It's the gut, stupid! Aligning the Immune Connection with Viral Infections

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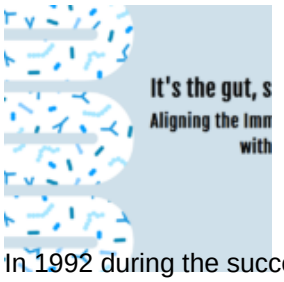

In 1992 during the successful presidential campaign of Bill Clinton, his campaign manager James Carville blurted out “it’s the economy, stupid”. As the story goes, Carville said this in a moment of frustration. The saying found its way onto a sign in Carville’s office and then instantly became part of popular culture as a symbolic rallying call for when the obvious is being overlooked in any debate. It is with that sentiment I will start this article by declaring “it’s the gut, stupid!”

Almost four decades ago the HIV virus was discovered by Luc Montagnier at the Pasteur institute in Paris in 1983 (Gallo and Montagnier., 2003). This discovery gave the world an answer to the questions of what was causing Acquired Immunodeficiency Syndrome (AIDs), which at the time was taking the lives of young men and women globally with stealth efficiency. From this discovery, it took only five years for the first antiretroviral medication to be approved by the FDA; azidothymidine (Oksendhendler., 1989). Five years may seem like a long time, but anyone who has been in drug development will tell you that is lightning speed from bench to bed side. Azidothymidine was a disease modifying treatment and its discovery ushered in a renaissance in infectious disease research. Up until this point, viral infections could be prevented with vaccinations but there were no effective acute or chronic treatments available once a deadly virus found its host.

The world continues to benefit from the breakthrough of HIV antiretroviral treatments. Now there are dozens of HIV treatments available. These discoveries helped to build a roadmap for antiviral treatments for conditions such as hepatitis C, which once was fatal for many. Death and disability as a result of HIV viral infections was no longer a certainty. In fact, the antiretroviral medications were so good that patients were said to be “cured” with non-detectable serum titers of the virus, so long as they continued the lifelong treatment. While acquiring HIV was no longer a life sentence, the need to stay on HIV medications could be viewed as such. These medications were good at maintaining a patient, but once stopped there would be fierce viral rebound.

> These Medications Were Good At Maintaining A Patient, But Once Stopped There Would Be Fierce Viral Rebound

In 1999 I was sitting in war memorial hall at the University of Guelph. Professor Krell was lecturing on virology. He said something then, that now makes a lot of sense to me “viruses are alive. They adapt, they evade, they target, and they thrive. All these characteristics are key features of a living organism”. His argument was that we underestimate this foe by reducing it to a molecular entity comprised of DNA or RNA. As he saw it, anything on this planet that could

learn and evolve in the way a virus can deserves to be looked at as a living organism. Perhaps nothing defines this resilience better than HIV's persistence in the face of potent antiretroviral medications. We now know that the virus retreats, it waits and proliferates in what many have proposed to be the largest and most dynamic immune organ, the gut.

Gut-associated lymphoid tissue (GALT) provides the HIV virus a refuge (Chun et al, 2008). It is a haven for the virus because exposure of the tissue to antiretroviral medications is minimal (Smith et al., 1992). Residual replication in this unique immune compartment can propagate the viral infection systemically leading to ongoing stealth immune derangement. A few years ago, this would have been a very controversial hypothesis. It was thought that HIV latency with compromised immune memory cells such as helper T cells were the main driver in persistent HIV infection (Miles et al., 2016). However, we now know that the GALT may be one of the most likely sources of persistent HIV replication, as it has a high number of HIV target cells (Chun et al, 2008). It is also one of the earliest sites of HIV infection. This has been established in multiple studies utilizing tissue biopsy analysis (Lapenta et al., 1999). Several studies have also shown that even with undetectable levels of the virus in serum, biopsy of GALT tissue will show a high concentration of virus (Alzahrani et al., 2019). This may be the reason for why any treatment interruptions result in an impressive rebound of the virus and symptoms.

Treatments That Focus Only On The Respiratory Or Systemic Circulation May Not Adequately Address Viral Reservoirs In The Gut

Could the lack of targeted gastrointestinal antiviral treatments have contributed to the continuation of the HIV epidemic without a cure? It is imperative that we address this question now, because HIV is not the only virus of global concern that may have benefited from this scientific oversight. The last three years have challenged the world with the COVID pandemic. There is a great deal of scientific evidence emerging on the gut-brain connection as a driver for long COVID (Leppkes et al., 2022). Public health teams are using sewer water with examination of viral particles in fecal matter as an assessment of the prevalence of COVID infection in the community (Rooney et al., 2021). If the virus is in the stool than it's in the gastrointestinal tract. Treatments that focus only on the respiratory or systemic circulation may not adequately address viral reservoirs in the gut.

I will end this article as I began it by declaring what my gastrointestinal colleagues have known all along; "it's the gut, stupid". We cannot continue to overlook this important immune organ when treating viral infectious diseases. We ignore it at our own peril and especially to the detriment of the patients we serve.

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