Short-Term Effects of Cannabinoids in Patients with HIV-1 Infection
A Randomized, Placebo-Controlled Clinical Trial

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Background: Cannabinoid use could potentially alter HIV RNA levels by two mechanisms: immune modulation or cannabinoid–protease inhibitor interactions (because both share cytochrome P-450 metabolic pathways).

Objective: To determine the short-term effects of smoked marijuana on the viral load in HIV-infected patients.

Design: Randomized, placebo-controlled, 21-day intervention trial.

Setting: The inpatient General Clinical Research Center at the San Francisco General Hospital, San Francisco, California.

Participants: 67 patients with HIV-1 infection.

Intervention: Participants were randomly assigned to a 3.95%-tetrahydrocannabinol marijuana cigarette, a 2.5-mg dronabinol (delta-9-tetrahydrocannabinol) capsule, or a placebo capsule three times daily before meals.

Measurements: HIV RNA levels, CD4+ and CD8+ cell subsets, and pharmacokinetic analyses of the protease inhibitors.

Results: 62 study participants were eligible for the primary end point (marijuana group, 20 patients; dronabinol group, 22 patients; and placebo group, 20 patients). Baseline HIV RNA level was less than 50 copies/mL for 36 participants (58%), and the median CD4+ cell count was 340 x 10^3 cells/L. When adjusted for baseline variables, the estimated average effect versus placebo on change in log_{10} viral load from baseline to day 21 was -0.07 (95% CI, -0.30 to 0.13) for marijuana and -0.04 (CI, -0.20 to 0.14) for dronabinol. The adjusted average changes in viral load in marijuana and dronabinol relative to placebo were -15% (CI, -50% to 34%) and -8% (CI, -37% to 37%), respectively. Neither CD4+ nor CD8+ cell counts appeared to be adversely affected by the cannabinoids.

Conclusions: Smoked and oral cannabinoids did not seem to be unsafe in people with HIV infection with respect to HIV RNA levels, CD4+ and CD8+ cell counts, or protease inhibitor levels over a 21-day treatment.

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Marijuana has been smoked for medicinal purposes for centuries (1). Introduced into western medicine in 1842, marijuana was used to treat various illnesses on the basis of its purported analgesic, anticonvulsant, sedative, hypnotic, and anti spasmodic properties. With the passage of the Marihuana Tax Act in 1937, use of marijuana as a therapeutic agent in the United States waned until the substance was removed from the U.S. Pharmacopoeia in 1942. The Controlled Substances Act of 1970 placed marijuana in the Schedule I category along with other substances deemed to have no medicinal value and high potential for abuse.

In 1986, the U.S. Food and Drug Administration approved a synthetic, oral form of marijuana’s main psychoactive component, delta-9-tetrahydrocannabinol (dronabinol, Marinol, Roxane Laboratories, Columbus, Ohio), for treating chemotherapy-induced nausea and vomiting (2–5). A randomized, controlled trial demonstrated that dronabinol increased self-reported appetite but not weight in patients with AIDS-related wasting syndrome; these findings led to an expansion of the labeling indication for this use in 1992 (6, 7). Before the advent of highly active antiretroviral therapy in the 1990s, many patients infected with HIV-1 experienced wasting as a preterminal manifestation of the disease (8). Patients with AIDS-related wasting syndrome often reported that they preferred smoked marijuana to dronabinol because it was easier to titrate the dose to achieve the desired effect; smoked marijuana delivers cannabinoids to the bloodstream much more rapidly than dronabinol (9). By the mid-1990s, cannabis buyers’ clubs in the San Francisco Bay area were reportedly selling marijuana to 11,000 patients with HIV infection (10–12).

With the increased availability of protease inhibitor-containing antiretroviral regimens in the mid-1990s, the incidence of AIDS-related wasting syndrome decreased markedly, as did most of the other late-stage opportunistic manifestations of advanced HIV disease (13–15). Protease inhibitors, which can inhibit or stimulate the hepatic cytochrome P-450 enzyme system, are subject to many significant drug–drug interactions with other agents used in treating HIV infection and its complications (16, 17). The potential for a drug–drug interaction between protease inhibitors and marijuana is worrisome since many HIV-infected patients continue to smoke marijuana as an appetite stimulant or to decrease nausea associated with their antiretroviral therapy (18, 19). The likelihood of such an interaction is supported by the facts that cannabinoids are metabolized by some of the same cytochrome P-450 enzyme isoforms that metabolize the more widely prescribed protease inhibitors and that tetrahydrocannabinol has been shown to inhibit the metabolism of other drugs (20–23).

Although few recent clinical trials have evaluated the potential therapeutic effects of smoked marijuana, significant progress has been made in understanding the pharmacology of cannabinoids in humans. Of the two cannabinoid receptors identified, CB1 (found mainly in cells of the central nervous system) is thought to be responsible for the neurologic and behavioral effects of marijuana (24, 25).
The identification of a CB2 receptor, found predominantly on B lymphocytes and natural killer cells, suggests that cannabinoids may also affect the immune response. Some studies suggest that marijuana can impair the immune system through B-lymphocyte modulation, tumor necrosis factor inhibition, or changes in the phenotype and function of circulating lymphocytes (26–29).

The hallmark of successful antiretroviral therapy is sustained suppression of HIV RNA levels associated with increasing CD4\(^+\) cell counts (30–32). Considering the potential for both a protease inhibitor–cannabinoid interaction and an effect of smoked marijuana on the immune system, we designed a study to determine the safety or toxicity profile of cannabinoids (smoked and oral) in persons with HIV infection. We chose HIV RNA levels as our primary outcome because an intervention that interacted unfavorably with either the antiretroviral agent pharmacokinetics or the immune system directly could cause a perturbation of viral suppression. We report the overall safety results of this randomized, controlled inpatient clinical trial.

**METHODS**

**Study Group**

Study participants were recruited by referrals from local physicians and advertisements in newspapers. Volunteers from across the country telephoned to determine whether they might be eligible to participate. Participants were required to be at least 18 years of age, have documented HIV infection, and be receiving a stable antiretroviral treatment regimen of either indinavir (Crixivan, Merck & Co., Inc., North Wales, Pennsylvania) or nelfinavir (Viracept, Agouron Pharmaceuticals, Inc., La Jolla, California) for at least 8 weeks before enrollment. When enrolled, participants who had been taking the recently recommended dose of nelfinavir, 1250 mg twice daily, were switched to 750 mg three times daily for consistency of our pharmacokinetic evaluations (33). No additional protease inhibitors were allowed for the duration of the study. Participants were also required to have a stable viral load, defined as less than a threefold (0.5 log\(_{10}\) change in HIV RNA level for the 16 weeks before enrollment. All participants were required to have previous experience smoking marijuana (defined as six or more times) to ensure that they knew how to inhale and what neuropsychiatric effects to expect. The institutional review board of the University of California, San Francisco, approved the study. Participants randomly assigned to the oral regimens, methadone maintenance, use of tobacco or cannabinoids (smoked or oral) within 30 days of enrollment, history of serious pulmonary disease, pregnancy, or stage II or higher AIDS dementia complex. Laboratory exclusion criteria were hematocrit less than 0.25 and elevation of hepatic aminotransferase levels to greater than five times the upper limit of normal. Therapeutic exclusions were concurrent use within the past 8 weeks of anabolic hormones, prednisone, interleukin-2, or other agents known to alter immune system function.

**Study Medications**

The National Institute on Drug Abuse provided pre-rolled marijuana cigarettes, weighing on average 0.9 g and containing 3.95% delta-9-tetrahydrocannabinol. These cigarettes were kept in a locked and alarmed freezer until they were dispensed to a locked freezer in the General Clinical Research Center at the San Francisco General Hospital, where the inpatient study was conducted. The frozen marijuana cigarettes required rehydration overnight in a humidiﬁer. Participants randomly assigned to the smoked marijuana group were housed in a room with a fan ventilating to the outside. To maximize standardization of inhaled doses, research staff monitored participants while they followed the uniform puff procedure outlined by Fol tin and colleagues (34). Research staff weighed the marijuana cigarettes immediately before and after they were administered to participants and returned all leftover material to the pharmacy. Study participants smoked up to three complete marijuana cigarettes daily, as tolerated, 1 hour before meals. Study participants were randomly assigned in a double-blind fashion to the oral regimens, which were given on the same schedule as the smoked marijuana. Research staff observed participants taking all treatments.
Research Design and Procedures

Study clinicians admitted study participants to the General Clinical Research Center for a 4-day lead-in period to obtain baseline variables. A urine sample obtained on the day of admission (day −4) had to be negative for tetrahydrocannabinol. The second phase of the trial was a 21-day intervention period beginning with random assignment of treatments on day 0. Patients were stratified by protease inhibitor (indinavir or nelfinavir) and then allocated with equal probability in blocks of 12 to the study agents (marijuana, dronabinol, and placebo). The statistician generated the random allocation sequences, and the pharmacists maintained the sequences in a secure location and distributed the assignments to the study coordinator on day 0.

Study participants were not permitted to have visitors or to leave the General Clinical Research Center unless accompanied by research personnel during the 25-day study. All clinical laboratory tests and study procedures were obtained or performed in the center. Patients were weighed on the same calibrated scale each morning while wearing a hospital gown.

Baseline blood specimens were collected on days −4 and 0 to examine within-participant variation in HIV RNA level in the absence of experimental therapies. Follow-up specimens were obtained on days 2, 5, 8, 11, 14, 17, 19, and 21. Samples were stored at −70 °C and batch-tested for HIV RNA at the end of the trial by using branched DNA (bDNA) technology (VERSANT HIV-1 RNA 3.0 Assay, Bayer Diagnostics, Emeryville, California) with a lower detection limit of 50 copies/mL.

Baseline samples for CD4+ and CD8+ cell counts were collected on days −4 and 0, and follow-up specimens were drawn on days 7, 14, and 21. Assays were performed in the San Francisco General Hospital Clinical Laboratory. Complete blood counts with differential were performed by using an automated hematology analyzer (Bayer Technicon H3 system, Bayer Corp., Tarrytown, New York) according to the manufacturer’s directions. The CD4+ and CD8+ cell counts were measured by using MultiTEST CD3/CD8/CD45/CD4 with Trucount tubes (BD Biosciences, San Jose, California) according to the manufacturer’s directions. Data acquisition and analysis were performed by using a FACSCalibur (BD Biosciences) flow cytometer and MultiSET software (BD Biosciences).

Pharmacokinetic methods are described elsewhere (35).

Statistical Analysis

This randomized trial was designed to compare the marijuana and dronabinol groups with the placebo group with respect to mean changes in log_{10} HIV RNA levels between days 0 and 21. We planned the sample size for two one-sided Bonferroni-adjusted 0.05-level t-tests of the null hypothesis of no difference against the alternative that the cannabinoid effect is larger than 0.3 log_{10} copies/mL, each with 80% power. This design, which assumed an SD of 0.3 log_{10} copies/mL for within-participant changes, required 21 participants per group. To allow for potential dropouts, we enrolled two additional patients per group. The between-group difference of 0.3 log_{10} copies/mL represents a doubling of the viral load on the natural scale and a clinically significant and potentially unsafe effect of cannabinoid on HIV RNA levels (30). Changes less than 0.3 log_{10} copies/mL are considered to be within the natural range of variability of log_{10} HIV RNA measurements (36, 37).

To evaluate the success of the randomization procedures, we examined the distributions by group of several baseline variables, including CD4+ and CD8+ cell counts and HIV RNA levels on day 0 and protease inhibitor used. When a participant’s viral load level was undetectable, a value of 49 copies/mL was assumed. HIV RNA levels were transformed to the log_{10} scale, and each participant’s change in viral load level on day 21 relative to day 0 was calculated. We summarized the raw changes by group using means, 95% CIs of differences between mean changes, and P values. We used multiple regression to model the cannabinoid effects while controlling for the effects of baseline covariates, including age (<40 years, 40 to 49 years, and ≥49 years), race or ethnicity (white, African American, Latino, or other), protease inhibitor, viral load detectability on day 0, small or large RNA change during the lead-in period (≤0.5 versus >0.5 log_{10} copies/mL), and baseline log_{10} CD4+ and log_{10} CD8+ cell counts. Similarly, we modeled log_{10} HIV RNA levels at day 0 and all eight follow-up time points, using a random intercept repeated-measures model. This model allowed baseline covariates to modify either the intercept or the slope and included a quadratic time trend for patients with large RNA changes during the lead-in period. This subgroup showed marked benefit from participation in the clinical trial during the lead-in period and early part of the follow-up period; their RNA levels were typical of all study participants. The simpler model compared HIV RNA levels at the start and end of the trial (two levels per participant), whereas the repeated-measures model used nine levels per participant to estimate the changes from day 0 to day 21; therefore, the latter cannabinoid effect estimates were less influenced by measurement error at any one time point. Because we were concerned about violations of model assumptions of normality and homoscedasticity, all CIs and P values reported were calculated by using the bias-corrected, accelerated bootstrap method with participant-level resampling and 2000 bootstrap iterations (38). These are valid even when the assumptions are violated. Finally, each model was examined for the effects of influential observations, identified through the algorithm of Lefflieg and Verbeke (39).

The cannabinoid groups also were compared with the placebo group with respect to changes in CD4+ and CD8+ cell counts, adjusted for the covariates above and for baseline HIV RNA level. The model of CD4+ cell
counts was additionally adjusted for baseline CD8+ counts and vice versa. We added 10 to the cell counts to reduce the influence of very small values and then transformed to the log10 scale to ensure model validity. These models estimate multiplicative effects on geometric means, which we described as percentage effects by converting the effect on the original log scale with the formula \(10^{\text{effect}} - 1\) \times 100%. For example, an effect of 0.05 is a 12% greater increase in cell count for a cannabinoid than a placebo participant with the same initial count, regardless of whether it was 0.005 or 0.5 \times 10^9 cells/L. We used medians and ranges to describe within-group changes in body weight over the study period and Mann–Whitney tests to compare the cannabinoid and placebo groups. All \(P\) values reported are two-sided.

To investigate the effect of imputing a single fixed value of 49 copies/mL for undetectable viral loads, we used the SAS Lifereg procedure (SAS Institute, Inc., Cary, North Carolina) to instead treat undetectable viral loads as left-censored at the detection limit. Although this method is usually used for survival time analysis, we obtained the needed models by using viral load as the time variable and specifying a log-normal distribution.

**Role of the Funding Source**

The funding source reviewed and funded the protocol and provided the marijuana cigarettes for the trial.

**RESULTS**

**Characteristics of Patients**

A total of 603 individuals volunteered for the study, but most did not meet the eligibility criteria (Figure 1). Of the 69 study participants admitted to the inpatient study unit, 67 were randomly assigned between May 1998 and May 2000. Thirty-seven patients were receiving nelfinavir-containing regimens and 30 patients were receiving indinavir-containing regimens. Of these, 3 and 2 patients, respectively, left the study before the pharmacokinetic analysis on day 14. The remaining 62 study participants completed the 21-day inpatient intervention phase and were eligible for all end points (marijuana group, 20 patients; dronabinol group, 22 patients; and placebo group, 20 patients).

Most patients were men (89%) older than 40 years of age (68%), and half were of nonwhite ethnicity (Table 1). More patients in the marijuana and dronabinol groups...
than in the placebo group had previous AIDS diagnoses and detectable HIV RNA than in the placebo group. Overall, 58% of the participants had undetectable HIV RNA levels (<50 copies/mL); only 5 patients had HIV RNA levels greater than 10,000 copies/mL, 4 of whom were receiving nelfinavir-containing regimens. Baseline CD4+ and CD8+ cell counts were similar in all groups.

During the 4-day lead-in phase, no participant’s HIV RNA level increased by 0.5 log10 copies/mL (3.2-fold). However, HIV RNA levels decreased by at least this amount in 5 patients (marijuana group, 3 patients; dronabinol group, 2 patients; placebo group, 0 patients): 1 of 28 patients receiving indinavir, 1 of 13 patients receiving nelfinavir three times daily, and 3 of 21 patients originally receiving nelfinavir twice daily. Changing the nelfinavir regimen from two to three doses per day seemed to have a large effect on HIV RNA levels. However, since large decreases in HIV RNA occurred in participants receiving all three regimens, they also might be due to the fact that therapy was directly observed.

Change in HIV RNA Levels
HIV RNA was undetectable at days 0 and 21 in 50% to 55% of patients in each group (Table 2). Although the median change in each group was 0, the mean changes were decreases in both cannabinoid groups: marijuana group, −0.14 log10 copies/mL (95% CI, −0.42 to 0.03 log10 copies/mL), and dronabinol group, −0.18 log10 copies/mL (CI, −0.51 to −0.04 log10 copies/mL). These findings were due mainly to five study participants with 0.5 log10 copies/mL or greater decreases in viral load during follow-up. The mean change among patients receiving placebo, 0.06 log10 copies/mL (CI, −0.03 to 0.24 log10 copies/mL), was an increase, and no patient experienced a large decrease during follow-up. The unadjusted mean change in the marijuana group was −0.19 log10 copies/mL (CI, −0.48 to 0.01 log10 copies/mL) lower than in the placebo group, and the corresponding mean difference between the dronabinol and placebo groups was −0.24 log10 copies/mL (CI, −0.55 to −0.06 log10 copies/mL). After we controlled for the large change in HIV RNA level during the lead-in period (≤0.5 vs. >0.5 log10 decrease) and other covariates previously mentioned, the mean marijuana–placebo difference was −0.06 log10 copies/mL (CI, −0.26 to 0.13 log10 copies/mL) and the mean dronabinol–placebo difference was −0.07 log10 copies/mL (CI, −0.24 to 0.06 log10 copies/mL). Models treating undetectable viral loads as left-censored produced slightly higher upper confidence bounds of 0.23 for the marijuana–placebo difference and 0.09 for the dronabinol–placebo difference.

The repeated-measures models of nine measurements per study participant seemed to fit adequately with only linear terms for treatment effects over time, since quadratic terms did not approach statistical significance. A quadratic term was needed only for the five patients with large change in HIV RNA level during the lead-in period. Before adjustment, the cannabinoids seemed to reduce viral load, whereas after adjustment they seemed to have little effect on this outcome. In particular, on the basis of the adjusted model, both upper confidence bounds for the treatment effects (marijuana group, 0.13 [34%]; dronabinol group, 0.14 [37%]) excluded cannabinoid-associated

Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Marijuana Group (n = 20)</th>
<th>Dronabinol Group (n = 22)</th>
<th>Placebo Group (n = 20)</th>
<th>All Groups (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>41.5 (33–54)</td>
<td>43 (34–52)</td>
<td>44.5 (26–80)</td>
<td>43 (26–80)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>17 (85)</td>
<td>19 (86)</td>
<td>19 (95)</td>
<td>55 (89)</td>
</tr>
<tr>
<td>Women</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Transgender (male-to-female)</td>
<td>1 (5)</td>
<td>2 (9)</td>
<td>1 (5)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Race or ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (65)</td>
<td>9 (41)</td>
<td>9 (45)</td>
<td>31 (50)</td>
</tr>
<tr>
<td>African American</td>
<td>3 (15)</td>
<td>6 (27)</td>
<td>3 (15)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Latino or Latina</td>
<td>1 (5)</td>
<td>4 (18)</td>
<td>5 (25)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (15)</td>
<td>3 (14)</td>
<td>3 (15)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Median body mass index (range), kg/m²</td>
<td>25.6 (21.9–53.3)</td>
<td>25.0 (14.8–38.2)</td>
<td>25.4 (18.7–33.0)</td>
<td>25.5 (14.8–53.3)</td>
</tr>
<tr>
<td>Use of protease inhibitor, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>11 (55)</td>
<td>12 (55)</td>
<td>11 (55)</td>
<td>34 (55)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>9 (45)</td>
<td>10 (45)</td>
<td>9 (45)</td>
<td>28 (45)</td>
</tr>
<tr>
<td>Previous opportunistic infection or malignant condition, n (%)</td>
<td>12 (60)</td>
<td>12 (55)</td>
<td>6 (30)</td>
<td>30 (48)</td>
</tr>
<tr>
<td>Median HIV RNA level (range), log₁₀ copies/mL</td>
<td>3.5 (2.0–4.5)</td>
<td>3.5 (1.7–4.3)</td>
<td>3.7 (1.8–4.6)</td>
<td>3.6 (1.7–4.6)</td>
</tr>
<tr>
<td>Undetectable HIV RNA levels, n (%)</td>
<td>12 (60)</td>
<td>11 (50)</td>
<td>13 (45)</td>
<td>36 (58)</td>
</tr>
<tr>
<td>Median CD4+ cell count (range), ×10⁹ cells/L†</td>
<td>0.345 (0.026–0.9)</td>
<td>0.315 (0.052–0.771)</td>
<td>0.378 (0.007–0.906)</td>
<td>0.34 (0.007–0.906)</td>
</tr>
<tr>
<td>CD4+ cell count &lt; 200 ×10⁹ cells/L, n (%)</td>
<td>5 (25)</td>
<td>5 (24)</td>
<td>5 (28)</td>
<td>15 (24)</td>
</tr>
<tr>
<td>Median CD8+ cell count (range), ×10⁹ cells/L†</td>
<td>0.736 (0.433–1.987)</td>
<td>0.91 (0.223–2.23)</td>
<td>0.708 (0.3–1.987)</td>
<td>0.757 (0.223–2.23)</td>
</tr>
</tbody>
</table>

* Among patients with baseline viral load levels > 50 copies/mL.
† Three patients had missing data for CD4+ and CD8+ cell counts on day 0: dronabinol group, 1 patient, and placebo group, 2 patients.
increases in viral load of 0.3 log_{10} copies/mL (100%), our a priori threshold for concern.

**Change in CD4+ and CD8+ Cell Subsets**

Figure 2 shows the median changes in absolute numbers of CD4+ and CD8+ cells over the 21-day experimental intervention. Compared with patients receiving placebo, the unadjusted mean increases in CD4+ cell counts were greater for patients receiving cannabinoids than for patients receiving placebo (marijuana group, 20% [CI, 7% to 55%]; dronabinol group, 17% [CI, 5% to 45%]) (Table 3). The adjusted two-point model and the repeated-measures model showed similar findings.

Over the 21-day follow-up period, increases in CD8+ cell counts were on average 20% (CI, 7% to 38%) greater for patients receiving marijuana than for patients receiving placebo and marginally greater (10% [CI, −5% to 29%]) for patients receiving dronabinol than for those receiving placebo. In the adjusted repeated-measures model, the cannabionoid effects were similar (lower confidence bounds: marijuana group, 4%; dronabinol group, −3%). An analysis of expanded immune system phenotypes and functions revealed few statistically significant effects (40).

**Pharmacokinetics**

The detailed results of the effects of the cannabinoids on the pharmacokinetics of the protease inhibitors have been described elsewhere (35, 41). No clinically significant alterations of nelfinavir or indinavir levels were noted.

**Change in Weight**

Although safety was the primary end point of this trial, study participants underwent many evaluations to assess the effect of cannabinoids on appetite, caloric intake, weight, and body composition. Over the 21-day study period, the placebo recipients gained a median of 1.1 kg (range, −1.4 to 5.2 kg). The participants in the marijuana and dronabinol groups gained significantly more weight, a median of 3.0 kg (range, −0.75 to 8.6 kg; P = 0.021) and 3.2 kg (range, −1.4 to 7.6 kg; P = 0.004), respectively. Dual-energy x-ray absorptiometry demonstrated that most of the weight gained in all groups was fat mass (42).

![Figure 2](http://annals.org)
Table 3. Changes in CD4⁺ and CD8⁺ Cell Counts Relative to the Placebo Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Marijuana Group (n = 20)</th>
<th>Dronabinol Group (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative change in CD4⁺ cell count between day 0 and day 21 (2 time points)</td>
<td>20 (7 to 55)</td>
<td>17 (5 to 45)</td>
</tr>
<tr>
<td>Unadjusted estimated effect, %</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted estimated effect, %†</td>
<td>13 (−1 to 28)</td>
<td>12 (−2 to 28)</td>
</tr>
<tr>
<td>P value</td>
<td>0.06</td>
<td>0.09</td>
</tr>
<tr>
<td>Relative change in CD4⁺ cell count at day 21 (repeated measures: 4 time points)</td>
<td>16 (2 to 33)</td>
<td>14 (−1 to 32)</td>
</tr>
<tr>
<td>Adjusted estimated effect, %†</td>
<td>0.025</td>
<td>0.064</td>
</tr>
<tr>
<td>Relative change in CD8⁺ cell count between day 0 and day 21 (2 time points)</td>
<td>20 (7 to 38)</td>
<td>10 (−5 to 29)</td>
</tr>
<tr>
<td>Unadjusted estimated effect, %</td>
<td>0.002</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Adjusted estimated effect, %†</td>
<td>16 (2 to 36)</td>
<td>8 (−5 to 27)</td>
</tr>
<tr>
<td>Relative change in CD8⁺ cell count at day 21 (repeated measures: 4 time points)</td>
<td>20 (4 to 42)</td>
<td>10 (−3 to 32)</td>
</tr>
<tr>
<td>Adjusted estimated effect, %†</td>
<td>0.016</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* The placebo group included 18 participants. All values in parentheses are 95% CIs.
† Multivariable models included the following covariates: age; race; protease inhibitor; viral load detectability at day 0; small or large viral load change during the lead-in period; baseline log10 HIV RNA level; and baseline log10 CD8⁺ and log10 CD4⁺ cell counts for log10 CD4⁺ and log10 CD8⁺ cell models, respectively. The models yielded results similar to those of the models that included all independent variables and led to the same conclusions.

DISCUSSION

This study provides evidence that short-term use of cannabinoids, either oral or smoked, does not substantially elevate viral load in individuals with HIV infection who are receiving stable antiretroviral regimens containing nelfinavir or indinavir. Upper confidence bounds for all estimated effects of cannabinoids on HIV RNA level from all analyses were no greater than an increase of 0.23 log₁₀ copies/mL compared with placebo. Because this study was randomized and analyses were controlled for all known potential confounders, it is very unlikely that chance imbalance on any known or unknown covariate masked a harmful effect of cannabinoids. Study participants in all groups may have been expected to benefit from the equivalent of directly observed antiretroviral therapy, as well as decreased stress and, for some, improved nutrition over the 25-day inpatient stay.

Neither CD4⁺ nor CD8⁺ cell counts seemed to be adversely affected by the cannabinoids during the study; lower confidence bounds on estimated cannabinoid effects typically exceeded 0, indicating benefit rather than harm. Increases in CD8⁺ cell counts in the marijuana group seen in our study differ from findings reported in earlier studies conducted in participants without HIV infection (29). The clinical significance and mechanism accounting for these changes are unclear.

The pharmacokinetic component of this study did not demonstrate clinically significant interactions with cannabinoids that would warrant dose adjustments of protease inhibitors in the context of smoked marijuana or dronabinol use (35). However, given the great variability of the pharmacokinetics of protease inhibitors, the long-term significance of the short-term concentration decreases observed is not known.

Although the primary objective of this study was to assess the safety of cannabinoids in patients with HIV infection treated with protease inhibitor—containing antiretroviral regimens, a secondary aim was to obtain some information on activity, particularly about appetite stimulation and weight gain. Whereas previous studies of dronabinol have demonstrated significantly increased appetite and only a trend toward weight gain, this trial shows increased weight in both cannabinoid groups compared with the placebo group. However, the weight gained by the cannabinoid recipients was not in the desired lean body mass but in fat.

Our conclusions are limited by the short duration of this study. Also, few women participated, so our results may apply mainly to men. The results of this study, which evaluated government-supplied marijuana of known potency and content, cannot be extrapolated to the potential effects of marijuana available on the street. In addition, the lack of a blinded control group for the smoked marijuana arm could bias the interpretation of some of our results, such as the weight changes; however, it is difficult to attribute effects on HIV RNA level and CD4⁺ and CD8⁺ cell counts to any such potential bias. We chose not to include a smoked placebo group because we thought it would be impossible to blind marijuana in study participants with previous marijuana experience. Of interest, most of the patients receiving dronabinol (17 of 22) could identify their blinded treatment correctly, whereas the patients in the placebo group had more difficulty (9 of 20). This suggests that placebo-controlled studies of the efficacy of smoked marijuana could be considered in the future.

The Institute of Medicine reviewed accumulated data on the safety and effectiveness of marijuana as medicine in a recent comprehensive report (43). The discussion of medicinal marijuana is a polarizing one that is confounded by emotion and politics, usually unsupported by data. Our short-duration clinical trial suggests acceptable safety in a vulnerable immune-compromised patient population. Further studies investigating the therapeutic potential of marijuana and other cannabinoids in patients with HIV infection and other populations are ongoing and should provide additional safety information over longer exposure periods (44).

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