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How to Rouse a Sleeping Virus

Dormant reservoirs of HIV are hiding inside infected cells—and represent our biggest barrier to eradicating HIV/AIDS

BY ANNE D. HOLDEN, PHD

October 30, 2013—We've entered the fourth decade since AIDS was first recognized, and we still do not have a strategy to eliminate it. AIDS and the virus that causes it, HIV, have taken the lives of more than 35 million people worldwide. The virus has now joined a very exclusive club: only smallpox, the Spanish flu and bubonic plague have killed more people in the history of our species.

That is not to say we haven't made extraordinary progress. With 30 anti-HIV drugs on the market, each targets a specific step in the HIV lifecycle. When taking these so-called *antiretroviral* (ARV) drugs in combination, a patient's viral load can drop to almost undetectable levels—effectively downgrading HIV from a death sentence to a chronic disease.

But a strategy focused solely on ARV treatments is a losing one, particularly in Africa. Of the more than [34 million people](#) worldwide infected with HIV, nearly 70% of them live in sub-Saharan Africa. Many in this region and in other parts of the developing world have limited access to expensive ARVs. Recent estimates are that for every 10 people in the developing world who *do* receive ARVs, 16 new people become infected.

Perhaps even more troubling, however, is that even the best ARVs cannot eliminate HIV completely; a small percentage hides inside the host, beyond the reach of even the most potent drugs.

In the latest issue of the journal [Cell](#), the Gladstone Institutes' [Warner C. Greene, MD, PhD](#), describes how the problem of dormant, or "latent," HIV is perhaps the biggest barrier to finding a cure—and what steps researchers must take if they are to break down that barrier and lay the foundation of a world without AIDS.

Sleeper Cell

The human body's immune system, led by a class of white blood cells called CD4 T cells, is adept at defending against foreign invaders, such as bacteria, viruses or other pathogens. But these cells are also HIV's primary targets. And in a cruel evolutionary twist, what makes these cells so effective at fighting pathogens is also what makes them ideally suited to housing dormant HIV.

When HIV first infects CD4 T cells, it inserts its viral genome into the DNA of the host cell. And then, one of two things happens: 1) the virus directs the host cell to produce, or

“transcribe” more virus, which eventually kills the cell, or 2) it goes into a holding pattern, entering a long-lived latent state within the cell.

Without treatment to halt production of the virus, the HIV patient’s T cells will die at a faster rate. Multiple mechanisms promote the loss of these CD4 T cells. Eventually they are so low that the disease progresses to AIDS. And usually just a few years after that, the severely weakened patient succumbs to opportunistic infection and dies.

But the development of ARVs has been a game changer.

“We initially predicted that just two to three years of ARVs was adequate to eliminate the virus,” explained Dr. Greene, who directs virology and immunology research at Gladstone. “But we soon found that within just *a few weeks* of stopping treatment, the latent HIV reservoir wakes up. The cycle in infection begins all over again.”

Purging the Reservoir

One of major challenges towards an HIV cure is that latency’s underlying mechanisms, of which there are likely many, remain shrouded in mystery. In particular, researchers have sought to understand precisely what triggers the latent virus to “wake up” and infect new cells.

“If we understood precisely how the latent virus is activated, we could then explore ways to artificially induce the process,” said the review paper’s lead author Debbie Ruelas, a University of California, San Francisco, graduate student and member of the [Greene laboratory](#). “With the latent virus then active, we could then administer ARVs that target it for destruction. Scientists have taken to calling this the ‘shock-and-kill’ approach.”

There are multiple families of proteins that likely play a role in latent HIV activation, such as the protein Tat, which regulates HIV transcription. A few years ago, Gladstone virologist [Melanie Ott, MD, PhD](#), and her colleagues revealed that modifying Tat at particular locations could induce HIV transcription. Recently, researchers found that Tat also likely plays a role in regulating HIV latency. If scientists could artificially induce Tat, thereby activating latent HIV, they could theoretically employ ARVs to flush out the newly activated virus.

And just [today](#), Dr. Greene and Gladstone Postdoctoral Fellow Jonathan Chan, PhD, announced their discovery of a set of molecular signals that together can awaken latent HIV. In cells taken from HIV patients and cultured in a dish, the researchers stimulated the calcium/calcieneurin-signaling pathway to activate a complex of proteins called NF-κB. This would then induce HIV transcription from latently infected cells. However, they found that the success of this activation also depended on a compound called prostratin.

[Prostratin](#), a naturally occurring compound that is extracted from the Samoan mamala tree, helps to activate latent HIV, while at the same time preserving the health of the infected CD4 T cells. But prostratin is difficult to procure and, as of right now, impossible to synthesize on an industrial scale. But the experiments performed by Drs. Greene and Chan suggest a potential workaround.

“When we stimulated the calcium/calcineurin pathway in the presence of low levels of prostratin, we in turn boosted prostratin’s effectiveness,” explained Dr. Chan. “Our findings, while preliminary, hold promise that we could develop a way to purge the latent HIV reservoir.”

These results, and many more, hold much hope; however, there have been setbacks. For example, new research from [Johns Hopkins University](#) reveals purging the entire latent reservoir more difficult than previously estimated (see Sidebar). Nevertheless, this strategy represents a promising way of flushing out the majority of the remaining virus and thus providing a “functional” cure to HIV/AIDS.

Hope for a Cure

There have been several unique cases of patients with HIV being cured, including Timothy Brown (the so-called “[Berlin Patient](#)”) and the [baby girl](#) from Mississippi infected with HIV who received ARVs within 31 hours of birth and remains free of any detectable viral load even after stopping treatment. While these cases are unique and not scalable on a worldwide, they could also yield new understanding of HIV latency.

Ruelas, Dr. Greene and many others believe that defeating HIV/AIDS should focus on developing solutions to HIV latency that are workable in the developing world—especially in Africa, where most new infections occur. The recent discoveries outlined above are promising, and with continued efforts by scientists at Gladstone and around the world, Dr. Greene is cautiously optimistic.

“This war between humans and HIV has been long and slow—and fraught with victories and losses on both sides,” continued Dr. Greene. “We’ve come a long way in last few decades towards defeating this devious virus. As we continue to focus on HIV latency and the developing world, I firmly believe that not only can we develop a functional cure—we will.”