A rare group of HIV-positive individuals need no medicine to keep the virus in check. Their good fortune could point the way to more powerful treatments—and perhaps a vaccine

By Bruce D. Walker
Photographs by Richard Renaldi

UNIQUE STATUS: The genetic makeup of the individuals shown here has allowed them to fight the virus to a standstill without needing combination anti-HIV therapy. Scott Wafrock (top left) has lived with HIV for 26 years, Bob Massie (top right) for 34 years and Loreen Willenberg (bottom right) for 20 years. Doug Robinson (bottom left) learned he was HIV-positive in 2003.
One day in early 1995 a man named Bob Massie walked into my office at the outpatient clinic of Massachusetts General Hospital in Boston. Massie told me he had been infected with HIV—the virus that causes AIDS—for 16 years and yet had never shown any symptoms. My physical examination confirmed he was healthy, in stark contrast to all other patients I saw that day. At that time, a new combination of drugs was being tested that would eventually slow the progressive decline in immune function that HIV caused. In 1995, however, most people who had been infected with HIV for a decade or more had already progressed to AIDS—the stage marked by the inability to fight off other pathogens. The young man standing before me had never taken anti-HIV medication and strongly believed that if I learned the secret to his good fortune, the information could help others to survive what was then generally thought to be a uniformly fatal disease.

Massie was born with hemophilia, a blood-clotting disorder. In those days, nearly all hemophiliacs were HIV-positive because they were infused repeatedly with blood products agglomerated from thousands of donors—none of whom were screened for HIV until the mid- to late 1980s. (Today hemophiliacs receive artificial clotting factors, which pose no risk of HIV contamination.) Some of Massie's blood samples that had been stored for a study revealed that he had contracted HIV in 1978. Yet every test I conducted on him or his stored samples showed that the amount of virus in his blood was vanishingly small and that his immune responses seemed as strong as ever.

I was stunned. This was the first time I had ever come face to face with a patient whose body appeared to be controlling HIV on its own and had been doing so for a decade and a half. Massie, as it turned out, was not alone. Investigators in California, Maryland, Italy and France had all come across similarly unusual individuals in the early 1990s and were studying them intently. We eventually determined that these extraordinary people divided into two main groups: one set of “long-term nonprogressors,” whose bodies were able to fight off an HIV infection for an extra long time but who ultimately became ill, and a much smaller group of even more astonishing “elite HIV controllers,” who, like Massie, simply did not develop AIDS year after year after year despite never having taken any anti-HIV medication.

Somehow the elite controllers maintain extremely low—or even undetectable—levels of virus in their blood. If scientists can

**IN BRIEF**

One out of 300 people infected with HIV are naturally able to control the virus without having to take antiviral medications. **Investigators believe** the key to the good fortune of such elite controllers lies in the complex workings of their immune system. **Genetic studies** reveal the precise reasons why the targeting and destruction of HIV-infected cells occur more quickly in the body of an elite controller. **Understanding** this efficient, powerful immune response in greater detail might one day lead to better methods for preventing and treating AIDS.

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figure out how these rarest of rare individuals can pull off such a feat, they may learn how to create an effective vaccine or develop therapies that strengthen a patient’s immune system, as opposed to just attacking the virus with drugs.

Such an accomplishment would come not a moment too soon. Currently about 33 million people are living with HIV worldwide. More than six million of them have access to anti-HIV medication, but these drugs are unable to cure HIV infection, and they must be taken for life. The likelihood is slim that drug treatment can be supplied to everyone who needs it for as long as they need it. We desperately require a solution to prevent infection in those who are not yet infected and to prevent disease from developing in those who are.

After two decades of studying elite controllers like Massie, my colleagues and I are more persuaded than ever that research into their unique biochemical makeup offers phenomenal insights for the prevention and treatment of AIDS. This scientific journey has broad implications for the ultimate ability to harness the human immune system to combat a myriad of other human infectious diseases and perhaps even some cancers.

**NOT ENOUGH GENERALS**

To understand how unusual Massie and other elite HIV controllers are and why their story offers hope for conquering AIDS and other diseases, it helps to first understand how HIV attacks the body and how the body tries to defend itself. In the past 30 years researchers have learned that the immune systems of most people infected with HIV—not just elite controllers—fight back very hard against the initial infection, producing lots of antibodies against the virus. Unfortunately, the antibodies are not effective, which is why the infection persists—even in elite controllers. The exact mechanisms of control without good antibodies are rather convoluted and at times mysterious. Yet in essence, two different immune cells—known as helper T (or CD4+) cells and killer T (or CD8+) cells—and molecules known as human leukocyte antigen (HLA) receptors—seem to play the most important roles.

As a virus, HIV is unable to reproduce on its own. When it infects cells, it takes over their machinery and instructs them to make new viruses instead of performing their usual cellular functions. These infected cells, however, contain an early-warning system to alert the body to the invaders. In the earliest hours of a viral invasion, the infected cells ferry pieces of the viral proteins that they are being forced to manufacture up to their surface. Here these bits and pieces of foreign material are displayed by HLA receptors. The presence of viral proteins attached to the HLA molecules of these cells quickly attracts the attention of the immune system, programming the helper T cells to mobilize a group of killer T cells that are then specifically primed to destroy HIV-infected cells. The now activated helper T cells also gradually trigger the production, by yet other immune cells, of antibody molecules that latch on to specific components of the viruses being released from infected cells in a separate, though futile, attempt to eliminate the invaders.

This defensive effort works pretty well for most viral infections. Yet HIV performs an unusual trick that ultimately defeats the immune system: the virus preferentially targets helper T cells for infection, including those that are specifically primed to help defend against it. This particular act of viral sabotage leads directly or indirectly to the eventual destruction of most of the available helper T cells. If one thinks of helper T cells as the generals of the immune system and of killer T cells as the foot soldiers, then HIV takes laserlike aim at the generals, disrupting their ability to give the foot soldiers effective orders on how to proceed. In the simplest sense, HIV is an infection of the immune system, and the results are predictable: the ultimate inability of the body to defend itself, not just against HIV but against hundreds of other invaders as well.

When Bob Massie showed up in my office in the mid-1990s, my laboratory was focused on the role of the killer T cells in fighting HIV. If Massie’s immune system were really controlling HIV, we surmised, he would have to have mounted an unusually strong killer T cell response. We enrolled him in a study we were conducting and quickly discovered that he had the strongest HIV-specific killer T cell response we had ever encountered. In other words, his immune system produced a large infantry specifically trained to recognize HIV. This result fit with our hypothesis, but other HIV-positive men and women also sometimes had strong killer T cell responses, and yet they went on to develop AIDS, as if the infantry could be present in large numbers but could not fight effectively.

This observation, in turn, led to a second hypothesis. Maybe Massie’s killer T cells were particularly effective because they had received the appropriate directions from especially effective helper T cells. In other words, both his generals (helper T cells) and his infantry (killer T cells) were strikingly well trained.

As it happens, the first project I undertook when I began my research career in the mid-1980s examined the specific steps by which helper T cells coordinated the immune response against HIV. My colleagues and I studied blood samples from dozens of AIDS patients to look for evidence that helper T cells were orchestrating a counterattack. We found nothing, however—even

Of the 1.3 million DNA measurements made per patient in a study aiming to explain astonishingly good HIV control in some of them,

- 300 genetic variables were significantly different in the elite HIV controllers.
- Further testing narrowed the focus to four independent DNA snippets.
- Final analysis led to variations in one key protein that preserve immune control of HIV.
Plugging a Gap in the Body’s Defenses

Unlike most people infected with HIV (top panel), a few rare individuals (bottom panel) can limit the amount of virus in their body to low or undetectable levels because their immune system is exquisitely equipped to recognize and destroy infected cells.

More Questions

As with many discoveries in science, our finding that an effective killer T cell response against HIV required a robust cadre of helper T cells generated lots of new questions and hypotheses. Had Massie actually cleared the virus from his body? The answer was no, because we could detect viral genetic material in his blood. [To learn why some people, unlike Massie, are actually immune to HIV, see “Blocking HIV’s Attack,” by Carl June and Bruce Levine; SCIENTIFIC AMERICAN, March.] Could Massie still be infectious to others? We did not know but had to assume he was—an important issue for him and his wife (they eventually had a daughter). Was his immune system somehow supercharged, able to fight off all invaders? The answer here, sadly, was no, because he also suffered from hepatitis C virus infection—another result of contaminated treatments for hemophilia—and his body was completely unable to control that virus. (Massie later received a liver transplant, which cured both his hepatitis and—because the new liver could make the necessary clotting factor—his hemophilia.)

We considered the possibility that every infected person actually did produce HIV-specific helper T cells but that these highly trained generals were targeted and killed in the earliest stages after the initial invasion. If that were the case, then hitting the virus early and hard with a new drug cocktail that could completely inhibit viral production should protect the helper T cells of newly exposed individuals. Such a powerful first strike would allow the immune system to quickly gain the upper hand over the virus and maintain that control as effectively as Bob’s body did naturally. We performed clinical trials with a few dozen volunteers and showed that early treatment rapidly brought the amount of HIV in the blood to undetectable levels and, within a few weeks, allowed a massive scale-up in the production of helper T cells able to direct the killer T cells to combat HIV. In other words, nearly everyone’s immune system was capable of producing highly trained generals (the HIV-specific helper T cells), but they were eliminated almost as soon as they were produced.

Unfortunately, the newfound protection did not produce the kind of durable immune control we were seeing in Massie. As part of a follow-up clinical trial, we stopped treatment in a handful of patients (with their informed consent and after re-
Killer T cell
Helper T cells become activated and recruit killer T cells (CD8+ cells), instructing them to destroy any cell that makes HIV proteins.

Like the immune cells in infected cells, infected cells display bits of HIV protein on their surface. Unfortunately, in most HIV-positive people, the killer T cells are relatively inefficient at recognizing the HLA–viral protein combination, allowing many infected cells to continue making viruses.

In addition, HIV preferentially infects helper T cells. After years of infection, as more and more helper T cells disappear, killer T cells become clueless about how and what to attack.

Elite controllers have a slight variation in their HLA molecules that enables infected cells to be more easily recognized and targeted for destruction by killer T cells.

Most helper T cells are spared infection, which allows them to help the killer T cells to more efficiently find and destroy infected cells. This combined effort keeps the viral level in the body low.
ceivng permission from an ethical review board). As our study subjects stayed off therapy for a year or more, most of them experienced a gradual rise in the level of virus in their blood, so that the HIV drug cocktail had to be restarted. Nevertheless, the results, which were published in Nature in 2000, showed that it was possible to enhance, at least temporarily, the body’s control of HIV. Furthermore, the same mechanisms that allowed Massie to control his infection could be made to work in other people.

How could we make this new level of immune control more durable, more like that of the elite controllers? Up until this point, we had been looking at immune responses—helper and killer T cells—that we already knew how to measure. We needed to go deeper into the workings of the immune system to learn, once and for all, what was different about elite controllers that protected them against the ravages of HIV.

A NEW APPROACH

DIGGING DEEPER into the basis for HIV control was made possible by a series of lucky encounters. Around this time, I was invited to a dinner hosted by Lawrence Summers, then president of Harvard University, to discuss the school’s expanding mission in global health. Also attending the dinner was Eric Lander, a former classmate of Massie’s at Princeton University and an expert in applying the latest advances in human genetics to medical research. I had never before met Lander—the leader of the then newly established Broad Institute, a joint endeavor of Harvard and the Massachusetts Institute of Technology—but had long wanted to because it seemed that his new technology might provide insights into the HIV problem.

Our mutual acquaintance with Massie was the starting point for an extended conversation that night on the sidewalk outside Summers’s house. Lander explained that it was possible to compare the DNA of different people—specifically using natural variations in the A, T, C, G letters of the DNA code called SNPs (for single-nucleotide polymorphisms)—to try to identify genetic influences on an individual’s responses to a disease. The SNPs would function as pointers—or markers—for sections of the genome of elite controllers like Massie that allowed them to keep damage from HIV infection to a minimum. If we could find a unique pattern of SNPs that was associated with control, the pattern might help us locate the genes that were responsible, if they existed. To do these studies, we would need to obtain a swab of saliva or a blood sample from elite controllers and HIV-positive patients who had progressed to AIDS and then extract some DNA from those samples. At a minimum, we would need to sort through about one million SNPs for each of perhaps 1,000 elite controllers and about twice as many AIDS patients to get an adequate statistical sample.

Obtaining DNA from large numbers of people with AIDS was certainly not a problem. The issue that seemed insurmountable was finding large numbers of elite controllers. By this time we and other researchers around the world knew of a handful of such unusual people, but the idea of finding 1,000 elite HIV controllers was more than daunting.

At about the same time, I was invited to give a lecture in New York City to a group of 300 health care providers who had large HIV practices. My assigned task was to update these clinicians on what we knew about how HIV causes AIDS. During my talk, I happened to mention the case of Massie—someone who at that time had been infected for nearly a quarter of a century, who had never been treated, who still had a normal helper T cell count and undetectable amounts of virus in his blood. (At that point, testing for HIV had become much more sensitive, detecting as few as 50 copies of the virus per milliliter of blood. And Massie was always below this number.) On a whim, I asked for a show of hands as to whether any of the physicians or nurses in the audience had ever seen such a case.

I must have audibly gasped when more than half of the people in the room raised their hands. Here was the answer to our problem of finding 1,000 elite HIV controllers! Through the health care providers in this auditorium alone, we could potentially reach 200 of these unusual individuals. If we could go directly to physicians and nurses in private practice across the country and ask them to refer their HIV controllers to us, we believed we could easily reach the number necessary to perform a statistically significant search to determine whether specific genetic variants existed that either boosted or impaired the immune system’s ability to fight HIV to a permanent standstill.

Massachusetts General Hospital (MGH) gave us the institutional approval to proceed with such a study. We quickly hit another roadblock, however. Our requests for funding from numerous agencies and organizations went nowhere. They seemed to think our goals were too vague because we did not know what we were looking for and the odds of success seemed minuscule.

As we were struggling with this disappointing stall, Mark Schwartz, a former chairman of Goldman Sachs (Asia), invited me to breakfast with him at a hotel in New York City. Schwartz and his wife, Lisa, had begun to fund some of MGH’s and Harvard’s efforts to train scientists and clinicians in Africa to help tackle the AIDS crisis. During our meeting, Schwartz asked me what else I was working on. While answering, I expressed my frustration over the elite controller project and noted that I saw it as holding key information to guide our path forward. Schwartz immediately perked up when I explained the logic for the study. Why didn’t he and his wife fund it, he asked. To my amazement, by the time we parted the Schwartzs had made a commitment of $2.5 million over the next five years to launch our study of elite HIV controllers. The funds would be spent to recruit patients from across the country, and we would point to their successful enrollment to convince other funders to pay for the genetic analyses.

We immediately began the study, contacting all the major HIV doctors and nurses across the U.S. and eventually collecting DNA samples from patients in Europe, Asia, Australia and South America. We tried to include elite controllers from Africa but had trouble finding them because viral testing of blood was not routinely performed in many African countries at that time. Florencia Pereyra, a physician-scientist at Harvard Medical School, organized the colossal recruitment effort with the aid of at first one, then two and, later, three assistants. The Bill & Melinda Gates Foundation provided us with a five-year grant for $20 million to complete the studies.

It took almost as long to process and analyze the data as to collect the specimens. For each of the 974 elite controllers and 2,648 progressors in our study, we measured about 1.3 million SNPs in their DNA with an automated chip system. We relied on massive computing services at the Broad Institute to make comparisons between the two groups’ SNPs. Paul DeBakker, who...
is a geneticist at the institute, led the computational analysis.

By 2009 we had an initial answer. Of the three billion nucleotides in the human genome, there were 300 SNPs that were significantly different in elite controllers compared with people who were much more susceptible to developing AIDS. Further analysis whittled these 300 SNPs down to a mere four that were independently highly correlated with control of the infection. All four lay within chromosome 6, which is known to contain many genes that affect immune function. But we still did not know which gene, or genes, was important and why.

At least we now knew where to look. Next we needed to determine the complete genetic sequence of the region of chromosome 6 that our SNPs told us was important. Although we did not have funding to do this additional detailed sequencing, a remarkable medical student, Xiaoming “Sherman” Jia, solved the problem for us. Using massive data sets from other large genetic studies, he was able to develop a computer algorithm that, based on the combination of SNPs in each person, accurately inferred the sequence of DNA nucleotides, or code letters, for this particular stretch of the chromosome and, in turn, the sequence of amino acids in a protein encoded by the DNA in that region.

Like going to higher power on a microscope, Sherman’s analysis suddenly brought the picture into crisp view. The major genetic difference between elite HIV controllers and progressors came down to a change in amino acids that affected the shape in a groove of the HLA receptors that sat on the surface of infected cells. This particular groove held the bits of HIV proteins that are displayed by the HLA receptor. Something about this shape made the HLA-HIV combination on infected cells in elite controllers extraordinarily good for being seen by killer T cells, which then destroyed the infected cell. It is as if a factory worker, wanting to notify the outside community that the plant has been taken over by terrorists who are making bombs, paints his hand and a piece of the bomb bright orange and then waves them out the window for passersby to see. His action helps the authorities notice that something bad is happening, so they can come in and take care of the threat.

Here, at last, was another missing piece of the puzzle and the reason why Massie and other elite controllers are still healthy after all these years. From the earliest days of their infection, their immune systems maintain a critical number of healthy HIV-specific helper T cells, which provide vital instructions to the newly activated killer T cells. These foot soldiers of the immune system, in turn, are able to effectively find and destroy HIV-infected cells because the HLA molecules on the surfaces of those doomed cells are genetically endowed to advertise the presence of the invader to killer T cells better than the HLA molecules of the vast majority of people.

As a consequence, by keeping viral levels low, these highly efficient killer T cells protect the remaining helper T cells from infection. The foot soldiers guard the generals, allowing the immune system to fight the virus to a standstill. Our long-shot genetic approach—which began with no clear hypothesis and depended on the collaboration of more than 300 investigators around the world—revealed that the major genetic basis for durable control of HIV infection came down to the characteristics of a single protein, the HLA molecule.

Once again, the findings, which were published in *Science* in 2010, have raised new questions. We need to figure out how to re-create the elite controllers’ immune response in most infected people. In addition, we are beginning to understand just what it takes to fine-tune the body’s defenses against specific illnesses, starting with the need to boost the appropriate actions by helper and killer T cells. [To learn more about T cell therapy in cancer, see “A New Ally against Cancer,” by Eric von Hofe; *Scientific American*, October 2011.]

The immune system has long been a powerful if imperfect partner in the fight against disease. We still have much to learn, but soon, we hope, we will be able to help it fill in the gaps.

**MORE TO EXPLORE**


**SCIENTIFIC AMERICAN ONLINE**

Walker talks about the seesaw struggle of HIV and the immune system at ScientificAmerican.com/jul2012/elite-hiv-controllers