Finding a Cure for HIV [1]

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**What Does "Cure" Mean?**

You may think it's fairly simple. Depending on whom you talk to, a cure for people living with HIV [3] can be defined as:

- Living without treatment
- Not transmitting HIV [4] to others
- No longer having any virus in the body

There are several terms that are currently used in HIV cure research. All of them assume that a person no longer needs to take today's HIV drugs, at least for long periods of time:
• Eradication – getting rid of all virus from all locations in the body; sometimes referred to as 'complete cure'
• Functional cure – HIV may still be in the body, but it is not active; the body is not fully 'rid' of HIV, but the virus cannot affect one's health and cannot be transmitted to others
• Remission – a term borrowed from the cancer field, it means that HIV is not active in the body; there is no guarantee of lifelong control of the virus, and it suggests the need for continued monitoring (to make sure HIV is still inactive)
• Therapeutic vaccines – these would allow people already living with HIV to control the virus without needing to take HIV drugs (Note: it may also be possible to develop preventive vaccines that would keep those not living with HIV from getting HIV; for more information, see our fact sheet on Vaccines [5])

Why Is It Taking So Long to Find a Cure?

For those living with HIV, it may seem like it's taking scientists forever to find a cure for HIV. Considering how many drugs are out there to treat HIV, surely they would have found a way to knock it out once and for all, right?

Unfortunately, several factors contribute to why it is taking so long to find a cure. The first set of these is more about the research to find a cure than the virus itself. These include limitations in our global capacity to study HIV in laboratories, to fund cure research, and even to find willing study participants.

HIV-specific factors

There are also several factors specific to HIV and how it acts in the body that contribute to the time it is taking to find a cure. First, HIV produces proteins specifically designed to defeat our natural immune responses. Secondly, HIV not only exists in several different strains, but also mutates (makes changes in its genetic code) so quickly that it can bypass our immune system’s attacks and develop drug resistance [6].

HIV 'hides' from our immune system [7] by inserting its genetic material into our own. Its genetic material can remain in our bodies in inactive infected cells that our immune systems do not recognize (viral reservoirs; more details below). HIV can also remain where the immune system has limited access, such as in the brain and in certain important parts of our lymph nodes.

Current HIV drugs cannot remove HIV's DNA from these cells or directly kill infected cells, but it does keep the virus from reproducing in large amounts. To provide a cure, we would need to understand where these viral reservoirs are located, how they form, and how to get rid of them.

HIV reservoirs

HIV persists in the body by forming a 'reservoir.' The HIV reservoir refers to a collection of inactive, 'resting,' or latent HIV-infected cells. HIV may not be in the bloodstream, but it can still hide in a reservoir. At some point, HIV may re-activate, return to the bloodstream, and infect other cells. One cure for HIV would be eliminating all HIV in the reservoirs so that this cannot happen.

There are several known reservoirs, including immune cells in the gut, lymphoid tissue, blood, the brain, the genital tract, and bone marrow. It is unclear when reservoirs are established, but recent research suggests that it could be as early as three days after initial infection.

Research also suggests that the earlier a person receives HIV treatment, the smaller the size of their reservoirs. Early treatment may also prevent reservoirs from forming in some areas of the body. It is important to keep the reservoir size small because people with larger reservoirs experience greater and more persistent immune activation.

Keeping the immune system constantly activated or 'turned on' can lead to fatigue and chronic
inflammation. Chronic inflammation in people living with HIV is thought to be responsible for several conditions normally seen at older ages [8], including heart disease [9], bone loss [10], kidney disease, and certain non-AIDS-related cancers [11].

Because some current cure strategies aim to knock out HIV reservoirs, these strategies may work better in people who start HIV treatment [12] very early and have fewer or smaller reservoirs that need to be eliminated.

**The Mississippi Baby**

It is clear that early treatment of HIV is not a cure for HIV. A patient known as the 'Mississippi baby,' for example, acquired HIV at birth and started taking HIV drugs only 30 hours after birth. The baby took HIV drugs for 18 months, then stopped. It was thought that the infant was cured of HIV, since they had no detectable HIV in their bloodstream for more than two years without HIV treatment. However, at four years old, the child had a detectable viral load [13] and showed a decrease in its CD4 count. The case of the Mississippi child, while not a story of a successful HIV cure, does show that early HIV treatment can eliminate the reservoirs for a period of time in which HIV drugs may not be needed.

**Current Cure Research Strategies**

**Kick and kill**

Also called 'shock and kill' (or, more gently, 'poke and clear'), the game plan here is to 'kick' or 'poke' the resting cells in the reservoirs into action, then 'kill' or 'clear' the newly activated cells when HIV returns to the bloodstream. Once the cells become active, they are no longer hidden from the immune system. The substances that provide the ‘kick’ are called latency reversing agents, as they interrupt HIV's ability to remain inactive within cells.

At the same time, regular antiretroviral therapy would prevent uninfected cells from becoming infected with the newly active virus that has been 'kicked' into action. Ideally, this strategy would empty the reservoirs and thereby rid the body of infection.

Challenges with this approach:

- Finding substances (latency reversing agents) that will safely and effectively activate, or kick the resting cells into action
- Ensuring that every cell infected with HIV is reactivated when 'kicked,' leaving no infected cell untouched
- Ensuring that infected cells that are kicked into action to start producing virus end up dying (i.e., the 'kill' part of kick and kill); approaches to bolstering the immune system's ability to recognize and kill the newly activated cells are listed below

**Gene therapy/alteration**

There are three broad approaches to gene therapy: (1) knocking 'out' genes in the virus that allow it to enter and infect immune cells; (2) knocking 'in' genes to our immune cells that make them resistant to infection; and (3) cutting out the genetic pieces of HIV that have become integrated into the DNA of infected immune cells.

The first strategy looks to disable HIV and make it unable to enter cells in your body by editing the genetic code of the virus. The genes that code for or provide the manufacturing instructions for HIV's ability to enter cells would be deleted or 'knocked out.' Thus, HIV would remain in the body, but it would be unable to infect cells in your or other people's bodies.

The second approach involves adding, or 'knocking in' genes to a person's immune cells that would
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protect them against HIV. We know what those protective genes look like because some people are
naturally born with them. These people are protected by their inability to produce a receptor called
CCR5 on the outside of their immune cells that HIV needs to enter and infect the cells.

One popular example of this approach is Timothy Brown, once known as the ‘Berlin patient.’ He
received a stem cell transplant after he was diagnosed with leukemia (a form of blood cancer). Stem
cells are cells that have not yet received instructions to make them into a specific type of cell. Stem
cells can not only renew themselves, but also develop and grow into several different types of cells,
including several different kinds of immune cells.

The stem cells Brown received were from a person who was naturally protected from HIV by having
genes that lacked the ability to produce the CCR5 receptor that HIV needs to enter and infect cells.
Brown is considered 'functionally cured' - he may still have some HIV in his body, but his cells are
now unable to be infected by HIV and he does not take any HIV drugs to control his HIV. Experts are
trying to produce the same result by genetically altering a person’s own stem cells and giving them
back rather than giving them someone else's stem cells.

Two other people living with HIV and cancer who received stem cell transplants are commonly
referred to as the 'Boston patients.' These people stopped taking HIV drugs for a couple of years
after their transplants and were able to go for several weeks or months without the virus
reappearing. Unlike Timothy Brown, however, they did not receive donor stem cells from a person
resistant to HIV. As a result, although they appeared to have no evidence of HIV after their
transplants, the virus ultimately returned in both of them after they stopped taking their HIV drugs.

The third approach uses a relatively new technology called CRISPR that is able to latch precisely onto
the HIV genes that have integrated into human DNA and cut them out without harming the cell or
causing it to malfunction.

Challenges with these approaches:

- Finding the appropriate genes to knock out; researchers are studying elite controllers (those
  who have nearly undetectable viral loads without taking HIV drugs) and long-term non-
  progressors (those who maintain normal CD4 counts for a minimum of ten years without
  taking HIV drugs) to find potential targets
- Changing the genetic sequence or code can produce unexpected results, including
  unintended side effects
- Stem cell therapies require wiping out a person's existing immune cells. This process can
  involve several types of drugs as well as radiation to create a 'clean slate' for the newly
  transplanted stem cells to flourish and grow. It is a lengthy, uncomfortable, and dangerous
  process. In addition, there are few individuals naturally immune to HIV (few potential stem
  cell donors), and the process is very costly.
- Virus-removal techniques would need to be highly specific (removing only HIV genetic
  material and not human genetic material) and highly sensitive (able to find almost all the
  infected cells)

Therapeutic vaccines

Therapeutic vaccines work by making the immune system capable of killing infected cells and
achieving a cure. Scientists are looking at two approaches:

- Broadly neutralizing antibodies: When our immune cells attack and destroy invaders like HIV,
  they display pieces of the virus — known as antigens (from antibody-generating) — on their
  surfaces. An antibody is a protein that attaches to an antigen like a key fits a lock. When an
  antibody has matched up with an antigen, it has marked the intruder for destruction by
  immune cells. Broadly neutralizing HIV antibodies can recognize and target for destruction
  several different strains of HIV, unlike standard antibodies, which are usually only able to
  latch onto antigens from a single strain of the virus.
Natural killer (NK) cells and interferon-gamma: NK cells destroy infected cells and are an important part of the body's early response to viral infections. They kill infected cells while the body is prodding killer T cells into action. Unlike some immune cells, NK cells do not need to be infected by HIV in order to effectively identify or kill HIV. Scientists are hoping that this new understanding of how NK cells work can lead to a therapeutic vaccine or functional cure.

Challenges with this approach:

- Both broadly neutralizing antibodies and 'post-treatment controller' NK cells are hard to find. They occur in only a small minority of people and may not be able to get into all parts of the body where HIV hides.
- Stimulating the immune system can increase the number of cells that HIV can target for infection
- There are many different strains of HIV, and HIV mutates, or changes, very rapidly. This may make even broadly neutralizing antibodies ineffective over time. Experts believe people may need to receive a combination of broadly neutralizing antibodies just as today's effective HIV treatment regimens include multiple drugs.

**Where Are We Now?**

In some ways, the struggle to find a cure for HIV and end the pandemic resembles the fight against cancer. A few decades ago, HIV infection was almost always fatal. Then we began to find therapies that could slow disease progression. Now, there are multiple antiretroviral therapies that can be used to treat HIV. People who are living with HIV and taking HIV drugs can live long, healthy lives – in many cases as long as those who are not living with HIV.

While we do not yet have a cure, scientists are both cautious and optimistic. Researchers have been humbled by events that appeared to be advancements and were not. Nevertheless, we know so much more about HIV than we did in the past, we continue to expand upon that knowledge, and we have several good leads. Perhaps most important, we have determination and hope.

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**Tags:**

- HIV cure
- HIV gene therapy
- HIV genes
- HIV stem cell transplant
- Therapeutic vaccine
- Broadly neutralizing antibodies
- Kick and kill
- Shock and kill
- Natural killer cells
- NK cells
- HIV research
- HIV reservoirs
- Latent cells
- Inactive cells
- HIV eradication
- HIV functional cure
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Additional Resources

Select the links below for additional material related to Finding a Cure for HIV.

Is There a Cure for HIV and AIDS? (Avert) [33]
The Countdown for a Cure for AIDS (amfAR) [34]
Can AIDS Be Cured? (The New Yorker) [35]
The Only Cases of HIV Cure or Remission (TheBodyPRO) [36]
5 Strategies to Cure HIV (Desmond Tutu HIV Foundation) [37]
The Search for the Cure (POZ) [38]
Curing HIV (TheBody) [39]
We May Need to Combine Many Approaches to Achieve a Cure (AIDSmap) [40]
What Is the CUREiculum? (AVAC) [41]
Harnessing the Power of Antibodies (TheBodyPRO) [42]
With HIV Cure as the Goal, Gene Therapy Research Expands (TheBody) [43]
'Classic' HIV Cure Remains a Challenge, NIH Expert Says (Medpage Today) [44]

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