# Elusive secret of HIV long-term immunity

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Scientists have discovered a critical new clue about why some people are able to control the HIV virus long term without taking antiviral drugs. The finding may be useful in shortening drug treatment for everyone else with HIV.

These rare individuals who do not require medicine have an extra helping of a certain type of immune protein that blocks HIV from spreading within the body by turning it into an impotent wimp, Northwestern Medicine® scientists report. The new finding comes from analyzing cells from these rare individuals and HIV in the lab.

Scientists have been trying to solve the mystery of why 1 percent of people with HIV—called "controllers"—have enduring control of the virus without medications, in some cases for life. The controllers' early defense against HIV is quickly extinguished by the virus, so how do they have long-term immunity? The Northwestern discovery represents what scientists have long sought: a second line of defense deep in the immune system backing up the short-lived early defense.

This discovery suggests a novel approach involving much earlier treatment that could potentially make every HIV-infected person into a controller for the long term by protecting the reserves of this defensive immune protein. The goal would be for them to eventually be free from anti-retroviral drugs.

Currently most HIV patients need to take powerful anti-retroviral drugs every single day for life. If the medicines are stopped, the virus quickly

reactivates to harmful levels even after years of treatment.

"Preserving and even increasing this defense in cells may make more HIV-infected persons into controllers and prevent HIV from rebounding to high and damaging levels when anti-HIV medications are stopped," said Richard D'Aquila, M.D., the director of the Northwestern HIV Translational Research Center. He is the senior author of the study, which will be published Oct. 16 in the journal *PLOS ONE*.

D'Aquila also is the Howard Taylor Ricketts Professor of Medicine at Northwestern University Feinberg School of Medicine and a physician at Northwestern Memorial Hospital.

D'Aquila and colleagues now are working to develop a medicine that would boost this defensive immune protein called APOBEC3G, or A3 for short.

## The Missing Second Defensive Line

Much is known about how the immune system of controllers initially fights the virus. But HIV quickly escapes from that first line of defense by mutating and evading the adaptive immune system. How these individuals control HIV long term without medications to keep from developing AIDS has been under study by many researchers. It seemed there must be a second defensive line in the immune system.

## Turning HIV Into a Wimp

In the new study, D'Aquila and his team have found that controllers, long after they have acquired HIV, have a more abundant supply of the critical immune protein A3 in specific white blood cells called resting memory T cells. This is where the virus lies silently in an inactive form

and roars back when anti-retroviral drugs are stopped. In controllers, though, their bounty of A3 means that any new HIV made from those cells inherits a helping of A3, which turns the new viruses into harmless wimps that can't infect other cells.

## You Can't Fool A3

The feisty A3 is a critical part of the newly characterized intrinsic immune system, and it resides in many cells of the immune system including resting T cells. Unlike the adaptive immune system, which fails to recognize the virus once it mutates its pieces, the intrinsic immune system can't be fooled.

"The intrinsic immune system recognizes the basic guts of the virus—the nucleic acids—that HIV can't change and then damages those nucleic acids," D'Aquila said.

D'Aquila theorizes that the controllers' first line of defense slows down the ability of HIV to destroy all the A3.

"Perhaps starting anti-HIV drugs very soon after HIV is caught, rather than the current practice of waiting until later to start, would work like the controllers' first line of defense," D'Aquila suggested. "If we preserve A3, it could minimize HIV's spread through the body as this protein seems to do in controllers."

Otherwise, D'Aquila theorizes, all reserves of the protein are wiped out if HIV replicates unchecked for several months.

## Babies and Other Controllers

D'Aquila pointed to several recent examples of early treatment

sometimes resulting in lasting control of HIV in humans that are consistent with this theory.

In January 2013, a baby was born to an HIV-positive woman in Memphis who didn't take preventive medicines that are routinely given to these women. The baby got infected, and doctors began anti-HIV drug treatment within 36 hours of birth. After some treatment, the baby is now off anti-HIV medicines and appears to be cured of HIV.

Two studies published earlier this year show the protective effect of starting the medicines within three to four months after infection for a relatively short course, resulting in a lower level of HIV in the blood and better control of the virus for some who stopped the anti-retroviral medication.

A group of patients in a European study were started on anti-HIV drugs very early after infection. Their medications were stopped after three years but some continued to have a suppressed virus at such low levels it did not cause any damage.

## Earlier Detection Just Got Easier

"Early-as-possible detection—much easier with our new technology—and early drug treatment will be the future of HIV therapy," D'Aquila said. He added that the Affordable Care Act mandates that insurance companies pay for routine HIV testing, which they did not always cover in the past.

## D'Aquila Helped Developed Personalized Approach to HIV Medicine

D'Aquila is a leading HIV scientist who began investigating AIDS in

1982, the first year it was identified. He was a senior resident in Philadelphia when the early cases appeared at the hospital where he was working. D'Aquila began investigating, calling other area hospitals to see if they had seen similar cases. He discovered there were lots of them. The same month, Morbidity and Mortality Weekly Report sounded the first alarm that a new disease had erupted.

Over the last 30 years, D'Aquila has helped develop anti-HIV medicines and resistance testing for HIV—the latter is the first widely used clinical application of DNA sequencing in personalized medicine. Since the 1990s, HIV patients have their virus sequenced to determine which medicines are going to work best for them at that time—a result of research done by D'Aquila and others.

D'Aquila was also a leader and virologist for many NIH-supported clinical trials in the AIDS Clinical Trials Group. His laboratory studies were also among the first to characterize effects of resistance mutations on HIV's replicative fitness and to show that resistant virus persisted in HIV's latent reservoir.

The new study was done in collaboration with MariaPia De Pasquale and Yordanka Kourteva, formerly at Vanderbilt University School of Medicine, where D'Aquila did the experiments.

**More information:** dx.plos.org/10.1371/journal.pone.0076002

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