# Learning lessons from an HIV cure

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For doctors confronting the AIDS epidemic, past ambitions always boiled down to two main goals: prevention, or finding ways to protect people not yet exposed to HIV, through vaccines, safe sex education or other means; and treatment, or discovering effective drugs and providing them to people with HIV/AIDS, helping them live longer.

Now, thanks primarily to one test case, many doctors are beginning to think about a new possibility: finding a *cure*.

This case involved an American living in Germany, Timothy Brown, known popularly as the "Berlin patient," whose infection appears to have been eradicated after two carefully planned bone marrow stem cell transplants in 2007 and 2008.

"There's no evidence of HIV in my body after three years, even though dozens of tests have been done to look for it," said Brown, now a San Francisco Bay area resident and a patient at UCSF and San Francisco General Hospital (SFGH). To this day, Brown is believed to be the only person ever cured of HIV.

While experts agree that the procedure used to cure Brown is not generally applicable to the tens of millions living with HIV worldwide, his story has changed the thinking of many scientists at the forefront of HIV/AIDS research.

Several UCSF-affiliated researchers interviewed for this story pointed to Brown's experience as a seminal shift, giving them renewed hope for the

possibility of developing a cure.

## A Surprising New Hope

Halfway down a long corridor at UCSF Medical Center, Jay Levy, MD, a professor in UCSF's Department of Medicine, and his colleagues in the Laboratory for Tumor and AIDS Virus Research, co-discovered HIV as the cause for AIDS in 1983.

Twenty-five years later, the news of the successful cure came as a surprise even to him. "I felt that a cure was not possible," said Levy. "But the Berlin patient made me reevaluate that conclusion."

Levy was not the only one inspired by Brown's story. According to UCSF immunologist Mike McCune, MD, PhD, the case has galvanized many researchers to think about how to extend, improve and repeat the achievement.

Even researchers already working on cure research have been influenced. Brown's case is a vindication of their work – even if their approaches are fundamentally different.

For instance, scientists at the UCSF-affiliated Gladstone Institute of Virology and Immunology (GIVI) have begun to consider something short of a complete cure: the wholesale eradication of the virus from all tissues in the body. That would be a "functional cure," where the virus is knocked down enough and the immune system enhanced to the point where the virus stays permanently in check.

"A functional cure might be a more reasonable goal," said Warner C. Greene, MD, PhD, a UCSF professor and director of the GIVI.

"If you were to do this successfully, you might be able to remove therapy

altogether," said Eric Verdin, MD, a senior investigator at GIVI and a professor of medicine at UCSF.

At the same time, Greene warned, any eventual cures or functional cures could only realize the dream of ending the AIDS epidemic if they worked in the places hardest hit by the virus – regions like sub-Saharan Africa, home to about two-thirds of all people living with HIV/AIDS.

"We have to be constructing a therapy that is usable throughout the world," said Greene, who also is the Nick and Sue Hellmann Distinguished Professor of Translational Medicine.

## Failed Cures of the Past

For Steven Deeks, MD, a professor of medicine at UCSF and a clinician in the Positive Health Program at the UCSF-affiliated SFGH, the Berlin patient case raised as many questions as it answered.

What subtle biological processes were in play, and more importantly, how does this one case illuminate an expanded approach to curing HIV? Deeks and his team have now enrolled Brown in a series of ongoing UCSF-based studies and are overseeing a group of collaborators in the hope of addressing these and other questions.

In the last three years, Deeks has pondered these questions again and again. It was not the first time doctors had dreamed of curing someone with HIV – just the first time it actually worked.

Long-shot ambitions to cure HIV first ballooned into great hope in the mid-90s, as highly-active antiretroviral therapy (HAART) emerged as the standard care in treating AIDS. HAART is an umbrella term for numerous combinations of the two dozen or so FDA-approved antiretroviral drugs, which block HIV at various stages of the infection's

life cycle.

For Deeks, who started treating patients at SFGH in 1993, the impact of HAART on the lives of people with HIV is hard to overstate. He calls it one of the great milestones in HIV/AIDS – perhaps in all of medical history.

“It’s a different disease today,” Deeks said, “a chronic, manageable disease – there’s no comparison.”

According to Greene, almost any patient now can be treated to where he or she has no detectable levels of virus, and some of the newest drugs are less toxic than those used in the early days of treatment.

At the same time, HAART also provides a valuable lesson in failed cures.

When the earliest clinical trials using combinations of drugs appeared in the mid-1990s, they showed that HAART could drive down the virus to undetectable levels in the bloodstream. This led many scientists to wonder if the drugs might be able to actually cure people of the virus, allowing patients to stop taking their drugs.

After years of carefully designed trials, however, not a single person was ever cured of HIV. Moreover, one of the largest-ever clinical trials of HIV/AIDS patients showed that people who take the drugs continuously fare far better than those who go on and off their treatment.

Doctors now know that HIV can persist dormant in the body. When people stop taking the drugs, the virus rebounds – often in just a few weeks. And in the last 15 years, as the medical community came to realize that drugs alone would never be able to get rid of this hidden virus, the dreams of curing HIV through HAART quickly faded.

Then along came Brown. He had been on HAART since the 1990s, when he first was diagnosed with HIV. But he stopped the day of his first transplant operation in 2007 and has never taken the drugs again.

## How the Berlin Cure Worked

The opportunity to cure Brown emerged when he was diagnosed with leukemia in 2006. A transplant of stem cells from the bone marrow of a donor was needed, giving his doctors the idea of choosing a donor resistant to HIV.

In operations like these, patients undergo chemotherapy and radiation to kill off the existing cells in their own bone marrow. Then they receive an infusion of new stem cells taken from a healthy donor who is "compatible" with the patient. Essentially, the transplant replaces the body's source of T cells, the primary targets of HIV.

In Brown's case, the donor's cells were resistant to HIV thanks to a rare genetic mutation that left the donor with an altered form of a protein called CCR5 – the main co-receptor HIV uses to enter cells. This mutation causes the CCR5 protein to go missing from the surface of T cells, blocking HIV's access.

A team led by Gero Hutter in Berlin in essence successfully transplanted into Brown an immune system resistant to HIV infection. While his leukemia reappeared the following year and he had to undergo a second stem cell transplant, the procedure appears to have wiped out all the HIV-infected cells in his body.

If asked five years ago, Levy said, many scientists would have been skeptical about the procedure, assuming HIV would simply shift to a second receptor – CXCR4. Why this didn't happen is just one of the unexplained riddles that intrigues investigators.

A similar 1995 experiment at UCSF and SFGH also had fallen short of a cure. Jeff Getty, a Bay Area resident and AIDS activist, was given bone marrow-derived stem cells from a baboon, a species naturally resistant to HIV. While Getty may have experienced some transient benefit from the transplant, the baboon cells did not survive, and he was never cured of HIV. Getty died in 2006 due to oral cancer and complications of AIDS.

## Moving Forward with Other Approaches

However much more promising Brown's story may be, UCSF experts interviewed for this article all agreed the procedure that cured him could not easily be used on other patients.

The operation carries a significant risk of death, and it is prohibitively expensive, putting it out of reach for most people with HIV. But perhaps the greatest barrier of all would be locating compatible donors for all of those people. Finding a donor whose stem cells are matched to the recipient is difficult in any case. Finding one who also has the CCR5 mutation, only present in a small percentage people of northern European descent, would prove impossible in most cases.

A different approach, which Levy and his UCSF colleagues are pursuing, seeks to circumvent the problem of finding matched donors by using stem cells from the patient with HIV. The CCR5 receptor would be removed from the stem cells before they are infused back into the patient.

The technique has shown promise in mouse studies and in early human clinical trials. Levy, with UCSF professor Y. W. Kan and others, is working to improve the basic techniques for manipulating the stem cells and to find the funding needed to advance the studies toward the clinic.

Some, including Greene, are less enthusiastic about the stem cell

approach because it would require immune-suppressing therapy and other procedures that must be performed in a sophisticated clinical setting with substantial laboratory support. While such resources are readily available in San Francisco and many other urban centers around the United States and Europe, they may be inaccessible in those parts of the world where the majority of people with HIV/AIDS live.

To really turn the tide of the pandemic, a cure would have to be accessible to millions, Greene said. Ideally, it would have to be non-toxic, available in a pill form, cheap to manufacture and not require refrigeration.

Toward that goal, Greene, Verdin and their colleagues at GIVI and UCSF are pursuing an approach they refer to as “shock and awe.”

## The Shock and Awe Approach

Earlier attempts to cure HIV infections using HAART didn’t work because, while the drugs prevent the virus from replicating, they don’t kill the “latent” virus, which lies dormant and can persist for years in a small number of cells.

The idea of shock and awe is to use drugs to activate the virus, flushing it out in the open. Once the HIV is reactivated, the HAART drugs and the immune system could take care of the rest.

“The virus will come up but will have no place to go,” Verdin said.

While this concept has been demonstrated in cell culture, using latently infected cells from patients, many scientific issues remain to be resolved before shock and awe can be tested in people.

“We need to understand all of the places and types of cells where the

virus can hide in the body, what the biological processes are that maintain HIV in its slumbering state and whether it is possible to rouse the virus without also activating its cellular host," Greene said.

Other unanswered questions include what role inflammation plays in the disease. The virus induces a widespread inflammatory response that feeds forward during an infection. This seems to play a role in the disease progression and damages tissues.

McCune and Deeks are among those looking at the possibility that blocking inflammation may have played role in the Berlin Patient's cure. Brown, like anyone undergoing a bone marrow transplant procedure, would have been given lots of anti-inflammatory drugs during the procedure. "That may have been important," Deeks said.

Deeks and his colleagues are now looking at the effect of anti-inflammatory drugs on the persistence of the virus. They want to know whether controlling inflammation might help better control the infection.

## Will Dreams of a Cure be Realized?

For his part, Brown is not satisfied with the mere fact that his HIV has been cured. He wants to see others to be cured as well and is exploring the possibility of starting a nonprofit foundation to raise awareness of and funding for HIV research into a cure.

"More money should be spent for cure research," he said. "I'm just hoping that what I've gone through will be a catalyst for others and that more people will be cured of HIV."

## How likely is it that we will get there eventually?

“I wouldn’t be spending time on this if I didn’t think we could succeed,” McCune said. But, he added, getting there is going to require insights from fundamental laboratory research and from clinical studies with diverse populations of patients of different ages and gender and from different regions. McCune compares the effort to that behind a monumental shift in computer use as businesses and institutions switched from mainframes to desktop and laptop computers. This massive change was realized only with time, patience – and tremendous innovation.

Still, if the history of the AIDS epidemic proves anything, McCune added, it is that great advances are possible with a clear vision, dedication and hard work.

It’s not going to happen tomorrow, next week, or next year, added Greene, but every journey starts with a single step. Whether or not Brown’s cure turns out to be that first step, research in the field is off and marching – and gaining its stride.

Provided by University of California - San Diego

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