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Contents

I INFLAMMATION, HIV AND MARIJUANA

A. Some research issues with marijuana, HIV and inflammation

The body produces many compounds that cells use to send information via signals to each other. One such system of signals is called the endocannabinoid system. To respond to chemical signals, cells have certain proteins on their surface called receptors. Cells of the immune system, brain, gut and some organs have receptors for endocannabinoids produced by the body.

The marijuana plant may contain up to 100 cannabinoids; likely many of these also bind to the body's endocannabinoid receptors. When the flowers of the marijuana plant are heated, cannabinoids such as THC (tetrahydrocannabinol) and CBD (cannabidiol) are formed. Since many cells have receptors for endocannabinoids, marijuana and its extracts can have effects on different organ-systems. In this issue of *TreatmentUpdate* we will largely focus on the impact of cannabinoids on the immune system. Before we do so, we first present some information about the immune system and its interaction with microbes, particularly HIV.

Inflammation and immune activation in general

When cells of the immune system discover the presence of an invading microbe or tumour, a normal response is to mobilize the rest of the immune system. This happens when the cells that discovered the germ or tumour release chemical

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555 Richmond Street West, Suite 505
Box 1104
Toronto, Ontario M5V 3B1 Canada
phone: 416.203.7122
toll-free: 1.800.263.1638
fax: 416.203.8284
www.catie.ca
charitable registration number: 13225 8740 RR

signals to alert other cells of the immune system that are nearby. As more cells converge on the microbe, they capture it and take it to nearby lymph nodes or lymphatic tissues (both of which house many cells of the immune system). Once inside the lymph nodes, the cells that captured the germ show it, or a key part of it, to other cells so that they are educated about what to look for and attack. These educated cells are stimulated to make many copies of themselves and follow a chemical trail to where the germ is located. One group of cells of the immune system, called B-cells, makes antibodies designed to attack the germ. Other cells of the immune system release chemical signals that incite inflammation, as this helps to mobilize the immune system to contain the microbe. In most cases, the invading microbe is contained and eliminated. Once this happens the immune system then releases further chemical signals to help dampen inflammation and decrease immune activation. Such dampening signals are necessary, as having high levels of inflammation and immune activation for prolonged periods uses up vital nutrients (particularly protein) and the immune response against the microbe could get out of control and harm healthy tissues.

Inflammation and immune activation with HIV

Chronic HIV infection is associated with excessive levels of inflammation and activation of the immune system. Initiating HIV treatment (ART) and achieving and maintaining an undetectable viral load helps to reduce inflammation and immune activation. However, despite the use of ART, these consequences of HIV infection do not fall to the low levels seen in healthy HIV-negative people.

Researchers are concerned that chronic HIV-related inflammation and immune activation may, over the long-term, contribute to an increased risk for the following conditions:

- cardiovascular disease (including heart attack and stroke)
- degenerative conditions of the brain (such as Alzheimer's and Parkinson's diseases)
- type 2 diabetes
- inflammatory diseases of the digestive tract (such as Crohn's disease)
- arthritis
- lung injury
- thinner bones
- psoriasis

As a result, researchers are planning or conducting studies to reduce excess HIV-related inflammation. Some of these studies are discussed in *TreatmentUpdate 223*. Marijuana and its extracts also have potential to be assessed for their anti-inflammatory effects in clinical trials.

Marijuana and HIV

Most of the studies done with herbal marijuana (as opposed to pharmacological preparations or extracts) in people with HIV have not been robustly designed. As a result, the conclusions that can be drawn from such studies are only suggestive. Still, such studies can be useful when designing future clinical trials. We will report on additional marijuana research later in this report.

What's in marijuana?

Researchers estimate that there may be as many as 100 different compounds in marijuana with potential medicinal application. These compounds are called cannabinoids. Commonly researched cannabinoids include THC and CBD.

Cannabinoids and the immune system—a possible point of intervention

Lab experiments with cells of the immune system have found that when these cells become activated they display a relatively high density of receptors for cannabinoids. This suggests that these cells could have a heightened sensitivity to marijuana or its extracts. This sensitivity could be exploited in clinical trials.

Further lab experiments with cells of the immune system from both HIV-positive and HIV-negative people have found that cannabinoids can reduce immune activation. In one series of experiments, researchers found that HIV-positive marijuana users had reduced levels of immune activation. In other experiments, researchers confirmed the dampening effect of marijuana or its extracts (particularly THC) on the activities of the immune system. Altogether, the results of these laboratory experiments suggest that marijuana or its extracts have the potential to be used in reducing immune activation and inflammation in HIV-positive people.

Bear in mind

As mentioned earlier, the vast majority of studies with herbal marijuana and HIV-positive people have been observational in nature. This means that the conclusions drawn from such studies are suggestive, not definitive. Observational studies are a good starting point to explore a potential biomedical issue and collect data that can be used to develop a study of a more robust design.

Researchers are aware of the issues that affect observational study designs but have to develop a body of evidence that can later be used to support the need for larger and more robustly designed studies. Such robust studies are expensive and take time to develop, must compete against other research proposals for limited funding and then, if funded, have to be executed. These processes take time and it could take five to 10 years for such studies to bear fruit.

It is noteworthy that while marijuana or its extracts may have beneficial effects on the immune systems of HIV-positive people, it is possible that in some cases marijuana may have harmful effects as well. For instance, the smoke from burning marijuana contains a mix of compounds somewhat similar to that produced when tobacco is burned. It is therefore possible that people who chronically smoke marijuana may increase their risk for cardiovascular and lung disease. The point about marijuana and cardiovascular disease is explored later in this issue of *TreatmentUpdate*.

Also explored later in this issue of *TreatmentUpdate*: Marijuana can also interfere with the immune system by weakening some aspects of its ability to carry out its functions. Will this weakening have any negative health consequences? Future studies need to pay attention to these and the following issues:

- Which strains of marijuana were used?
- What was the relative mix of cannabinoids in such strains?
- How was marijuana used—smoked, ingested (edibles) or vapourized?
- How much marijuana was used and how often?
- Did marijuana interact with ART and/or other medicines commonly used by HIV-positive people?
- Are there differences in the effect of marijuana by gender?

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B. Can marijuana reduce the risk for developing fatty liver?

Due to shared routes of transmission, co-infection with HIV and hepatitis C virus (HCV) is relatively common. HCV infects and injures the liver. If HCV infection becomes chronic, liver injury gradually spreads throughout this vital organ. Eventually the liver becomes dysfunctional, causing complications including an increased risk for liver cancer, liver failure and death.

People with HIV alone or both HIV and HCV can have an increased risk of developing fatty liver. This is an excess accumulation of fat (steatosis), which can injure the liver. If the cause of fat accumulation in the liver is not addressed, the liver becomes injured and over time this injury caused by steatosis spreads through the organ. This can lead to serious complications.

According to a team of researchers in France, some co-infected people have risk factors that increase their chances of developing fatty liver, including the following:

- exposure to one or more of an older group of anti-HIV drugs nicknamed "d-drugs"—ddC (Hivid), ddI (Videx, didanosine) and d4T (Zerit, stavudine)
- excess intake of alcohol
- the presence of pre-diabetes and diabetes
- infection with a strain of HCV called genotype 3

In a previous study, the French researchers found that some co-infected people who used marijuana over the long-term were at decreased risk for developing pre-diabetes. A similar association has been seen with marijuana use among people

without HIV or co-infection with HIV and HCV. The researchers therefore suspected that exposure to marijuana might reduce the risk for fatty liver. To explore this issue, they conducted an observational study with 838 people co-infected with HIV and HCV. The researchers used ultrasound scans of the liver. Participants regularly visited study clinics where additional tests were performed and surveys about marijuana use were undertaken.

The researchers found that participants who disclosed daily marijuana use had a reduced risk of developing fatty liver. A much larger American study with HCV- and HIV-negative people, none of whom consumed excess alcohol, also found that marijuana users had a reduced risk for fatty liver.

Bear in mind

Both the French and American studies were observational in design. Such studies cannot prove "cause and effect"—that is, they cannot prove that exposure to marijuana resulted in a reduced risk for fatty liver. Still, these studies form a good foundation from which robustly designed (and expensive) studies of marijuana can be planned.

In the French study, researchers found that daily marijuana use was the apparently beneficial frequency. However, in the American study, researchers asked less precise questions so it is unclear how much marijuana may be needed to have an effect on preventing fatty liver. Future marijuana studies with co-infected people need to ask at least the following questions:

- Which strains of marijuana were used?
- What was the relative mix of cannabinoids in such strains?
- How was marijuana used—smoked, ingested (edibles) or vapourized?
- How much marijuana was used and how often?
- Did marijuana interact with ART and/or other medicines commonly used by co-infected people?
- Are there differences in the effect of marijuana by gender?

Resources:

French study hints at marijuana's potential for reducing diabetes risk – *CATIE News*

Canadian survey compares marijuana use across different conditions – *CATIE News*

Alcohol, not marijuana, linked to liver injury in women with both HIV and hepatitis C – *CATIE News*

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C. Heavy marijuana use linked to heart problems in HIV-positive people

HIV-positive people are generally at heightened risk for cardiovascular disease because of a number of contributing risk factors, including the following:

- high rates of smoking and/or substance use
- abnormal levels of cholesterol and triglycerides in the blood
- elevated levels of inflammation
- insufficient exercise

Furthermore, some studies suggest that marijuana use is relatively common among HIV-positive people. Also, some studies suggest that the use of this herb may contribute to cardiovascular disease in HIV-negative people. It is possible that the same may be true of marijuana use by HIV-positive people.

Researchers at Harvard University conducted an observational study with 558 HIV-positive men between 1990 and 2010. They found that "heavy" marijuana use increased the risk for complications of cardiovascular disease—including heart attack and stroke—regardless of whether the men also smoked tobacco and regardless of the presence of other traditional risk factors.

Study details

The researchers used the database of a study called MACS (Multicenter AIDS Cohort Study), which has been ongoing for many years.

Participants visited study clinics every six months where they underwent interviews and physical examinations and had blood and other fluids collected for analysis.

There are thousands of participants in MACS and researchers excluded from their analysis people with hepatitis C virus (HCV) co-infection as well as people who used other substances such as cocaine and heroin because they wanted to try to focus on the effect of marijuana.

Based on participants' disclosure, researchers placed them into the following categories:

- heavy users – daily or weekly use at 50% or more of study visits
- occasional users – used marijuana less frequently than once a month
- non-users

Participants who disclosed smoking at least a quarter of a pack of cigarettes daily were classified as "heavy" tobacco users by the researchers.

At the start of the study, participants were an average of 41 years old and about 20% were classified as heavy marijuana users.

Researchers focused on what they called "cardiovascular events," which included heart attacks, stroke, heart pain, heart failure and related events.

Results

After taking into account many factors, researchers found the following associations:

- heavy marijuana use was linked to a 2.5-fold increased risk of a cardiovascular event
- participants who used both marijuana and smoked tobacco had a nearly five-fold increased risk of a cardiovascular event

These associations were statistically significant.

Blood cells

Other studies, with HIV-negative people, have found an association between having elevated white blood cells (WBC) and serious cardiovascular disease. In the present study, participants who were marijuana or tobacco users generally had increased WBC. Furthermore, participants (regardless of substance used) who had a WBC of 6,500 cells/mm^3 or greater had a four-fold increased risk for a cardiovascular event.

Other issues

There was no significant association between long-term heavy marijuana use and changes in viral load, CD4+ cell count, the risk for developing AIDS, cancer or death. In contrast, cigarette smokers had an increased risk for both heart attack and cancers unrelated to AIDS.

Bear in mind

The present study found associations between heavy marijuana use and an increased rate of cardiovascular events in men aged 40 to 60 years. This increase was independent of smoking tobacco.

Additional studies will be needed to uncover the reason(s) for this association between heavy marijuana use and cardiovascular events.

The present study is observational in design. Such studies cannot prove that marijuana (or anything else) caused cardiovascular events. However, the present study provides a foundation for further investigating any connections between cardiovascular health, marijuana use and HIV. Such future studies need to include women and ask at least the following questions:

- Which strains of marijuana were used?
- What was the relative mix of cannabinoids in such strains?
- How was marijuana used—smoked, ingested (edibles) or vapourized?
- How much marijuana was used and how often?
- Did marijuana interact with ART and/or other medicines commonly used by co-infected people?
- Are there differences in the effect of marijuana by gender?

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2. Lorenz DR, Dutta A, Mukerji SS, et al. Marijuana use impacts midlife cardiovascular events in HIV-infected men. *Clinical Infectious Diseases*. 2017 Aug 15;65(4):626-635.

D. Heavy marijuana use associated with a reduction in immune activation

Marijuana is a widely used substance, particularly among some HIV-positive people who use it to reduce chronic pain, nausea and anxiety/depression and to improve appetite.

As mentioned in *TreatmentUpdate 223*, excess inflammation and immune activation in HIV-positive people is only partially reduced with treatment (ART). Therefore, researchers are studying additional options to try to reduce these consequences of HIV infection.

Lab research suggests that marijuana or its extracts can reduce inflammation and immune activation, and there is interest in finding out if marijuana can have the same effect in people.

A team of researchers in San Francisco analysed stored blood samples from 185 HIV-positive ART users, some of whom disclosed that they used marijuana. The researchers found that participants had decreased levels of activated cells of the immune system, specifically T-cells, in their blood. They also found that there were decreased levels of other cells of the immune system that could incite and maintain inflammation.

These findings should be considered preliminary because the present study was not able to prove that marijuana use resulted in the decreased immune activation. However, the present study was necessary and provides a foundation for designing robust studies to find out if heavy or light use of marijuana can lead to a reduction in inflammatory conditions and better health.

Study details

As part of an ongoing study with more than 1,500 HIV-positive people, researchers analysed blood samples from 198 participants. Among this latter group, 65 participants disclosed daily marijuana use (which the researchers classified as "heavy"). Researchers subjected the blood samples to extensive analysis, including testing for the presence of several cannabinoids—the compounds in marijuana responsible for its effects.

The average profile of participants upon entering the study was as follows:

- 87% men, 13% women
- age – 53 years
- CD4+ count – 533 cells/mm^3
- CD8+ count – 972 cells/mm^3
- viral load – less than 75 copies/mL (the lower limit of quantification used in this study)
- duration of viral suppression – four years
- length of time since HIV diagnosis – 17 years

Results—Verifying marijuana exposure

As mentioned earlier, researchers subjected the blood samples of participants to extensive testing, including analysing the blood for the presence of cannabinoids.

Among five people who reported not using marijuana, researchers found the presence of two or more cannabinoids in their blood. Among eight other people who reported daily marijuana use, researchers did not find significant levels of cannabinoids in their blood. Therefore, they decided to exclude these 13 people from further analysis, leaving 185 people's samples to be used for the study.

Results—Inflammation and immune activation

- Researchers found that heavy marijuana users had significantly reduced levels of activated CD4+ and CD8+ cells (written as CD4+ HLA-DR+ CD38+ and CD8+ HLA-DR+ CD38+) compared to non-users.
- Levels of another group of cells (monocytes) of the immune system that displayed the proteins CD14+ and CD16+ on their surface were decreased among moderate and heavy marijuana users compared to non-users.
- Another group of cells of the immune system are called dendritic cells. Researchers found that a subset of these called myeloid dendritic cells were "significantly lower in the moderate and heavy cannabis-using groups as compared to non-users."

- Another group of cells of the immune system called APCs (antigen-presenting cells), which produce chemical signals of inflammation, were significantly reduced in heavy cannabis users vs. other participants.

Bear in mind

Taken together, the findings from the present study are highly suggestive of marijuana's ability to reduce immune activation and to some extent inflammation. The study was strengthened by the researchers' ability to assess the blood samples of participants for the presence of key compounds found in marijuana. The reduction in immune activation and inflammation occurred because certain compounds in marijuana were able to interfere with the functioning of the immune system. There was no signal from the present study that this interference with the immune system was harmful (though the researchers did not appear to assess that). Studies are needed to assess the short-term and long-term safety of marijuana.

However, as the present study was observational in design, it does not prove that the use of marijuana caused the reduction in immune activation and inflammation. The present study does provide a foundation for designing a more robust future study. Such a study needs to examine at least the following:

- Which strains of marijuana were used?
- What was the relative mix of cannabinoids in such strains?
- How was marijuana used—smoked, ingested (edibles) or vapourized?
- How much marijuana was used and how often?
- Did marijuana interact with ART and/or other medicines commonly used by co-infected people?
- Are there differences in the effect of marijuana by gender?

REFERENCE:

Manuzak JA, Gott TM, Kirkwood JS, et al. Heavy cannabis use associated with reduction in activated and inflammatory immune cell frequencies in antiretroviral therapy-treated human immunodeficiency virus-infected individuals. *Clinical Infectious Diseases*. 2018; *in press*.

E. Clinical trials in Canada to explore reducing inflammation in HIV

A number of clinical trials are underway to study therapies that can help reduce inflammation and have other beneficial effects in people on HIV treatment (ART). Here are some in Canada:

Reprieve

Pitavastatin is approved in the U.S. but not in Canada for the management of cholesterol levels. Small clinical trials suggest that pitavastatin not only helps to normalize cholesterol levels but can also reduce some measures of inflammation. Also, pitavastatin does not increase the risk of developing type 2 diabetes, a problem with some other statins.

The main purpose of the Reprieve study is to find out if the use of pitavastatin can reduce deaths from heart attack, stroke or other complications of cardiovascular disease.

Researchers are seeking volunteers with the following basic profile:

- living with HIV between the ages of 40 and 75
- on antiretroviral therapy (ART) for at least 6 months prior to study entry
- no history of cardiovascular disease (including heart attack or stroke)
- not currently using a statin drug
- low-to-moderate risk for developing heart disease
- not pregnant or planning on becoming pregnant

To find out more about Reprieve and consider participation, readers can contact study centres in Canada: http://www.hivnet.ubc.ca/clinical-trials/ctn-293-reprieve-trial/

CTNPT 028

Researchers at McGill University in Montreal are studying the safety of two compounds found in marijuana on the immune systems of people with HIV. For further information about this study, visit: http://www.hivnet.ubc.ca/clinical-trials/ctnpt-028-cannabinoids-hiv-infected-individuals-effective-art-safety-tolerability-effect-immune-function/

CTNPT 022B

This study, taking place in Toronto, involves the use of friendly bacteria (probiotics) that researchers hope to show will reduce inflammation in the gut and possibly general inflammation in HIV-positive men with the following profile:

- At least 18 years of age
- Have been taking standard anti-HIV treatment for at least two years
- Have an undetectable HIV-1 viral load (less than 50 copies/ml) for the past 2 years (rare "blips" are OK)
- Consistently low blood CD4 T cell counts (less than 350 cells/mm^3 observed in at least 70% of tests during the previous 2 years)

For further information about enrolment contact Bryan Boyachuk (bryan.boyachuk@uhn.ca), or with questions about the study in general contact Rodney Rousseau (r.rousseau@utoronto.ca). For more information about this study, visit: http://www.hivnet.ubc.ca/clinical-trials/ctnpt022b/

Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

CATIE provides information resources to help people living with HIV and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

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Writer **Sean Hosein**
Editor **RonniLyn Pustil**

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For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

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