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AIDS cure seen as possible

By Erin Lounsbury, LA Times

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An influential group of scientists gathered last week at the International AIDS Conference in Washington committed to a goal that just five years ago would have seemed ludicrous: to cure HIV.

After studying the virus for more than 30 years and developing potent drugs that transformed the disease from a death sentence into a manageable chronic condition, a growing number of researchers now say the search for a cure should be a major research priority. While acknowledging substantial challenges, they argue that the effort is necessary because the epidemic cannot be contained through treatment and prevention alone. And recent medical and scientific advances — including the case of the first man definitively cured of the human immunodeficiency virus— offer proof that it's possible.

Spearheading this audacious challenge is the International AIDS Society, which developed a research agenda in collaboration with more than 40 scientists led by French virologist Françoise Barre-Sinoussi, who won the Nobel Prize in physiology or medicine in 2008 for her role in the discovery of HIV. Among the tasks: investigating where and how the virus can hide out in the body and studying the immune response of the select group of people who are naturally immune to HIV.

Developing drugs that keep HIV in check has so far proved more feasible than trying to eradicate it, said Dr. Steven Deeks, a member of the AIDS Research Institute at the University of California, San Francisco. But now that more than 20 antiretroviral therapies can prolong the lives of people with HIV for decades, he said, it's time to aim higher.

“I think these drugs have gotten as good as they're going to get,” said Deeks, who worked with Barre-Sinoussi to develop the research plan. “We need to shift from blocking the virus from replicating to essentially getting rid of the virus.”

The antiretroviral drugs are lifesaving, but they have problems. Treatment is toxic and expensive, and only about half of the world's 34 million people living with HIV who need

the drugs can get them. Patients must take the drugs daily for the rest of their lives to keep the virus at bay.

“It’s just practically difficult to treat people all their life with therapy, even if it’s very simple therapy,” said Dr. David Margolis, director of the Program in Translational Clinical Research at the University of North Carolina at Chapel Hill.

But for a long time, there has been no alternative. HIV researchers were set back in the 1990s when they discovered that the strongest drug cocktails could substantially knock down a patient’s viral load but couldn’t wipe it out completely. If people stopped taking medication, the disease came back.

Pessimism about finding a cure set in, said Paula Cannon, a molecular biologist at USC’s Keck School of Medicine. Even five years ago, a scientist who proposed HIV cure research “would be laughed out of the room,” she said. “Nobody would give you money.”

What changed? “It’s come down to one man,” Cannon said.

That man is Timothy Brown, known to the medical world as the Berlin Patient.

Brown was an HIV-positive American who was living in Germany when he developed leukemia. After failing to respond to first-line cancer treatments, he chose to have a bone marrow transplant in 2007. As his doctors searched for a suitable donor, they looked for one with a rare genetic mutation that disables a receptor known as CCR5, which HIV needs to gain entry into immune cells. Brown had two transplants that not only put his leukemia into remission but replaced his HIV-susceptible immune system with one that could ward off the disease.

Brown no longer takes antiretroviral drugs and no longer tests positive for HIV. Essentially, he is cured.

“There’s nothing like success to galvanize the research,” Cannon said. “People are daring to hope again that with a lot of hard work and ingenuity, scientists can deliver.”

Bone marrow transplants aren’t suitable for widespread use: The procedure Brown received ends in death 20 percent of the time, and finding an appropriate donor would be a long shot in most cases. So scientists are working on alternatives.

There are two general approaches. One, an elimination cure, would rid the body of all HIV-infected cells. The other, a functional cure, would engineer a patient's own immune system to resist HIV, even if the virus remains present in the body.

For an elimination cure to work, researchers must learn to identify the dormant HIV that hides in immune cells and tissues, evading assault from drugs. Much of the International AIDS Society's plan focuses on this problem.

Efforts to flush the virus from its hiding places are showing signs of progress. For example, Margolis and his colleagues have found that giving patients a drug called a histone deacetylase inhibitor can prompt HIV to wake up and start producing proteins. Drugs and the immune system can then recognize those proteins and mount an attack.

But it's far from clear how long this activation would last, or how to empty all of the hiding places. An effective elimination cure would also have to root out every last speck of HIV, including those in hard-to-reach areas like the brain and spleen.

One approach to a functional cure involves using gene therapy to modify a patient's DNA so that it produces immune cells with a disabled CCR5 gene. In theory, the result would be the same as with the Berlin Patient, said Dr. Jay Levy, who co-discovered the AIDS virus in 1983 and directs the Laboratory for Tumor and AIDS Virus Research at UCSF.

There are various hurdles, including finding ways to safely knock out the CCR5 gene.

"It's going to be like going to the moon again, but it's so important that we do this," said Cannon, who is working on a gene-therapy project that could be ready for clinical trials in two years.

Dr. Bernhard Schwartlander, a director with the Joint United Nations Program on HIV/AIDS, said the recent scientific developments make an HIV cure an exciting prospect. "It's the right point in time to actually make that a special topic in the AIDS response," he said. "If you don't focus on [a cure] now ... you will never get there."

It won't come cheap. Writing recently in *Nature*, Deeks and Barre-Sinoussi estimated that governments and foundations invested \$75 million in HIV cure research in 2011, but said the effort would require hundreds of millions of dollars in annual funding until a cure is found.

Dr. Anthony Fauci, director of the National Institute for Allergy and Infectious Diseases, called the search for an HIV cure an “aspirational goal.” He emphasized that finding a cure is not necessarily synonymous with turning the tide on the AIDS epidemic.

“You can end the AIDS pandemic without necessarily curing anybody,” by preventing new transmission and treating those with HIV, he said. “Or you can cure a small number of people and still have the epidemic be raging.”

Levy acknowledged that even if a cure were discovered, it could take years to become practical in low- and middle-income countries, where 97 percent of the people with HIV live. But right now, he said, finding a cure is like “the four-minute mile — what we need to do is just show it’s possible” — and after that, “there’s enough creativity out there to find a way of having it applied in all parts of the world.”