AIDS RESEARCH

HIV Survives Drug Onslaught By Hiding Out in T Cells

As the war against HIV, the virus that causes AIDS, nears the end of its second decade, researchers and clinicians have wheeled powerful new cannons onto the battlefield. Potent cocktails of anti-HIV drugs have led the counterattack, pounding the virus down to undetectable levels in the blood of many HIV-positive patients. But a pair of papers published in this issue of *Science* (pp. 1291 and 1295) have both good and bad news for commanders on the front lines.

Two research teams—one led by immunologist Robert Siliciano at The Johns Hopkins University School of Medicine in Baltimore and the other by virologist Douglas Richman of the University of California, San Diego, School of Medicine in La Jolla—report that many patients taking the new drug cocktails, known as combination therapy, for as long as 30 months show no signs of developing drug-resistant strains of HIV. They do, however, still harbor latent virus in a small number of their T cells—immune cells that are HIV's primary target—despite having undetectable blood levels of HIV. And, in the test tube at least, these viruses can be induced to wake up and begin reproducing, simply by stimulating the T cells to become immunologically active—a condition known to be required for HIV to replicate.

Although several research groups had previously demonstrated that HIV was still lurking in these cells, some scientists had speculated that it might exist in a damaged, nonviable form. But the new findings show that these viruses are fully capable of replicating and infecting other cells. Moreover, even in patients who adhered rigidly to their drug regimen for up to 30 months, the percentage of latently infected cells did not decrease significantly. This is not good news for hopes that combination therapies would be able to eradicate the virus quickly: Either the current drug regimens may take many years to eliminate HIV totally, or they are not powerful enough to do so. "The idea that the drugs can hit every infected site in the body is unrealistic," says Simon Wain-Hobson of the Pasteur Institute in Paris.

On the other hand, AIDS researchers are quick to stress the positive side of the results: The sequences of the viral genomes in the patients' T cells showed little evidence of mutational changes over the course of their treatment, as would be expected if drug-resistant strains were emerging. "The drugs are doing their job, but the reservoir is quite slow in its turnover," says David Ho, director of the Aaron Diamond AIDS Research Center in New York City. Ho, who with Richman is a co-author on the Siliciano paper, adds that the next task will be to "think of strategies to flush out this cellular compartment." And Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, says the results "should not have any impact on what we recommend to patients. We are reaping enormous benefits for patients by keeping the virus as low as possible for as long as possible."

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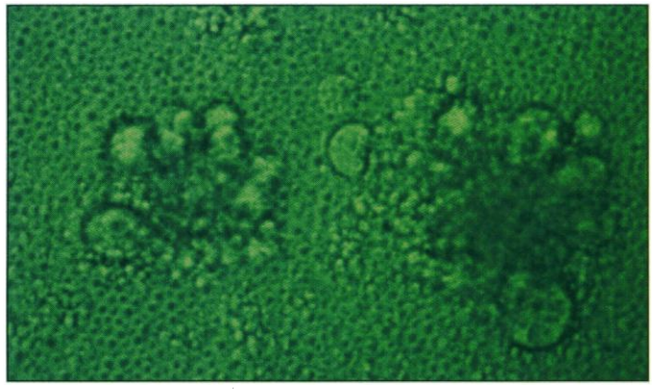
> **—David Ho**

Despite this optimism, new work from Fauci's laboratory—soon to be published in the *Proceedings of the National Academy of Sciences*—will sound yet another cautionary note. Fauci's group found the same hidden reservoirs as the Siliciano and Richman teams, but also uncovered evidence suggesting that some of the hidden virus may not be latent, but still replicating at a slow rate.



FINZI *ET AL.*

Ambushed. T cells killed by HIV that was hiding in the latent reservoir of a patient on antiviral treatment.

The Siliciano and Richman teams adopted the same basic approach in looking for HIV in so-called memory T cells, which help lead the attack when the body encounters microbial invaders it has seen before. The researchers took blood cells from HIV-positive patients who were on a strict regimen of combination therapy and cultured them together with blood cells from HIV-negative donors, along with reagents that trigger memory T cells to become immunologically activated. The researchers observed virus from latently infected memory cells quickly replicating and infecting the HIV-negative cells, even though the original level of infection of the HIV-positive cells was very low—the Siliciano team measured no more than 16 infected cells per 1 million T cells.

Researchers say these results clearly indicate that it is much too early to consider taking patients off combination therapy. "The results are not surprising," says retrovirologist John Coffin of Tufts University in Medford, Massachusetts. "We knew that patients over this time frame would become virus positive if treatment is removed. The virus has to still be somewhere." Adds Wain-Hobson: "We must assume that HIV infection is forever until we know to the contrary."

Researchers are far from sure how long infected memory T cells will live before finally dying out, perhaps taking the virus into oblivion with them. Several years ago, immunologists Angela McLean of Oxford University and Colin Michie at London's Ealing Hospital showed that while the average memory T cell lives for about 200 days, some individual cells could survive for many years. "If these cells are left on their own, they are going to last at least a decade, or maybe two or more," says Richman. But leaving these cells on their own is the last thing AIDS researchers intend to do. "We must hasten the demise of these cells," says Coffin.

Fauci suggests that some patients, particularly those treated early in their infection, might be able to mount an effective immune response against the few infected memory cells once they are taken off combination therapy—especially if their immune systems could be boosted with an anti-HIV vaccine. Another approach, Fauci says, would be to develop new drugs against HIV enzymes called integrases—which allow the virus to take over the genetic machinery of its target cells—hence stopping the formation of hidden HIV reservoirs. Says Ho: "These new results tell us what we must do in the upcoming year. They shed light on the path to eliminating the virus from an infected person, the ultimate goal for those of us working on HIV therapeutics."

–Michael Balter