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FEATURE

HIV/AIDS

The slow and unknown route to a cure for AIDS

Progress on several ways that a cure for AIDS might be developed was a source of optimism at the recent international AIDS conference, reports **Bob Roehr**

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Washington, DC

A growing acceptance that the "Berlin patient," Timothy Ray Brown, is the first person to have purged the virus from his body has sparked a renewed interest in a cure for HIV infection.[1] Brown has also announced the formation of a charity to promote the search for a cure.

This, and other tantalising evidence that a cure for HIV infection might be possible, inspired optimism among almost 24 000 delegates at the recent 19th international AIDS conference in Washington, DC. But the route to a cure is unclear and likely to take decades.

Conference participants revelled in the expansion of treatment to eight million people in the developing world, which was unimaginable less than a decade ago, when only tens of thousands were being treated. They took hope from new prevention tools, such as a rollout of voluntary circumcision, approval of the first drug treatment for pre-exposure prophylaxis[2]—tenofovir/emtricitabine (Truvada)—and solid evidence that treatment contributes to prevention by lowering HIV viral load. When combined with other prevention tools, it seems that the number of new infections might be held in check until a vaccine can be developed.

Brown's regimen was an arduous one designed to treat his leukaemia. It involved chemotherapy, radiation, and bone marrow transplantation, with a one in a million match that contained a rare naturally occurring genetic mutation (ccr5Δ32) that confers resistance to HIV.[1] When he stopped the treatment the virus did not reappear.

The regimen is not easily replicated, but it did generate the first tangible proof that a cure is possible. And it opened the door to explore other approaches that fall into two broad categories: eradication and "functional cure." The International AIDS Society has initiated a collaborative effort focused on research into a cure,[3 4] which it launched at a two day meeting immediately before the main conference.

The Harvard researcher Daniel Kuritzkes has tried a variation on the Berlin treatment in two patients with lymphoma. He used a milder chemotherapy regimen that allowed the patients to continue taking anti-HIV drugs and then infused allogeneic stem cells, which "were fully susceptible to HIV."

Over eight months, as the new stem cells engrafted, the "transplanted donor cells replaced the patients' own lymphocytes, and as this occurred, the amount of HIV DNA that was detectable in the patients' blood cells decreased and eventually became undetectable," he told the meeting. "We believe that continuous administration of effective antiretroviral therapy protected the donor cells from becoming HIV infected.

"In addition, we observed a significant decline in HIV antibody," Kuritzkes said. That suggests there is no or an extremely low level of viral replication going on. The real test will come if and when the patients stop their HIV therapy. Will the virus rebound? Other patients have been enrolled in the study but their transplantations are too recent to allow meaningful evaluations.

Eradication approach

An eradication approach to curing HIV focuses on flushing latent virus from reservoirs in resting CD4 T cells, a key part of the adaptive immune system. HIV drugs don't work on resting T cells. So the theory is that activating resting cells while the patient is taking antiretroviral drugs might clear this viral reservoir.

David Margolis, a researcher at the University of North Carolina at Chapel Hill, told the conference that it is possible to activate resting T cells in patients using the anticancer drug vorinostat.[5] But the drug "was not very effective" in activating T cells, he said, and he has no plans to pursue further research with that drug. Other molecules that might work have been identified by screening compound libraries. Margolis said, "The real challenge is going to be moving these through testing and development in a rational and efficient way."

Some researchers are sceptical about the eradication approach. They remember initial euphoria over the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s and the hope that it might cure HIV disease. Instead it led to

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discovery of the CD4 reservoir. They suspect that eliminating the CD4 pool of virus will reveal other sanctuaries in different types of cells.

The brain is an obvious candidate because some HIV drugs do not penetrate the blood-brain barrier well; separate genetic variants of the virus can evolve behind it. The barrier may also impede molecules used to activate resting T cells.

Living with the virus

The "functional cure" approach is based on the observation that monkeys can live with the simian version of the virus for many years without getting sick. A small percentage of humans—called "elite controllers"[6]—are capable of doing the same. If researchers could figure out how their immune systems manage to control the virus, then it might be possible to find a way to modify other people's immune systems to act in the same way.

Last year researchers supported by the company Sangamo BioSciences managed to modify patients' CD4 cells so that they contained the ccr5Δ32 mutation, which confers resistance to HIV.[7] The trial was only a small safety study of six patients, but their immune systems and health improved. The modified cells have continued to survive for more than a year while unmodified T cells fall victim to the infection. However, it is not known if the modified CD4 cells can hold the virus in check without drugs.

The ideal would be a single procedure that conferred lifetime control of the virus without using drugs. But even a procedure that has to be renewed every year or two might offer benefits over current treatments.

Early intervention

Two new studies presented at the conference suggest that if patients start HAART early enough—within a few weeks of becoming infected—that might help the immune system develop responses that are better able to control the virus. It might also help reduce seeding of the reservoirs, which seems to occur very early in the process, probably during the acute infection stage. This could make the process of eradication easier.

The French Visconti cohort study was a retrospective look at about 700 patients who began treatment during acute HIV infection—a median of 40 days after being exposed to the virus. Some 75 of them continued that therapy for at least a year before stopping, explained Asier Saez-Cirion, an investigator at the Pasteur Institute. Fourteen of them have been able to continue off therapy for an average of six years with little or no detectable HIV in their blood. He is seeking to find out why.

The patients do not have immune system genetic markers associated with HIV elite controllers, though Saez-Cirion acknowledged that they might carry other as yet unidentified genetic variations that protect against the disease.

Martin Markowitz retrospectively looked at 31 patients at the Aaron Diamond AIDS Research Center in New York who started treatment early—19 to 155 days after exposure to the virus. He examined levels of plasma markers that are normally raised in patients infected with HIV regardless of whether they are receiving antiretroviral therapy (CD8+ and soluble CD14) and found that they were similar to those in HIV negative people.

"These data suggest that very early initiation of combination therapy may overcome perceived limitations of current therapies, and could potentially result in superior outcomes," Markowitz concluded. If the findings from these small studies of early interventions hold true, then it increases the importance of testing and identifying people very early in the course of their infection.

Financing cure research

In Washington, hundreds marched from the conference to the White House pressing for more resources. Although many middle income countries are taking more responsibility for their own HIV programmes, many of the poorest and often hardest hit nations lack the financial resources to do so.[8] And wealthy nations are facing their own economic crises, which limit their political will and financial capacity to raise money for treatment and research.

The research budget at the US National Institutes of Health has been essentially flat for a decade. Its director, Francis Collins, told the conference, "Inflation has eaten away; we are about 20% down in terms of purchasing power." But the National Institute of Allergy and Infectious Diseases has committed $70m (£45m, €57m) to cure related research over five years. It recently signed a letter of intent with French researchers "to collaborate on a global effort towards an HIV cure," said director Anthony Fauci. The American Foundation for AIDS Research and the Bill and Melinda Gates Foundation are also leaders in funding cure research.

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