr. Sharma, in collaboration with the research team, the DSMB, and the NIH, will review all pertinent data to determine whether to continue accrual.

Early Study Termination
A decision to stop the study may be made at any time that the research team and DSMB agrees that an unacceptable type and/or frequency of adverse events has been observed. Dr. Sharma will report the decision to terminate the study to the DSMB, IRB and NIH within 48 hours of this determination. She will submit a narrative description of the reasons for early termination of the study to the IRB and NIH within 10 days.

C. Data and Safety Monitoring

Responsibility for Data and Safety Monitoring

We will establish a data and safety monitoring board (DSMB) for the proposed study, which will meet every 6 months. The DSMB will meet and vote on approval of the protocol prior to initiation. It will review safety and trial progress and provide advice with respect to study continuation, modification, and/or termination. Dr. Sharma will be responsible for convening the DSMB, providing all research-related materials and reports to the DSMB every 6 months during the project period, and communicating DSMB activities and recommendations to the Einstein IRB and NIA.

Frequency of Data and Safety Monitoring

Data and safety monitoring will be ongoing, and will include formal reviews every 6 months by Dr. Sharma, Co-Investigators, and the DSMB. For each formal review, Dr. Sharma will create a report documenting any quality assurance breaches or AEs that were discovered in the previous 6 months. Quality assurance breaches will be assessed through inspections of study forms, logs, and datasets. AEs will be assessed and compiled continually, through monitoring all study activities and through notification from the research team; study participants; participants' family members, friends, or colleagues; participants' physician or other health care provider involved in their care; or other persons who may have knowledge of such adverse events.

Content of data and safety monitoring report

Semiannual DSM reports will include a brief description of the trial, baseline sociodemographic characteristics of participants, participant recruitment and retention rates, any quality assurance issues that might occur, summary of adverse events and serious adverse events, any changes to the protocol, any IRB actions, and data comparing active cannabis vs. placebo.

A formal report containing the recommendations for continuation or modifications of the study will be prepared and sent to the DSMB members not later than four weeks after the meeting. Once approved by the DSMB members, the DSMB Chair or NIA Program Official will forward the formal DSMB recommendation to Dr. Sharma. Dr. Sharma will be responsible for distributing the DSMB recommendation to all co-investigators and to ensuring that copies are submitted to all the IRBs associated with the study (Einstein, SUNY Downstate, and Columbia University IRBs).

The DSMB report will include a recommendation to continue or to terminate the study. This recommendation will be made by formal majority vote. The DSMB may recommend termination of the study at any time by majority vote. In the event of a split vote in favor of continuation, a minority report will be included within the regular DSMB report. The DSBM report will not include either unblinded data nor discussion of the unblinded data.

DSMB membership and affiliation

The DSMB will be comprised of individuals at who are not employees of any of the organizations involved in the study, who are unaffiliated with the study, and have no financial or other conflicts of interest. Members of the DSMB have been carefully selected based on scientific and clinical backgrounds and expertise in substance use and misuse and clinical trials.

Members of the DSMB will be:

1) Erin E. Krebs, MD, MPH. Associate Professor of Medicine, University of Minnesota Medical School and Women's Health Medical Director, Minneapolis Veterans Affairs (VA) Health Care System, Minnesota. Dr. Krebs provides expertise on opioid use and misuse, particularly in relation to pain, physical function, falls, and fracture in older adults.

2) Alain H. Litwin, MD, MPH, MS. Professor of Medicine, University of South Carolina Greenville School of Medicine and Vice Chair of Academics and Research, Department of Medicine, Greenville Health System (GHS), and Professor, Clemson University School of Health Research, South Carolina. Dr. Litwin is board certified in internal medicine and addiction medicine, has received funding from NIDA, PCORI, CDC, SAMHSA, AHRQ, CMS, Robert Wood Johnson Foundation, and local and state governments, to study treatment of treatment of hepatitis C virus (HCV) among persons actively injecting drugs. He has

served as the Medical Director of a large methadone maintenance treatment program and is currently Medical Director of an integrated addiction treatment program, and is an international leader in implementing and studying interventions for people who use drugs in heterogeneous settings while incorporating stakeholder input. Dr. Litwin is the PI of PCORI-funded national, multi-site HCV randomized controlled trial focused on improving HCV outcomes in people who inject drugs (8 states and 26 sites).

3) Madhu Mazumdar, Ph.D. Professor, Department of Population Health Science and Policy, Icahn School of Medicine at Mt-Sinai, NY, NY. Dr. Mazumdar is founding Director of the Institute of Healthcare Delivery Science at Mount Sinai Health System (MSHS), with experience in sources of variation in clinical practice and risk adjusted outcomes across hospitals, prospects for reducing patient harm, and opportunities to improve outcomes by conducting comparative- and cost-effectiveness research regarding new practices and interventions. Her additional research interests include methodology development in the fields of meta-analysis, diagnostic test comparison, and clinical trial design.

4) Sachin Patel, M.D., Ph.D. is Associate Professor of Psychiatry and Behavioral Sciences, Molecular Physiology & Biophysics, and Pharmacology at Vanderbilt University Medical Center. He is the James G. Blakemore Chair in Psychiatry Research and Director of the Division of Addiction Psychiatry. Dr. Patel's overall research seeks to understand the role of neuronal cannabinoid signaling in brain function relevant to psychiatric disorders. Research specifically focuses on the role of the cannabinoid system in the regulation of stress response physiology, and the subsequent development of anxiety and depressive phenotypes relevant to affective disorders, as well as understanding the mechanisms by which cannabis exposure early in life leads to an increased risk for the development of psychiatric disorders during adulthood. Dr. Patel will provide expertise on effects of cannabis for this study.

Conflict of interest

Members of the DSMB have no relevant interests or activities with the study. None of the DSMB members are employees of any of the organizations involved in the study (paid or unpaid, part-time or full-time). DSMB members have no financial interests or assets in any organizations involved in the study; nor do the members' spouses or dependent children. All DSMB members have signed a conflict of interest statement.

Protection of Confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

DSMB responsibilities

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the National Institute of Aging (NIA) Director to monitor participant safety, data quality and evaluate the progress of the study. The DSMB responsibilities are to: (1) review the research protocol, informed consent documents and plans for data safety and monitoring; (2) advise the NIA on the readiness of the study staff to initiate recruitment; (3) evaluate the progress of the study, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome; (3) consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial; (4) review study performance, make recommendations and assist in the resolution of problems reported by Dr. Sharma; (5) protect the safety of the study participants; (6) report to NIA on the study safety and progress; (7) make recommendations to the NIA, the PI, and, if required, to the Food and Drug Administration (FDA) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study; (8) review interim analyses in accordance with stopping rules; (9) ensure the confidentiality of the study data and the results of monitoring; and, (10) assist the NIA by commenting on any problems with study conduct, enrollment, sample size and/or data collection. The DSMB will discharge itself from its duties when the study is complete.

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