COLLEGE OF PHARMACY
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EVIDENCE REVIEW:

Experimental Evidence for the Treatment of HIV/AIDS with Cannabis-based Products

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I have no conflicts of interest to disclose

BRIEF EVIDENCE REPORT OBJECTIVE & METHODS

- **Objective:**
  - Summarize recent clinical evidence for the use of cannabis- or cannabinoid-based products (CBPs) in people living with HIV or AIDS (PLWHA) using a hierarchy-of-evidence approach
  - Assist the CRRB with updating guidance

- **Methods:**
  - Searched for SRs of experimental controlled trials (ETs) published from database inception to May 2024 or ETs (eg, RCTs) published since 2021*
  - Included ETs of any design with:
    - PLWHA
    - Treatment with CBPs (natural or synthetic) for any duration;
    - Any efficacy or safety outcome
  - Summarized select efficacy and safety results from ETs
  - Extracted ROB ratings from published SRs[1,2]

*Narrowed RCT search dates to 2021-2024 based on the search dates of SRs

Abbreviations: AIDS, acquired immune deficiency syndrome; CBP, cannabis- or cannabinoid-based product; CRRB, Utah Cannabis Research Review Board; ET, experimental (controlled) trials; PLWHA, people living with HIV or AIDS; RCT, randomized controlled trial; ROB, risk of bias; SR, systematic review

INCLUDED TRIALS

- **12 experimental controlled trials[3-14] (16 citations)[15-18]**
  - Primarily RCTs (N=11) that were parallel group (N=5), or cross-over (N=7), including 2 trials that used staggered cross-over treatment periods
  - Double-blinded (N=9), open-label (N=2), or partially blinded (N=1)
  - Median treatment duration of about 25 days (range 1 to 84 days)*
  - Median of 34 participants per trial (range 7 to 139)
  - Participants enrolled to manage:
    - HIV-related neuropathic pain (N=4)
    - HIV-associated anorexia and weight loss and/or wasting, primarily PLWA (N=3)
    - General trials, focused on safety or other that enrolled PLWHA without specific complaints (N=5)
  - Concurrent use of ART and degree of HIV viral suppression varied, when reported
- 6 trials were <u>not</u> addressed/cited by the existing CRRB guidance:
  - *General trials:* Haney et al. 2005, Haney et al. 2007, Bedi et al. 2010, and Mboumba et al. 2022
  - *HRNP trials:* Eibach et al 2020, and NCT03099005 (unpublished)

*Based on 10 trials; two staggered cross-over trials lacked sufficient detail about duration

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CRRB, Utah Cannabis Research Review Board; HIV, human immunodeficiency virus; HRNP, HIV-related neuropathic pain; PLWA, people living with AIDS; PLWHA, people living with HIV or AIDS; RCT, randomized controlled trial;

OVERVIEW OF TRIALS IN PLWHA WITH HRNP

Trial and design	Population (total/completed n)	Approx. tx. duration
Abrams et al 2007*[3] Parallel, DB RCT[#]	• Adults (87% male) with chronic HRNP (pain ≥ 30/100) (n=55/50) • Most receiving ART (76.4%) • Cannabis-experienced, most with recent use	5 days
Ellis et al 2009*[4] Cross-over, DB RCT[#]	• Adults (97% male) with presumed chronic HRNP (pain ≥ 5/20), that is refractory to 2+ analgesics (n=38/28) • Most receiving ART (93%) • Most were cannabis-experienced, but <u>without</u> positive urine cannabinoid test	5 days *2-week washout*
Eibach et al 2020[5] Cross-over, DB, RCT[#]	• Adults (97% male) with chronic HRNP (pain ≥ 4/11) (n=34/32) • Receiving ART • History of cannabis use not reported	4 weeks *3-week washout*
NCT03099005[6] Cross-over, QB, RCT	• Adults (80% male) with chronic HRNP (mean baseline pain of 2.2-2.8/11) (n=44/5?) • Unknown ART status • Current cannabis users	1 day (single dose)

[#]Confirmed other analgesics allowed during the trial

*Trial addressed by current CRRB guidance

Abbreviations: ART, (combination) antiretroviral therapy; CRRB, Utah Cannabis Research Review Board; DB, double-blinded; HRNP, HIV-related neuropathic pain; RCT, randomized controlled trial; Tx, treatment; QB, quadruple blinded

HRNP - SELECT PAIN EFFICACY RESULTS

Study	Intervention(s)	Efficacy – pain
Abrams 2007[3]	Smoked cannabis (3.6% THC) vs PBO TID	• 30% pain reduction: **Can. > PBO** • Median % pain reduction: **Can. > PBO**
Ellis 2009[4]	Smoked cannabis (1-8% THC) vs PBO QID	• 30% pain reduction: **Can. > PBO** • Change from BL in pain: **Can. > PBO**
Eibach 2020[5]	Oral CBDV 400 mg vs PBO daily	• 20% pain reduction: PBO > Can. • Change from BL in pain: No difference
NCT 03099005[6]	Vaporized cannabis, single dose: "Low" CBD vs "Medium" CBD vs "High" CBD	• Change in pain up to 4 hours later: numerical reductions in each group • PGIC: score range 2.8 to 3.4 (out of 7)

Key: green/bold, efficacy favors CBP over comparator (statistically); red, efficacy favors neither CBP or comparator (statistically); grey, no formal statistical comparisons reported

Abbreviations: BL, baseline; Can., cannabis; CBD, cannabidiol; CBP, cannabis- or cannabinoid-based product; CBDV, cannabidivarin; PBO, placebo; TID, three times daily; QID, four times daily;

OVERVIEW OF TRIALS IN PLWA WITH ANOREXIA OR WASTING

Trial and design	Population (total/completed n)	Approx. tx. duration
Struwe et al 1993*[7] Cross-over, DB RCT	• Adults (100% male) with HIV who lost ≥ 2.3 kg and remained at ≥ 70% of IBW; 80% of final population with wasting • Able to feed self and consume a normal diet (n=12/5) • Receiving ART (60%)[a] • No cannabis use in the prior month	35 days *2-week washout*
Beal et al 1995*#[8] Parallel, DB RCT	• Adults (93% male) with AIDS who lost ≥ 2.3 kg from a normal body weight (n=139/88 [”evaluable population”]) • Able to feed self and consume normal diet • ART allowed; unknown proportion of patients on ART[a] • 40-48% without prior cannabis use; no use within prior 20 days	42 days
Timpone et al 1997*[9] Parallel, open-label, safety-focused, RCT	• Adults (88% male) with HIV-wasting and anorexia who lost 10% of body weight or had a low BMI for age group • Able to tolerate oral intake and no diarrhea (n=52/39) • Receiving ART (89%)[a] • No cannabis use in the prior month	84 days

*Trial cited by review addressed by current CRRB guidance

#Pivotal trial that led to FDA approval of dronabinol for AIDS-associated anorexia with weight loss

[a] ART regimens unknown; likely used ART regimens that were less effective than modern combination ART regimens

Abbreviations: ART, antiretroviral therapy; AIDS, acquired immunodeficiency syndrome; BMI, body mass index; CRRB, Utah Cannabis Research Review Board; DB, double-blinded; HIV, human immunodeficiency virus; IBW, ideal body weight; PLWA, people living with AIDS; RCT, randomized controlled trial; Tx, treatment;

WASTING AND/OR ANOREXIA IN PLWA – SELECT EFFICACY RESULTS

Study	Intervention(s)	Efficacy – Appetite	Efficacy – Weight
Struwe 1993[7]	Dronabinol 5 mg **vs** PBO BID	• Daily caloric intake and patient-reported appetite: Slight increase favoring DRO. (+4.2 kcal/kg) > PBO, *NSS*	• Increased weight at 5 weeks, DRO. > PBO by +1 kg, *NSS* • Increased body fat, **DRO. > PBO**
Beal 1995[8]	Dronabinol 2.5 mg **vs** PBO BID	• Patient-reported appetite: **DRO. (37% increase) > PBO (17% increase)** • Patient-reported nausea: **DRO. > PBO**	• % with 2kg weight gain in evaluable population: DRO. (22%) vs PBO (10.5%), *NSS*
Timpone 1997[9]	Dronabinol 2.5 mg BID **vs** megestrol acetate 750 mg daily[a]	• Patient-reported hunger: both groups significantly improved from BL to 1 week	• Mean weight gain at 12 weeks: **megestrol (+6.5 kg) > DRO. (–2 kg)**

Key: green/bold, efficacy favors CBP over comparator (statistically); red, efficacy favors neither CBP or comparator (statistically); blue, efficacy favors active comparator over CBP (statistically)

[a] Timpone et al also included 2 treatment groups that received dronabinol + megestrol acetate. Megestrol acetate is FDA-approved for treatment of anorexia, cachexia, or significant weight loss in PLWA (at doses of 625-800 mg/day).

Abbreviations: BID, twice daily; BL, baseline; CBP, cannabis- or cannabinoid-based product; DRO., dronabinol; NSS, non-statistically significant; PBO, placebo; PLWA, people living with AIDS

OVERVIEW OF GENERAL TRIALS IN PLWHA

Trial and design	Population (total/completed n)	Approx. tx. duration
Haney et al 2005[10] Staggered, cross-over, double-dummy, DB RCT	• Adults (89% male) with HIV; medically stable (n=30/29?) • 44% with low body cell mass/height (<90% of normal) • Smoked cannabis at least twice weekly • Prescribed ≥ 2 ART	8 sessions over 3-4 weeks; likely 3 sessions/tx, non-sequentially
Haney et al 2007[11] Staggered, cross-over, double-dummy, DB RCT	• Adults (90% male) with HIV; medically stable (n=10/10?) • 20% of participants had low body mass • Smoked cannabis at least twice weekly • Prescribed ≥ 2 ART	Two sequential 4-day treatment periods at each dose PBO for 4 days between active doses
Bedi et al 2010[12] Cross-over, DB, CT	• Adults (100% male) with HIV; medically stable (n=7/7) • Smoked cannabis at least twice weekly • Prescribed ≥ 2 ART	16 days *5-15 days between tx*

Abbreviations: ART, antiretroviral therapy; CT, controlled trial (randomization status unknown); DB, double-blinded; HIV, human immunodeficiency virus; PBO, placebo; PLWHA, people living with HIV or AIDS; RCT, randomized controlled trial; Tx, treatment;

OVERVIEW OF GENERAL TRIALS IN PLWHA

Trial and design	Population (total/completed n)	Approx. tx. duration
Abrams et al 2003[13] Parallel, DB (oral regimen only), RCT	• Adults (89% cisgender male) with HIV/AIDS (n=67/62) • No acute issues or unintentional weight loss of ≥ 10% • 58% with undetectable HIV RNA at BL; stable levels for ≥ 16 weeks • On stable ART with nelfinavir or indinavir • Experience using cannabis ≥ 6 times	3 weeks
Mboumba et al 2022[14] Pilot, open-label, safety, RCT	• Adults (80% male) with HIV (n=10/8) • Suppressed viral load (<40 copies/mL) • Chronic ART for ≥ 3 years • 70% with history of cannabis use; no cannabis use allowed within 4 weeks prior to the study	12 weeks Trial stopped early due to medication supply issues

Abbreviations: ART, antiretroviral therapy; BL, baseline; DB, double-blinded; HIV, human immunodeficiency virus; PLWHA, people living with HIV or AIDS; RCT, randomized controlled trial; Tx, treatment;

BODY WEIGHT AND/OR CALORIC INTAKE IN PLWHA FROM GENERAL TRIALS

Study	Intervention(s)	Efficacy – Caloric intake	Efficacy – Weight
Abrams 2003[13]	Smoked cannabis (3.9% THC) **vs** DRO 2.5 mg **vs** PBO, all TID	NR	• Body weight after 21 days: **DRO and Can. (median +3-3.2kg) > PBO (median +1.1kg)** • Associated with increased fat mass
Haney 2005[10]	Smoked cannabis (0-3.9% THC) x 3 puffs **vs** DRO. 0 – 30 mg **vs** matched PBO	• Acute caloric intake (4 hrs): **Can. & DRO > PBO in people with low** but not normal body mass	NR
Haney 2007[11]	Smoked cannabis (0-3.9% THC) 3 puffs **vs** DRO 0-10 mg **vs** matched PBO, all QID	• Mean caloric intake: **DRO (5,10 mg) and Can. (2.0, 3.9%) > PBO** • Increased calories from fat	• Body weight after 4 days: **DRO 10 mg and Can. 3.9% > PBO**
Bedi 2010[12]	DRO 10 mg **vs** PBO, each QID	• Caloric intake from day 1 to 8: **DRO. > PBO** • Caloric intake day 9 to 16: no diff.	• Weight from day 1 to 8: no diff. • Weight from day 9 to 16: no diff.

Key: green/bold, efficacy favors CBP over comparator (statistically); red, efficacy favors neither CBP or comparator (statistically)

[a] In the staggered trials, details about the number of experimental sessions was poorly reported. For Haney 2005, participants appeared to have received one dose of the same active drug at 3 non-sequential sessions. For Haney 2007, participants appeared to have received the same active drug at two separate 4-sequential day sessions.

Abbreviations: Can., cannabis; CBP, cannabis- or cannabinoid-based product; DRO., dronabinol; PBO, placebo; PLWA, people living with AIDS; NR, not reported; TID, three times daily; QID, four times daily;

SAFETY: T LYMPHOCYTES AND HIV VIRAL LOAD

- **T lymphocytes**
  - Overall, no significant changes in CD4+ or CD8+ counts associated with CBPs[7,9,13,14]
    - Dronabinol in PLWA, or oral THC/CBD (15 mg/15 mg) or CBD 200-800 mg for up to 12 weeks in PLWH
    - Smoked cannabis for up to 21 days in PLWHA
  - Smoked cannabis and oral THC/CBD or CBD associated with changes in some T-cell or other immune cell phenotypes[15,17]

- **HIV viral load**
  - CBPs not associated with significant changes (versus placebo or baseline) in viral load in the short-term[4,13,14]
    - Among PLWHA who were virologically suppressed (Mboumba 2022), or mixed (58% with undetectable viral load) (Abrams 2003), or had an unknown status at baseline (Ellis 2009)
    - Smoked cannabis for 5 or 21 days, dronabinol for 21 days, or oral THC/CBD or CBD for 12 weeks

Abbreviations: AIDS, acquired immune deficiency syndrome; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; HIV, human immunodeficiency virus; PLWA, people living with AIDS; PLWHA, people living with HIV or AIDS; THC, delta-9-tetrahydrocannabinol;

SAFETY: ART PHARMACOKINETICS AND COGNITION

- **ART pharmacokinetic (PK) parameters**
  - Modest changes to PK parameters of 2 protease inhibitors* from baseline to day 14 during treatment with smoked cannabis and dronabinol[13,18]
    - Authors considered the changes to be **clinically insignificant**
    - Statistically significant decreases (-14.1%; range –58 to +7) in indinavir maximum concentration during cannabis treatment

- **Cognition**
  - No studies targeted or reported including people with HAND
  - Cognitive performance tests in 2 trials suggests high-dose dronabinol *might* worsen acute digit recall, processing speed, rapid acquisition, and increase false responses to distractors[10,12]
    - Results inconsistent between trials[10-12] and may not be reliable[#]
  - Smoked cannabis was not associated with significantly altered cognitive performance versus placebo[10,11]

*Tested protease inhibitors included indinavir and nelfinavir that are used uncommonly in the US today; other ARTs used with these agents was not specified.
[#] Results from trials of highly-experienced cannabis users, with only only acute performance tested during/near peak cannabinoid concentrations. Two trials allowed use of cannabis at home between testing periods (Haney 2005 and Haney 2007).

Abbreviations: ART, antiretroviral therapy; HAND, HIV-associated neurocognitive disorder; PK, pharmacokinetic;

SAFETY: DISCONTINUATIONS DUE TO AES

Trial	Discontinuation due to AE
PLWHA with no specific complaints	
Abrams 2003[13]	• *Smoked cannabis:* **grade 2 neuropsychiatric symptoms** (1/21, 4.8%) • *Dronabinol:* **grade 2 paranoia** (1/25, 4%); persistent headache/nausea (1/25, 4%) • *PBO:* none
Haney 2005[10]/2007[11]	• *Dronabinol or smoked cannabis:* None reported
Mboumba 2022[14]	• *Oral CBD:* anemia and mild transaminitis (1/5, 20%); **life-threatening acute hepatitis** (1/5, 20%) • *Oral THC/CBD:* none reported
PLWHA with HIV-related neuropathic pain	
Ellis 2009[4]	• *Smoked cannabis:* **psychosis, in a cannabis-naïve person** (1/34, 2.9%); intractable cough (1/34, 2.9%) • *PBO:* none
Eibach 2020[5]	• *Oral CBDV:* cough (1/32, 3.1%) • *PBO:* none

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; d/c, discontinued; HIV, human immunodeficiency virus; PBO, placebo; PLWHA, people living with HIV or AIDS; THC, delta-9-tetrahydrocannabinol;

SAFETY: DISCONTINUATIONS DUE TO AES

Trial	Discontinuation due to AE and/or illness
PLWA with weight loss and/or wasting	
Struwe 1993[7]	• *Dronabinol:* **mood changes and sedation** (2/12, 16.7%) • Select other discontinuations (unclear if AE) during unspecified treatment period (*dronabinol or PBO*): HIV progression, including HIV encephalopathy in 1 case (2/12; 16.7%)
Beal 1995[8]	• *Dronabinol:* **unspecified toxicities** (6/72, 8.3%); unspecified intercurrent illness (5.6%) • *PBO:* unspecified toxicities (3/67, 4.5%); unspecified intercurrent illness (4.5%)
Timpone 1997[9]	• *Dronabinol:* lymphoma (1/11, 9.1%); **hallucinations** (1/11, 9.1%); tuberculosis (1/11, 9.1%); low-grade **somnolence** (1/11, 9.1%); • *Dronabinol + megestrol 750 mg: candida* esophagitis (1/13, 7.7%); cryptosporidiosis (1/13, 7.7%) • *Dronabinol + megestrol 250 mg:* seizure (1/13, 7.7%); dyspnea (1/13, 7.7%); tuberculosis (1/13, 7.7%) • *Megestrol 750 mg:* dyspnea (1/11, 9.1%); lymphoma (1/11, 9.1%)

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; d/c, discontinued; HIV, human immunodeficiency virus; PBO, placebo; PLWHA, people living with HIV or AIDS; THC, delta-9-tetrahydrocannabinol;

SELECT OTHER SAFETY

- *When described*, most AEs appeared to be of mild-moderate severity[3,4,8,14]
  - *Overall AEs* with cannabis > PBO: impaired concentration, fatigue, sedation. Increased sleep duration, reduced salivation, thirst (Ellis 2009)[4]

- Severe AEs (not reported by all trials)
  - Trend toward more moderate-to-severe AEs with smoked cannabis vs PBO (Ellis 2009)[4]
  - Incidence of of grade 3 or 4 AEs (Timpone 1997)[9]:
    - Dronabinol: 63.6%, dronabinol + megestrol or megestrol only (80 to 84.6%)
      - Most serious dronabinol-related AEs were neuropsychiatric in nature
  - 1 myocardial infarction during oral CBDV treatment in a patient with pre-existing cardiovascular risk factors[5]

- Transient significant increases in HR by ≥ 30 bpm (46%) with smoked cannabis versus placebo (4%) (Ellis 2009)[4]

- Worsened glycemic control during oral THC/CBD or CBD (1 case each out of 5 patients per group) in people with pre-existing T2DM[14]

Abbreviations: AIDS, acquired immune deficiency syndrome; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; HIV, human immunodeficiency virus; PLWA, people living with AIDS; PLWHA, people living with HIV or AIDS; T2DM, Type 2 Diabetes Mellitus; THC, delta-9-tetrahydrocannabinol;

ROB ASSESSMENT

- ROB by an SR[1,2] was available using Cochrane tool for **8 of 12 trials**
  - Only 2 of 8 without any domain rated as high risk (Abrams et al 2007 and Haney et al 2005), although Haney 2005 was rated unclear on all domains
  - Trials rated as high risk for:
    - blinding (N=4),[4,7,11,13] incomplete outcome data (N=2),[8,9] bias from randomization/allocation concealment (N=1),[9] or other (N=2)[4,11]

- Qualitative quality assessment for trials with ROB rating by SR:
  - **Moderate quality**: N=2, Abrams et al 2007 and Ellis et al 2009
  - **Low quality**: N=6, Abrams et al 2003, Haney et al 2005/2007, Struwe et al 1993, Beal et al 1995, Timpone et al 1997

- Noted concerns (not comprehensive) for trials without ROB assessment:
  - Randomization/allocation concealment (N=3)[6,12,14]
  - Blinding (N=2)[12,14]
  - Very little information available for the unpublished trial (NCT03099005)[6]

Abbreviations: ROB, risk of bias; SR, systematic review;

SELECT LIMITATIONS

- Most trials are considered low quality with concerns for significant bias
- Lack of long-term *experimental data*
  - Beal et al 1997: single-arm 12-month follow-up on dronabinol use in PLWHA[19]
- Limited data about the impact on mortality and/or major morbidity (eg, incidence of AIDS)
- Some results may not be generalizable to PLWHA in Utah who desire to use medical cannabis
  - Differences in the type of or use of ART, particularly for the older trials from the 1990s

Abbreviations: ART, antiretroviral therapy; AIDS, acquired immune deficiency syndrome; PLWHA, people livening with HIV or AIDS;

CONCLUSIONS FROM AN EXPERT OPINION GUIDANCE (2023)[20]

- Guidance from Canadian experts focused on the management of chronic pain, and comorbidities in people with chronic pain

- Recommendations for PLWHA informed by 2 RCTs (Abrams et al 2007 and Ellis et al 2009) and 1 cross-sectional study

- Recommended CBPs for:
  1. Patients with HIV with **muscular or neuropathic pain and an inadequate response or intolerance** to other treatments (strong recommendation; moderate quality evidence)
  2. Patients with **HIV-related symptoms of nausea, poor appetite, weight loss, anxiety, or depression** (strong recommendation; low quality evidence)

Abbreviations: AIDS, acquired immune deficiency syndrome; CBPs, cannabis- or cannabinoid-based product; HIV, human immunodeficiency virus; PLWHA, people living with HIV or AIDS; RCT, randomized controlled trial

CURRENT UTAH CRRB GUIDANCE FOR HIV/AIDS

Includes 3 formal (ie, graded) conclusions:

1. "There is *limited evidence* to support the conclusion that medical cannabis is effective in the treatment of symptoms of painful HIV-associated neuropathy" (page 5)[21]

2. "There is *limited evidence* to support the conclusion that medical cannabis is effective in the treatment of HIV/AIDS wasting syndrome" (page 5)[21]

3. "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…" (page 6)[21]
   - This statement is not specific to PLWHA and is identical to the statement in the CRRB's persistent pain guidance

Abbreviations: AIDS, acquired immune deficiency syndrome; CRRB, (Utah) Cannabis Research Review Board; HIV, human immunodeficiency virus; PLWHA, people livening with HIV or AIDS;

CONSIDERATIONS FOR UPDATES TO CRRB GUIDANCE FOR HIV/AIDS

- Statement about medical cannabis for HIV-associated peripheral neuropathy:
  - Maintain "limited" LOE
  - Consider adding details: "chronic" neuropathic pain in the "short-term"

- May consider additional statement about oral CBDV for HRNP
  - "Insufficient" evidence of ineffectiveness

- Determine whether to keep graded statement about neuropathic pain in general
  - Current graded statement is identical to the persistent pain document, but the elaborations in the HIV/AIDS guidance slightly differs from the persistent pain guidance

Abbreviations: AIDS, acquired immune deficiency syndrome; CBDV, cannabidivarin; CRRB, Utah Cannabis Research Review Board; HIV, human immunodeficiency virus; HRNP, HIV-related neuropathic pain; LOE, level of evidence;

CONSIDERATIONS FOR UPDATES TO CRRB GUIDANCE FOR HIV/AIDS

- Statement about medical cannabis for HIV/AIDS wasting syndrome:
  - May consider *replacing* "medical cannabis" with "oral cannabinoids" or "dronabinol," *or adding* it to cannabis
    - Majority of evidence in people with probable wasting is from trials with dronabinol
  - *May consider* maintaining "limited" LOE and adding specific efficacy outcomes (ie, increased caloric intake/appetite and body weight)*

OR

  - *May consider* changing the LOE to "insufficient" for 1 or both outcomes*
    - Evidence limited to 5 *low quality* RCTs[7-10, 13]
    - Appetite/hunger increased in 4 studies,[7-10] but the effect was only SS in 2 trials[8,10] and increased hunger plateaued at 1 week in a 3rd 12-week trial[9]
    - Weight increased with dronabinol or cannabis vs PBO in 3 of 4 trials,[7,8,13] but the effect was SS in only 1 of 3 trials.[13]
      - The 4th trial showed SS more weight gain with megestrol acetate versus dronabinol; dronabinol-treated patients lost weight on average[9]

*Please note that the recommendation and reported details for this consideration differ from the written report.

Abbreviations: AIDS, acquired immune deficiency syndrome; CBDV, cannabidivarin; CRRB, Utah Cannabis Research Review Board; HIV, human immunodeficiency virus; HRNP, HIV-related neuropathic pain; LOE, level of evidence; PBO, placebo; SS, statistically significant;

CONSIDERATIONS FOR UPDATES TO CRRB GUIDANCE FOR HIV/AIDS

- Additional considerations for elaboration in guidance:
  - Elaborate about the characteristics of available experimental controlled trial evidence, including the study design and participants (see report section 3.1)
  - Comment on generalizability or limitations, for example:
    - Limited long-term *experimental* evidence
    - Limited evidence about the effect of cannabis on cognition, mortality, and major morbidity in PLWHA
    - Limited robust evidence about drug-drug interactions between cannabis and ART – patients/providers should exercise caution (see report pages 18-19)
    - Generalizability of anorexia/cachexia findings to people receiving current ART
  - Cannabis is not an ART replacement

Abbreviations: ART, antiretroviral therapy; AIDS, acquired immune deficiency syndrome; CRRB, Utah Cannabis Research Review Board; HIV, human immunodeficiency virus; PLWHA, people living with HIV or AIDS

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Extra slides

NATIONAL ACADEMIES LOE RATINGS*[22]

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).
"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).
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).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[22]

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).
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).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[22]

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).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report.

Abbreviations: LOE, level of evidence;

OVERVIEW OF STUDIED CBPS

Trial *Approx. tx duration*	Studied Cannabinoid- or Cannabis-based Product (CBP)
PLWHA without specific complications	
Abrams et al 2003[13] *21 days*	Smoked* cannabis (0.9 grams with 3.95% THC) **or** oral dronabinol 2.5 mg up to three times daily as tolerated, 1 hour before meals *Followed the Foltin puff procedure (Foltin et al 1998; PMID 3228283)
Haney et al 2005[10] *1 day, with multiple non-sequential treatments*	Smoked cannabis (with 1.8%, 2.8% or 3.9% THC), 3 puffs with 5 second inhalations, 10 seconds held in the lung, and 40 seconds between puffs once daily; **or** oral dronabinol 10 mg, 20 mg or 30 mg# once daily
Haney et al 2007[11] *4 days per period, with 2 staggered treatment periods*	Smoked cannabis (with 2.0% or 3.9% THC), 3 puffs with 5 second inhalations, 10 seconds held in the lung, and 40 seconds between puffs four times daily; **or** oral dronabinol 5 mg mg or 10 mg# four times daily
Bedi et al 2010[12] *16 days*	Oral dronabinol 5 mg four times daily x 2 days, then 10 mg four times daily
Mboumba et al 2022[14] *84 days*	Oral purified (>98%) cannabinoids in oil, self-titrated per the following schedules: 1. **THC/CBD** 5 mg/5 mg x 2 weeks (as 2.5/2.5 twice daily), followed by 10 mg/10 mg x 2 weeks (as 5 mg/5 mg twice daily), then 15 mg/15 mg x 8 weeks (as 5 mg/5 mg three times daily) 2. **CBD:** 200 mg x 2 weeks (once daily), then 400 mg x 10 weeks (as 200 mg twice daily) **or** 400 mg x 2 weeks followed by 800 mg x 8 weeks (400 mg twice daily)* *Investigators changed the dose from a maximum of CBD 800 mg/day to a maximum of 400 mg/day during the trial due to hepatotoxicity at the highest dose of 800 mg

The number of dronabinol capsules administered daily is unclear, but we infer that it was 1 capsule per day for each strength

Abbreviations: AIDS, acquired immune deficiency syndrome; Approx., approximate; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; HIV, human immunodeficiency virus; PLWHA, people living with HIV or AIDS; THC, delta-9-tetrahydrocannabinol; Tx, treatment

OVERVIEW OF STUDIED CBPS

Trial *Approx. tx duration*	Studied Cannabinoid- or Cannabis-based Product (CBP)
PLWHA with HRNP	
Abrams et al 2007[3] *5 days*	Smoked* cannabis (0.9 grams with 3.56% THC) as tolerated three times daily[a] *Followed the Foltin puff procedure (Foltin et al 1998; PMID 3228283)
Ellis et al 2009[4] *5 days*	Smoked cannabis (with 1-8% THC; most patients used 8%) four times daily, titrated according to patient response[b]
Eibach et al 2020[5] *28 days*	Oral cannabidavarin* 400 mg once daily in the morning *Inferred that used plant-derived CBDV – administered as a 50 mg/mL solution in sesame oil with <0.2% THC.
NCT03099005, unpublished[6] *1 day*	Vaporized cannabis*, single dose once in the morning, using one of 3 different regimens: 1. THC 1.9% + CBD 0.01% x 8 puffs (low CBD) 2. THC 1.9% + CBD 0.01% x 4 puffs and THC 1.4% + 5.1% CBD x 4 puffs (medium CBD) 3. THC 1.4% + CBD 5.1% x 8 puffs (high CBD) *Administered using a volcano vaporizer

[a] The number of inhalations per administration was not specified. Patients were allowed to smoke the cannabis or placebo cigarettes as tolerated (Abrams 2007)

[b] The number of inhalations per administration was not specified; patients titrated the dose according to effectiveness and tolerability and followed inhalation instructions from a staff nurse. On day 1 of treatment, patients starting with a 4% THC cannabis by weight, and were allowed to titrate up to higher or lower potency cannabis based on patient response. (Ellis 2009)

Abbreviations: AIDS, acquired immune deficiency syndrome; Approx., approximate; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; HIV, human immunodeficiency virus; PLWHA, people living with HIV or AIDS; THC, delta-9-tetrahydrocannabinol; Tx, treatment

OVERVIEW OF STUDIED CBPS

Trial *Approx. tx duration*	Studied Cannabinoid- or Cannabis-based Product (CBP)
PLWHA with anorexia and weight loss and/or wasting	
Struwe et al 1993[7] *35 days*	Oral dronabinol 5 mg twice daily 30 minutes before lunch and dinner
Beal et al 1995[8] *42 days*	Oral dronabinol 2.5 mg twice daily 1 hour before lunch and dinner
Timpone et al 1997[9] *84 days*	Oral dronabinol 2.5 mg twice daily 1 hour before lunch and dinner, as monotherapy or in combination with megestrol acetate (250 mg daily or 750 mg daily)

Abbreviations: AIDS, acquired immune deficiency syndrome; Approx., approximate; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; HIV, human immunodeficiency virus; PLWHA, people living with HIV or AIDS; THC, delta-9-tetrahydrocannabinol; Tx, treatment