The search for a cure

For the past several years, researchers in Canada, the U.S., Western Europe and Australia have intensified efforts to understand how HIV might be cured. Some of these efforts have gone toward lab studies with cells and HIV, while other studies have been done in HIV-positive people. The movement toward a cure has been encouraged by the successful experiment with a patient in Berlin, Timothy Brown (sometimes called “the Berlin patient”). His HIV infection was cured after two stem cell transplants of cells naturally resistant to HIV infection and intensive and sometimes dangerous rounds of chemotherapy and radiation.

Repeated attempts to cure people using similar regimens have not worked. However, scientists are planning many other different experimental approaches with monkeys infected with SIV (simian immunodeficiency virus; a close relative of HIV that causes an AIDS-like disease in susceptible monkeys) and in some people with HIV. The vast majority of these experiments with people are being conducted in the U.S.

In the quest for a cure for HIV, many different approaches are being tested, such as combinations of drugs that attempt to flush HIV out of hiding, antibodies that help capture HIV, and drugs and vaccines that enhance the ability of the immune system to detect and destroy HIV-infected cells. There are also attempts to cure HIV with gene therapy, with many clinical trials underway in the U.S.

From press release to news

It is important to note that in recent years the funding environment for all biomedical researchers has become much more competitive. At large agencies that provide research funds, only about 20%, often less, of research grant applications get highly reviewed and receive funding. This means that many good ideas do not get funded. In this highly competitive environment, teams of scientists increasingly have their university media relations offices issue press releases about their work. This helps the scientists get noticed by media and, in a few lucky cases, results in an interview. They likely hope that such publicity incites interest in their work that perhaps helps them get additional funding in the future. These press releases simplify the scientific advances made and are sometimes republished on media websites as “news” and often changed in the process by people who do not fully understand the subject matter. In some cases over the years, some media outlets have misunderstood press releases or what was said in an interview and have claimed that HIV has been cured or that a cure is very close, when that is not the case.

The hidden virus

In the past, media outlets have arrived at the erroneous conclusion that HIV has been cured after scientists involved in cure experiments have revealed that they are unable to find HIV in the blood of participants in clinical trials. However, this finding is not novel: Only about 2% of CD4+ cells are in the blood; the vast majority of these cells are in lymphatic tissue and lymph nodes scattered around the body, particularly around the gastrointestinal tract. Most HIV is also in the cells of the immune system within these tissues and lymph nodes. The inability to find HIV in the blood, therefore, does not mean that the virus has been purged from the body or that people were cured.

The tests and techniques used to try to find residual HIV in clinical trials of potential cures are imperfect. In nearly all cases in which scientists initially said that they were unable to find HIV, the virus subsequently became detectable after participants had stopped using potent combination anti-HIV therapy (ART) for several months or years. Researchers do not know all the tissues and types of cells where HIV might remain after intensive rounds of experimental cure therapy. They cannot sample every bit of lymphatic tissue, lymph node and delicate and important tissues such as the brain, ovaries or testicles where HIV might be lurking at low levels. This is why in cure research supervised treatment interruptions are necessary. The only way that researchers can be certain about the effectiveness of a potential cure is to take the risky step of withholding ART from participants to see if HIV once again becomes detectable in blood samples. Therefore, participants in cure research experiments need to be
monitored, sometimes intensively, for months and years.

In published results so far, HIV has almost always eventually been detected after ART has been withdrawn—the exception being the Berlin patient. These findings suggest that based on currently available technology, scientists are not certain where HIV lurks in the body despite attempts at purging the virus. As a result, in the absence of a breakthrough, it is unlikely that scientists will be able to produce a cure safely, cheaply and effectively in vast numbers of people within the next 10 years.

**Changing the goals**

However, what may be possible is that with a future experimental therapy, scientists could significantly reduce the amount of HIV in ART users to a level so low that for a time—perhaps weeks, months or hopefully years—participants may not subsequently need to use ART and their immune systems would remain healthy with no chance of transmitting HIV. Researchers refer to such a goal as a “functional cure.”

**Bear in mind**

Many of the drugs and/or therapies that have been and will be used in clinical trials attempting to cure HIV are experimental; they may not have been approved for routine use and/or they likely have toxicities. Drugs and techniques that have potential for cure research today may not appear that way a few years from now and might be quickly discarded from a clinical trial program as scientists search for a drug or combination of drugs that is likely to be more effective.

**Learning from advances in cancer research**

Advances in immunology were once led by scientists working in the field of HIV research in the 1980s to mid-1990s. Now the excitement in immunological discovery has moved to the field of cancer research. In this field, scientists have uncovered some of the ways that tumours can subvert the immune system. To counteract this, scientists have deployed a growing number of proteins, often specially designed antibodies, which block key molecules (called checkpoints) on cells of the immune system. These antibodies, called checkpoint inhibitors, unleash the immune system so that it can attack tumours. In some clinical trials, checkpoint inhibitors have greatly helped prolong survival in some HIV-negative people with cancer.

Enthused by the discoveries in the immunology of cancer, scientists working in the field of HIV plan to conduct experiments in their labs with HIV-infected cells, in SIV-infected monkeys and, in some cases, in HIV-positive people to assess the effect of intermittent use of checkpoint inhibitors. Note that checkpoint inhibitors have been priced incredibly high by pharmaceutical companies (around $15,000 CAN per person per month for cancer therapy) and can cause intense and complex side effects, so these experiments in HIV-positive people will likely proceed slowly and involve small numbers of people.

Another development from the cancer field is to create T cells that are trained to attack tumours. How this works is, scientists filter the blood of a person with cancer to extract T cells. Through genetic engineering these cells are made to produce a receptor that helps them focus only on attacking the specific tumour. These receptors are called chimeric antigen receptors (CARs). Scientists working in the field of HIV cure research plan to design experiments so that T cells from HIV-positive people can be genetically engineered to produce a receptor that helps them zero in on and attack HIV-infected cells.

**Back to finance**

Since the onset of the financial-economic crisis in 2008-09, economic growth in many Western countries has been diminished. This has led in some cases to a reduction or just small increases in general research funds in comparison to the era prior to the onset of the Great Recession. Scientists working hard in laboratories to try to find a cure for HIV must now also compete for research funds against proposals that seek to increase research on other infectious diseases, including newly (re)emerging viruses such as Ebola, Chikungunya and Zika and drug-resistant germs. All of these factors suggest that overall funding for HIV research will not significantly increase. This means that progress toward a cure for HIV will require a combination of hard work and more time. As a result of the long-term timeline that is likely needed for cure research, funding agencies must be patient with scientists and continue to support them for the many years it will take to create a safe, effective, affordable and widely available
In this issue

Many of the potential therapies being tested in the hope of finding a functional cure for HIV are experimental. However, some experiments for a cure are repurposing drugs approved for another use. For instance, one cure study underway in the U.S. is testing a drug approved for the treatment of inflammatory intestinal conditions—Crohn’s disease and ulcerative colitis—in HIV-positive people. The clinical trial of this drug may or may not result in a cure, but because the drug is already approved for use in people with a different condition, clinical trials with it in the context of curing HIV will likely move faster than studies with experimental drugs. We report on this exciting possibility later in this issue of TreatmentUpdate.

—Sean R. Hosein

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