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CANNABIS, CANNABIS-BASED PRODUCTS, OR CANNABINOIDS BRIEF EVIDENCE REPORT:

EVIDENCE FROM EXPERIMENTAL TRIALS IN PEOPLE LIVING WITH HIV OR AIDS

Report finalized: July 2024

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ABBREVIATIONS

AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ART	(Combination) antiretroviral therapy
AUC	Area under the concentration by time curve
BMI	Body mass index
CB1/CB2	Cannabinoid receptor type 1/type 2
CBD	Cannabidiol
CBDV	Cannabidivarin
CBP	Cannabis- or cannabinoid-based product
CI	Confidence interval
CNS	Central nervous system
CRRB	Utah Cannabis Research Review Board
CYP	Cytochrome P450 enzyme
DDI	Drug-drug interaction
FAHI	Functional Assessment of HIV Infection
FDA	(United States) Food and Drug Administration
HAND	HIV-associated neurocognitive disorders
HR	Heart rate
HRNP	HIV-related neuropathic pain
HSQ	Hunger-Satiety Questionnaire
HIV	Human immunodeficiency virus
KPS	Karnofsky performance status
LOE	Level of evidence
N/n	Number of trials/number of participants
NASEM	National Academies of Sciences, Engineering, and Medicines
NCT	National Clinical Trial (registry number)
PGIC	Patient's Global Impression of Change
PK	Pharmacokinetic
PLWA	People living with AIDS
PLWH	People living with HIV
PLWHA	People living with HIV or AIDS
QoL	Quality of life
RCT	Randomized controlled trial
RNA	Ribonucleic acid
ROB	Risk of bias
SD	Standard deviation
SEM	Standard error of the mean
SR	Systematic review
THC	(delta-9)-tetrahydrocannabinol
VAS	Visual analog scale

1.0 OBJECTIVE

Medical cannabis can be used in the management of human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) under Utah law.[1] The Utah Cannabis Research Review Board (CRRB) previously summarized evidence for the use of cannabis in people living with HIV or AIDS (PLWHA). Existing guidance from the CRRB includes 3 formal (ie, graded) conclusions about the use of cannabis in PLWHA, including[2]:

- "There is *limited evidence* to support the conclusion that medical cannabis is effective in the treatment of symptoms of painful HIV-associated peripheral neuropathy" (page 5).
- "There is *limited evidence* to support the conclusion that medical cannabis is effective in the treatment of HIV/AIDS wasting syndrome" (page 5).
- "There is moderate evidence to support the conclusion that medical cannabis and cannabinoids can have clinically significant beneficial effects in the management of chronic pain, particularly pain that is due to nerve damage or neuropathy. This is based on supportive findings from good to fair quality controlled clinical trials with very few opposing findings" (page 6).

The **objective** of this report is to summarize experimental (ie, nonrandomized or randomized) controlled trials of the use of cannabis- or cannabinoid-based products (CBPs) in PLWHA to assist the CRRB in updating existing guidance.

2.0 BACKGROUND

HIV is a lentivirus that infects the immune system, reducing the number of CD4+ T lymphocytes and increasing the risk of serious infections and cancer. Advanced HIV infection is called AIDS, which is typically defined as the presence of a CD4+ lymphocyte count below a threshold (<200 cells per mm^3) or the occurrence of an AIDS-defining illness, such as opportunistic infections or cancers, or HIV-attributed wasting syndrome.[3] Combination antiretroviral therapy (ART) for HIV became available in the US in 1996.[4] While ART reduces HIV progression by suppressing the HIV viral load and increasing CD4+ lymphocyte counts and its use is associated with reduced HIV-associated mortality, some people living with HIV (PLWH) receiving ART experience long-term complications that are often attributed to persistent immune system activation and inflammation.[3]

Complications of HIV or AIDS or their treatment that could potentially benefit from cannabis or cannabinoid-based therapy (CBPs) include, but are not limited to, neuropathy/neuropathic pain, HIV-associated neurocognitive disorder (HAND), nausea and/or anorexia, and cachexia/wasting syndrome.[5-7] The incidence of HIV-associated anorexia and cachexia has declined with the availability of ART; the average annual prevalence of HIV-associated anorexia/cachexia was 3% in a sample from 2012-2018.[8] Both HAND and HIV-related neuropathic pain (HRNP) are relatively common complications of HIV.[9,10] For patients who develop anorexia/cachexia, HAND, or neuropathy despite optimal ART, treatment options are primarily symptomatic.[11-13] Symptoms of HRNP typically include sleeve-like symmetrical pain and hyperalgesia of the extremities. The pathogenesis of HRNP is not fully understood, but it might develop from vascular inflammation and/or nervous system damage, particularly with long-standing disease, or from side effects of certain nucleoside reverse transcriptase inhibitors that are infrequently used to treat HIV in the US today.[7] The severity of HAND varies, including both patients with mild cognitive

impairment and patients with dementia. HAND is hypothesized to occur due to chronic inflammation from HIV proliferation in the central nervous system (CNS; an area with poor ART penetration).[6]

The oral synthetic delta-9-tetrohydrocannabinol (THC), dronabinol (Marinol, Syndros), is US Food and Drug Administration (FDA)-approved for treatment of AIDS-associated anorexia with weight loss. Notably, dronabinol was approved for use in patients with AIDS in 1993,[14] prior to the availability of modern highly effective ART for HIV.[5] A single pivotal randomized controlled trial conducted in the 1990s (Beal et al 1995) supported the approval of dronabinol for AIDS-associated anorexia.[15] Cannabis plant-derived cannabinoids other than THC and cannabidiol (CBD) might also have therapeutic applications. For example, the propyl analog of CBD, cannabidivarin (CBDV),[16] that has a relatively low affinity for cannabinoid type 1 (CB1) and type 2 (CB2) receptors (with much higher affinity for CB2)[17] and may also act on transient receptor potential (TRP) ion channels.[18] CBDV is considered a candidate for the treatment of inflammation, pain, seizures, and autism spectrum disorders.[16]

There are potential safety concerns for use of CBPs in PLWHA. Notable concerns include adverse respiratory outcomes from cannabis inhalation (especially from smoking), as well as cognitive, cardiovascular, and mental health outcomes. PLWHA have a disproportionately increased risk of chronic obstructive pulmonary disease (COPD), pulmonary infections, and lung cancer compared to the general population. While cannabis *might* have therapeutic applications in the treatment of HAND,[9,19] there are also concerns that it could worsen cognition.[5]

Anti-HIV ART regimens are potentially vulnerable drug-drug interactions (DDIs) through multiple mechanisms, including through interactions with drug-metabolizing enzymes or transporter proteins that are also known to interact with the major cannabis constituents THC and/or CBD. [4] The likelihood of interactions with cannabis depends on the type of ART regimen, cannabis regimen, and other concurrent medications. According to the US DHHS guideline on the treatment of HIV in adults and adolescents, all protease inhibitors and cobicistat-boosted elvitegravir can possibly interact with dronabinol causing increased dronabinol exposure and dronabinol-associated adverse events (AEs).[4] Monitoring for dronabinol-associated AEs during concurrent use with interacting antiretroviral agents is recommended. No information was provided by the DHHS about interactions between other cannabinoid products and ART, although the DHHS described that cannabis is not considered to interfere with most individual's ability to achieve HIV viral suppression in general.[4]

As of May 2024, of 86,571 Utahns who are medical cannabis card holders, HIV or AIDS was reported as a qualifying condition for 229 patients and <11 patients, respectively.[20] In a nationally representative sample of US adults (from 2005-2015) with HIV, 35% had taken cannabis (recreational or medicinal) within the past year and 26% of those surveyed between 2013-2015 endorsed taking medical cannabis within the past year.[21] PLWHA have endorsed using cannabis to help manage psychological distress, poor appetite, and pain.[5]

3.0 RESULTS

3.1 Overview of Included Trials

Our literature search identified 12 unique completed controlled experimental trials (with 15 citations) of CBPs in PLWHA with results. Of the 12 trials, 6 were not included/addressed as a primary study or as part of a cited review article by the existing CRRB guidance for the use of cannabis in patients with HIV/AIDS (see **Appendix A**). Identified trials that were not addressed by the current guidance include Haney et al 2005,[22] Haney et al 2007,[23] Bedi et al 2010,[24] Eibach et al 2020,[25] Mboumba et al 2022/2023,[26,27] and an unpublished trial (NCT03099005).[28]

The study designs of the included trials varied. Most trials were randomized controlled trials (RCTs),[22,23,25,27-34] except for the trial by Bedi et al 2010 that did not report any information about randomization.[24] The trials used both parallel (N=5 trials),[27,29-31,34] staggered (ie, with 3 treatments administered in a staggered order with multiple treatment sequences varying by participant) cross-over (N=2),[22,23] and non-staggered (ie, 2 treatments administered as a single consecutive sequence with a wash-out period between them) cross-over (N=5) designs.[24,25,28,32,33] Several trials administered the study medications and measured outcomes in a monitored inpatient setting, with participants inpatient for the duration of the trial (Abrams et al 2003)[29] or partially outpatient during washout periods between different treatments (Haney et al 2005, Haney et al 2007, Bedi et al 2010).[22-24] Most trials were described as double-blinded,[22-25,28,30-33] except for Mboumba et al 2022 and Timpone et al 1997 that were completely open-label and Abrams 2003 that was blinded to oral treatments (dronabinol and placebo capsules) but not to smoked cannabis.[27,29,34] Two staggered cross-over trials used double-dummy blinding with 2 different placebos matched to both the smoked cannabis and dronabinol oral capsule.[22,23] All 12 trials included adult participants, the majority of whom were male.[22-25,27-34] Total sample sizes ranged from 7 (Bedi et al 2010) to 139 (Beal et al 1995),[24,31] with a median size of 34 participants. Several trials reported including fewer participants in the data analyses than the number recruited (eg, due to drop-outs or non-adherence to the trial protocol); for example, Beal et al 1995 included only 88 of 139 recruited participants in their primary data analysis.[31]

Five of the 12 included experimental trials enrolled patients with HIV/AIDS without the requiring that they had specific complications (eg, cachexia, HRNP) to explore the safety/general effects of a CBP.[22-24,26,27,29] While it is possible that some patients in these trials had complications (eg, Bedi et al included 2 patients with low body mass that is suggestive of muscle wasting[24]), most participants appeared to be male PLWH without specific complaints who were receiving ART and had experience using cannabis. Although not explicitly defined, the trial by Haney et al 2005 likely included people living with AIDS (PLWHA) since the standard deviation (SD) of the mean CD4+ count extended to <200 cells/mm^3 and half of study participants were classified as having clinically low muscle mass (<90% body cell mass/height).[22] Participants in the Abrams et al 2003 trial had stable HIV ribonucleic acid (RNA) levels for at least 16 weeks upon entering the trial, no recent unintentional weight loss, and no opportunistic infection or malignancy that would have required acute treatment, although nearly half of participants had a history of an AIDS-associated illness.[29] Of the 5 trials, only the recent trial by Mboumba et al 2022 required participants to have a suppressed HIV viral load (<40 copies/mL) and to not have recently used cannabis within 4 weeks of the trial.[27] These trials reported a variety of outcomes, such as the effects of

a CBP on the immune system (eg, CD4+ lymphocyte counts), HIV RNA levels, hunger/satiety, body weight, and cognitive performance.[22-24,26,27,29]

Four of the included trials enrolled patients with HIV who had symptomatic HRNP.[25,28,30,32] Most trial participants appeared to have been receiving stable ART therapy.[25,30,32] Three of the 4 trials enrolled participants with a history of cannabis use,[28,30,32] including two trials with all or most participants reporting current cannabis use.[28,30] The 4th trial did not report information about the participant's historical or current cannabis use.[25] Primary efficacy outcomes were the change in pain intensity.[25,28,30,32]

The remaining 3 included trials primarily targeted PLWA with anorexia and/or cachexia.[31,33,34] Included participants in each trial had HIV/AIDS, and either had lost 10% or ≥ 2.3 kg of their usual body weight, were underweight per body mass index (BMI), or had a BMI in the lower range of normal. All participants tolerated oral food intake and lacked recent major medical complications (eg, opportunistic infections).[31,33,34] Each trial prohibited cannabis use within 20 days (Beal et al) or 30 days (Struwe et al and Timpone et al) before the trial[33,34]; only Beal et al described that about 42% of the treatment arm and 48% of the placebo harm had not previously used cannabis.[31] All 3 trials were conducted in the 1990s, which was before modern combination ART for HIV. Struwe et al 1995 and Timpone et al 1997 reported that most participants were receiving ART (but not necessarily combination highly-effective ART; 60% and 89%, respectively),[33,34] whereas Beal et al only reported that the proportion of participants receiving ART was well-balanced between treatment groups.[31] Beal et al 1995 is the pivotal trial that led to dronabinol's FDA approval for AIDS-associated anorexia with weight loss. The study by Timpone et al was focused on safety and pharmacokinetic (PK) outcomes,[34] whereas the co-primary outcomes in the trial by Beal et al was change in appetite on a visual analog scale (VAS) and change in weight,[31] and Struwe et al did not specify a primary outcome.[33]

Across the 12 trials, studied CBPs included dronabinol (n=7 trials),[22-24,29,31,33,34] smoked cannabis (N=5),[22,23,29,30,32] vaporized cannabis (N=1),[28] oral THC/CBD or CBD-only capsules (N=1),[27] and oral CBDV (N=1).[25] Most trials used a placebo comparator (N=9); of the studies without a placebo comparator, one used an active control, oral megestrol acetate[*],[34,35] and the remaining 2 trials studied multiple cannabis dosages, lacking a non-cannabinoid comparator.[27,28] Three trials compared the effects of both dronabinol and smoked cannabis with placebo,[22,23,29] and 1 trial administered both dronabinol monotherapy and dronabinol in combination with megestrol acetate.[34]

Overall, the treatment duration for most trials was short. The median treatment duration is approximately 24.5 days (range, 1 to 84 days) for the 10 trials providing sufficient information about the duration of treatment.[24,25,27-34] The two remaining trials used a staggered design (ie, alternating treatment sequences between dronabinol, smoked cannabis, and placebo) and provided insufficient information about the treatment duration and number of treatment sequences.[22,23] One of these trials (Haney et al 2005) reported administering 8 experimental sessions over 3-4 weeks,[22] which we estimate to have included 3 sessions per active treatment, likely with treatments administered on discrete, non-sequential days. The other staggered trial (Haney et al 2007) administered the same active treatment on 4 sequential days, possibly with 2 discrete 4-day treatment sequences per active treatment.[23]

[**] Megestrol acetate suspension is a progesterone derivative that is FDA-approved (at doses of 625-800 mg/day) for treatment of anorexia, cachexia, or significant weight loss in PLWA.

Refer to **Appendix B** for additional details about the study design and results from the 12 included trials. The following sections highlight efficacy and safety results from these trials. While we divided the summarized outcomes into those for "efficacy" versus "safety", some outcomes could be both.

3.2 Select Efficacy Outcomes

3.2.1 HIV-Related Chronic Neuropathic Pain (HRNP)

Mixed results were observed for the analgesic effects of CBPs among adults with chronic HIV-associated neuropathy, most of whom were men with chronic HIV receiving ART.[25,28,30,32] Participants in the 3 published trials had approximately moderate pain at baseline and were allowed to continue other analgesics during the trial.[25,30,32] Ellis et al 2009 included participants with pain refractory to at least 2 other analgesics.[32] Participants in the unpublished trial (NCT03099005) had mild pain at baseline (mean scores of 2.2–2.8/11), and insufficient information was reported about concomitant analgesics.[28]

Short-term 5-day treatment with smoked cannabis (1-8% THC by weight; most participants used 2-4%) administered three or four times daily significantly improved patient-reported pain scores from baseline compared to matched placebo cannabis cigarettes in 2 trials (Abrams et al 2007 and Ellis et al 2009). The proportion of participants who achieved a ≥ 30% reduction in pain from baseline was significantly greater from cannabis versus placebo use in both the Abrams et al (13/25 [52%] vs 6/25 [24%], respectively) and Ellis et al (46% vs 18%, respectively) trials.[30,32]

In contrast, Eibach et al 2020 found that 4 weeks of treatment with oral CBDV 400 mg daily did not significantly reduce patient-reported pain from baseline compared with matched sesame oil placebo. A higher proportion of placebo-treated participants achieved at least a 20% reduction in pain (61.3%) versus CBDV-treated participants (29%). Utilization of concomitant analgesics was similar between CBDV and placebo treatment periods. While this study was underpowered (the study enrolled 31 of 50 targeted participants) to detect a difference in pain outcomes between treatments, investigators felt that the null result is unlikely to change with more participants.[25]

Results from an unpublished trial examining outcomes after a single dose of vaporized cannabis at 3 different doses/ratios of THC and CBD (low CBD, medium CBD, and high CBD) suggest that the treatments *might* similarly reduce patient-reported pain acutely. Authors of this study did not report statistical comparisons, and the study appears to be very underpowered, with only 5 participants out of the target 120 enrolled.[28]

Two studies measured the patient's global impression of change (PGIC); however, interpretation of the results from one of these studies (NCT03099005) is limited because the study did not report statistical comparisons and lacked a non-cannabinoid control group.[28] Compared to placebo, 4 weeks of treatment with CBDV did not significantly improve the PGIC in participants with HRNP.[25] PGIC results from NCT0309905 suggest that single dose of the studied oral THC/CBD treatments might modestly improve the PGIC (mean score range of 2.6 to 3.4) in participants with HRNP.[28]

3.2.2 HIV-Associated Wasting/Cachexia, Anorexia, or Hunger/Satiety

3.2.2.1 Trials among people living with AIDS who had low body weight

Among PLWA who had a low body weight or clinically significant weight loss, dronabinol (2.5 mg twice daily or 5 mg twice daily) treatment tended to increase appetite/caloric intake without significantly increasing weight compared to placebo or megestrol acetate.[31,33,34] Notably, results from 2 out of 3 trials were likely underpowered to detect differences in efficacy outcomes; Struwe et al 1993 included only 5 participants (7 dropped out), and Timpone et al 1997 included complete results from 39 participants (of 52 randomized).[33,34] The trial by Timpone et al was designed to primarily evaluate PK and safety parameters. Nonetheless, Timpone et al found that megestrol acetate 750 mg significantly increased weight from baseline to 12 weeks, unlike dronabinol 2.5 mg twice daily.[34]

Weight**:** Non-statistically significant increases in weight from baseline to 5 or 6 weeks were observed with dronabinol versus placebo.[31,33] In the larger trial by Beal et al 1995 (including 139 total and 88 'evaluable' participants), 22% of the dronabinol-treated evaluable participants gained 2 kg from baseline to 6 weeks compared to 10.5% of placebo-treated participants (P=0.11).[31] Struwe et al reported that dronabinol 5 mg twice daily significantly increased body fat versus placebo (1% vs 0.06% increase, respectively).[33] In the longest 12-week trial by Timpone et al, megestrol 750-mg-treated participants gained significantly more weight from baseline (mean ± standard error [SEM]: +6.5 ± 1.1 kg; mean 11% weight gain) than participants who received dronabinol 2.5 mg twice daily (mean ± SEM: –2.0 ± 1.3 kg). Increases in weight from baseline were similar among participants who received megestrol acetate 750 mg monotherapy and megestrol 750 mg plus dronabinol 2.5 mg twice daily.[34]

Appetite/caloric intake: Compared to placebo, dronabinol 5 mg twice daily non-significantly (ie, no statistically significant difference) increased daily caloric intake from baseline to 5 weeks (daily median kcals/kg/24 hours: dronabinol 3.84 versus placebo 0.84).[33] Dronabinol 5 mg twice daily also non-significantly improved patient-reported appetite on a VAS versus placebo.[33] In the larger trial by Beal et al 1995, mean appetite scores on a VAS were significantly improved from baseline to 6 weeks with dronabinol 2.5 mg twice daily vs placebo (37% increase vs 17% increase in the total population, respectively; P=0.05).[31] Timpone et al found similar improvements in VAS scores for hunger with dronabinol and megestrol acetate from baseline to 1 week, with no changes found after 1 week of treatment. Unlike for dronabinol, megestrol acetate PK parameters (maximal plasma concentration and area under the concentration by time curve [AUC]) was positively correlated with breakfast and dinner hunger scores.[34]

Nausea: Dronabinol 2.5 mg twice daily treatment significantly decreased nausea compared to placebo from baseline to 12 weeks among patients with mild nausea at baseline (20% vs 7% decrease from baseline; P=0.05 in the evaluable population).[31] There were no statistically significant differences in patient-reported nausea scores during treatment with dronabinol and megestrol acetate throughout the 12-week trial.[34]

3.2.2.2 Other trials among people living with HIV or AIDS (PLWHA)

Four small (7 to 67 randomized participants) short-term trials among PLWHA with experience using cannabis and without specific complaints (ie, enrolled regardless of having anorexia or cachexia)

reported weight or appetite outcomes among patients treated with smoked cannabis, oral dronabinol, or placebo.[22-24,30] Most of these trials (Haney et al 2005, Haney et al 2007, Bedi et al 2010) enrolled participants with recent frequent (≥ 2 times weekly) cannabis use to explore the efficacy and safety of higher dronabinol doses (10 to 40 mg daily).[22-24] Notably, participants were allowed to use cannabis at home between treatment sessions in the trials by Haney et al 2005 and Haney et al 2007,[22,23] which could have biased the results toward a finding of no difference versus placebo.

Weight: Two trials (Abrams et al 2003 and Haney et al 2007) found cannabis (3.9% THC) three to four times daily or dronabinol (7.5 or 10 mg per day) significantly increased body weight after 4 days or 3 weeks compared to placebo.[23,29] In contrast, a third trial by Bedi et al 2010 found that changes in body weight from baseline to day 8 or from day 9 to day 16 were not significantly different between dronabinol (up to 10 mg four times daily)- and placebo-treated groups.[24]

Caloric intake: Haney et al 2005 divided participants into subgroups of low body mass (<90% of normal) and normal body mass (>90% of normal), finding that a single treatment of cannabis (with 1.8% or 2.9% THC) or dronabinol (10, 20, or 30 mg) was significantly associated with increased acute caloric intake versus placebo among patients with low, but not normal, body mass.[22] Among 7 participants, Bedi et al found that dronabinol (10 mg four times daily) was associated with significantly increased daily caloric intake (average $\pm$ SEM: 3579 $\pm$ 563 calories/day) versus placebo (average $\pm$ SEM: 3227.6 $\pm$ 385/day) on treatment days 1 through 8, but no differences between treatments were observed for treatment days 9 through 16. Bedi et al proposed that participants might develop tolerance to dronabinol-associated increases in appetite.[24] In a third trial by Haney et al 2007, both dronabinol 5 or 10 mg and smoked cannabis (with 2.0% or 3.9% THC) four times daily for 4 consecutive days significantly increased mean daily caloric intake from baseline versus placebo; dronabinol and cannabis use was associated with increased intake of calories from fat.[23]

Hunger/satiety: Three trials measured patient-reported hunger, fullness, nausea, thirst and dry mouth on the 6-item Hunger-Satiety Questionnaire (HSQ). Studies by Haney et al 2005 and Haney et al 2007 measured these effects 15 or 45 minutes after a dose (of cannabis; it is unclear if the same methods were used during dronabinol treatment), and Bedi et al reported maximal daily HSQ scores during both cannabis and dronabinol treatment.[22-24] Results on subscale scores (eg, hunger, thirst) versus placebo were inconsistent between studies, with some cannabis or dronabinol doses but not others eliciting differences versus placebo. Neither dronabinol nor cannabis was consistently associated with increased hunger versus placebo (only 1 study reported this on days 9-16 with dronabinol only).[24] The most consistent finding was that at least one dose of cannabis and/or dronabinol was associated with increased dry mouth compared to placebo.[22-24]

A separate study by Riggs et al 2012 assessed the impact smoked cannabis (1-8% THC) on appetite hormones in a subset (n=7; 25% of completers of the parent trial) of patients with HRNP with a median BMI of 25 from the Ellis et al 2009 trial. Because this study did not enroll all randomized participants and did not control for caloric intake, the study should be considered observational in nature. Authors reported that cannabis use was associated with plasma level increases in the hormones ghrelin and leptin and decreases in peptide YY compared to placebo. Increases in ghrelin and decreases in peptide YY are associated with increased hunger, whereas increases in leptin is associated with decreased

appetite. Cannabis use was not associated with significant differences in insulin levels compared to placebo use, which could suggest that the results were not confounded by food intake.[36]

3.2.3 Quality of Life or Functional Status

Many studies (N=7 trials), including PLWHA with HRNP, wasting, or no specific complaints, measured changes in patient-reported quality of life (QoL) or functional status using variable assessment scales, limiting comparisons across trials. Three trials (Mboumba et al 2022, Eibach et al 2020, Timpone et al 1997) measured patient-reported QoL using general (ie, 36-item short form [SF-36] or Euro-Qol-5 Dimension [EQ-5D]) or HIV-specific (ie, World Health Organization Quality of Life – HIV Brief Scale [WHOQOLHIV-BREF], Functional Assessment of HIV Infection [FAHI][†]) questionnaires. Whereas, other studies that reported "QoL" made inferences about QoL by administering one or more non-QOL-specific scales, such as psychological (eg, Brief Symptom Inventory) or functional status (eg, Karnofsky performance status [KPS]) assessments.[32] It is possible that studies were underpowered to detect changes in QoL or related outcomes because the study sizes were mostly small (range of 5 to 139 participants) and the measures were considered secondary outcomes.

Overall, results suggest that the studied CBPs do not improve QoL or related outcomes significantly more than placebo or megestrol acetate. Using specific QoL measures among small samples of participants with virologically suppressed HIV (Mboumba et al) or participants with HRNP (Eibach et al 2020), oral THC/CBD treatment did not significantly improve QoL from baseline to 12 weeks, nor did CBDV significantly change QoL from baseline to 4 weeks versus placebo.[25,27] No differences in FAHI scores were observed between dronabinol, megestrol acetate, or dronabinol plus megestrol active treatment arms over 12 weeks in patients with AIDS-associated wasting.[34] Although, when FAHI perception scores for all patients who received dronabinol or megestrol were pooled together, there were significant improvements from baseline to week 4 in the sub-scores for social/family and other concerns affecting QoL that remained unchanged until the end of the study at week 12.[34] Smoked cannabis (1-8% THC) four times daily for 5 days in participants with HRNP failed to significantly improve QoL-related symptoms (using multiple non-QoL-specific measures) versus placebo.[32]

Mixed results were found for the effect of studied CBPs on different functional status measures among patients with AIDS-associated wasting or anorexia. Neither dronabinol nor megestrol acetate significantly improved KPS from baseline to up to 12 weeks or compared to each other.[34] Beal et al 1995 found that dronabinol did not significantly improve KPS from baseline to 6 weeks compared to placebo.[31] However, the smallest study by Struwe et al 1993 found that dronabinol (at double the daily dose versus the 2 aforementioned studies) significantly improved the combination of patient-reported distress, mood, and function from baseline to 5 weeks on a 330-point total scale (median decrease in total score: dronabinol, –31 versus placebo, –3.5; P=0.04).[33]

3.2.4 Sleep

Few studies reported sleep-related secondary outcomes, and these studies did not specifically select participants with insomnia or sleep disturbances at baseline.

[†] The 'FAHI' questionnaire was not described well by investigators (Timpone et al 1997), but we interpreted the measure as being an HIV-specific health-related QoL questionnaire.

Based on small (7-10 participants) studies among PLWH, high-dose dronabinol (10 mg four times daily) and/or cannabis (at the highest studied concentration of THC, 3.9%) *might* improve patient-reported sleep satisfaction in the short-term of up to 8 days.[23,24] However, the statistical significance of the effects of dronabinol on patient satisfaction varied between studies; in one study, dronabinol 40 mg daily significantly improved satisfaction through treatment day 8,[24] whereas in the second study, dronabinol 40 mg numerically improved patient satisfaction versus placebo over 4 days but the difference failed to reach statistical significance.[23] Among participants with HRNP, CBDV did not significantly improve patient-reported sleep severity on the Insomnia Severity Index (ISI) at 4 weeks versus placebo.[25]

Two studies measured sleep parameters objectively (eg, sleep latency, total sleep time, time in rapid-eye movement [REM] or non-rapid eye movement [NREM] sleep) with Nightcap sleep monitors worn in an inpatient setting among PLWH.[23,24] In the first study (Haney et al 2007), all studied oral dronabinol (5 or 10 mg four times daily) and smoked cannabis (with 2.0% or 3.9% THC, four times daily) dosages numerically improved total sleep time over 4 days versus placebo, but the differences versus placebo were not statistically significant.[23] The second study by Bedi et al 2010 reported that dronabinol 40 mg daily improved the proportion of sleep total time in NREM+REM sleep out of total time in bed ("sleep efficiency") over days 1-8, but not days 9-16, compared to placebo.[24] Bedi et al, who included participants with frequent cannabis use (≥ 2 times per week) before the trial, suggested that participants might have developed tolerance to the effects of dronabinol on sleep after 8 days.[24] Both Haney et al 2007 and Bedi et al 2010 did not report results for objective sleep outcomes other than the those addressed above.[23,24]

3.3 Select Safety Outcomes

3.3.1 HIV/AIDS-Related Mortality and Serious Morbidity

There is little information from experimental studies on the impact of the studied CBPs on mortality or serious morbidity (eg, incidence of AIDS, hospital admissions) in PLWHA. One unpublished trial of 5 participants who received a single cannabis dose reported there were no deaths,[28] and a 12-week trial of PLWA reported that 2 deaths occurred, which were both considered unrelated to study medications (megestrol acetate or megestrol + dronabinol).[34] No differences in the incidence of new AIDS-defining conditions were observed during treatment of PLWA with dronabinol or megestrol acetate over 12 weeks.[34] Beal et al 1995 reported that 35 PLWA (out of an unknown total participants; could be up to 139) treated with dronabinol or placebo developed a "significant intercurrent illness" during the trial.[31]

Overall, the 12 included trials were for short durations (maximum of 12 weeks), which might have precluded a meaningful assessment of these outcomes.[22-25,27-34] The most comprehensive SR of cannabinoids or cannabis for HIV/AIDS RCTs that we found, Lutge et al 2013, concluded that evidence for mortality and major morbidity outcomes from 7 included trials (each also included in our review) is lacking. Lutge et al suggested that additional long-term experimental trial data is needed.[37]

3.3.2 T Lymphocytes

Four small (between 5 and 67 participants) short-term trials examined changes in CD4+ T-lymphocytes and/or CD8+ T-lymphocytes among (1) PLWH, of whom 58% were virally suppressed on ART (Abrams et al 2003),[29] (2) PLWH who were all virally suppressed on modern ART therapy (Mboumba et al

2022/2023),[26,27] or (3) PLWA with wasting, of whom 60 or 89% of participants were receiving ART (Struwe et al 1993 and Timpone et al 1997).[33,34] Among PLWA, treatment with dronabinol 10 mg per day for 5 weeks or dronabinol 5 mg per day for 12 weeks was not associated with significant changes to CD4+ lymphocyte counts compared to placebo or megestrol acetate.[33,34] Timpone et al described that patient's CD4+ lymphocyte counts fluctuated throughout the 12-week study and the mean concentration at week 12 did not significantly differ from baseline in the total study population.[34]

Both CD4+ lymphocyte and CD8+ lymphocyte concentrations did not significantly change from baseline to 12 weeks with oral THC/CBD (up to 15 mg/15 mg daily) or CBD 200-800 mg per day, in a small study of PLWH by Mboumba et al 2022.[26,27] Abrams et al found that cannabis and dronabinol were both associated with modest increases in CD4+ and CD8+ lymphocytes from baseline to day 21 compared to placebo, but the differences were not statistically significant after adjustment for covariates in a multivariable model.[29] Two additional publications (Bredt et al 2002 and Mboumba et al 2023) reported secondary analyses of immunophenotypes and/or systemic inflammatory markers from the trials by Abrams et al 2003 and Mboumba et al 2022; these studies differed in their methodologies, limiting comparisons of results.[26,38] In brief, comparing changes from baseline to day 21 of treatment for select subtypes of CD4+ and CD8+ cells, and natural killer cells, Bredt et al concluded that the few significant changes associated with dronabinol or cannabis treatment versus placebo "…do not constitute any meaningful changes in immune phenotypes or function (page 87S)".[38] Pooling results from 8 CBD-only and THC/CBD-treated participants, Mboumba et al reported changes from baseline to up to 14 weeks (2 weeks after the end of 12-week treatment), including reduced levels of select markers of systematic inflammation and damaged gut mucosa, and improved T-cell immunophenotypes for exhaustion and senescence (see **Appendix B** for details).[26]

3.3.3 HIV Viral Load

Three included experimental studies reported changes in HIV viral load. These studies included participants who (1) were virologically suppressed (ie, viral load <40 copies/mL) at baseline (Mboumba et al 2022),[27] (2) were mixed with 58% of patients with an undetectable viral load at baseline (Abrams et al 2003),[29] or (3) had an unknown virological status at baseline (Ellis et al 2009).[32] A limitation of the trials by Abrams et al and Ellis et al is that the treatment duration (5 days or 21 days) may not be long enough to detect significant changes in viral load.[29,32] The trial by Mboumba et al 2022 is limited by the lack of non-cannabinoid comparator group.[27]

Available short-term evidence suggests that smoked cannabis (1-8% THC) for 5 or 21 days, dronabinol 2.5 mg three times daily for 21 days, and oral THC/CBD (5/5-15/15 mg daily) or CBD (200-800 mg daily) for 12 weeks are not associated with significant changes in HIV viral load.[27,29,32] Abrams et al included patients receiving indinavir- or nelfinavir-based ART regimens, finding that the adjusted changes in HIV viral load (a primary outcome) from baseline to 21 days did not significantly differ from placebo for cannabis and dronabinol (adjusted average changes vs placebo: cannabis, –15% [95% confidence interval [CI], –50% to 34%]; dronabinol, –8% [95%CI, –37% to 37%]).[29] Among virologically suppressed patients receiving a variety of ART regimens[‡],[26] Mboumba et al reported that participant's HIV viral load

[‡] Mboumba et al trial participants were receiving ART regimens that are commonly used today, including bictegravir/tenofovir alafenamide/emtricitabine (n=5), dolutegravir/abacavir/lamivudine (n=1), tenofovir/emtricitabine/nevirapine (n=1), raltegravir/abacavir/lamivudine and bictegravir/tenofovir

was undetectable throughout the 12-week treatment with THC/CBD or CBD oral capsules.[27] Ellis et al 2009 primarily included patients receiving combination ART (94% of the randomized population) of unknown type and found no significant changes in viral load between cannabis-treated and placebo-treated patients after 5 days.[32]

3.3.4 *Antiretroviral Therapy Pharmacokinetic Parameters*

A sub-study of Abrams 2003 by Kosel et al 2002 evaluated changes in the PK parameters of 2 protease inhibitors (indinavir or nelfinavir)[§] before and after 2 weeks of smoked cannabis (3.9% THC) or dronabinol 2.5 mg three times daily among 62 participants, finding modest changes to indinavir and nelfinavir PK parameters that were considered unlikely to be clinically significant. Percent changes from baseline to day 14 in the median indinavir and nelfinavir maximum or minimum concentrations (Cmax or Cmin) and AUC were <10% among participants receiving dronabinol or placebo, whereas these parameters were slightly decreased (varying in the range of –10% to up to –33%) after cannabis treatment. Decreases in the median indinavir Cmax (–14.1%; range –58 to +7) from baseline to day 14 during cannabis treatment were statistically significant (P=0.039).[39]

3.3.5 *Cognition*

No included experimental studies evaluated use of CBPs among patients with HAND. Three short-term trials performed cognitive performance tests among PLWHA with recent frequent cannabis use (≥ 2 times weekly),[22-24] two of which may have been confounded by allowing patients to use cannabis at home between staggered treatment periods (Haney et al 2005 and Haney et al 2007).[22,23] Collectively, some of these studies suggest that high-dose dronabinol might worsen acute digit recall,[22] processing speed, and rapid acquisition, and increase false responses to distractors compared to placebo among frequent cannabis users.[24] However, the findings were inconsistent between trials. Unlike high-dose dronabinol, using smoked cannabis (up to 3.9% THC) up to 4 times daily for 4 days was not associated with significantly altered cognitive performance compared to placebo.[22,23]

3.3.6 *Select Other Adverse Events (AEs)*

Overall, other than the occurrence of AIDS-associated illnesses among patients with pre-existing AIDS,[33,34] the types of AEs reported during treatment with smoked cannabis, oral dronabinol, oral THC/CBD, oral CBD, and oral CBDV among PLWHA appear to be similar to those reported by clinical trials of CBPs in other patient populations. Hepatic AEs, particularly during treatment with high-dose oral CBD, might warrant particular attention among PLWHA. Two out of 5 participants with virologically suppressed HIV that were administered high-dose (up to 800 mg) oral CBD-only treatment developed transaminitis, including one case of life-threatening acute hepatitis in a patient with pre-existing metabolic dysfunction-associated steatotic liver disease. Since hepatic disease is potential complication of HIV infection,[40] investigators recommended that providers consider additional screening for liver disease (eg, performing transient elastography) in PLWHA with risk factors for hepatic steatosis before

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alafenamide/emtricitabine (n=1), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (n=1), or doravirine/lamivudine/tenofovir disoproxil fumarate (n=1).

[§] Nearly all participants were receiving either indinavir 800 mg every 8 hours (n=28) or nelfinavir 750 mg three times daily (n=34) as part of their ART regimen. Other ART medications taken by participants were not reported.

starting a CBP.[27] Detailed information about the type of and severity of AEs was not reported by all 12 included trials, but generally, among trials reporting this information, most AEs were of mild to moderate severity.[25,27,28,30,31]

Nine of 12 trials reported the frequency of trial discontinuations due to tolerability concerns and/or AEs. The following summarizes information about trial withdrawals or discontinuations due to an AE by trial:

- Abrams et al 2003: One of 21 (4.8%) participants who received smoked cannabis discontinued due to grade 2 neuropsychiatric symptoms; 1 of 25 (4%) participants who received dronabinol discontinued due to grade 2 paranoia and 1 of 25 (4%) discontinued due to persistent headache and nausea. No participants who received placebo discontinued due to AEs.[29]
- Haney et al 2005 and Abrams 2007: No withdrawals due to AEs occurred.[22,30]
- Mboumba et al 2022: Two of 5 (40%) participants in the CBD-only treatment group discontinued due to anemia (aggravated by frequent blood draws) and mild transaminitis (n=1) and life-threatening acute hepatitis (n=1). No participants discontinued during THC/CBD treatment.[27]
- Ellis et al 2009: Of 34 participants, 2 (5.9%) discontinued during the smoked cannabis treatment phase due to psychosis (n=1, in a cannabis-naïve participant) or intractable cough (n=1). No participants discontinued during the placebo treatment phase.[32]
- Eibach et al 2020: Of 32 participants, 1 (3.1%) discontinued during oral CBDV treatment due to cough and none during placebo treatment.[25]
- Struwe et al 1993: Of 12 participants, 2 (16.7%) discontinued due to mood changes and sedation during dronabinol treatment; 2 additional participants withdrew due to the progression of HIV disease (including developing HIV encephalopathy in 1 case) during an unspecified treatment period (dronabinol or placebo) during the trial.[33]
- Beal et al 1995: Six of 72 (8.3%) of dronabinol-treated participants and 3 of 67 (4.5%) of placebo-treated participants discontinued treatment for unspecified toxicities. Additional participants did not receive the total treatment due to unspecified intercurrent illness: 4 (5.6%) of dronabinol treatment arm and 3 (4.%) in the placebo arm.[31]
- Timpone et al 1997:
    - Discontinuations due to AEs or illness by treatment arm were (number of participants):
        - dronabinol only (5 of 11 [45.%]): lymphoma (n=1), hallucinations (n=1), tuberculosis (n=1), somnolence, not specified low-grade severity (n=1)
        - dronabinol plus megestrol 750 mg (2 of 13 [15.4%]): *candida* esophagitis (n=1), cryptosporidiosis (n=1)
        - dronabinol plus megestrol 250 mg (3 of 13 [23.1%]): seizure (n=1), dyspnea (n=1), and tuberculosis (n=1)
        - megestrol 750 mg only (2 of 11 [18.2%]): dyspnea (n=1), and lymphoma (n=1)
    - Other participants in each dronabinol arm including those who also received megestrol (n=37) required study treatment modification, mostly due to neuropsychiatric events including confusion/emotional lability (n=1), anxiety/depression (n=1), confusion (n=1), euphoria (n=1), anxiety (n=1), or other not specified low-severity event (n=1).[34]

Regarding serious or severe AEs, including events that may overlap with those that led to treatment discontinuation, two trials with a total of 60 participants reported that no serious AEs occurred during

treatment with smoked cannabis for 5 days, or vaporized cannabis for one day.[28,29] Among participants treated with smoked cannabis for 5 days, investigators described that there was a trend toward a higher incidence of moderate to severe AEs with cannabis treatment versus placebo.[32] Out of 32 participants, one experienced a serious AE (acute myocardial infarction) during treatment with oral CBDV (versus none during placebo) that was considered unrelated to CBDV because the participant had many pre-existing risk factors for a myocardial infarction.[25] The incidence of any drug-related severe AE was greater among the 72 participants who received dronabinol (n=6; 8.3%) compared to the 67 placebo recipients (0% severe AEs); dronabinol-related severe AEs were of the cardiovascular (n=1), digestive (n=1), nervous (n=4), integumentary (n=1), and special sense (n=1) systems.[31] The incidence of grade 3 or 4 AEs was numerically greater during treatment with megestrol acetate monotherapy or megestrol plus dronabinol (range 80% to 84.6% per group) than during dronabinol monotherapy (63.6%). Serious AEs considered dronabinol-related were neuropsychiatric in nature, compared to dyspnea, liver enzyme changes and hyperglycemic events that were associated with megestrol acetate treatment.[34] As previously described, high-dose oral CBD was associated with life-threatening acute hepatitis in a patient with pre-existing fatty liver disease.[27]

Increases in heart rate (HR) associated with cannabis and dronabinol were reported.[23,32] Ellis et al 2009 described that a heart rate increase by ≥ 30 beats within 30 minutes of treatment occurred more frequently during cannabis use (46%) than placebo (4%); no significant differences in blood pressure were found between treatment groups. The increases in HR measured during the Ellis et al trial were considered asymptomatic and they resolved without intervention.[32] Oral THC/CBD and CBD-only therapy were each associated with 1 case (out of 5 patients per treatment) of worsened glycemic control in patients with pre-existing type 2 diabetes mellitus at treatment weeks 6 or 9; one of the cases occurred in the participant who developed life-threatening acute hepatitis.[27]

4.0 RISK OF BIAS

Risk of bias (ROB) or quality ratings by a SR were found for 8 of 12 included trials. For each of these trials, the ROB assessment was performed using a Cochrane ROB assessment for RCTs, which includes 6-7 domains (depending on the version)[**] that are each rated as carrying a low, unclear, or high ROB. An assignment of "unclear" usually indicates that insufficient information was reported to determine the ROB.[37,41] Of these 8 trials, only 2 trials were rated as having no high-risk domains (Haney et al 2005 and Abrams et al 2007); however, the trial by Haney et al 2005 was rated as having an unclear risk on all domains. The other 6 trials were rated as high risk for the domains of blinding (Abrams et al 2003, Haney et al 2007, Ellis et al 2009, Struwe et al 1993), incomplete outcome data (Beal et al 1995 and Timpone et al 1997), bias arising from randomization and/or allocation concealment (Timpone et al 1997), or 'other' bias (Haney et al 2007, Ellis et al 2009).[37,41] 'Other' sources of bias assessed as high risk by Lutge et al included the fact that many patients were cannabis-treatment experienced and correctly guessed their treatment (Ellis et al 2009), which could have biased patients toward having high positive expectations

[**] The SR by Lutge et al 2013 performed ROB ratings for 7 of 8 trials, including the 6 domains of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and 'other' bias. The SR by Mücke et al 2018 performed ROB ratings for the Timpone et al 1997 trial using the same domains as Lutge et al except that blinding was separated into 2 categories (participants/personnel and outcome assessors), there was no 'other' category, and 'selection bias' was an additional category addressing both random sequence generation and allocation concealment.

of cannabis use, and that participants were allowed to use cannabis at home between staggered treatment periods (Haney et al 2007).[37] Qualitatively, the 8 trials are considered to be low quality (N=6 trials; based on having 0-2 domains rated as low risk) or moderate quality (N=2 trials; based on having 3-5 domains rated as low risk)[††].[41] Refer to **Appendix B** for details about ROB ratings by SRs.

Trials without a ROB or quality rating by an SR primarily included the most recently published or completed trials including Mboumba et al 2022, Eibach et al 2020, and the unpublished trial (NCT03099005), as well as Bedi et al 2010. Little information was reported about NCT03099005 since it is unpublished. Noted potential bias concerns (this is not comprehensive) with these trials include issues due to randomization and/or allocation concealment (Bedi et al, Mboumba et al, NCT03099005) and blinding (Bedi et al, Mboumba et al).[24,27,28] Bedi et al was possibly non-randomized and provided no information about randomization, whereas Mboumba et al and NCT03099005 described the trials as being randomized but provided no information about randomization or allocation concealment procedures.[24,27,28] Regarding blinding, Mboumba et al was an open-label trial, and Bedi et al was described as double-blinded but provided no information about who was blinded.[24,27]

5.0 SUMMARY

We included 12 parallel group (N=5)[27,29-31,34] or cross-over (N=7)[22-25,28,32,33] experimental controlled trials of CBPs with an approximate median duration of 25 days (range 1 to 84 days)[‡‡] that included a total of about 494 adult PLWHA. Of the 12 trials, 6 were not included/addressed as a primary study or as part of a cited review article by the existing CRRB guidance for the use of cannabis in patients with HIV/AIDS. Most trial participants were men, and many studies included participants with experience using cannabis; participant's concurrent use of ART and the degree of HIV viral suppression varied across trials. Studies primarily assessed the short-term safety (eg, impact on HIV viral load or CD4+ lymphocyte counts, incidence of AEs)[27,29] or the treatment of HRNP,[25,28,30,32] both primarily among PLWH, and the treatment of AIDS-associated anorexia or wasting.[31,33,34] Three additional studies also assessed the short-term effects of CBPs on appetite, weight, subjective effects, and cognitive performance among PLWHA *without* specific complaints (eg, wasting or pain). Studied CBPs included dronabinol (N=7 trials),[22-24,29,31,33,34] smoked cannabis (N=5),[22,23,29,30,32] vaporized cannabis (N=1),[28] oral THC/CBD capsules (N=1),[27] oral CBD (N=1),[27] and oral CBDV (N=1),[25] which were compared to placebo (N=9), active comparator (megestrol acetate; N=1),[34] and/or another CBP (N=5).[22,23,27-29]

Overall, there is moderate quality evidence from 2 RCTs that smoked cannabis (with 1-8% THC by weight) administered three to four times daily significantly reduces patient-reported HIV-related chronic neuropathic pain in the short-term (5 days).[30,32] A third unpublished trial evaluated a single vaporized dose of 3 different cannabis products (low CBD, medium CBD, high CBD) and found that cannabis might reduce chronic neuropathic pain, but firm conclusions from this study are lacking because it was very small (n=5 participants), lacked a non-CBP comparator, and did not report statistical comparisons.[28] In

[††] Per a qualitative rating system used by Mücke et al 2018, the trials by Abrams et al 2007 and Ellis et al 2009 are considered moderate quality, and the trials by Abrams et al 2003, Haney et al 2005, Haney et al 2007, Struwe et al 1993, Beal et al 1995, and Timpone et al 1997 are considered low quality.

[‡‡] This estimate is based on the treatment durations for 10 of 12 included trials. The estimated duration does not include the duration from 2 trials that used staggered cross-over designs and reported insufficient details to determine the treatment duration.

contrast to the studies of inhaled cannabis, oral CBDV 400 mg daily for 4 weeks failed to significantly reduce patient-reported pain compared to placebo.[25]

Low quality evidence from 2 RCTs among PLWA with a low body weight or significant weight loss suggests that oral dronabinol 2.5 to 5 mg twice daily for 5-6 weeks significantly increases appetite and might improve nausea versus placebo (based on 1 of the 2 RCTs); however, dronabinol did not significantly increase weight versus placebo.[31,33] In a third, low quality, open-label, safety-focused active comparator RCT, both megestrol acetate 750 daily and dronabinol 2.5 mg twice daily significantly increased patient-reported hunger from baseline to 1 week, but the benefit plateaued at 1 week.[34] Additionally, megestrol-treated patients gained significantly more weight from baseline to 12 weeks (mean +6.5 kg) than dronabinol-treated patients (mean –2.0 kg).[34] Notably, body composition analyses from a subset of trials that assessed this outcome among PLWH or PLWA suggest that weight gain associated with smoked cannabis or dronabinol is primarily from fat mass.[29,33]

Other short-term, low-quality trials, which primarily included PLWHA who did not necessarily have anorexia or cachexia and were frequent cannabis users (≥2 times/week), demonstrated mixed effects of high-dose oral dronabinol (7.5 to 40 mg daily) or smoked cannabis (with 1.8% to up to 3.9% THC) on weight gain and caloric intake.[22-24,30] Dronabinol and smoked cannabis significantly increased body weight versus placebo after 4 days or 3 weeks in 2 trials,[23,29] but dronabinol did not significantly increase body weight from baseline to 16 days versus placebo in a third trial.[24] Dronabinol 10-40 mg daily increased acute caloric intake from baseline versus placebo; however, this benefit was limited to patients with low body mass (not patients with normal body mass)[22] and the effect plateaued after treatment day 8, with no change from day 9 to 16, in a second trial.[24] Smoked cannabis with 2.0% or 3.9% THC four times daily for 4 days increased mean daily caloric intake versus placebo.[24]

Overall, regarding the impact of CBPs on QoL or functional status, which were assessed as secondary outcomes in select low-quality trials that were likely underpowered to measure these outcomes, the available experimental evidence does not suggest that CBPs improve QoL compared to placebo or megestrol acetate in the short-term.[25,27,32,34] Mixed results were found for the impact on functional status in PLWA; a small (n=5 participants) trial found dronabinol significantly improved a composite patient-reported measure for distress, mood, and function at 5 weeks versus placebo,[33] whereas dronabinol did not significantly improve Karnofsky performance status versus placebo in a second, larger trial (n=139).

Although there is interest in using cannabis in the management of HIV-associated neurocognitive disorders (HAND),[9,19] we found no experimental trials that specifically targeted patients with HAND or that acknowledged including patients with HAND. Two short-term studies among PLWH who were treatment-experienced frequent cannabis users found that smoked cannabis or high-dose dronabinol for up to 4 days might impair some aspects of cognitive performance versus placebo.[22,23] However, the impaired cognitive domains varied between studies and cannabinoid products, and the studies appeared to have only measured acute cognitive performance soon after cannabis or dronabinol use (eg, within 1 hour) when cannabinoid concentrations may be at or near peak levels.

Overall, the primarily low-quality trials suggest that the studied CBPs are probably tolerated by many PLWHA *in the short-term*. Limited evidence suggests that smoking cannabis for up to 21 days is not associated with significant changes in HIV viral load, decreases in CD4+ lymphocytes, or clinically

meaningful changes in the PK parameters of the protease inhibitors indinavir or nelfinavir compared to placebo in PLWH.[29] In a safety-focused small trial of patients with virologically suppressed HIV who were taking ART regimens that are commonly used today, oral THC/CBD (5/5-15/15 mg daily) or CBD (200-800 mg daily) for 12 weeks was not associated with significant changes to HIV viral load or CD4+ or CD8+ lymphocyte counts from baseline.[27] When reported, neuropsychiatric events (eg, sedation, confusion, dizziness, concentration difficulties) tended to be the most frequent type of AEs associated with dronabinol, smoked cannabis, oral THC/CBD, or oral CBD, which were primarily of mild to moderate severity.[27,30-32,34] Smoked cannabis was associated with asymptomatic acute increases in heart rate,[32] and oral THC/CBD and CBD-only therapy were each associated with 1 case (out of 5 patients per treatment) of worsened glycemic control in patients with pre-existing type 2 diabetes.[27] A high overall rate of any grade 3 or 4 AE (37 of 47 [79%]) among PLWA with wasting who received dronabinol and/or megestrol acetate was reported by 1 trial.[34] The majority of serious or severe AEs attributed to a CBP were neuropsychiatric in nature; for example, cases of paranoia, anxiety, or hallucinations.[30,31,34] Two of 5 patients with virologically suppressed HIV developed transaminitis during high-dose oral CBD (800 mg daily) therapy, including a case of life-threatening acute hepatitis in a patient with pre-existing metabolic dysfunction-associated steatotic liver disease.[27]

There are limitations to the body of experimental evidence. Most trials are of low-quality, with concerns for significant bias resulting from the lack of or unsuccessful blinding, incomplete outcome data, and/or other bias (eg, allowing use of cannabis between staggered treatment periods).[37,41] Long-term experimental studies are lacking[§§],[42] which is concerning due to the overlap between potential safety concerns of long-term cannabis use with comorbidities that occur at a higher rate among PLWHA compared to the general population (eg, cognitive impairment, cardiovascular disease, malignancy).[5] Results from the limited experimental studies may not be generalizable to PLWHA in Utah who desire to use medical cannabis. For example, the CBPs studied may differ from available or desired medical cannabis products and routes of administration in Utah, as the experimental studies primarily evaluated oral dronabinol (5 mg to 40 mg daily) or smoked cannabis (with 1-8% THC, three to four times daily). In addition, the majority of PLWHA included in the experimental trials may not be representative of most PLWHA today due to differences in the available ARTs. Especially for the experimental trials of PLWA with anorexia or cachexia that were conducted in the 1990s, participants were possibly not receiving ART or were receiving different ART regimens that are less effective than those used today.

5.1 Conclusions from an Expert Opinion Guidance

A 2023 clinical practice guidance for the management of chronic pain and co-morbidities from a panel of Canadian cannabis experts, which was informed by evidence from a systematic literature search, provided recommendations about the management of HIV in patients with chronic pain.[43] Based on evidence from 2 RCTs (Abrams et al 2007 and Ellis et al 2009) and an observational, cross-sectional study, the panel recommended cannabis-based medicines for patients with HIV and *muscular or neuropathic pain* who have an inadequate response or intolerance to other treatments (strong

[§§] We are aware of one 12-month open-label, single-arm, follow-up trial of Beal et al 1995 (Beal et al 1997) which supports the use of dronabinol 2.5 mg once or twice daily in PLWA. Beal et al 1997 reported that 2 of 94 participants had a severe AE during the follow-up and no life-threatening reactions occurred, although 3 participants died due to complications of AIDS. Additional long-term safety evidence may be available from observational studies, which could be addressed in the future.

recommendation; moderate quality evidence). Informed by the 3 studies, Bell et al also recommended cannabis-based medicines for managing other HIV-related symptoms including nausea, poor appetite, weight loss, anxiety or depression (strong recommendation; low-quality evidence). Despite the positive evidence for management of HIV-associated pain being exclusive to experimental studies of smoked cannabis with an unspecified concentration of CBD, Bell et al encouraged using oral dosage forms and starting with CBD-predominant cannabinoids to minimize potential pulmonary AEs associated with inhalation and toxicities associated with THC.[43]

6.0 CONSIDERATIONS FOR THE CRRB HIV GUIDANCE DOCUMENT

If desired, the CRRB may consider updating the current guidance document on the treatment of PLWHA with medical cannabis based on information from this review. Historically, the CRRB has used level of evidence (LOE) ratings (eg, "limited" or "insufficient") from the National Academies of Sciences, Engineering, and Medicines (NASEM) for formal recommendations. See **Appendix C** for summary of LOE categories and criteria from NASEM.

6.1 Considerations for Formal (ie, Graded) Recommendations

The CRRB may consider the following regarding updates to existing formal recommendations:

- **For the statement about medical cannabis effectiveness for HIV-associated peripheral neuropathy**:
  - Consider maintaining the LOE of "limited" regarding the use of cannabis.
  - Consider revisions to add that medical cannabis is effective for *chronic* neuropathic pain in the *short-term*, since positive RCTs are limited to treatment durations of 5 days among patients believed to have long-standing pain.[30,32] One trial included participants with a median pain duration of 7 years,[30] and the other did not describe the patient's duration of pain, but implied that patients had a chronic pain syndrome and required participants had to have failed at least 2 other analgesics to be included in the trial.[32]
  - May consider adding a separate graded statement to address the single 4-week cross-over RCT among patients with chronic HIV-associated neuropathic pain that found oral CBDV did not significantly improve pain versus placebo.[25] For example, that there is insufficient evidence that oral CBDV is ineffective for chronic HIV-associated neuropathic pain in the short-term.
  - May consider including information about the type of cannabis and route of administration that showed a benefit in trials.
- **For the statement about medical cannabis effectiveness for HIV/AIDS wasting syndrome:**
  - Consider maintaining the LOE of "limited" and replacing "medical cannabis" with "oral cannabinoids" or "dronabinol."
    - Experimental evidence from trials that targeted patients with probable HIV/AIDS anorexia and/or wasting syndrome is limited to treatment with oral dronabinol.[31,33,34] Another trial by Abrams et al 2003 found that smoked cannabis or oral dronabinol significantly increased median weight versus *oral* placebo (ie, without a true placebo comparator for cannabis). The trial by Abrams et al 2003 included patients with HIV without acute complications and excluded patients with unintentional weight loss by 10% or more in the prior 6 months. Yet,

some patients in the trial were underweight since the lower end of the BMI range of trial participants at baseline was 14.8 kg/m^2 (group median BMI was 25.5 kg/m^2).[29]

- May consider specifying which outcomes benefited from cannabinoid treatment in experimental trials of patients with probable HIV/AIDS wasting syndrome. For example, that there is limited evidence of increased caloric intake/appetite (with dronabinol), and insufficient evidence of increased body weight (with dronabinol).
  - Three low-quality RCTs among patients with probable HIV/AIDS anorexia and/or wasting syndrome found dronabinol did not increase body weight versus placebo or megestrol acetate by a statistically significant amount.[31,33,34] Non-statistically significant increases in body weight were observed with dronabinol versus placebo (eg, gain of +2 kg by 22% of the dronabinol group vs 10.5% of the placebo group at 6 weeks).[31] In a 12-week, open-label trial, on average, participants who received megestrol acetate gained weight (mean of +6.5 kg) whereas participants who received dronabinol lost weight (mean of –2.0 kg).[34]

- **For the statement about medical cannabis or cannabinoids effectiveness for chronic pain in general:**
  - The CRRB's current HIV/AIDS guidance document includes a graded recommendation about chronic pain in general, which is identical to the current graded statement in the CRRB's persistent pain guidance. The CRRB should consider whether to include this in the updated guidance for HIV/AIDS.

6.2 Additional Considerations

- Consider including additional information about characteristics of trial participants and details about the types of cannabis or cannabinoids from experimental studies. Refer to the trials overview in section 3.1 on pages 3-4.
  - May also consider including information about the generalizability or limitations of the reviewed experimental evidence. For example, there is limited experimental information about the effects of cannabis or cannabinoids on cognition, and major morbidity or mortality in PLWHA. Available experimental evidence in patients with AIDS-associated anorexia and/or wasting was conducted in the 1990s when patients were likely not receiving modern ART; it is unknown if the improvements in appetite and/or weight observed in these trials would occur in patients receiving modern ART regimens.
- May consider including brief information about additional outcomes/concerns, for example:
  - Medical cannabis is not intended to replace antiretroviral regimens.
  - Monitoring for potential DDIs between cannabis/cannabinoids and ART[***]:
    - Providers and patients should remain vigilant about the possibility of DDIs between cannabis and ART regimens, particularly when starting, stopping, or changing the dose of any agent. Although the available evidence is mostly reassuring about the lack of clinically significant DDIs between the studied cannabinoids and ART regimens, *robust evidence is*

[***]Notable cytochrome P450 (CYP)-based metabolism of major cannabinoids includes but is not limited to the following: (1) THC is metabolized by CYP3A4 and CYP2C9 and may induce metabolism by CYP1A2; and (2) CBD is metabolized by CYP3A4 and CYP2C19 and is an inhibitor of CYP3A4 and CYP2D6 (Mills et al 2021).

limited. Please note this this report was not focused on DDI evidence, so any information about DDIs should not be considered comprehensive.

- According to Mills et al 2021, extra caution is advised when using ART regimens containing the strong cytochrome P450 (CYP) 3A4 inhibitors, ritonavir or cobicistat; these agents could theoretically increase a patient's exposure to THC.[44] Potentially clinically significant interactions have been reported between THC/CBD and CBD and the antiretrovirals atazanavir and efavirenz: decreased atazanavir troughs without apparent changes to HIV viral load and CD4+ cell counts were associated with cannabis treatment, and efavirenz (a major CYP2C9 inducer) might increase exposure to THC.[44] The US HIV treatment guideline from the DHHS recommends monitoring for increased THC-associated side effects in patients receiving ART regimens containing cobicistat or a protease inhibitor.[4]

- Determine if changes to the section on chronic pain in general are needed.
  - The CRRB's current guidance for HIV/AIDS includes information about neuropathic pain in general. This information may be helpful to providers seeking to treat neuropathic pain in a PLWHA, but the section is lengthy compared to the section with specific evidence from PLWHA. Moreover, the information about general chronic pain differs slightly from the CRRB's guidance for persistent pain that was updated in 2022.

7.0 METHODS

We performed literature searches including free-text and controlled vocabulary search terms in 2 major bibliographic databases, Ovid-Medline and Embase. First, we queried databases for SRs of experimental studies published between database inception and May 1, 2024. Next, based on the results of the SR search, we performed a search for experimental trials published between January 2021 and May 20, 2024. We filtered the literature search results using an SR filter developed by McMaster University for Ovid-Medline and an independently derived filter for Embase[45]; filters for RCTs from the Cochrane Organization were used for searches in both Ovid-Medline and Embase.[46] Refer to **Appendix D** for our full search strategies.

Included studies were experimental (ie, randomized or non-randomized) controlled trials of cannabis or cannabinoids (plant-based or synthetic) used in patients with HIV and/or AIDS that reported any efficacy or safety outcomes. A single author reviewed the literature search results for inclusion in two phases: first titles and abstracts were considered, followed by the full texts of potentially relevant studies. We also searched for SRs that included experimental trial(s) meeting inclusion criteria. Experimental studies included by an SR or review article that was reviewed in full text were also considered for inclusion. Select efficacy and safety outcomes were extracted and summarized; although the outcomes were assigned to "efficacy" or "safety", some outcomes are both.

Major efficacy and/or safety outcomes were extracted from included experimental trials by a single author. Information from experimental studies was supplemented from a high-quality SR of RCTs by Lutge et al 2013 that included 7 of the 12 identified experimental trials.[37] For feasibility, due to time constraints, assessment of the ROB and/or quality of included experimental trials was limited to assessments performed by an SR, when available.

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APPENDIX A – OVERVIEW OF EXPERIMENTAL STUDIES INCLUDED BY SELECT REVIEW ARTICLES

Table A1. Comparison of Experimental Studies Included by Select Review Articles[a]

Review Article	Experimental Study Addressed by this Report											
	Struwe 1993[33]	Beal 1995[31]	Timpone 1997[34]	Abrams 2003[29]/ Kosel 2002	Haney 2005[22]	Abrams 2007[b,30]	Haney 2007[23]	Bedi 2010[24]	Ellis 2009[32]/ Riggs 2012[36]	Eibach 2020[25]	Mboumba 2022[27]/2023[26]	NCT03099005 (unpublished)[28]
Lutge 2013[37]	X	X		X	X	X	X		X			
Andrae 2015[b,47]						X			X			
Whiting 2015[b,48]	X	X	X	X		X			X			
Mücke 2018[41]		X	X	X								
Aly 2021[49]						X			X	X		X
Bell 2023[43]						X			X			

Abbreviations: AIDS, acquired immunodeficiency syndrome; CRRB, (Utah) Cannabis Research Review Board; HIV, human immunodeficiency virus

[a] *Includes systematic or narrative reviews cited by existing CRRB guidance for HIV/AIDS and select reviews identified from our literature search*

[b] *HIV/AIDS-specific study with experimental evidence that was mentioned/addressed in the original CRRB guidance on cannabis for HIV/AIDS*

APPENDIX B – EXPERIMENTAL TRIALS EVIDENCE

Table B1. Summary of the Study Design and Select Efficacy and Safety Outcomes from Included Experimental Trials among People Living with HIV or AIDS

Study: First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result	ROB per a SR
People with HIV/AIDS without specific targeted complications							
Abrams 2003 population: Adults (≥ 18; 89% cisgender male and 6% transgender female) with HIV receiving a stable ART regimen containing indinavir or nelfinavir with a stable viral load who had prior experience (use ≥ 6 times) with smoked cannabis							
Abrams 2003 and Kosel 2002 (reported PK outcomes)[29,37]	Parallel group, R, PC, DB (oral regimens only), inpatient, trial 21 days	67 (62)	Cannabis cigarette (3.95% THC) or dronabinol 2.5 mg, both TID	PBO capsule TID	HIV RNA levels (primary)	No SS difference between cannabis, dronabinol, and PBO	ROB: low risk for allocation concealment and incomplete outcome data; unclear risk for random sequence generation, selective reporting and other bias; and high risk for blinding.[37] Noted limitation(s): unlikely to see changes in HIV RNA or T-cell counts within the short study duration. Cigarette arm was not blinded.[37] Few women participants.[29]
					CD4+ and CD8+ T-cell counts	Difference in change from BL to 21 days vs PBO: • CD4: cannabis, +16 (2 to 33; P=0.025); dronabinol, +14 (– 1 to 32; P=0.064) • CD8: cannabis, +20 (4 to 42; P=0.016); dronabinol, +10 (– 3 to 32; P=0.015)	
					ART PK parameters	• Cannabis: ↓ indinavir Cmax by –14% (P=0.039); and ↓ AUC by –14.5% (P=0.074; not SS); nelfinavir: non-SS ↓ in Cmax (– 17.4; P=0.46), AUC (–10.2%; P=0.015); Cmin (–12.2%; P-0.28) --> unlikely to be clinically significant, per authors	
					Weight gain	• Dronabinol or cannabis (median + 3-3.2 kg) > PBO (median 1.1 kg); P <0.05	
					Discontinuation due to AE[29]	• Cannabis: grade 2 neuropsychiatric symptoms (n=1) • Placebo: none • Dronabinol: grade 2 paranoia (n=1); headache/nausea (n=1)	
Haney 2005 population: Adults (21-50 years; 3/27 female) with HIV receiving at least 2 ART who smoked cannabis at least twice weekly in the past 4 weeks who are medically stable. Mean CD4 counts (cells/mm3) were 400-500 and ~50% of patients were considered virally suppressed – based on the SD of the CD4 counts, some patients may have met criteria for AIDS. Participants were divided into those considered to have a low body mass (<90% of normal) and normal body mass (>90%).							
Haney 2005[22]	With-in participant, staggered, double-dummy trial in a hospital setting. Blinded to strength of capsule/cannabis. P<0.01 was SS. 8 sessions over 3-4 weeks	30 (? 1 participant not included in analysis) Low BIA group (15) Normal BIA group (15)	1. Dronabinol capsules with 0, 10, 20, or 30 mg 2. Cannabis cigarette with 0, 1.8, 2.8, or 3.9% THC On experimental session days, participants took dronabinol (of the assigned strength), then smoked 3 puffs of the assigned cannabis 1 hr later. Puffs included 5 second inhalations and 10 seconds held in the lung. Only 1 active dose was given per session.	Matched PBO (capsules and cigarettes) Mean outcome values for PBO were calculated from the 2 sessions.	Change from BL in mean caloric intake during 4 hours after drug administration	Low BIA: Dronabinol 10, 20, and 30 mg > PBO; cannabis 1.8% and 2.9% THC >PBO (P<0.01). Normal BIA: No SS difference with PBO vs any cannabis or dronabinol dose	ROB: unclear risk on all measures including random sequence generation, allocation concealment, blinding, incomplete outcome data, selecting reporting, and other bias. Noted limitations: Patients were allowed to continue using cannabis during the study (except on the morning of experimental
					Ratings of "hunger" and "satiety"	Low BIA and normal BIA: Both groups had increased dry mouth ratings (P<0.01) with cannabis 3.9% vs PBO. Low BIA group: Increased ratings vs PBO for thirst with cannabis 3.9% (P<0.004).	
					Ratings (on 5-item VAS) for feeling high or "good drug effect"	Low BIA and normal BIA: Both groups had higher ratings (P<0.01) for each active drug except dronabinol 10 mg vs PBO. Peak onset of effect was earlier with cannabis (30 min) vs dronabinol (180 min).	

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; AUC, Area under the plasma concentration by time curve; BID, twice daily; BL, baseline; BPI, brief pain inventory; CBD, cannabidiol; CBDV, cannabidivarin; CBP, cannabinoid- or cannabis-based intervention; CI, confidence interval; DB, double-blind; DDS, Descriptor Differential Scale; DN4i, Douleur Neuropathique 4 interview; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; ISI, Insomnia Severity Index; NSS, not statistically significant; PBO, placebo; PC, placebo-controlled; PGIC, Patient Global Impression of Change; PK, pharmacokinetic; R, randomized; RNA, ribonucleic acid; ROB, risk of bias; SD, standard deviation; SE, standard error; SEM, standard error of the mean; THC, (delta-9) tetrahydrocannabinol; SR, systematic review; SS, statistically significant; sTNFRII, soluble receptor for tumor necrosis factor type II; TID, three times daily; VAS, visual analog scale; QID, four times daily; QoL, quality of life;

Table B1. Summary of the Study Design and Select Efficacy and Safety Outcomes from Included Experimental Trials among People Living with HIV or AIDS

Study: First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result	ROB per a SR
					Other subjective ratings (each on a 5-item VAS)	*Cannabis* Low BIA: Scores on the following scales were increased (P<0.01) vs PBO: good drug effect (2.8 and 3.9% THC cannabis), strength (2.8% and 3.9% THC), liking (3.9% THC) Normal BIA: Scores on the same scales mentioned above were increased (P<0.001) vs PBO from each active cannabis dose. *Dronabinol* Low BIA: Scores on the strength scale were increased vs PBO (P<0.01) for only the highest dronabinol (30 mg) dose. Normal BIA: No differences vs PBO described	sessions). Many participants had a limited income and used the 4-hour sessions with access to unlimited food as an opportunity to eat as much as they could.
					Change in performance	Low BIA: No significant changes with cannabis. Decreased performance on digit substitutions test, digit recall task and maximal speed in attention task vs PBO from dronabinol 20 mg (P<0.01). No changes in word recall or recognition from dronabinol. Normal BIA: No significant changes with cannabis. Reduced number of digits recalled in recall task vs PBO with dronabinol 30 mg (P<0.01). No changes in word recall or recognition from dronabinol.	
					Withdrawal due to AE	None	
					AEs	Low BIA: dizzy (n=1; PBO); in another participant: nauseous (n=1; dronabinol 10 mg), very intoxicated (dronabinol 30 mg); another participant: nausea and headache (n=1; dronabinol 20 mg), intoxication and vomiting (dronabinol 30 mg). Normal BIA: diarrhea (n=1; 3.9% cannabis); another participant: nausea (n=1; PBO), headache (dronabinol 30 mg); very intoxicated (n=3; dronabinol 30 mg).	
Haney 2007 population: Adults (21-50 years; 1/10 female) with HIV receiving at least 2 ART who smoked cannabis at least twice weekly in the past 4 weeks who are medically stable. Mean CD4 count (cells/mm3) was 411. Two participants had low body mass.							
Haney 2007[23]	Within-participant, staggered, double-dummy, DB, trial in a monitored residential inpatient and outpatient laboratory setting. P<0.01 was SS.	10 (unknown, appears to be 10)	1. Dronabinol capsules with 0, 5, or 10 mg, four times daily during active treatment periods 2. Cannabis cigarette with 0, 2.0, or 3.9%,THC, four times daily during active treatment periods Participants inhaled 3 puffs per cannabis dose. Puffs included 5 second	Matched PBO (capsules and cigarettes)	Change from BL in mean daily caloric intake Mean of caloric intake was calculated from 4 sessions at each dose	Both dronabinol (5 mg, 10 mg) and cannabis (2.0% and 3.9% THC) increased mean daily caloric intake compared to PBO (P<0.01). • Authors report this was driven by an increase in the number of times participants ingested food throughout the day. • Active dronabinol and cannabis doses were associated with an increased proportion of calories from fat.	ROB: low risk for incomplete outcome data; unclear risk for random sequence generation and allocation concealment; and high risk for blinding, and other bias.[37] Noted limitations: During the outpatient phase, patients were
					Change in body weight	Dronabinol 10 mg and cannabis 3.9% treatment periods increased body weight (P<0.01) versus PBO; +1.2 kg after dronabinol and +1.1 kg after cannabis, for 4 days each.	

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; AUC, Area under the plasma concentration by time curve; BID, twice daily; BL, baseline; BPI, brief pain inventory; CBD, cannabidiol; CBDV, cannabidivarin; CBP, cannabinoid- or cannabis-based intervention; CI, confidence interval; DB, double-blind; DDS, Descriptor Differential Scale; DN4i, Douleur Neuropathique 4 interview; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; ISI, Insomnia Severity Index; NSS, not statistically significant; PBO, placebo; PC, placebo-controlled; PGIC, Patient Global Impression of Change; PK, pharmacokinetic; R, randomized; RNA, ribonucleic acid; ROB, risk of bias; SD, standard deviation; SE, standard error; SEM, standard error of the mean; THC, (delta-9) tetrahydrocannabinol; SR, systematic review; SS, statistically significant; sTNFRII, soluble receptor for tumor necrosis factor type II; TID, three times daily; VAS, visual analog scale; QID, four times daily; QoL, quality of life;

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	37 to 42 days total: treatment periods were 16 days each, which included 4 days at each active dose and a 4-day PBO washout between active doses.		inhalations and 10 seconds held in the lung. Only one active cannabis or dronabinol dose was administered at a time.		Scores on hunger-satiety questionnaire	Scores for the desire to eat and hunger were increased with cannabis 3.9% vs PBO (P<0.005); and dry mouth scores increased with dronabinol 10 mg and cannabis 2.0% vs PBO (P<0.005).	allowed to continue using cannabis.
					Subjective drug effects on 6-item VAS scales	Vs PBO: increased "good drug effect", "high", and "mellow" (P<0.005); and "can't concentrate" (P<0.01) with dronabinol 10 mg Vs PBO: Increased "good drug effect", "high", "mellow", "stimulated" and "friendly" (P<0.005) with cannabis (2.0% and 3.9%). The lower cannabis 2.0% also increased "anxious"	
					Marijuana rating form and drug effects questionnaire	Both dronabinol 10 mg and cannabis (2.0% and 3.9%) increased "good drug effect", "liking", "strength" and "desire to smoke again" vs PBO. Similar results were observed on the drug effects questionnaire, but only with dronabinol 10 mg and cannabis 3.9% vs PBO.	
					Cognitive performance	No significantly altered performance (learning, memory, vigilance, psychomotor tests) with any active treatment vs PBO	
					Sleep measures (ie, objective measures of sleep latency, total sleep time, and % REM; and subjective ratings on a 6-item VAS about sleep quality and satisfaction)	Objective ratings were only available from 7/10 participants: Sleep time increased vs PBO with all active conditions (maybe most with cannabis), but the difference was not SS. Subjective ratings: sleep satisfaction and time spent sleeping increased with cannabis 3.9% vs PBO (P<0.01).	
					HR by monitor	All active doses (dronabinol and cannabis) increased HR vs PBO in the afternoon and evening (P<0.005), and all active doses except dronabinol 5 mg increased HR vs PBO in the morning (P<0.01).	
Bedi 2010 population: Adults (21-50 years; all male) with HIV receiving at least 2 ART who smoked cannabis at least twice weekly who are medically stable. Mean CD4 count (cells/mm3) was 510. Two participants had low body mass.							
Bedi 2010[24]	Within-subject, DB, PC, trial in a monitored inpatient and outpatient setting. P<0.01 was SS.	7 (7)	Dronabinol 20 mg (5 mg QID) orally x 2 days, then 40 mg (10 mg QID) orally.	Matched PBO	Difference in average ± SEM daily caloric intake during waking hours	Treatment days 1-8: Dronabinol (average 3579 ± 563 calories) > PBO (average 3227.6 ± 385); P<0.01, attributed to eating more frequently. Treatment days 9-16: No differences between treatments	No ROB rating by an SR. Noted limitations: All participants were male, and no participants were anorexic. No information was provided about randomization. Possible impact of cannabis smoking withdrawal during the study; however,
					Change in body weight	Change from treatment day 1 to day 8: Dronabinol, +1.0 vs PBO –0.2, P= NSS. Change from treatment day 9 to 16: Dronabinol, –0.1 vs PBO, –0.4, P= NSS	

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; AUC, Area under the plasma concentration by time curve; BID, twice daily; BL, baseline; BPI, brief pain inventory; CBD, cannabidiol; CBDV, cannabidivarin; CBP, cannabinoid- or cannabis-based intervention; CI, confidence interval; DB, double-blind; DDS, Descriptor Differential Scale; DN4i, Douleur Neuropathique 4 interview; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; ISI, Insomnia Severity Index; NSS, not statistically significant; PBO, placebo; PC, placebo-controlled; PGIC, Patient Global Impression of Change; PK, pharmacokinetic; R, randomized; RNA, ribonucleic acid; ROB, risk of bias; SD, standard deviation; SE, standard error; SEM, standard error of the mean; THC, (delta-9) tetrahydrocannabinol; SR, systematic review; SS, statistically significant; sTNFRII, soluble receptor for tumor necrosis factor type II; TID, three times daily; VAS, visual analog scale; QID, four times daily; QoL, quality of life;

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	37-47 days total: treatment was for 16 days each (while inpatient), with 5-15 days outpatient between treatment periods.				Subjective ratings of hunger, satiety, thirst, dry mouth (Hunger and Satiety Questionnaire)	Treatment days 1-8: Significantly higher scores satiety (fullness) scores with dronabinol vs PBO. No differences between groups in hunger scores. Significantly greater thirst and dry mouth with dronabinol vs PBO. Treatment days 9-16: Significantly higher hunger scores with dronabinol vs PBO. No differences between groups in satiety. Significantly greater thirst and dry mouth with dronabinol vs PBO.	authors reported that their findings did not support a withdrawal in the placebo arm.
					Subjective mood and drug effects	Treatment days 1-8 and 9-16: Dronabinol significantly increased positive affect (on VAS), drug high, drug-liking, and sedation scores vs PBO. Treatment days 9-16: Dronabinol significantly increased strong drug effect vs PBO.	
					Objective (using a nightcap sleep monitor) and subjective sleep assessments	Treatment days 1-8: • Dronabinol significantly increased sleep efficiency (proportion of NREM+REM sleep out of total time in bed) vs PBO, attributed to increases in NREM sleep. • Dronabinol significantly increased patient-reported sleep satisfaction vs PBO on VAS	
					Cognitive performance tests	• Processing speed was significantly reduced with dronabinol vs PBO on days 9-16 (differences not significant on days 1-8) • Increased false alarms (P<0.01) to distractors with dronabinol vs PBO on days 1-8 (not significant on days 9-16) • Changes on the rapid acquisition task: fewer sequences entered with dronabinol vs PBO (on days 1-8 and 9-16) and more errors with dronabinol vs PBO (on days 9-16); all P<0.01	
Mboumba 2022/2023 population: Adults ≥ 18 years (80% male) with HIV and a suppressed viral load (<40 copies/mL) who were taking chronic ART for ≥ 3 years. No cannabis use within 4 weeks of the start of the study was allowed; 70% had cannabis use in the previous 6 months.							
Mboumba 2022[27] and Mboumba 2023[26]	R, open-label, pilot, safety trial 12 weeks	10 (8 with all 10 analyzed) Studied was stopped prematurely due to	1. THC/CBD oral capsules (2.5 to 15 mg/day), self-titrated per the schedule: 5 mg/5 mg x 2 weeks (as 2.5/2.5 BID), followed by 10 mg/10 mg x 2 weeks (as 5 mg/5 mg BID), then 15 mg/15 mg x 8 weeks (as 5 mg/5 mg TID) 2. CBD oral capsule (200 to 800 mg/day), self-titrated per the schedule: 200 mg x 2 weeks (once daily), then 400		Discontinuations due to AEs	2 in CBD-only arm: aggravated anemia and mild transaminitis (n=1), and life-threatening acute hepatitis that was possibly treatment related (n=1). Patient with acute hepatitis had other risk factors for hepatitis.	No ROB rating by a SR Noted limitations: There was no untreated/non-CBP comparator. The study was stopped early and did not reach the target sample size. Most of the sample was
					Incidence of at least 1 AE	THC/CBD: 80%; CBD: 80%. Most common AEs that were considered drug-related were difficulty concentrating, cognitive impairment, and increased appetite. Mostly mild-moderate.	

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		problems with medication supply	mg x 10 weeks (as 200 mg BID)*, or 300 mg x 2 weeks followed by 800 mg x 8 weeks (400 mg BID) Capsules contained purified (>98%) cannabinoids in oil *Amended protocol due the risk of hepatic toxicity		Biochemistry	As a group (both study arms combined), no clinically significant changes in biochemical labs. Two patients with diabetes had worsened blood glucose (one receiving CBD, the other receiving THC/CBD)	male. Patients who decided to participate may be more likely to be cannabis experienced.
					CD4 and CD8 counts	As a group, CD4+ and CDD8+ counts were not significantly different between baseline and the end of treatment. Mboumba 2023 reported more detailed analyses, finding decreases in PD1+ memory CD4+ T cells, CD73+ regulatory CD4+ T cells, and M-DC8+ intermediate monocytes from BL to end of treatment. Other cell types increased from BL during the treatment period (Ki-67+ CD4 T-cell, CCR2+ non-classical monocytes, and myeloid dendritic cells).	
					HIV viral load	As a group, the HIV RNA load remained undetectable during the treatment period (no changes from baseline)	
					Plasma markers of gut epithelial damage	As a group, plasma levels of REG-3alpha were lower at the end of treatment vs baseline. No observed changes in I-FABP.	
					Select other inflammatory markers	As a group, IFN-gamma, IL-1beta and STNFRII plasma levels declined from baseline to the end of treatment (P<0.05).	
					Change in QoL	As a group, the distribution of responses to the EQ-5D and WHOQoL-HIV BREF was not significantly different from baseline to the end of treatment.	
					Total mood disturbance on the POMS	As a group, 5/10 had a reduced total mood disturbance, whereas 3/10 had a slightly increased total mood disturbance.	
HIV-Related Neuropathy/Neuropathic Pain							
Abrams 2007 population: Adults (≥ 18) with HIV and symptomatic sensory neuropathy (average daily pain ≥ 30/100 on VAS), who had a stable health status including being on a stable HIV ART regimen and had prior cannabis experience (use ≥ 6 times in lifetime). Patients with current cannabis use were 78% in the cannabis group and 68% in the placebo group.							
Abrams 2007[30,37]	Parallel group, R, PC, DB, inpatient and outpatient trial Total duration 21 days: 7 days outpatients, 2-day inpatient lead-in, 5-day inpatient	55 (50)	Cannabis cigarette (3.56% THC; average weight 0.9g) 1 cigarette TID on study days (5 days)	Matched PBO cigarette	% with 30% reduction in pain on VAS (recorded in diary) from pre-intervention to post-intervention (primary)	**Cannabis, 13/25 (52%) vs. PBO, 6/25 (24%); P = 0.04**	ROB: low risk for random sequence generation, incomplete outcome data and other bias; unclear risk for selective reporting, blinding, and allocation concealment.[37]
					Median % reduction in neuropathic pain from BL (on VAS per diary) (co-primary)	**Cannabis, –34% (IQR –71 to –16); PBO, –17% (–29 to 8); P=0.03**	
					Withdrawal due to AE	None	

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	intervention, 7-day outpatient				AEs	**Significantly (P<0.05) more anxiety, sedation, disorientation, confusion, and dizziness with cannabis vs PBO**; and numerically more paranoia and nausea with cannabis vs PBO	
Ellis 2009 population: Adults with HIV-associated neuropathy (average pain score ≥ 5 on pain intensity scale for the descriptor differential scale (DDS); pain was refractory to ≥2 other treatments. Patients were allowed to continue other regular use of other analgesics. Patients with an AIDS-defining opportunistic infection were excluded. Most participants were receiving combination ART (93%). Most participants had prior cannabis experience (91% of those randomized, and 96% of trial completers), but patients who tested positive for urine cannabinoids during the week before starting treatment were excluded.							
Ellis 2009[32,37]	Crossover, R, DB, PC, outpatient trial 7 weeks total, including two 5-day treatment periods followed by two 2-week washout periods	34 (28)	Cannabis cigarettes (1-8% THC by weight; most patients used 8%) 1 cigarette four times daily during treatment (5 days). Participants started with 4% THC cannabis and titrated to a higher or lower potency depending on efficacy and tolerability.	Matched PBO cigarettes	Change from BL to end of treatment (day 5) in patient-reported pain scores (on the 0–20-point DDS) (primary)	**Median difference between change during cannabis vs PBO treatment: 3.3 DDS points (effect size 0.60); P=0.016 among completers.** No significant treatment effect based on order of treatment. Change in pain scores did not differ between the subgroups of patients with or without concomitant opioid use.	ROB: low risk for random sequence generation, allocation concealment, and incomplete outcome data; unclear risk for selective reporting; and high risk due to blinding; and other.[37] Noted limitations: Nearly all patients were male.[32] Many participants had used cannabis in the past, and most participants were able to correctly guess their treatment assignment.[37]
					Proportion with 30% reduction in pain on DDS from BL to day 5	**Cannabis: 0.46 (95% CI 0.28 to 0.65) vs PBO: 0.18 (95%CI 0.03 to 0.32); P = 0.043.**	
					Change from BL to end of treatment (day 5) per VAS pain scores	**Median change: cannabis, –17 (–58 to 52) vs. PBO, –4 (–56 to 29); P<0.001**	
					Other efficacy	Authors reported no differences (similar improvement) between treatments in scores on the POMS (Profile of Mood States), SIP (Sickness Impact Profile), BSI (Brief Symptom Inventory), mood disturbance, physical disability, and quality of life.	
					Withdrawal due to AE	During cannabis treatment: Psychosis in a cannabis-naïve person (n=1), intractable coughing that resolved after smoking stopped (n=1)	
					Other AE	AE more frequent with cannabis than placebo, including "concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, thirst" (page 677).[32] Also increases in heart rate by ≥ 30 points occurred more with cannabis (46%) vs PBO (4%).	
Riggs 2012 (Ellis trial subgroup analysis of hormones)[36]	See Ellis 2009	7 (out of 28 from the full study), 2 patients did not complete the PBO week	See Ellis 2009		Based on comparisons of morning (pre-treatment) and afternoon levels (after last treatment of the day), **cannabis use was associated with significant increases in plasma ghrelin and leptin and decreases in peptide YY versus PBO use**. No differences were observed in insulin plasma levels during periods of cannabis vs PBO use.		Additional limitations include this study being only a subgroup analysis of the primary study. The study did not control for caloric intake.

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Eibach 2020 population: Adults (18-65 years) with HIV and HIV-associated neuropathy (pain ≥ 4/11 on NRS). Participants were allowed to co-treat with analgesics (antidepressants and anticonvulsants) as-needed during the study. All patients were receiving ART. Patients currently using "conventional cannabinoids" were excluded; whether patients had a history of cannabis use was not reported.							
Eibach 2020[25]	Crossover, R, DB, PC, outpatient trial 13 weeks total, including two 4-week treatment phases and a 3-week washout. Each treatment phase was preceded by 1 week baseline measurement phase.	34 (32 included in analysis; 2 excluded from analysis and 4 additional dropped out but were included in the analysis)	400 mg CBDV orally once daily in the morning Administered as a 50 mg CBDV/mL solution with sesame oil and <0.2% of THC. Inferred it was plant-derived CBDV.	Matched PBO in sesame oil	Change from BL to end of treatment in mean pain intensity on 11-point NRS (primary) (calculated using average values from the last 2 days of the baseline and treatment phases)	Difference between CBDV and PBO: + 0.62 (95%CI –0.27 to 1.51; P = 0.16)	No ROB rating by a SR. Noted limitations: study was underpowered (aimed to enroll 50), although authors suggested that higher recruitment was unlikely to affect the outcome of the study.
					% of patients with at least 20% reduction in pain from BL	CBDV: n=9/31 (29%); PBO: n= 19/31 (61.3%)	
					Other secondary efficacy	No significant difference between CBDV and placebo treatment periods in scores on questionnaires for neuropathic pain (painDETECT, DN4i), pain intensity (BPI), pain influence on daily living, depression or anxiety symptoms (HADS), insomnia (ISI), or the patient's global impression of change (PGIC)	
					% with ≥ 1 AE	CBDV: 91.2% vs PBO: 79.4%	
					Serious AE	CBDV: 1 acute MI, considered non-study drug related	
					Other AEs	Similar incidence of AE with both CBDV and PBO. One patient withdrawal due to cough during CBDV treatment.	
NCT03099005 Population: Adults (≥ 18 years; 20% female) with HIV and HIV-associated sensory neuropathy who were currently using cannabis, had stable medical conditions, and were willing to respond to text messages. No information was documented about patient's use of ART.							

NCT03099005, **unpublished**[28]	Crossover, R, quadruple-blinded, phase 2 trial
	
	Each treatment was administered 1 time in the morning
		44 (5?)	Vaporized cannabis with 3 different doses of THC and CBD:
			1. THC 1.6% + CBD 0.09% x 8 puffs (low CBD)
			2. THC 1.6% + CBD 0.09% x 4 puffs and THC 1.73% + 5.4% CBD x 4 puffs (medium CBD)
			3. THC 1.73% + CBD 5.4% x 8 puffs (high CBD)
			Cannabis was administered using a Volcano vaporizer, with each treatment administered <u>one time.</u>
					Change from BL to <u>up to</u> 4 hours later in pain intensity on an 11-point NRS
					(primary)
					BL = start of experimental treatment day before treatment
						Mean score (SEM) at BL//after single dose of cannabis use:
						• Low CBD: 2.2 (0.7)//1.4 (0.6)
						• Medium CBD: 2.6 (1.0)//1.2 (0.6)
						• High CBD: 2.8 (0.8)//1.2 (0.4)
							No ROB rating by an SR.
							
							Noted limitations: **At the time of review, results submitted by investigators were not yet fully vetted by quality control**. No statistical comparisons reported. There was no PBO or non-cannabis comparator. Study did

					Patient Global Impression of Change (PGIC) on 7-point ordinal scale	• Low CBD: 2.8 (0.6) • Medium CBD: 2.6 (0.4) • High CBD: 3.4 (0.7)	

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					Score on VAS pain scale after Von Frey filament test on the dorsum of the more painful foot	Mean score (SEM) at BL//after single dose of cannabis use:
						• Low CBD: 28 (11.1)//7.4 (3.8)
						• Medium CBD: 13.4 (9.4)//10.8 (5.7)
						• High CBD: 14.5 (6.4)//8.8 (5.4)
							not meet the enrollment target of 120 participants.

					Incidence of SAE	0/5 (0%) in each treatment group, including no deaths	
					Incidence of non-serious AE	• Low CBD: 3/5 (60%) • Medium CBD: 2/5 (40%) • High CBD: 2/5 (40%)	
					Reported AEs collected systematically	• Low CBD: drowsiness (1/5; 20%); dry mouth (2/5; 40%); cognitive impairment (1/5; 20%) • Medium CBD: drowsiness (1/5; 20%); dry mouth (2/5; 40%); cognitive impairment (0/5; 0%) • High CBD: drowsiness (1/5; 20%); dry mouth (2/5; 40%); cognitive impairment (0/5; 0%)	
People with AIDS and Anorexia and/or Cachexia							
Struwe 1993 population: Men with HIV who had lost 2.25 kg of their usual body weight (and remained at ≥ 70% of their ideal body weight) who could feed themselves and tolerate a regular diet; at least some patients met criteria for AIDs based on baseline CD4 counts (2/5 patients with CD4 count <200/μL; both <50). Four of five patients were considered to have wasting; 3/5 patients were receiving ART.							
Struwe 1993[33]	Crossover, R, DB, PC trial 70 total days, including 35 days each with treatment or PBO. 2-week washout period.	12 (5; only completers included in the analysis)	Dronabinol 5 mg orally BID (before lunch and dinner)	Matched PBO	Median difference in change from BL to end of treatment between treatment periods (all were considered 'main' outcome measures):		ROB: low risk for incomplete outcome data and selective reporting; unclear risk for allocation concealment, and other bias; and high risk due to blinding.[37] Noted limitations: many patients were correctly able to identify the dronabinol treatment, which could have led to behavioral changes (eg, eating more); and failed to recruit many patients because they did not want to stop cannabis, suggesting the study population tended to benefit from cannabis already. Study was underpowered to detect a difference in weight with 80% power.
					Weight (kg)	+1 favoring dronabinol; P=0.13	
					Body fat (%)	+0.76 favoring dronabinol; P=0.04	
					Caloric intake (kcal/kg/24h)	+4.2 favoring dronabinol; P=0.50	
					Serum prealbumin (mg/L)	+26 favoring dronabinol; P=0.11	
					Functional limitations (higher score out of 340 points = more distress)	–33.5 favoring dronabinol; P=0.04	
					Appetite (0-100 scale; with lower scores = increased)	–19.5 favoring dronabinol; P=0.14	
					Withdrawal due to AEs	Dronabinol: 2 (sedation and mood effects). No treatment-limiting AE in the 5 people who completed the study	

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Beal 1995 population: Adults (93% male) with AIDS (per 1987 CDC criteria) who lost at least 2.3 kg from a normal body weight and had the ability to feed themselves and consume a normal diet. Patients on a stable ART regimen for at least 2 weeks could continue ART. No cannabis was allowed during the trial, and 41.7% (dronabinol arm) or 47.8% (PBO arm) endorsed no prior cannabis use. (For AIDS-related anorexia)							
Beal 1995[31]	Parallel, R, multicenter, DB, PC trial 6 weeks	139 (88 [63%] in the 'evaluable' population, including 50 [72%] randomized to dronabinol and 38 [57%] randomized to PBO)	Dronabinol 2.5 mg orally BID (before lunch and dinner)	Matched PBO	Change in mean appetite from BL to last evaluable endpoint (per 100-point VAS) (primary)	Among all patients: Dronabinol: 37% increase; PBO: 17% increase; P = 0.05 Among evaluable patients: Dronabinol: 38% increase; PBO: 8% increase; P = 0.015 • Increases in appetite were considered independent from baseline CD4 count	ROB: low risk for other bias; unclear risk for allocation concealment, random sequence generation, blinding, and selective reporting; and high risk due to incomplete outcome data.[37]
					Change in mean weight from BL to last evaluable endpoint (primary)	Among evaluable patients: Dronabinol: 0.1 kg increase; PBO: –0.4 kg loss; P = 0.14 Among patients without intercurrent illness (unknown #) Dronabinol: 1.1 kg increase; PBO: –0.1 kg loss; P = 0.12	
					Change in mean mood from BL to last evaluable endpoint (per 100-point VAS)	Among all patients: Dronabinol: 7% increase; PBO: 2% increase; P=0.14 Among evaluable patients: Dronabinol: 10% increase; PBO: 2% decrease; P = 0.06	
					Change in mean nausea from BL to last evaluable endpoint (per 100-point VAS)	Among all patients: Dronabinol: 22% decrease; PBO: 4% decrease; P=0.26 Among evaluable patients: Dronabinol: 20% decrease; PBO: 7% decrease; P = 0.05	
					Change in mean Karnofsky performance status (0 [death] to 100 [normal])	Among all patients: Dronabinol: –2.5 point decrease; PBO: no change; P=0.18 Among evaluable patients: Dronabinol: –1.0 point decrease; PBO: 0.3 point increase; P = 0.07	
					Discontinuation due to AEs	Dronabinol: n=6 (8.3%); PBO: n= 3 (4.5%)	
					Any treatment-related AE (%)	Dronabinol: 43.1%; PBO: 13.4%, primarily due to more nervous system AEs with dronabinol	
					Drug-related nervous system AEs (%)	Dronabinol: 34.7%; PBO: 9%. Most events were mild-moderate. Most common AEs with dronabinol: euphoria, dizziness, thinking abnormality, somnolence	

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; AUC, Area under the plasma concentration by time curve; BID, twice daily; BL, baseline; BPI, brief pain inventory; CBD, cannabidiol; CBDV, cannabidivarin; CBP, cannabinoid- or cannabis-based intervention; CI, confidence interval; DB, double-blind; DDS, Descriptor Differential Scale; DN4i, Douleur Neuropathique 4 interview; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; ISI, Insomnia Severity Index; NSS, not statistically significant; PBO, placebo; PC, placebo-controlled; PGIC, Patient Global Impression of Change; PK, pharmacokinetic; R, randomized; RNA, ribonucleic acid; ROB, risk of bias; SD, standard deviation; SE, standard error; SEM, standard error of the mean; THC, (delta-9) tetrahydrocannabinol; SR, systematic review; SS, statistically significant; sTNFRII, soluble receptor for tumor necrosis factor type II; TID, three times daily; VAS, visual analog scale; QID, four times daily; QoL, quality of life;

Table B1. Summary of the Study Design and Select Efficacy and Safety Outcomes from Included Experimental Trials among People Living with HIV or AIDS

Study: First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result	ROB per a SR
Timpone 1997 population: Adults (88% male) with HIV-associated wasting syndrome including anorexia, including ≥ 10% of body weight loss or an underweight BMI who could tolerate oral intake, and lacked severe diarrhea. Mean baseline CD4 count was <250 in each study arm (range 56 to 123). Patients were allowed to continue stable doses of ART (86% were receiving ART) or other medications. Cannabis use within 1 month before the study was prohibited, and patients could not have a major opportunistic infection in the past 2 months or active neoplasms (except for localized cutaneous neoplasms) (HIV-related cachexia/wasting syndrome)							
Timpone 1997[34]	Parallel, multicenter, R, open-label outpatient trial 12 weeks	52 (39 completed entire treatment)	1. Dronabinol 2.5 mg orally BID (D) 2. Dronabinol 2.5 mg orally BID + megestrol acetate 750 mg daily (D+M750) 3. Dronabinol 2.5 mg orally twice daily + megestrol acetate 250 mg daily (D+ M250)	4. Megestrol acetate 750 mg once daily (M750)	Mean weight change ±SE from BL to 12 weeks	D: –2.0 ± 1.3 kg D+M750: +6.0 ± 1.0 kg (about 11% weight gain) P=0.0001 D+M250: –0.3 ± 1.0 kg M750: +6.5 ± 1.1 kg (about 11% weight gain)	ROB: no low risk; unclear risk for random sequence, allocation concealment, blinding of participants/personnel, blinding of outcome assessors, and selective reporting; high risk for incomplete outcome data and selection bias[41] Noted limitations: study was focused on PK and safety, and was not powered to assess efficacy outcomes.
					Correlation of PK parameters with efficacy parameters	After 2 weeks of treatment, megestrol PK parameters (Cmax and AUC) were positive correlated with weight change and hunger at breakfast and at dinner on VAS. Correlations were not observed with these dronabinol parameters.	
					Other efficacy	No significant differences between treatment groups in VAS mood or nausea scores. As an overall group (ie, all study arms), VAS hunger scores improved from baseline to week 1 and not after week 1. No differences in QoL between groups.	
					Discontinued treatment due to AEs (not necessarily treatment related)	D: hallucinations (n=1), somnolence (n=1); other patients d/c due to lymphoma (n=1), tuberculosis (=1), or unknown (n=1) D+M750: none; other patients d/c due to unknown (n=1), *Candida* esophagitis (n=1), cryptosporidiosis (n=1) D+M250: seizure (n=1), dyspnea (n=1); other patients d/c due to unknown (n=1) and tuberculosis (n=1) M750: dyspnea (n=1); other patients d/c due to lymphoma (n=1)	
					Deaths	2 deaths; M750 (n=1; lymphoma) and MR750+D (n=1; respiratory failure) – both considered unrelated to study treatment	
					Incidence of grade 3 or grade 4 AEs	D: 63.6% M750: 80% D+M750: 84.6% D+M250: 84.6%	
					Grade 3 CNS AEs	Of the 37 patients who received dronabinol, 5 (14%) experienced drug-related confusion, anxiety, emotional lability, euphoria or hallucinations	

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; AUC, Area under the plasma concentration by time curve; BID, twice daily; BL, baseline; BPI, brief pain inventory; CBD, cannabidiol; CBDV, cannabidivarin; CBP, cannabinoid- or cannabis-based intervention; CI, confidence interval; DB, double-blind; DDS, Descriptor Differential Scale; DN4i, Douleur Neuropathique 4 interview; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; ISI, Insomnia Severity Index; NSS, not statistically significant; PBO, placebo; PC, placebo-controlled; PGIC, Patient Global Impression of Change; PK, pharmacokinetic; R, randomized; RNA, ribonucleic acid; ROB, risk of bias; SD, standard deviation; SE, standard error; SEM, standard error of the mean; THC, (delta-9) tetrahydrocannabinol; SR, systematic review; SS, statistically significant; sTNFRII, soluble receptor for tumor necrosis factor type II; TID, three times daily; VAS, visual analog scale; QID, four times daily; QoL, quality of life;

APPENDIX C – NATIONAL ACADEMIES LEVEL OF EVIDENCE CATEGORIES

Previously, the CRRB developed LOE categories for graded statements using evidence rating categories from the 2017 National Academies of Sciences, Engineering, and Medicine (NASEM) report for therapeutic recommendations.[50] Refer to **Table C1** for details about these evidence categories.

Table C1. Levels of Evidence for Therapeutic Effects from the 2017 NASEM Cannabis Report

Conclusive Evidence
• "There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).[50] • "For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitation of the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence" (page 7).[50]
Substantial Evidence
• "There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).[50] • "For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence" (page 7).[50]
Moderate Evidence
• "There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8). • "For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence." (page 8).[50]
Limited Evidence
• "There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[50] • "For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors" (page 8).[50]
No or Insufficient Evidence
• "There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[50] • "For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors" (page 8).[50]

Abbreviations: NASEM, The National Academies of Sciences, Engineering, and Medicine

APPENDIX D – LITERATURE SEARCHES

Table D1. Ovid-Medline Literature Search Strategy for Systematic Reviews

Ovid-Medline Session Results

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to May 1, 2024

Date of search: May 2, 2024

#	Searches	Results
1	(hiv* or human immun* virus).ti,ab,kw,kf.	389284
2	(acquired immun* adj3 syndrome).ti,ab,kw,kf.	27480
3	exp HIV/	109040
4	exp HIV Infections/	322217
5	1 or 2 or 3 or 4	465649
6	exp Cannabis/ or exp cannabinoids/ or exp Medical Marijuana/ or exp "Marijuana Use"/ or exp Marijuana Abuse/	39731
7	(mari?uana or pot or hash* or bhang* or gan?a* or weed* or hemp*).ti,ab,kw,kf.	90964
8	(Tetrahydrocannab* or cannabi* or THC or CBD or CBN or CBG or CBC, or THCV or CBDV or CBCV or CBGV or THCA or CBDA or CBGA or CBNA).ti,ab,kw,kf.	69966
9	(THC and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	683
10	(nabilone or dronabinol or marinol or syndros or cesamet or epid#olex or nabiximol* or Sativex or bedrocan or bedrobinol or bedica or bediol or bedrolite or dexanbinol).ti,ab,kw,kf.	1285
11	6 or 7 or 8 or 9 or 10	156912
12	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "systematic review"/ or ((sytematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	526032
13	(MEDLINE or Embase or Pubmed or systematic review).tw. or meta analysis.pt.	543618
14	12 or 13	652768
15	5 and 11 and 14	**68**

Table D2. Embase Literature Search Strategy for Systematic Reviews

Embase Session Results

Date of search: May 2, 2024

#	Searches	Results
1	'human immunodeficiency virus'/exp	224,353
2	'human immunodeficiency virus infection'/exp	825,102
3	hiv*:ti,ab,kw OR 'human immun* virus':ti,ab,kw	502,972
4	('acquired immun*' NEAR/3 syndrome):ti,ab,kw	27,548
5	#1 OR #2 OR #3 OR #4	1,019,071
6	'cannabinoid'/exp OR 'cannabis use'/exp OR 'cannabis smoking'/exp OR 'cannabis addiction'/exp	106,955

Table D2. Embase Literature Search Strategy for Systematic Reviews

Embase Session Results

Date of search: May 2, 2024

#	Searches	Results
7	mari?uana:ti,ab,kw OR pot:ti,ab,kw OR hash*:ti,ab,kw OR bhang*:ti,ab,kw OR gan?a*:ti,ab,kw OR weed*:ti,ab,kw OR hemp*:ti,ab,kw	112,972
8	tetrahydrocannab*:ti,ab,kw OR cannabi*:ti,ab,kw OR thc:ti,ab,kw OR cbd:ti,ab,kw OR cbn:ti,ab,kw OR cbg:ti,ab,kw OR cbc:ti,ab,kw OR thcv:ti,ab,kw OR cbdv:ti,ab,kw OR cbcv:ti,ab,kw OR cbgv:ti,ab,kw OR thca:ti,ab,kw OR cbda:ti,ab,kw OR cbga:ti,ab,kw OR cbna:ti,ab,kw	106,667
9	thc:ti,ab,kw AND (analog*:ti,ab,kw OR enantiomer*:ti,ab,kw OR isomer*:ti,ab,kw)	886
10	nabilone:ti,ab,kw OR dronabinol:ti,ab,kw OR marinol:ti,ab,kw OR syndros:ti,ab,kw OR cesamet:ti,ab,kw OR epid?olex:ti,ab,kw OR nabiximol*:ti,ab,kw OR sativex:ti,ab,kw OR bedrocan:ti,ab,kw OR bedrobinol:ti,ab,kw OR bedica:ti,ab,kw OR bediol:ti,ab,kw OR bedrolite:ti,ab,kw OR dexanabinol:ti,ab,kw	2,051
11	#6 OR #7 OR #8 OR #9 OR #10	240,768
12	cochrane*:jt OR 'systematic review*':jt OR 'meta analysis'/exp OR 'systematic review'/exp OR ((systematic* NEAR/3 review*):ti,ab,kw) OR ((systematic* NEAR/2 search*):ti,ab,kw) OR 'meta analys*':ti,ab,kw OR metaanalys*:ti,ab,kw OR ((overview NEAR/4 (review OR reviews)):ti)	774,332
13	#5 AND #11 AND #12	**198**

Table D3. Ovid-Medline Literature Search Strategy for Experimental Trials

Ovid-Medline Session Results

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to May 17, 2024

Date of search: May 20, 2024

#	Searches	Results
1	(hiv* or human immun* virus).ti,ab,kw,kf.	389987
2	(acquired immun* adj3 syndrome).ti,ab,kw,kf.	27493
3	exp HIV/	109167
4	exp HIV Infections/	322612
5	1 or 2 or 3 or 4	466368
6	exp Cannabis/ or exp cannabinoids/ or exp Medical Marijuana/ or exp "Marijuana Use"/ or exp Marijuana Abuse/	39842
7	(mari?uana or pot or hash* or bhang* or gan?a* or weed* or hemp*).ti,ab,kw,kf.	91276
8	(Tetrahydrocannab* or cannabi* or THC or CBD or CBN or CBG or CBC, or THCV or CBDV or CBCV or CBGV or THCA or CBDA or CBGA or CBNA).ti,ab,kw,kf.	70218
9	(THC and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	686
10	(nabilone or dronabinol or marinol or syndros or cesamet or epid#olex or nabiximol* or Sativex or bedrocan or bedrobinol or bedica or bediol or bedrolite or dexanbinol).ti,ab,kw,kf.	1292

Table D3. Ovid-Medline Literature Search Strategy for Experimental Trials

Ovid-Medline Session Results

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to May 17, 2024

Date of search: May 20, 2024

#	Searches	Results
11	6 or 7 or 8 or 9 or 10	157459
12	(randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1648333
13	5 and 11 and 12	211
14	limit 13 to yr="2021 -Current"	39

Table D4. Embase Literature Search Strategy for Experimental Trials

Embase Session Results

Date of search: May 20, 2024

#	Searches	Results
1	'human immunodeficiency virus'/exp	224,566
2	'human immunodeficiency virus infection'/exp	826,892
3	hiv*:ti,ab,kw OR 'human immun* virus':ti,ab,kw	504,313
4	('acquired immun*' NEAR/3 syndrome):ti,ab,kw	27,571
5	#1 OR #2 OR #3 OR #4	1,021,486
6	'cannabinoid'/exp OR 'cannabis use'/exp OR 'cannabis smoking'/exp OR 'cannabis addiction'/exp	107,353
7	mari?uana:ti,ab,kw OR pot:ti,ab,kw OR hash*:ti,ab,kw OR bhang*:ti,ab,kw OR gan?a*:ti,ab,kw OR weed*:ti,ab,kw OR hemp*:ti,ab,kw	113,366
8	tetrahydrocannab*:ti,ab,kw OR cannabi*:ti,ab,kw OR thc:ti,ab,kw OR cbd:ti,ab,kw OR cbn:ti,ab,kw OR cbg:ti,ab,kw OR cbc:ti,ab,kw OR thcv:ti,ab,kw OR cbdv:ti,ab,kw OR cbcv:ti,ab,kw OR cbgv:ti,ab,kw OR thca:ti,ab,kw OR cbda:ti,ab,kw OR cbga:ti,ab,kw OR cbna:ti,ab,kw	107,185
9	thc:ti,ab,kw AND (analog*:ti,ab,kw OR enantiomer*:ti,ab,kw OR isomer*:ti,ab,kw)	890
10	nabilone:ti,ab,kw OR dronabinol:ti,ab,kw OR marinol:ti,ab,kw OR syndros:ti,ab,kw OR cesamet:ti,ab,kw OR epid?olex:ti,ab,kw OR nabiximol*:ti,ab,kw OR sativex:ti,ab,kw OR bedrocan:ti,ab,kw OR bedrobinol:ti,ab,kw OR bedica:ti,ab,kw OR bediol:ti,ab,kw OR bedrolite:ti,ab,kw OR dexanabinol:ti,ab,kw	2,062
11	#6 OR #7 OR #8 OR #9 OR #10	241,760
12	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	3,336,206
13	#5 AND #11 AND #12	**666**
14	#5 AND #11 AND #12 AND [2021-2024]/py	137