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HIV/AIDS Research at Gladstone: It's Time for a Cure

As the pandemic continues, Gladstone scientists are laser-focused on curing HIV/AIDS.

BY WARNER C. GREENE, MD, PHD

One of the biggest misconceptions about HIV/AIDS today is that fight is over. Nothing could be further from the truth—or more detrimental to our work to stop one of the greatest plagues in recorded history.

Since 1981, HIV/AIDS has killed approximately 35 million people. New HIV infections among young gay and bisexual men in the United States, meanwhile, increased a full 22% from 2007 to 2010, as the global number of people living with HIV in 2011 rose nearly 16% from a decade earlier to 34 million. And in 2011 alone, the world logged 2.5 million new HIV infections and 1.7 million AIDS-related deaths.

While antiretroviral medications (ARVs) have saved millions of lives, they do not *cure* HIV/AIDS. HIV often still lingers in a *latent* or dormant state in the cells of those taking ARVs—many of whom suffer prematurely from diseases associated with aging. Plus while nearly 10 million are being treated, more than 16 million HIV-infected adults and children around the world who need treatment are not getting ARVs—most of these individuals live in Sub-Saharan Africa. And finally, because ARVs have worked so well, many have dropped their guard—they carry HIV but don't get tested. So they don't take the medications they need, and may even be spreading the virus further.

We have gone very far, very fast to stop HIV/AIDS. But our work is by no means done. At Gladstone, we are taking a multi-pronged approach to find new preventions, treatments and a cure for HIV/AIDS.

Preventing HIV/AIDS

At a research institute focused on basic science, all of our HIV/AIDS work is predicated on a thorough understanding of the virus' basic biology. Some of our scientists, such as [JJ Miranda, PhD](#), and [Nevan Krogan, PhD](#), have made seminal contributions to the understanding how HIV and other viruses turn on and off their genes.

In applying what we know to help patients, Gladstone Investigator [Robert Grant, MD, MPH](#), recently played a critical role in securing FDA's approval for [the first preventative drug](#) to curb the spread of HIV/AIDS. Dr. Grant directed the international [iPrEx study](#) a few years earlier that led to Truvada's 2012 approval. Meanwhile, Gladstone Postdoctoral Fellow Nadia Roan, PhD, and I—together with Drs. Jan Munch and Frank Kirchoff in Germany—[discovered](#) that protein fragments in semen enhance HIV's ability to infect cells. We're now investigating ways to reduce the levels of these HIV-enhancers with an effective microbicide for use by women.

While we don't have an HIV/AIDS vaccine yet, Gladstone Investigator [Leor Weinberger, PhD](#), is testing something that might be more effective. He wants to use therapeutic interfering particles, or TIPs, to outsmart the virus. To create TIPs, Dr. Weinberger uses genetic engineering to eviscerate HIV's damaging payload—while retaining its viral characteristics of contagion and mutation. As a result, he expects TIPs to replicate more efficiently than HIV—thereby stealing the resources the virus needs and preventing HIV from destroying the human immune system. His mathematical models indicate that TIPs could be far more effective in ending the HIV/AIDS pandemic than a vaccine.

Gladstone immunologist [Shomyseh Sanjabi, PhD](#), meanwhile, is building on the Nobel-prize-winning stem cell discoveries of Gladstone's Shinya Yamanaka, MD, PhD, to genetically engineer laboratory animals to have human immune systems. In collaboration with researchers at Yale, Dr. Sanjabi's development of "humanized" mice gives Gladstone an exclusive opportunity to study why some HIV-positive people never develop AIDS—without help from medications. This knowledge could help us mimic these individuals' protective response in a new therapy to prevent AIDS.

Moving Towards Better Treatment—and a Cure

In [Gladstone's Center for HIV & Aging](#), [Eric Verdin, MD](#), is leading our work to determine exactly how HIV promotes the premature onset of conditions such as cardiovascular disease, dementia and liver disease—and what can be done to arrest the process. HIV-induced chronic inflammation may be to blame, and/or the HIV medications themselves. Our research holds the promise of a greater "healthspan" for those with HIV—and could ultimately contribute to an HIV/AIDS cure.

In my own laboratory, Gladstone Staff Research Investigator [Gilad Doitsh, PhD](#), and I are building on our [2010 research](#), which showed that most "bystander" immune cells—once thought to be uninfected by HIV—are actually abortively infected with HIV. This failed attempt at infection drives an innate immune response against the virus and promotes *pyroptosis*—a fiery and highly inflammatory form of cellular suicide. This, in turn, attracts more CD4 T cells, a type of immune cell that HIV can attack, for new rounds of abortive infection and death. This sets up a vicious cycle that underlies CD4 T-cell depletion and the development of AIDS.

Our recent tests suggest that existing anti-inflammatory drugs may be able to circumvent this fiery cell death and thereby prevent HIV from progressing to AIDS—meaning a life-saving solution for the millions without current access to ARVs. Controlling inflammation may also lead to new way to stop the premature onset of aging-related diseases. If successful, this work could also lead to a functional cure—in which HIV does not progress to AIDS, even when ARVs are discontinued.

And Gladstone Investigator [Melanie Ott, MD, PhD](#), Dr. Verdin and I are all working to solve the problem of HIV [latency](#), finally making it possible to cure HIV-infected patients.

We are also investigating if HIV-induced inflammation expands the body's reservoir of latent HIV. If it does, the same anti-inflammatories may be key to clearing the latent virus.

For the 34 million people infected with HIV around the world—and the millions more who will become infected this year and the next and the next—there is no time to lose. At Gladstone, we think it's time to end the HIV/AIDS pandemic, once and for all.