What Does "Cure" Mean?

It may seem fairly simple. Depending on whom you talk to, a cure for people living with HIV 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 currently used in HIV cure-related 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 or complete elimination – getting rid of all virus from all locations in the body; sometimes referred to as "complete cure"
• Durable antiretroviral (ART)-free control – 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; also sometimes called “functional"cure"
• 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)

Why Is It Taking So Long to Find a Cure?

For those living with HIV, it may seem like it is 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 the virus 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. It includes limitations on 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 [5].

HIV "hides" from our immune system [6] by inserting its genetic material into our own genes. Its genetic material (DNA) can hide in our bodies in inactive infected cells that our immune system does 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 clear infected cells, but they do 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 reservoirs. HIV reservoirs refer to a collection of inactive, "resting," or latent HIV-infected cells. HIV may not be in the bloodstream, but it can still hide in reservoirs. 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 in the body, including immune cells in the gut, lymphoid tissue, blood, the brain, the genital tract, and in 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 may be. 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 usually seen at older ages [7] in people without HIV, including heart disease [8], bone loss [9], kidney disease, and certain non-AIDS-related cancers [10].

Because some current cure strategies aim to knock out HIV reservoirs, these strategies may work better in people who start HIV treatment [11] very early and have fewer or smaller reservoirs that need to be eliminated.

The Mississippi Child

It is clear that early treatment of HIV is not a cure for HIV. A patient known as the "Mississippi child," for example, acquired HIV at birth and started taking HIV drugs only 30 hours after birth. The child took HIV drugs for 18 months, then stopped. It was thought that the infant was cured of HIV, since she had no detectable HIV in her bloodstream for more than two years without HIV treatment. However, at four years old, the child had a detectable viral load [12] and showed a decrease in her CD4 count. The case of the Mississippi child, while not a story of a successful HIV cure, does show that early HIV treatment can reduce the reservoirs for a period of time in which HIV drugs may not be needed.

Current Cure-Related Research Strategies

Latency reversing agents ("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. Latency reversing agents would need to be taken along with strategies that enhance the immune system.
CAPTAIN LRA SAVES THE DAY!

The immune system is on the lookout for HIV, which has entered the body...

Now that the cell is asleep, HIV is invisible to the immune system. Who can help them find the sneaky HIV? ...

CAPTAIN LRA HAS COME TO SAVE THE DAY!!!

I’m a master of disguise.

Captain LRA awakens the cells to try and find HIV.

AHHHHH!!

I CAN’T TAKE THIS!!

When an infected cell is ZAPPED, it reveals the pesky HIV inside!

Thanks, Captain LRA! Now the immune system can finish the job...

Key:

**Immune System**
A system of cells, tissues and organs within the body that help fight off infections.

**HIV**
Human Immunodeficiency Virus: A virus that enters the body and attacks cells that help the body fight off infections, making the body highly susceptible to diseases and infections.

**DNA**
Genetic material found in all living organisms that contains the main constituents of chromosomes. It is self-replicating and contains all genetic information.

**LRA**
Pharmacological approach to eliminating the HIV reservoir. This strategy attempts to flush the virus out of the resting cells by reawakening the dormant viruses in the latent reservoirs.

Story by: Eric Lee, Matylda Mai & Jazmin Guzman
(Pencils) (Inks&Lettering) (Colors)
Finding a Cure for HIV
Published on The Well Project
(https://www.thewellproject.org)

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.

Block and lock strategies

Rather than activating and clearing off cells as with latency reversal strategies, the "block and lock" approach aims to permanently silence latent virus using latency promoting agents (LPAs) to "block" the transcription step in the cell's lifecycle [13]. Over time, this would "lock" the part of the cell or the gene responsible for HIV transcription into a deep latent state. Permanent control of that part of the cell means HIV drugs would no longer be necessary. Another key aspect of these "block and lock" approaches is that the agent would be specific to HIV (e.g., Tat gene), so it would not block other processes needed to overcome other infections.

Studies in humans will be needed to test whether this kind of approach could work to achieve ART-free durable suppression. However, unlike latency reversal approaches that are studied in HIV after being used to manage other health conditions, no block and lock strategy has been approved by the US Food and Drug Administration (FDA). Therefore, clinical trials of these therapies have lagged behind.
AGENT "BLOCK 'N` LOCK"

They look like they could use some help...

The immune system is fighting HIV which has entered the body...

Introducing ME! I'm BLOCK 'N` LOCK!

And I'm here to offer my assistance.

Once I've located HIV in a cell...

...And for extra protection, Lock it in place!

Thanks for your help!

Anytime!

The HIV won't bother anyone now, and will disappear at the end of the cell life cycle.

KEY

Immune System
A system of cells, tissues and organs within the body that help fight off infections and diseases.

HIV
(Human Immunodeficiency Virus)
A virus that enters the body and attacks cells that help the body to fight off infections, making the body highly susceptible to diseases and infections.

DNA
Genetic material found in all living organisms that contains the main constituents of chromosomes. It is self-multiplying and contains all genetic information.

Latently-Infected Cell
A cell that is infected by the HIV but not actively producing the virus. It's hard for the immune system cell to recognize it as an affected cell because of its inactivity.

Block and Lock Strategy
A strategy that targets and silences the HIV virus DNA in the latently-infected cell. The cell can return to its normal activity if the viral DNA stays silent.

Story by: Eric Lee, Matylda Mai & Jazmin Guzman
(Pencils) (Inks&Lettering) (colors)
Gene therapy

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 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 from the body 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 a functional CCR5 receptor, one of two T-cell receptors that HIV needs bind to in order to enter and infect cells. Brown was considered cured of HIV, though he died of cancer in September 2020.

A similar procedure appears to have been successful in two other people. The first one is known as the "London patient" – a man named Adam Castillejo. The second person, called the "Dusseldorf patient," is discussed less often in articles on the topic of HIV cure. 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.

In early 2022, researchers announced that a fourth person – and the first woman – has reached ART-free control of HIV following a procedure. The "New York patient," who at this point wishes to remain anonymous, is of mixed race and was also diagnosed with leukemia. She underwent a transplant using stem cells from umbilical cord blood, but from an individual with a CCR5 mutation like in the three previous cases. She has been in remission without HIV medications for more than a year at the time of this writing.

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 gene therapy approach uses relatively new technologies (e.g., CRISPR) that are 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.
The immune system and cells are being taken to a training school to learn how to defend the body against HIV...

The immune system learns how to locate and protect against HIV...

The other cells learn how to shield themselves against HIV.

After their training, they are taken back to teach and assist the other cells how to find, protect and defend against HIV.

Story by: Eric Lee, Matylda Mai & Jazmin Guzman

(Pencils) (Inks & Lettering) (Colors)
Challenges with these approaches:

- 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)

**Immune-based approaches**

Immune-based approaches work by enhancing the immune system's ability to clear infected cells and achieve a cure. Scientists are looking at three main approaches:

- Broadly neutralizing antibodies (bNAbs): 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 clear 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 clear HIV. Scientists are hoping that this new understanding of how NK cells work can lead to a therapeutic vaccine or durable ART-free control of HIV.

Chimeric with a low viral load and a high CD4 count without ever having taken HIV drugs. She had been participating in research studies for many years, hoping that a path to an HIV cure might include what scientists could learn from her unique cells (elite controllers make up about 0.5 percent of people living with HIV). In 2011, researchers realized they could not find any virus inside Willenberg's body that could make copies of (replicate) itself - including in reservoirs. The virus had entirely cleared from her body by itself. This was found in 2021 to have occurred with a second woman in Argentina, known as the "Esperanza patient." Now, the job of scientists is to figure out how to repeat the process in other people. These cases are inspiring research efforts towards "block and lock" approaches (see above) to keep HIV from replicating inside the body.
IMMUNOTEAM: POWER UP!

The immune system is fighting a losing battle against HIV, which is rapidly reproducing...

But it looks like help is on the way!

The body has been injected in an effort to help the immune system control the spread of HIV more effectively.

KEY

**Immune System**
A system of cells, tissues and organs within the body that help fight off infections and diseases.

**HIV** (Human Immunodeficiency Virus)
A virus that enters the body and attacks cells that help the body to fight off infections making the body highly susceptible to diseases and infections.

**Immune Base Strategy**
Designed to boost an immune response against HIV in someone who already has the virus.

**Killer T-Cell**
An immune system cell that can clear certain cells. The injection gives the Killer T-Cell more strength to fight off the HIV.

**Helper T-Cell**
An immune system cell that activates the majority of the immune system. The injection gives the Helper T-Cell better tools to fight the virus.

**B-Cell**
An immune system cell that makes antibodies and develops from the stem cells in the bone marrow. The injection gives the B-Cell a better way to create the antibodies to help the immune system find HIV.

Story by: Eric Lee, Matylida Mai & Jazmin Guzman
(Pencils) (Inks & Lettering) (colors)
Challenges with immune-based approaches:

- 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.

**Combination approaches**

Most likely, we will need a combination of approaches to achieve ongoing control of HIV without HIV drugs. Scientists are investigating safe ways to combine different HIV cure research approaches.

**Cure-Related Research and Women Living with HIV**

Globally, women represent approximately 51 percent of all people living with HIV; however, very few women have ever participated in HIV cure research. It is important to many researchers to be sure that when the time comes for an HIV cure, women will have an opportunity to benefit.

In the early days of the HIV epidemic, people living with HIV joined clinical trials of HIV drugs that could help them and others in their communities stay alive. In the case of HIV cure studies, people with HIV are asked to participate to advance science so that someday, other people with HIV can be cured – but participants now will not get these clinical benefits. In fact, being part of cure research could even expose them to health risks, because some cure studies may require participants to stop taking their HIV drugs (known as “analytical treatment interruption”) for some period of time during the study. During this time, participants are no longer considered “viral suppressed” and could possibly transmit HIV to sexual partners. As a result, there are additional considerations for sexual partners of people who participate in ATI studies to minimize risk of HIV transmission during the ATI, including offering pre-exposure prophylaxis (PrEP) and other options for HIV prevention.

In 2020, a group of US researchers studied whether or not people living with HIV would be willing to participate in HIV cure studies based on potential risks and benefits. The researcher group included people with HIV and community organizations like The Well Project that represent them. Survey participants were much more diverse than in past studies. The researchers found differences in preferences and reasons for participating based on gender – which would not have been found if women (cisgender and transgender) had not been included in the study.

For example, cis and trans women were less likely than cis men to want to try a new HIV cure strategy over their daily HIV drugs. In general, a majority of people in the study were unlikely to switch to an HIV cure method if there were even a very small increase in risk of transmitting HIV to a partner. Especially in the era of Undetectable Equals Untransmittable [14] (U=U), when being on effective HIV drugs makes transmission to a sexual partner impossible, fear of interrupting HIV treatment and transmitting HIV remains one of the most important factors that could keep people living with HIV from participating in cure research. Another study conducted by a diverse group of researchers found that it will be important to pay attention to power dynamics between partners – including concerns around disclosure [15] or potential intimate partner violence [16] – when women (or their partners) participate in cure research involving ATIs.

The features that led cis and trans women to be interested in joining a clinical trial were different than for cis men. They included supports like regular nurse visits, being paid, help with transportation to the study location, and having a meal while there. In one ongoing study in an area...
of South Africa where rates of poverty, unemployment, and HIV are extremely high, researchers have worked with community members to develop an empowerment program for young sexually active women that has been successful in providing life and job skills training as well as HIV prevention support. Women take weekly blood tests and, when HIV cases do occur, participants have immediate access to HIV drugs while scientists are able to study immune responses very soon after HIV acquisition. This information will be valuable in developing cure strategies.

It is extremely important for women living with HIV to be involved at every level of research into a cure for HIV – including designing studies. When a diverse range of people that will be affected by a drug or process being studied are included in figuring out how the study will be carried out, every aspect of the study will be more useful, successful, and safe.

**Where Are We Now?**

In some ways, the search for 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](#)
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- [HIV genes](#)
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- [HIV eradication](#)
- [HIV functional cure](#)
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- [HIV remission](#)
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) [40]
- Are Scientists Getting Closer to an HIV Cure? (TheBody) [41]
- Research Toward a Cure Trials (Treatment Action Group) [42]
- HIV Cure Illustrations (Youth4Cure, University of California, San Francisco) [43]
- An HIV Cure May Work Differently for Women and Men (aidsmap) [44]
- #Cure (POZ) [45]
- 5 Strategies to Cure HIV (Desmond Tutu HIV Foundation) [46]
- Meet the Scientists: Women and HIV Cure Research (amfAR; includes video) [47]
- The Dose Response: Perceptions of People Living with HIV in the United States on Alternatives to Oral Daily Antiretroviral Therapy (AIDS Research and Human Retroviruses) [48]
- A Third Person Living With HIV Has Been Cured by Transplant (Medscape - free registration required) [49]
- What Does the 'New York Patient' Mean for Everyone Else Who’s Living With HIV? (TheBody) [50]
- Durable HIV Remission in London Patient, the Second Person Cured of HIV (TheBodyPro) [51]
- The Often-Overlooked Düsseldorf Patient (CATIE) [52]
- HIV Cure Research Strategy for Women: Where Are We? (Positively Aware) [53]
- Considerations for Increasing Racial, Ethnic, Gender, and Sexual Diversity in HIV Cure-Related Research with Analytical Treatment Interruptions (AIDS Research and Human Retroviruses) [54]
- An Exception to the Rule (POZ) [55]
- There's a Second Woman Whose Immune System Seems to Have Cured Her HIV. What Does This Mean for the Rest of Us? (TheBody) [56]
- FRESH Cohort (Ragon Institute) [57]
- Research on HIV Cure: Mapping the Ethics Landscape (PLOS Medicine) [58]
- With HIV Cure Research on the Horizon, Exploring Ethical Questions in Advance (TheBodyPro) [59]
- 'Classic' HIV Cure Remains a Challenge, NIH Expert Says (Medpage Today) [60]
- The Countdown to a Cure for AIDS (amfAR; video) [61]
- Can AIDS Be Cured? (The New Yorker) [62]
- The Search for the Cure (POZ) [45]

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Links
[3] https://www.thewellproject.org/hiv-information/what-are-hiv-aids