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
- 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.

—Sean R. Hosein

REFERENCES:


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