TreatmentUpdate 226

Vol. 30, No. 3 · March/April 2018

Available online at
www.catie.ca/en/treatmentupdate

Contents

I INFLAMMATION

A. Focus on bugs in the gut

Initiating HIV treatment (ART) and achieving and maintaining an undetectable viral load by taking ART every day brings many benefits. Scientists increasingly expect that a young adult who is diagnosed today *and* who begins ART shortly thereafter *and* achieves and maintains an undetectable viral load, *and* who keeps regular doctor and lab appointments, *and* who does not have untreated mental health issues (including addiction) will likely have a near-normal life expectancy. There is also another benefit from ART: Studies have shown that people who achieve and maintain an undetectable viral load do not pass on HIV to their sexual partners.

Despite these immense benefits arising from the use of ART, treatment can only partially correct changes that HIV causes deep within the body and immune system. In particular, HIV causes inflammation and activation of the immune system. ART partially reduces this but does not eliminate it. As HIV-related inflammation and immune activation become chronic, some scientists are concerned that this may contribute to other health problems over the long-term, including the following:

- 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

produced by

CATIE
Canada's source for HIV and hepatitis C information

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

- lung injury
- thinning 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. In this issue of *TreatmentUpdate* we focus on another potential intervention to reduce inflammation—manipulating the population of bacteria and fungi that live in the gut.

Inside the gut

Many germs can enter the body through eating food or drinking water that has been contaminated. These germs pass through the intestine. As a result, much of the immune system has evolved to be distributed around the intestine in lymph nodes and lymphatic (or lymphoid) tissues.

The gut contains trillions of microbes—mostly bacteria but also some fungi and viruses—that live off of fibre and other substances in food. For this report, we will focus mostly on gut bacteria. The technical term for the bacteria that normally live in the gut is the *gut microbiome*. There is a balance of bacteria and fungi living in the gut, generally favouring microbes that are either usually harmless or in some way helpful to human health. Friendly bacteria (and fungi) release chemicals that reduce the growth of unfriendly microbes. Friendly bacteria and fungi take up physical space in the gut, making it difficult for unfriendly microbes to grow.

The full benefit of carrying trillions of friendly microbes in the gut is being explored by scientists. Emerging research suggests that some friendly bacteria (and fungi) have the potential to do the following:

- reduce general inflammation
- release compounds that directly or indirectly affect mood
- play a role in reducing the risk for cardiovascular disease
- strengthen the immune system and make it more responsive to compounds called checkpoint inhibitors. These compounds are emerging therapies for cancer and are being studied to assess their impact on the immune systems of healthy HIV-positive people.

A shifting balance

Scientists have found that, in general, HIV-positive people have a reduced diversity of gut bugs compared to healthy HIV-negative people. In some cases, this decreased diversity of microbes has been linked to lower-than-ideal levels of CD4+ cells in the blood of HIV-positive people who have not had a robust immunological response to ART despite having an undetectable viral load.

As mentioned earlier, there are many lymph nodes and small collections of lymphatic tissue around the intestines. HIV accumulates in those tissues because many cells of the immune system are located there. As HIV attacks cells in those tissues, this causes inflammation, which also affects the intestines, weakening the barrier in the gut and causing it to become "leaky."

This inflammation also likely plays a role in the malabsorption that is a feature of untreated HIV infection. Due to HIV infection, certain bacteria that are naturally present in the intestine in small proportions can grow as the balance of bacteria is altered. These bacteria produce proteins that can incite and prolong inflammation. These proteins can cross a weakened gut barrier and become absorbed into the blood and spread throughout the body. The scientific term for the passage of high levels of bacterial proteins across the gut to the blood is called bacterial translocation. Researchers have found that over time ART can greatly reduce the passage of these proteins across the gut to the blood. However, ART does not decrease the level of these bacterial proteins to very low levels seen in healthy HIV-negative people.

Scientists are conducting many experiments in animals and people (both HIV negative and HIV positive) to better understand the impact of shifting the populations of gut bugs. A recent systematic review of 39 randomized controlled trials with more than 9,000 HIV-positive participants found no evidence of harm. The results of this review should be reassuring for doctors and nurses planning clinical trials or counselling their patients about considering participation in such trials.

In this issue of *TreatmentUpdate*, we explore some immunological issues related to shifting the balance of bacteria (and some fungi), mostly in people with HIV.

REFERENCES:

1. Williams B, Landay A, Presti RM. Microbiome alterations in HIV infection—a review. *Cellular Microbiology*. 2016 May; 18(5):645-651.

2. Bandera A, De Benedetto I, Bozzi G, Gori A. Altered gut microbiome composition in HIV infection: causes, effects and potential intervention. *Current Opinion in HIV/AIDS*. 2018 Jan;13(1):73-80.

3. El-Far M, Tremblay CL. Gut microbial diversity in HIV infection post combined antiretroviral therapy: a key target for prevention of cardiovascular disease. *Current Opinion in HIV/AIDS*. 2018 Jan;13(1):38-44.

4. Desai SN, Landay AL. HIV and aging: role of the microbiome. *Current Opinion in HIV/AIDS*. 2018 Jan;13(1):22-27.

5. Hager CL, Ghannoum MA. The mycobiome in HIV. *Current Opinion in HIV/AIDS*. 2018 Jan;13(1):69-72.

6. Sereti I, Krebs SJ, Phanuphak N, et al Persistent, albeit reduced, chronic inflammation in persons starting antiretroviral therapy in acute HIV infection. *Clinical Infectious Diseases*. 2017 Jan 15;64(2):124-131.

7. Angelidou K, Hunt PW, Landay AL, et al. Changes in inflammation but not in T cell activation precede non-AIDS-defining events in a case-control study of patients on long-term antiretroviral therapy. *Journal of Infectious Diseases*. 2018; *in press*.

8. Barouch DH, Ghneim K, Bosche WJ, et al. Rapid inflammasome activation following mucosal SIV infection of rhesus monkeys. *Cell*. 2016 Apr 21;165(3):656-667.

9. 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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):463-471.

20. 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.

21. 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.

22. Mamik MK, Power C. Inflammasomes in neurological diseases: emerging pathogenic and therapeutic concepts. *Brain*. 2017 Sep 1;140(9):2273-2285.

23. 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):10550-10561.

24. 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):1177-1185.

25. 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.

B. A clinical trial of friendly yeast

In low- and middle-income countries, clinical trials of the friendly microbe *S. boulardii* (a yeast) have found that it can generally reduce diarrhea.

Researchers in Barcelona, Spain, conducted a randomized, double-blind, placebo-controlled trial with 44 HIV-positive people taking HIV treatment (ART). Participants took supplements of *S. boulardii* for 12 weeks. Most participants who received *S. boulardii* had reduced levels of bacterial proteins in their blood. Levels of the immunological signal IL-6 (interleukin-6), which is associated with inflammation, decreased modestly. These changes persisted for at least three months after the cessation of the study.

Study details

All participants had been taking ART and had a viral load of less than 20 copies/mL for at least two years prior to entering the present study. Researchers reported that half of the participants entered the study with more than 400 CD4+ cells/mm^3.

Participants took about 5 billion units of *S. boulardii* daily. This probiotic was taken in capsules three times daily.

Key findings

The use of *S. boulardii* was associated with the following changes compared to placebo:

- a decrease in IL-6 levels in the blood
- a decrease in levels of bacterial proteins in the blood
- a decrease in activation of the immune system (this was shown as a decrease in the level of a protein called beta2-microglobulin in the blood)

These changes were statistically significant.

There were no other notable and significant changes in the study, including CD4+ and CD8+ cell counts.

The researchers found that the friendly yeast was well tolerated and did not cause harm.

Bear in mind

Supplements of *S. boulardii* were used in the time before ART was available to try to reduce the severity of AIDS-related diarrhea.

In the current era when ART is widely available in high-income countries, perhaps *S. boulardii* supplements may have another use, such as reducing inflammation in the immune system. However, note that the present study was relatively small and adherence to a thrice-daily regimen of probiotics was not directly measured. Despite this, the overall design of the Barcelona study suggests that there is modest benefit. The researchers said that a longer study may be useful with this probiotic.

REFERENCES:

1. Villar-García J, Hernández JJ, Güerri-Fernández R, et al. Effect of probiotics (Saccharomyces boulardii) on microbial translocation and inflammation in HIV-treated patients: a double-blind, randomized, placebo-controlled trial. *Journal of Acquired Immune Deficiency Syndromes*. 2015 Mar 1;68(3): 256-263.

2. Villar-García J, Güerri-Fernández R, Moya A, et al. Impact of probiotic *Saccharomyces boulardii* on the gut microbiome composition in HIV-treated patients: A double-blind, randomised, placebo-controlled trial. *PLoS One*. 2017 Apr 7;12(4):e0173802.

C. Intestinal bacteria and the brain

Scientists who study brain-related issues suggest that some bacteria that normally live in the gut have an influence on human health. They are not certain precisely how this effect occurs but perhaps studies in animals can provide clues.

Experiments with mice and rats suggest that chronic stress can change the balance of microbes in the gut. In turn, as different bacteria become more common because of stress, the walls of the intestine may become weaker and allow the entry of harmful bacteria. These harmful bacteria can release proteins that are absorbed by the blood and spread throughout the body, causing inflammation. The scientists who study brain-related issues have noted that "emotional stress and depression have been shown to increase prevalence of disorders of the digestive system."

Researchers have found that some bacterial proteins can interact with cells of the immune system that travel to, and in some cases take up residence in, the brain. In turn, these cells of the immune system release chemical signals that influence brain cells.

Scientists have conducted experiments with mice that do not have any bacteria in the gut and found that these animals have altered levels of neurotransmitters—compounds that the brain and nerves use to communicate—compared to mice with gut bacteria. This suggests that gut bacteria play some role in the health of the brain and nerves.

In other experiments, scientists have found that giving large doses of harmful bacteria to animals can cause what they describe as "anxiety-like behaviour." They have also found that giving friendly bacteria to the same animals can result in apparent relief from anxiety.

When researchers conducted further experiments to better understand these findings, they found that in order for the bacteria to have helpful or harmful effects on the brain, the nerves that reach from the intestine to the brain must be intact. Scientists think that bacteria release proteins that have an indirect or direct effect on nerve cells in the intestine and these effects are relayed to the brain.

Depression

Some studies have found that there is a difference in the population of bacteria in the gut of people with depression vs. healthy people without depression. Whether this difference in gut bacteria was a factor that contributed to the onset of depression or is a result of depression is not clear. In experiments with young rats who have depression, certain friendly bacteria appear to relieve depression, perhaps by reducing inflammation. That there is a link between inflammation and depression is suggested by the results of pilot studies of the antibiotic doxycycline, which has anti-inflammatory activity, in some people with depression.

Thinking and gut bacteria

Other experiments with mice suggest that gut bacteria, particularly a group of bacteria called lactobacilli, can have an impact on memory and learning. As yet there is no evidence for a similar effect of these bacteria on people. However, research in this area is slowly advancing and one team of scientists has found that giving people probiotics "can alter the functional activity of the areas in the brain that are involved in cognitive functions."

Understanding the effect of gut bacteria on the brain is still in its infancy; many clinical trials lie ahead.

A note about clinical trials

Most recent studies of probiotics and their effects on the brain or immune system have tested one, two or three strains of bacteria or fungi. Since the gut contains many different types of bacteria (and fungi), clinical trials with many strains of probiotics are likely to have a greater effect than just a few strains.

REFERENCES:

1. Bauer KC, Huus KE, Finlay BB. Microbes and the mind: emerging hallmarks of the gut microbiota-brain axis. *Cellular Microbiology*. 2016 May;18(5):632-644.

2. Yarandi SS, Peterson DA, Treisman GJ, et al. Modulatory effects of gut microbiota on the central servous system: How cut could play a role in neuropsychiatric health and diseases. *Journal of Neurogastroenrology and Motility Association*. 2016 Apr 30;22(2):201-212.

D. A pilot study of Visbiome on some aspects of brain health

As mentioned earlier in this issue of *TreatmentUpdate*, experiments with animals suggest that bacteria in the gut can somehow affect memory and mood. These experiments involved giving the animals antibiotics to wipe out their intestinal bacteria or some of their intestinal bacteria, as well as other experiments where supplements of friendly bacteria were given.

Researchers in Rome, Italy, conducted a six-month pilot study with a sophisticated mix of friendly bacteria (Visbiome, Vivomixx) to assess their impact on memory and thinking processes in 10 HIV-positive people who had been taking HIV treatment (ART) for several years and had undetectable viral loads.

The researchers found that there was significant improvement in several neuropsychological test results over time, including memory and verbal fluency. They also found that there was a decrease in anxiety. The probiotic was safe. The study's small size and other design limitations mean that its results are suggestive, not definitive. However, the results of this study can be used to design larger studies of Visbiome to confirm these findings.

Study details

Researchers recruited HIV-positive adults who did not have diagnoses of the following:

- intestinal disorders
- neurological disorders
- mental health conditions
- cancer

Participants had samples of the fluid that surrounds the brain and spinal cord (cerebrospinal

fluid, or CSF) removed before and after the study for analysis.

Participants took Visbiome twice daily. Visbiome contains the following bacteria:

- *Lactobacillus plantarum*
- *Streptococcus thermophilus*
- *Bifidobacterium breve*
- *Lactobacillus paracasei*
- *Lactobacillus delbrueckii, subspecies bulgaris*
- *Lactobacillus acidophilus*
- *Bifidobacterium longum*
- *Bifidobacterium infantis*

Participants underwent complex neurological testing at the beginning and end of the study.

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

- all male
- age – 42 years
- duration of ART – six years
- all participants had an undetectable viral load for at least the past year
- CD4+ count – 674 cells/mm^3

Results

Visbiome was well tolerated and no side effects were reported. Furthermore, analysis of CSF samples found no increase in inflammation in the blood or brain.

Researchers found that the level of bifidobacteria in the stool samples of participants rose significantly during the study, suggesting that participants were taking Visbiome.

Neuropsychological testing

Researchers found that there were some improvements in memory, verbal fluency and anxiety. However, they were cautious about the apparent change in measures of anxiety—they felt it was possible that participants may have become more aware of their feelings from being asked questions about anxiety and that perhaps the changes reported were influenced by the questioning.

Bear in mind

The results of the present study are promising but not definitive. A more robust study design will be needed before researchers can be certain about Visbiome's usefulness.

REFERENCES:

1. Ceccarelli G, Fratino M, Selvaggi C, et al. A pilot study on the effects of probiotic supplementation on neuropsychological performance and microRNA-29a-c levels in antiretroviral-treated HIV-1-infected patients. *Brain and Behavior*. 2017 Jul 16;7(8):e00756.

2. Bauer KC, Huus KE, Finlay BB. Microbes and the mind: emerging hallmarks of the gut microbiota-brain axis. *Cellular Microbiology*. 2016 May;18(5):632-644.

3. Yarandi SS, Peterson DA, Treisman GJ, et al. Modulatory effects of gut microbiota on the central nervous system: How gut could play a role in neuropsychiatric health and diseases. *Journal of Neurogastroenrology and Motility Association*. 2016 Apr 30;22(2):201-212.

E. Visbiome and immune activation

As mentioned earlier in this issue of *TreatmentUpdate*, experiments with animals suggest that bacteria living in the gut can affect several aspects of health, including inflammation in the gut, general inflammation, the health of the immune system and perhaps even the brain.

Researchers in Rome and Bologna, Italy, conducted a sub-study of a slightly larger study, with eight HIV-positive participants and supplements with a sophisticated mix of friendly bacteria (called Visbiome in North America or Vivomixx in the European Union). The bacteria were taken for six months. Researchers found increased levels of the neurotransmitter serotonin in the blood of participants. Other blood tests found reduced levels of activation of CD4+ cells in the blood. Levels of an enzyme in the blood that can weaken the immune system were also reduced.

This pilot study suggests that Visbiome holds promise. A more robustly designed clinical trial of Visbiome is underway in Toronto.

Study details

The average profile of participants was similar to that in the previous reported study in this issue of *TreatmentUpdate*. Participants took Visbiome twice daily for six months.

Results—Immune activation

Over the course of the study, researchers found that there was a decrease in the proportion of activated CD4+ cells in the blood. This decrease approached statistical significance.

The researchers found significantly decreased levels of an enzyme called IDO-1 (indoleamine 2,3-dioxygenase-1) in the blood. In many lab experiments with cell cultures, IDO-1 can weaken the immune system, particularly in cancer and HIV infection.

Bear in mind

This sub-study suggests that Visbiome may be able to reduce levels of immune activation and levels of an important enzyme that can weaken the immune system. However, due to design issues, firm conclusions cannot be drawn from this study. But it has provided the foundation for a more robustly designed study underway in Toronto. In this study, researchers hope to better understand Visbiome's potential to reduce excess immunological activation.

REFERENCES:

1. Scheri GC, Fard SN, Schietroma I, et al. Modulation of tryptophan/serotonin pathway by probiotic supplementation in human immunodeficiency virus-positive patients: Preliminary results of a new study approach. International *Journal of Tryptophan Research*. 2017 May 30;10:1178646917710668.

2. d'Ettorre G, Rossi G, Scagnolari C, et al. Probiotic supplementation promotes a reduction in T-cell activation, an increase in Th17 frequencies, and a recovery of intestinal epithelium integrity and mitochondrial morphology in ART-treated HIV-1-positive patients. *Immunity, Inflammation and Disease*. 2017 Sep;5(3):244-260.

3. Prendergast GC, Malachowski WP, DuHadaway JB, et al. Discovery of IDO1 inhibitors: From bench to bedside. *Cancer Research*. 2017 Dec 15;77(24):6795-6811.

F. Probiotics and the response to immunotherapy for cancer

As mentioned earlier in this issue of *TreatmentUpdate*, emerging research suggests that bacteria that live in the gut can have an impact on several organ-systems, including the intestine, brain and immune system. There are teams of scientists around the world studying how bacteria in the gut can be manipulated to produce beneficial effects for the immune system and perhaps to help moderate certain conditions. In particular, some scientists hope to be able to decrease inflammation and immune activation with gut bugs. Other scientists hope to improve the anti-cancer response of the immune system when people with cancer are given an emerging class of drugs call checkpoint inhibitors. We will discuss checkpoint inhibitors later in this report, but first some background about the immune system is necessary.

Checkpoints within the immune system

During a typical response to an infection or tumour, the immune system needs to be mobilized. This mobilization is done through the release of chemical signals of inflammation. Certain cells of the immune system that fight microbes and tumours—including CD8+ T cells, natural killer cells and macrophages—become activated. Eventually, after an infection or tumour has been contained and destroyed, the immune system needs to dampen and shut down the response to the infection/cancer or else cells that remain activated could inadvertently injure healthy tissue. Also, excess inflammation could slowly degrade vital organs.

To help turn off these immune responses, cells of the immune system begin to display checkpoints. These are proteins on the surface of cells that signal to CD8+ and other cells to decrease and eventually cease their activity.

The interest in checkpoint inhibitors

Commonly studied checkpoints include PD-1 and PD-L1 (these are called programmed cell death protein-1 and programmed cell death ligand-1, respectively). Some research suggests that HIV infection causes cells of the immune system to display these and other checkpoints. It is possible that, in the vast majority of people, these

checkpoints may play a role in the immune system's inability to contain and clear HIV. Scientists in the U.S. are conducting small studies of checkpoint inhibitors in people with HIV as part of attempts at curing this infection.

Responders and non-responders

Some tumours also display checkpoints on their surface, thwarting the immune system's ability to vanquish tumours. In some people with cancer, checkpoint inhibitors can be powerful; they can cause tumours to shrink, and, in some cases, tumours disappear entirely. This occurs because in some people, called "responders," checkpoint inhibitors unblock the immune system, unleashing a robust immunological response against the tumour. Unfortunately, this immune response can sometimes get out of control and cause intense side effects.

Scientists are trying to find out which people with cancer will have a beneficial response when treated with checkpoint inhibitors. Such studies may one day be useful in HIV cure research.

Clues from cancer treatment

Research teams in France and the U.S. have been studying the gut bacteria of people with different cancers, all of whom were treated with checkpoint inhibitors. Participants were divided into responders and non-responders. Some of the most interesting aspects of this research came from the team in France with scientist Bertrand Routy, PhD. He and his colleagues studied participants who were receiving treatment with checkpoint inhibitors for the following cancers:

- non-small cell lung cancer
- renal cell carcinoma
- urothelial carcinoma

They found that when participants took antibiotics to treat infections, they had a relatively weak response to tumours elicited by checkpoint inhibitors. This finding suggests that some species of bacteria can interfere with the effectiveness of checkpoint inhibitors.

Routy's team analysed the feces of participants (feces contain a representative sample of gut bacteria) and found that participants with a favourable response to checkpoint inhibitors against PD-1 had relatively high levels of the bacteria *Akkermansia muciniphila*. These bacteria are thought to have anti-inflammatory activity. In separate and unrelated experiments, researchers fed mice different diets and found that those mice fed a diet rich in fish oil had relatively high levels of these bacteria in their gut.

Engaging in fecal microbiota transplants

Culturing bacteria from the feces of healthy people or from people who are immune to certain bacterial infections, and then transferring these bacteria to other people is called fecal microbiota transplant (FMT). This technique has been used to treat some cases of severe and prolonged diarrhea caused by overgrowth of the bacteria *C. difficile*.

Routy, as well as another team of researchers in the U.S., cultured bacteria from the feces of cancer patients who were treated with checkpoint inhibitors. They then gave mice with human tumours FMT with these bacteria. Only the mice that received FMT from people who had responded to checkpoint inhibitors showed improved responses to those tumours when they too were treated with checkpoint inhibitors. The mice that showed poor responses despite FMT were then given supplements of *A. muciniphila* and their responses to checkpoint inhibitors improved.

These and other experiments strongly suggest that for checkpoint inhibitors to have beneficial effects, people with cancer may need to have the right mix of bacteria.

Readers should note that other scientists studying people with other cancers (such as malignant melanoma) found that other bacteria, such as *Faecalibacterium*, enhanced the activity of checkpoint inhibitors in subsequent studies with mice. Thus, it is possible, likely even, that there is no one ideal variety of gut bacteria that can help people who use checkpoint inhibitors. Rather, a mix of bacteria with one strain predominating may be useful in some cancers, while in others types of cancer, a diverse mix of bacteria may be more useful.

A difficult road ahead

The experiments with gut bacteria and checkpoint inhibitors are exciting and underscore the importance of such bacteria for the immune system. Now much work lies ahead in this aspect of cancer research. Scientists need to study precisely how friendly bacteria can help enhance the immune response in cases of cancer treatment with checkpoint inhibitors.

Also, as mentioned earlier in this issue of *TreatmentUpdate*, there are factors that can affect the mix of bacteria that live in the gut. It is one thing to study mice confined to cages, but another to study complex human beings with cancer and the many factors that can affect the composition of gut bacteria, including use of antibiotics and other medicines, diet, stress, use of supplements, and so on. Scientists have their work cut out for them as they try to move experimental results with mice to clinical trials with people with cancer being treated with checkpoint inhibitors. Due to the complex and poorly understood ways that gut bacteria can affect human health, it could take years before supplements of friendly bacteria are routinely used with checkpoint inhibitors or other immune-based therapy in clinical trials. In some cases, if scientists can uncover how gut bacteria exert their effects on the immune system, it may not be supplements of bacteria that are tested in clinical trials, but instead proteins derived from such bacteria.

HIV cure research

Researchers in France and the U.S. are conducting clinical trials of checkpoint inhibitors in people who have HIV and cancer. As checkpoint inhibitors can cause intense side effects, researchers are proceeding cautiously with these studies. If the results from these studies are positive, then researchers can plan on investigating the role of gut bacteria and checkpoint inhibitors in this population.

REFERENCES:

1. Wykes MN, Lewin SR. Immune checkpoint blockade in infectious diseases. *Nature Reviews. Immunology*. 2018 Feb; 18(2):91-104.

2. Thomas S, Izard J, Walsh E, et al. The host microbiome regulates and maintains human health: A primer and perspective for non-microbiologists. *Cancer Research*. 2017 Apr 15;77(8):1783-1812.

3. Jobin C. Precision medicine using microbiota. *Science*. 2018 Jan 5;359(6371):32-34.

4. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science*. 2018 Jan 5;359(6371):104-108.

5. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science*. 2018 Jan 5;359(6371):91-97.

6. Zitvogel L, Daillère R, Roberti MP, et al. Anticancer effects of the microbiome and its products. *Nature Reviews. Microbiology*. 2017 Aug;15(8):465-478.

7. Sage PT, Schildberg FA, Sobel RA, et al. Dendritic cell PD-L1 limits autoimmunity and follicular T cell differentiation and function. *Journal of Immunology*. 2018; *in press*.

G. 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, or with questions about the study in general contact Rodney Rousseau. 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.

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.

Permission to Reproduce

Credits

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

ISSN 1181-7186 (print)
ISSN 1927-8918 (online)
CATIE Ordering Centre Catalogue Number ATI-60257E
(*Aussi disponible en français, ATI-60257F*)

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

What CATIE Does

CATIE is Canada's source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life.

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.

CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

CATIE Publications

TreatmentUpdate
CATIE's flagship treatment digest on cutting-edge developments in HIV/AIDS and hepatitis C research and treatment. Subscribe to *TreatmentUpdate* and automatically receive an email notifying you the moment a new issue is available online or contact us at 1.800.263.1638 to receive a print subscription.

CATIE News
CATIE's bite-sized HIV and hepatitis C news bulletins.

HepCInfo Updates
CATIE's bi-weekly electronic newsletter highlighting key hepatitis C prevention, treatment and epidemiology information.

A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

***The Positive Side* magazine**
Holistic health information and views written by and for people living with HIV.

Fact Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

Contact CATIE

By e-mail:	info@catie.ca
On the Web:	www.catie.ca
By telephone:	416.203.7122 1.800.263.1638 (toll-free)
By fax:	416.203.8284
By social media:	www.facebook.com/CATIEInfo; www.twitter.com/CATIEInfo
By post:	505-555 Richmond Street W Box 1104 Toronto, Ontario M5V 3B1 Canada