

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

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