CATIE Canada's source for HIV and hepatitis C information
La source canadienne de renseignements sur le VIH et l'hépatite C

From *TreatmentUpdate 225*

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 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?

—Sean R. Hosein

REFERENCES:

1. Dimopoulos Y, Moysi E, Petrovas C. The lymph node in HIV pathogenesis. *Current HIV/AIDS Reports* . 2017 Aug;14(4):133-140.
2. Barouch DH, Ghneim K, Bosche WJ, et al. Rapid inflammasome activation following mucosal SIV infection of rhesus monkeys. *Cell*. 2016 Apr 21;165(3):656-67.
3. Boritz EA, Darko S, Swaszek L, et al. Multiple origins of virus persistence during natural control of HIV infection. *Cell*. 2016 Aug 11;166(4):1004-1015.
4. Castellano P, Prevedel L, Eugenin EA. HIV-infected macrophages and microglia that survive acute infection become viral reservoirs by a mechanism involving Bim. *Scientific Reports* . 2017 Oct 9;7(1):12866.
5. Hunt PW, Lee SA, Siedner MJ. Immunologic biomarkers, morbidity and mortality in treated HIV infection. *Journal of Infectious Diseases*. 2016 Oct 1;214 Suppl 2:S44-50.
6. Schechter ME, Andrade BB, He T, et al. Inflammatory monocytes expressing tissue factor drive SIV and HIV coagulopathy. *Science Translational Medicine* . 2017 Aug 30;9(405). pii: eaam5441.
7. Lorenzo-Redondo R, Fryer HR, Bedford T, et al. Persistent HIV-1 replication maintains the tissue reservoir during therapy. *Nature*. 2016 Feb 4;530(7588):51-56.
8. Estes JD, Kityo C, Ssali F, et al. Defining total-body AIDS-virus burden with implications for curative strategies. *Nature Medicine* . 2017 Nov;23(11):1271-1276.
9. Deleage C, Schuetz A, Alvord WG, et al. Impact of early cART in the gut during acute HIV infection. *JCI Insight* . 2016 Jul 7;1(10). pii: e87065.
10. Somsouk M, Estes JD, Deleage C, et al. Gut epithelial barrier and systemic inflammation during chronic HIV infection. *AIDS*. 2015 Jan 2;29(1):43-51.
11. Booiman T, Wit FW, Girigorie AF, et al. Terminal differentiation of T cells is strongly associated with CMV infection and increased in HIV-positive individuals on ART and lifestyle matched controls. *PLoS One* . 2017 Aug 14;12(8):e0183357.
12. Cobos Jiménez V, Wit FW, Joerink M, Maurer I, et al. T-cell activation independently associates with immune senescence in HIV-infected recipients of long-term antiretroviral treatment. *Journal of Infectious Diseases* . 2016 Jul 15;214(2):216-25.
13. Wada NI, Jacobson LP, Margolick JB, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. *AIDS*. 2015 Feb 20;29(4):463-71.
14. Castillo-Mancilla JR, Brown TT, Erlandson KM, et al. Suboptimal adherence to combination antiretroviral therapy is associated with higher levels of inflammation despite HIV suppression. *Clinical Infectious Diseases* . 2016 Dec 15;63(12):1661-1667.
15. Nasi M, De Biasi S, Gibellini L, et al. Ageing and inflammation in patients with HIV infection. *Clinical and Experimental Immunology* . 2017 Jan;187(1):44-52.
16. Mamik MK, Power C. Inflammasomes in neurological diseases: emerging pathogenic and therapeutic concepts. *Brain*. 2017 Sep 1;140(9):2273-2285.
17. Festa L, Gutoskey CJ, Graziano A, et al. Induction of interleukin-1β by human immunodeficiency virus-1 viral proteins leads to increased levels of neuronal ferritin heavy chain, synaptic injury, and deficits in flexible attention. *Journal of Neuroscience* . 2015 Jul 22;35(29):10550-61.
18. Jiang W, Lederman MM, Hunt P, et al. Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection. *Journal of Infectious Diseases*. 2009 Apr 15;199(8):1177-85.
19. Tawakol A, Ishai A, Li D, et al. Association of arterial and lymph node inflammation with distinct inflammatory pathways in human immunodeficiency virus infection. *JAMA Cardiology* . 2017 Feb 1;2(2):163-171.
20. Fisher BS, Green RR, Brown RR, et al. Liver macrophage-associated inflammation correlates with SIV burden and is substantially reduced following cART. *PLoS Pathogens.* 2018 Feb 21;14(2):e1006871.
21. Acharya N, Penukonda S, Shcheglova T, et al. Endocannabinoid system acts as a regulator of immune homeostasis in the gut. *Proceedings of the National Academy of Sciences USA.* 2017 May 9;114(19):5005-5010.
22. Pacher P, Steffens S, Haskó G, et al. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nature Reviews. Cardiology* . 2018 Mar;15(3):151-166.
23. Rizzo MD, Crawford RB, Henriquez JE. HIV-infected cannabis users have lower circulating CD16+ monocytes and IFN-γ-inducible protein 10 levels compared with non-using HIV patients. *AIDS*. 2018 Feb 20;32(4):419-429.

24. Henriquez JE, Rizzo MD, Schulz MA, et al. Δ9-tetrahydrocannabinol suppresses secretion of IFNα by plasmacytoid dendritic cells from healthy and HIV-infected individuals. *Journal of Acquired Immune Deficiency Syndromes.* 2017 Aug 15;75(5):588-596.
25. Sido JM, Nagarkatti PS, Nagarkatti M. Production of endocannabinoids by activated T cells and B cells modulates inflammation associated with delayed-type hypersensitivity. *European Journal of Immunology* . 2016 Jun;46(6):1472-9.
26. Sido JM, Jackson AR, Nagarkatti PS, et al. Marijuana-derived Δ-9-tetrahydrocannabinol suppresses Th1/Th17 cell-mediated delayed-type hypersensitivity through microRNA regulation. *Journal of Molecular Medicine* . 2016 Sep;94(9):1039-51.
27. Cabral GA, Rogers TJ, Lichtman AH. Turning over a new leaf: Cannabinoid and endocannabinoid modulation of immune function. *Journal of Neuroimmune Pharmacology* . 2015 Jun;10(2):193-203.
28. Croxford JL, Yamamura T. Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? *Journal of Neuroimmunology* . 2005 Sep;166(1-2):3-18.
29. Börner C, Höllt V, Kraus J. Activation of human T cells induces upregulation of cannabinoid receptor type 1 transcription. *Neuroimmodulation.* 2007;14(6):281-6.
30. Eisenstein TK, Meissler JJ. Effects of cannabinoids on T-cell function and resistance to infection. *Journal of Neuroimmune Pharmacology.* 2015 Jun;10(2):204-16.
31. 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.
32. 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* .
33. Nordmann S, Vilotitch A, Roux P, et al. Daily cannabis and reduced risk of steatosis in human immunodeficiency virus and hepatitis C virus-co-infected patients (ANRS CO13-HEPAVIH). *Journal of Viral Hepatology* . 2018 Feb;25(2):171-179.
34. Kim D, Kim W, Kwak MS, et al. Inverse association of marijuana use with nonalcoholic fatty liver disease among adults in the United States. *PLoS One* . 2017 Oct 19;12(10):e0186702.

Produced By:

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

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.

CATIE endeavours to provide the most up-to-date and accurate information at the time of publication. However, information changes and users are encouraged to ensure they have the most current information. Users relying solely on this information do so entirely at their own risk. Neither CATIE nor any of its partners or funders, nor any of their employees, directors, officers or volunteers may be held liable for damages of any kind that may result from the use or misuse of any such information. Any opinions expressed herein or in any article or publication accessed or published or provided by CATIE may not reflect the policies or opinions of CATIE or any partners or funders.

Information on safer drug use is presented as a public health service to help people make healthier choices to reduce the spread of HIV, viral hepatitis and other infections. It is not intended to encourage or promote the use or possession of illegal drugs.

Permission to Reproduce

Production of this content has been made possible through a financial contribution from the Public Health Agency of Canada.

Available online at:
http://www.catie.ca/en/treatmentupdate/treatmentupdate-225/inflammation-hiv-and-marijuana/some-research-issues-marijuana-hi