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The Safety and Efficacy of Marijuana in Persons Living with HIV

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Abstract

The prevalence of the use of marijuana throughout the world is substantial. In light of ongoing increases in accessibility to marijuana, safety and efficacy must be established to guide recommendations for safe use. Of particular interest is at-risk populations such as persons living with HIV (PLWH) in whom there are higher rates of marijuana use and inherent risks of comorbid conditions. Databases and reference lists were searched for relevant studies investigating marijuana or cannabinoid use, HIV, and/or pulmonary diseases. The effect of marijuana on the human body is complex and not yet fully understood. The principal components, tetrahydrocannabinol, and cannabidiol interact with cannabinoid receptors. As some cannabinoid receptors are located in the immune system, many have investigated the effect of marijuana on the immune system. Although marijuana would appear to have anti-inflammatory properties, there are conflicting findings on its immune effect in PLWH. In the lung, marijuana smoke is thought to cause harm. Marijuana smokers have shown increased rates of respiratory symptoms, and a variety of changes on lung function has been reported. Limited data are available specific to the safety of marijuana on the lung, cognition, malignancy risk, and cardiovascular disease in PLWH who are already at increased risk of chronic diseases. Marijuana use is common in PLWH, but significant research gaps exist with regard to its safety and efficacy. Until further evidence on its safety is available, recommendations should be to avoid the use in PLWH. (AIDS Rev. 2019;21:84-92)

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Key words

Drug addiction. Marijuana. Cannabis. Pulmonary disease.

Background

Recreational and medical cannabis are a controversial topic around the world where in many countries its usage remains illegal. Throughout the world, there is a movement toward the decriminalization of marijuana culminating in its legalization in certain countries and states, most recently in Canada. The prevalence of use is expected to increase with the changes in regulations and accessibility. The long-term health implications of these new policies are still to be determined. Marijuana usage rates are highly dependent on population subgroups and location. Moreover, both the health benefits and adverse effects of marijuana use may also vary according to the patient group. In this review, we explore in depth the impact of marijuana on persons living with HIV (PLWH) among whom there is a two- to threefold increase in use[1,2]. For these patients, marijuana has

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been used to treat HIV-related conditions such as cachexia or wasting syndrome and chronic pain[3]. However, the safety concerns that apply to the general population such as cognitive impairment, psychiatric illness, lung diseases, and diminished quality of life[4] may be heightened in PLWH. PLWH may face greater health consequences as a result of marijuana.

The legalization of marijuana could have the benefit of taking away responsibility from the medical community as the current gatekeepers of medical marijuana. Medical providers may feel a certain level of discomfort surrounding marijuana, its health benefits, and its complications due to a paucity of evidence in literature. However, the responsibility for counseling around marijuana use still rests with the medical community, especially for those patients affected by complex medical conditions. The objective of this review is to comprehensively summarize the available information to guide recommendations to PLWH concerning the safety and efficacy of marijuana use.

Search methods

A database search of Embase, PubMed, Google Scholar, and MEDLINE was performed using the following keywords: marijuana, cannabis, cannabinoid, dronabinol, Marinol, nabilone, Cesamet, tetrahydrocannabinol (THC), cannabidiol (CBD), Sativex, HIV, human immunodeficiency, AIDS, lung and pulmonary disease. A total of 226 articles were found. Additional searches were performed for the section addressing the physiologic effects of marijuana and the epidemiology of marijuana use.

Epidemiology of HIV and marijuana

Despite improvements in the care of PLWH, HIV remains a global public health issue with a total of 36.7 million PWLH worldwide[5]. Of PLWH, many use marijuana, although significant geographic variation exists. In Australia, the prevalence of use was 60% in the past 6 months[6], while in Europe; it was estimated as high as 27% within the previous 12 months[7]. In the United States, 47% of PLWH reported marijuana use in the past month[8] and HIV infection was associated with a three-fold higher risk of marijuana use[2]. Similarly, in Canada, 37% of PLWH reported current use[9,10], with most using recreational marijuana (92%) in comparison to medical cannabis (14.5%)[10]. PLWH who use marijuana are more likely to use other illicit substances[2], more likely to be tobacco smokers[8], more likely to have lower income, and are younger[6]. As for their motivation to use marijuana, most PLWH reports recreational use, but when compared to the general population, rates of medicinal use are also higher[11]. The reasons most cited for use include psychological distress, appetite stimulation, and pain relief[9,10].

Physiologic effects of marijuana

The full effect of cannabis on the human body is not yet fully understood due to the variable concentrations of its multiple components; until now, over 500 have been identified[12]. Delta-9-THC is the primary psychotropic agent causing the short-lived sensation of euphoria and sedation[13], but it is also responsible for the undesirable effects of psychosis[14] and addiction[4]. The effects of THC are mediated through the endogenous cannabinoid system. THC binds to the G-protein coupled cannabinoid receptors: CB1 located in the central nervous system (CNS) and CB2 located in the immune system[15]. THC is a partial agonist of both CB1 and CB2; however, the psychotropic effects occur when THC binds with CB1 receptors in the CNS. This mostly inhibits neurotransmitter release, although it has also been found to increase the release of other neurotransmitters in different neurons, leading to a combination of inhibition and stimulation of neurotransmitter release[16].

CBD is another important constituent of cannabis. It has low affinity but high potency as an antagonist to CB1 and CB2 receptors[16,17]. It is thought to counteract the adverse reactions of THC with its antipsychotic and anxiolytic properties[18], at least partially explained by its ability to antagonize CB1 receptors[18]. Higher ratios of CBD to THC are known to reduce the rate of psychosis from cannabis[18].

Marijuana can be inhaled and ingested. The main physiologic difference between these is the time of onset and duration of effect[19]. Inhaled THC travels quickly from the lung to the CNS, achieving a peak effect time of around 20-30 min. The edible form takes longer to act and peaks around 2-4 h[20]. THC concentration in the blood appears lower with oral use in comparison to inhaled forms[21]. However, the hepatic metabolism of the oral form is thought to increase quantities of a potent by-product of THC, which easily crosses the blood–brain barrier and could explain the stronger and longer lasting effects[22]. The delay in effect of the oral form can lead to difficulties with titration and a higher risk of intoxication as many

patients do not wait until full absorption before taking more[23]. This can lead to more undesirable effects, such as psychosis[24].

Marijuana and the immune system in HIV

With CB2 receptors located in the immune system, many have attempted to understand the effects of cannabis or cannabinoids on the immune system. *In vitro* studies have suggested a protective effect of marijuana within the context of HIV, working to provide anti-inflammatory properties by reducing CD16 expression in HIV-infected monocytes[25] and by diminishing HIV-1 infection of differentiating macrophages[26]. Animal studies, however, have yielded much more mixed results. In simian immunodeficiency virus (SIV)-infected macaques, chronic marijuana exposure has been shown to augment anti-inflammatory microRNA responses in the gastrointestinal tract and reduce oxidative stress responses[27], attenuate SIV viral replication[28], and improve mortality[28]. On the other hand, murine models, such as gp120-expressing mice and severe combined immunodeficient (SCID) mice, have shown fewer beneficial effects. In fact, in the presence of marijuana use, SCID mice demonstrate increased HIV coreceptor expression allowing for a greater number of HIV-infected leukocytes[29]. Variability between animal models designed to mimic HIV infection may account for these conflicting results.

The impact of cannabis and cannabinoids on immunity in PLWH on antiretroviral treatment has also been investigated, yet results have varied considerably. *In vitro*[26] and animal studies[30] have shown that marijuana can decrease viral replication. Clinical studies, however, have demonstrated conflicting results, as summarized in table 1. While some studies have shown that marijuana could have beneficial effects in increasing CD4 and decreasing CD8 cell count, others have shown no significant differences in T cell numbers. Similarly, while some authors have reported lower viral loads[31,32], other larger studies have not shown significant differences in viral loads between marijuana users and non-users[33,34].

Marijuana and the lung in HIV

Marijuana is most commonly used by inhalation, favored by users for its easy titration to effects[10,35], but the implications for overall lung health are important to consider. The broad categories of inhalation methods include inhalation of combusted product such as with a water pipe, joint, or hookah pipe, or non-combusted product using a vaporizer. The latter involves heating the cannabis plant, concentrate, or oil below the combustion threshold to produce an aerosolized vapor. This vapor can be inhaled without smoke, reducing the exposure to combustion-related toxins and presenting a theoretically safer alternative to smoking cannabis[36]. Fewer respiratory problems have been reported when vaporizing is used in comparison to other methods of use[37]. However, there are other safety concerns, including increased intoxication due to the higher potency of concentrated product used and exposure to other toxins such as solvents used to produce the concentrate[38]. When compared to smoking tobacco, in general patients use less marijuana[39] such that smoking tobacco is calculated in pack-years and marijuana by joint-years. However, the technique of inhaling combusted cannabis deeper with a longer breath hold increases tar deposition in the lung and carboxyhemoglobin in the blood[40]. Adding to potential lung injury is the fact that many smoke marijuana in conjunction with cigarettes. Such practices expose marijuana users to the complications of cigarette smoking, such as chronic obstructive pulmonary disease (COPD), lung cancer, and accelerated atherosclerosis. For PLWH in particular, those smoking marijuana are twice as likely to also smoke tobacco[1].

Few studies have assessed the safety of smoking marijuana on the lung, specifically in PLWH who are already at higher risk of chronic pulmonary diseases. A review by Tashkin in 2001[41] of the effects of marijuana on the lung in PLWH proposed that frequent marijuana use could cause increased respiratory symptoms, lung injury, and inflammation; however, these conclusions were extrapolated from data from HIV-negative populations. Speculation that marijuana could increase AIDS-related malignancies and opportunistic infections has largely come from studies that predated modern antiretroviral therapy (ART). In fact, the studies included in this review were all done before combination therapy was widely used and early initiation of ART was recommended.

Mouse studies suggest that marijuana smoke exposure can have a deleterious effect on the airway epithelium, disrupting gene expression along with oxidative stress, xenobiotic metabolism, DNA damage, and inflammatory pathways[42]. The potency of marijuana appears to be significantly higher than cigarette smoke to elicit these changes. Human lung pathology specimens from marijuana smokers demonstrate marked abnormalities including basal cell and gob-

Table 1. Summary of studies of marijuana and the immune system in PWLH

Studies	Participants	Study design	Exposure/intervention	Outcomes
Abrams, et al., 2013[35]	n = 67 PWLH on ART for > 8 weeks	RCT (1998-2000)	21 days intervention Intervention: smoking marijuana or Dronabinol Control: placebo capsule	↔ Viral load ↔ CD4
Chao, et al., 2008[94]	n = 289 Participants in multicenter AIDS cohort study	Longitudinal cohort (1984-1991)	Marijuana use in the past 6 months, grouped by: – None – ≤ monthly – ≥ weekly	↓ CD8 ≥ weekly use ↔ CD4
Milloy, et al., 2015[31]	n = 88 Recently seroconverted illicit drug users in Vancouver	Longitudinal cohort (1996-2012)	Cannabis use in 6 months, grouped by: ≥ daily vs. < daily	↓ Viral load ≥ daily use
Thames, et al., 2016[32]	n = 55 HIV community care clinics patients	Cross-sectional	Cannabis use, grouped by – No use – Light use (2-14 times/week) – Moderate-to-heavy use (18-90 times/week)	↑ CD4 ↓ Viral load In all users
Okafor, et al., 2017[33]	n = 1902 PLWH in Florida	Cross-sectional (2009-2013)	Marijuana use in the past 12 months grouped by: – None – < Daily – Daily	↔ Viral load
Nolan, et al., 2017[34]	n = 202 PLWH from the Boston cohort with substance dependence or injection drug use	Cross-sectional (2012-2014)	Past 30 days use of marijuana	↔ Viral load
Manuzak, et al. 2018[95]	n = 198 PLWH enrolled in an ART cohort study	Cross-sectional	Reported Marijuana use confirmed by plasma cannabis metabolite: – None – Occasional – Medium – Heavy	↓ (HLA)-DR+CD38+CD4+ ↓ CD8 in heavy marijuana user

PLWH: Persons living with human immunodeficiency virus; ART: Antiretroviral therapy; AIDS: Acquired immune deficiency syndrome; HIV: Human immunodeficiency virus; ↓: Unchanged; ↓: Decreased; ↑: Increased.

let cell hyperplasia, inflammation, squamous cell metaplasia, and basement membrane thickening when compared to non-smokers[43,44]. Furthermore, Fligiel et al.[43] showed that the combination of marijuana and tobacco smoking resulted in a greater degree of airway damage in comparison to smoking each substance alone. While there are case reports of bullous formation in marijuana smokers[45], the prevalence of bullae in pathologic specimens does not conclusively appear to be significantly higher when compared to non-marijuana smokers[44]. Radiographically, there also appears to be no increased risk of emphysema[39,46]. Pulmonary function in marijuana users has been investigated thoroughly, although the evidence remains somewhat conflicting. Some have shown no significant difference in spirometry between cannabis smokers and controls[47,48]. Others have shown airflow limitation with a reduction in the forced expiratory volume in one second

(FEV1) to forced vital capacity (FVC) ratio[46,49]. The most commonly seen spirometric change is an elevation in FVC[39,50-53]. Differences in lung function results between studies may be a result of the difficulty controlling several confounding factors including comorbidities, concomitant tobacco use, or other substance use. Smoking marijuana is also difficult to control with variation in its different constituents, the method of inhalation, the timing of use in relation to the lung function test and the dose or joint-year history. In fact, recent data suggest there is a dose-dependent association with marijuana smoking and reduction in FEV1/FVC ratio[54,55].

Despite the variability in lung function results, increased rates of respiratory symptoms have commonly been reported with smoking marijuana. Several observational studies have found an increase in symptoms of chronic bronchitis when compared to non-tobacco smoking controls or when adjusted for tobacco use. These symptoms included wheezing[39,46,48,49,54], cough[46,48,49,54], sputum production[46,48,49,54], and dyspnea with marijuana use[49]. However, Tan et al. only saw an increase in respiratory symptoms when marijuana was combined with tobacco use[52].

Many studies have also investigated the association of marijuana use and lung cancer, although the results appear to be mixed. A large cohort study found a two-fold increase in lung cancer in marijuana smokers of over 50 times in their lifetime[56]. However, most recently, a pooled analysis of six studies of 2159 lung cancer patients and 2985 controls showed only a weak association between cannabis use and lung cancer[57].

Even with limited evidence on how marijuana smoking impacts the lung health of PLWH, it is imperative that clinicians consider the potential increased risks within the unique context of HIV. In particular, we must adjudicate the use of marijuana (and its possible associations with airway abnormalities, respiratory symptoms, and lung cancer) against a background of increased pulmonary infections, COPD, and lung cancer in this population. COPD now appears to affect PLWH at disproportionate rates compared to the general population, with a prevalence of up to 22%[58]. Even after adjustment for smoking, PLWH was just over 2.5 times more likely to develop COPD, with increased risk with higher viral loads[59]. PWLH are also at higher risk of many non-AIDS related malignancies[60]. For example, a higher risk of lung cancer seen in the HIV population independent of smoking[61,62] and a 3.3-fold increase has been estimated[60]. A recent meta-analysis showed higher mortality of lung cancer in PLWH[63]. As with COPD, the risk for lung cancer in HIV persists even after adjustment for smoking, suggesting additional mechanisms of injury predisposing PLWH to lung cancer[64]. While few studies have fully assessed the impact that marijuana has on these mechanisms of lung injury in HIV, one recent study looking at marijuana use in the Multicenter AIDS Cohort found that PLWH who recently smoked marijuana had a higher risk of pulmonary infections and chronic bronchitis while uninfected marijuana smokers had no such higher risk[65]. This would suggest that the risk of pulmonary complications secondary to marijuana use may be elevated in PLWH compared to the general population.

Other safety concerns of marijuana in PLWH

Several other adverse health effects in marijuana users have been identified, predominantly affecting neurocognition and mental health. These include cognitive impairment, impaired short term memory, acute paranoia and psychosis, chronic psychotic disorders, altered judgment, impaired motor coordination, and increased poly-substance use[4]. It is the most common first drug used in males and older youth[66]. Marijuana is hypothesized to act as a gateway drug[66,67] possibly due to a genetic predisposition to addiction[67] but may also lead to higher rates of poly-substance use due to exposure to other illicit drug users[68] through the proposed string of opportunity theory[67].

HIV-associated neurocognitive disorder (HAND) is well documented, and while the severity of neurocognitive impairment has declined since effective ART, its milder forms remain prevalent with reported rates of 54% and 63% of neuropsychologic impairment seen in the era of combination therapy[69,70]. Cognitive impairment is of particular concern in PLWH who use marijuana due to the independent association of both HIV and marijuana with cognitive dysfunction[71]. HIV patients who use marijuana before the age of 18 are over 8 times more likely to have learning impairment in comparison to non-users or late-onset users[72]. Cognitive dysfunction in PLWH using marijuana has also been observed in one out of three measures of cognition tested in a cross-sectional study[73]. There may also be an additive effect as patients with advanced HIV who use marijuana appear to have increased rates of cognitive dysfunction when compared to PLWH without marijuana use and HIV-uninfected patients with marijuana use[15]. Others have suggested that it is the HAND itself that can lead to substance use[74].

Medication compliance is crucial to the treatment of HIV, and substance use disorders have been shown to correlate with ART non-compliance[75]. This could be explained by the cognitive impairment from substance use and/or by a higher likelihood of other risky behaviors. Marijuana use alone and ART adherence has been more controversial, however[75]. The most recent studies have shown no impact of marijuana use on ART adherence measured by pharmacy refilling[76], self-report[77], and questionnaires[78]. However, daily marijuana use has been associated with a higher risk of missing HIV clinic visits[79]. The efficacy of ART when combined with marijuana and its pharmacokinetics is not fully understood. Cannabinoids have been shown to affect CYP isoforms[80], and smoked THC has shown decreased protease inhibitors maximal concentration in a small randomized controlled trial[81]; however, more research is required to determine the clinical relevance.

Marijuana use has been linked with accelerated cardiovascular aging measured by an increase in arterial stiffness measures[82]. In fact, an increased risk of 4.8-fold of myocardial infarction in the hour after marijuana use has been observed[83]. However a prospective study of 5113 young adults followed for more than 25 years showed no increase in cardiovascular disease in marijuana smokers in comparison to non-marijuana smokers[84]. PLWH using marijuana on a daily or weekly basis had increased risk of cardiovascular events independent of other risk factors including smoking tobacco although the risk was significantly higher in users of both marijuana and tobacco[85]. In hepatitis C infection, the regular use of marijuana has been associated with increased liver fibrosis[86]. However, this association has not been observed in marijuana users with HIV and hepatitis C coinfection[87,88].

Are there benefits to the use of marijuana in PLWH?

Several researchers have looked at the utility of marijuana for medical purposes in PLWH, but many of these studies were done before the widespread access to effective ART[3]. The most common medicinal use of marijuana in PLWH has been for HIV-related wasting and appetite stimulation. However, the weight gain seen in AIDS-related wasting might not be applicable to current PLWH on modern ART. Currently, there is low-quality evidence for cannabinoids in weight gain for PLWH[89,90]. This was concluded from a recent systematic review and meta-analysis which assessed the utility of cannabinoids for several medical conditions. Out of the 79 included articles in their systematic review, four looked at the effect of cannabinoids as an appetite stimulant in PLWH and showed overall improvements in weight. However, all of the included studies were considered at high risk of bias by the authors and were published between 1993 and 2003 in the pre-ART era[90]. In a different review assessing dronabinol for the treatment of HIV-associated weight loss, ten studies were included and showed variability in weight change between –2.0 and 3.2 kg[91]. Others have also suggested that marijuana might be an effective sleep aid and that it could help reduce chronic pain as well as psychologic distress associated with HIV although no research, to the best of our knowledge, has specifically addressed these issues in PLWH.

Systematic reviews have subsequently followed to determine the efficacy and safety of marijuana in overall health. In a Cochrane review by Lutge[3], the impact of medical marijuana in PLWH was assessed based on seven randomized controlled trials. All study participants were diagnosed with HIV infection and the interventions included smoked cannabis and or use of other cannabinoids. The authors were unable to conclude that marijuana provided significant morbidity or mortality reduction. However, the included studies were small, of short duration (21-84 days) and patients were at variable stages of HIV control. Secondary outcomes were heterogeneous and difficult to compare, but positive results were seen for weight gain and decreased peripheral neuropathy symptoms when studies were interpreted individually.

In an attempt to determine, if persistent changes in well-being occur with marijuana use, another systematic review and meta-analysis looked at the effect of cannabis on health-related quality of life[92]. This included a total 11 randomized controlled trials and nine cross-sectional studies, two of which were done with PLWH and the remainder of studies addressed a variety of other conditions including cancer, multiple sclerosis, and chronic pain. The authors found no significant change in the quality of life in patients using medical cannabis or cannabinoids for a variety of medical conditions, although in PLWH there was a reduction in mental quality of life identified in one study[93]. Included studies varied significantly in terms of interventions, patient population, diseases, as well as measurements of quality of life. The short duration of studies also limited the interpretation of the sustained effects of cannabis on well-being.

With the increasing interest in determining the safety of marijuana, more researchers have attempted to clarify

this. A cross-sectional study of PLWH on ART with undetectable viral loads compared to recent marijuana users (n = 93) to non-users (n = 266) in regard to healthy aging[1]. In the recent marijuana use group, there was the lower mental quality of life and social functioning measured by Short Form 36 as well as an increase in smoking tobacco. No significant differences were seen between groups with regard to CD4 counts, functional status or disease burden. Due to the cross-sectional design, though, it was impossible to determine causality.

Future directions and conclusions

Marijuana use is common in PLWH, but significant research gaps exist with regard to its safety and efficacy. PLWH have inherent risks for chronic lung and cognitive diseases that may very well be exacerbated by the potential harms of marijuana use observed in the general population. In the era of modern ART, the benefits of marijuana use in PLWH are also unclear, and our understanding of these benefits is limited by observational, cross-sectional studies. With the growing legalization, there is an opportunity to institute rigorous studies on the impact of marijuana in PLWH. This will include translational studies where we can now evaluate the acute and chronic effects of marijuana use on immune cell function and the structure and function of the airway, particularly in the latter how airway injury related to marijuana might differ from that incurred in tobacco smokers. We can also now start to collect the longitudinal data required to determine whether marijuana is beneficial or detrimental to overall survival and quality of life in PLWH. Researchers will need to take into consideration the many barriers in conducting marijuana research such as the different forms of cannabis and cannabinoids with variable THC to CBD ratios, different techniques of use, and separating its effect from tobacco which is commonly used alongside marijuana, and the difficulty with blinding psychoactive effects. To fully understand the harms and benefits of marijuana in PLWH, though, these barriers will need to be addressed and overcome as we anticipate the growth of use in the coming era of legal marijuana.

Conflicts of interest

None

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None

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