

## Searching for a cure for HIV and AIDS



### KEY POINTS

- A cure has not yet been discovered for HIV. However, there is optimism that breakthroughs will lead to a way of controlling or eradicating the virus without the need for further HIV treatment.
- There is only one person known to have been 'cured' of HIV.
- Significant discoveries about the body's immune system have been made on the road to finding a cure with some very promising attempts to create a vaccine, antibodies or effective gene therapy against HIV.

Explore this page to find out more about [how HIV has evaded a cure](#), [functional](#) and [sterilising cures](#), [existing research and development strands](#), [what the future might hold](#) and [ethical considerations for HIV trials](#).

There is still no known cure for HIV. However, scientific efforts to improve treatment, prevention and awareness tools are continuing to have a positive impact on the lives of many until a cure is discovered.

There are many logistical limitations and cost challenges that come with providing life-long care to those living with HIV. So continuing research to find a cure that controls the virus in the absence of antiretroviral treatment (ART) remains an important step to ending the epidemic.<sup>1</sup>

Cure research is still at an early but promising stage, and scientists are working on two broad types of HIV cure research - a '[functional cure](#)' and a classic, '[sterilising cure](#)' (see below).

# How HIV has evaded a cure

Due to the complex nature and structure of HIV, locating and quantifying the amount of virus in the body is proving to be a daunting task.

HIV evades the immune system by staying dormant in infected T- lymphocyte cells (T-cells) until they are activated to respond to infections. This state is called latent infection. Some of these cells may live for decades without becoming activated. Cells that are latently infected are described by scientists as the `HIV reservoir`. Detecting and eliminating these cells are the biggest challenges facing cure research.

## T-cell reservoirs

A reservoir of HIV-infected T-cells can be found in the lymphoid tissue of people living with HIV, even if HIV is undetectable on viral load tests in the blood. It is here that lymphocytes are produced and primed to fight infections in the body. The main concentrations of lymphoid tissue in the body are found in the thymus, spleen and lymph nodes in the gut, neck, under the arms and in the groin. HIV-infected T-cells can also be found in the bone marrow and the brain.

## Macrophage reservoirs

Studies have also shown that HIV does not only infect T-cells – the virus can also persist in macrophages, cells which are found in virtually every tissue in the body.<sup>2</sup> As a result, other sites in the body, such as the lungs, brain and genital tract, are also important reservoirs of latently-infected cells.

Macrophage cells infected with HIV have been shown to persist under ART – giving them the ability to harbour ‘hidden HIV’ in latent reservoirs despite treatment. This poses another major obstacle to virus eradication, because if an individual’s treatment stops or is interrupted, dormant HIV can re-establish itself by leaking out of these reservoirs.<sup>3</sup>

The discovery of latent HIV residing in these cells gives us new insight into why locating viral reservoirs has been so difficult. Macrophage cells are present everywhere, which unfortunately makes their isolation and analysis challenging. The long lifespan of these cells also constitutes the perfect environment for HIV to exist in difficult to detect ‘viral sanctuaries’ where the virus can hide out and proliferate for many years.<sup>4</sup>

## Technology gaps

Tests that are sensitive enough to identify the presence of the virus at an undetectable level are limited and tools that can reveal the true scale and depth of these reservoirs are as yet unknown.<sup>5</sup>

This, of course, provides limits to the advances of cure research. Without the ability to sufficiently monitor what is happening to the virus at this undetectable level, it would be impossible to verify if curative strategies have made a lasting impact as there is always the potential for the virus to re-emerge from undetected reservoirs.<sup>6</sup>

## Functional cure research

Progress towards creating a 'functional cure' focuses not on the elimination of HIV from the body, but rather on reducing the virus to a level that is undetectable; where the person no longer needs to take HIV-related medication, nor has any risk of progressing to AIDS or transmitting the virus.

This can more precisely be described as a level of 'remission'. Some advisory bodies have further suggested that this term be prioritised over calling it a 'cure', as suppressing viral replication still leaves traces of dormant HIV in the body which have the potential to re-emerge.<sup>7</sup>

Early antiretroviral treatment (ART), which is initiated close to the time-point of primary infection, certainly does not cure HIV, but there has been some success in individuals achieving temporary and long-term remission through this strategy. These people are called post-treatment controllers.

In a 2012 study, 14 French people living with HIV known as the 'Visconti cohort', started taking ART within 10 weeks of infection. After three years of medication, they stopped taking treatment, which would normally result in HIV re-emerging.<sup>8</sup> Remarkably, they maintained low levels of HIV in their systems for an average of seven years before a recurrence of the virus emerged.<sup>9</sup>

The 2018 'Control of HIV After Antiretroviral Medication Pause' (CHAMP) study yielded similar results – some 13% of those treated in early infection were considered post-treatment controller.<sup>10</sup>

### Early treatment for new-born babies living with HIV

The potential benefits of early treatment have also been seen in two new-born babies. In March 2014, it was reported that a nine-month-old baby born in California with HIV may have been functionally cured as a result of treatment that doctors administered just four hours after birth.

Similarly, in March 2013, researchers announced that a Mississippi baby born with HIV and given high doses of three antiretroviral drugs (ARVs) shortly after delivery still appeared to be functionally cured two years on.<sup>11</sup> But progress towards a functional cure took a significant blow in July 2014, when detectable levels of HIV were found in the Mississippi baby.<sup>12</sup>

More recently, in July 2015, researchers announced that a French teenager who was infected with HIV at birth was still in good health 12 years after she last took ART. However, it is not yet known why she has fared better than the Visconti cohort or the Mississippi baby.<sup>13</sup>

Researchers from these studies are still unable to distinguish if it was the treatment, the patients' genes or just random chance that the people in the study were able to prevent viral rebound for an extended period of time.<sup>14</sup> What has been noted, however, are that these people were different from those with natural immunity – otherwise known as 'elite controllers'.

Hypotheses include the fact that early treatment limits the building of viral reservoirs – and specifically long-lived cells in the reservoirs – which preserves the immune response for a longer period without treatment, and protects them from developing chronic infection.<sup>15</sup>

## Sterilising cure research

Unlike a functional cure, a 'sterilising cure' hopes to eradicate HIV from the body by measurably eliminating cells from latent reservoirs. This has proved a very difficult challenge for scientists, who believe it may be unattainable in most people living with HIV.[16](#)

### The Berlin Patient

Timothy Brown - also known as the 'Berlin Patient' - is the only documented case of a person living with HIV to have been successfully 'cured'. Through a combination of chemotherapy to destroy most of Brown's HIV-infected immune cells and two bone marrow transplants to treat leukaemia, the treatment also seemed to have removed all traces of HIV in Brown's body.[17](#)

In selecting a stem cell donor, Brown's doctors deliberately sought out someone with a rare HIV-resistant genetic mutation, whose CD4 cells had a resistance to the CCR5 co-receptor. The most common variety of HIV uses CCR5 as its 'docking station', attaching to it in order to enter and infect CD4 cells. Individuals with a specific mutation on the CCR5 (CCR5-delta32) are known to be naturally resistant to many HIV-1 strains because it renders deficient this co-receptor needed to inject HIV into the cell.[18](#)

Brown continued to receive immunosuppressive treatment to prevent the rejection of these new stem cells for 38 months, after which his viral load tests confirmed that this treatment had effected a successful 'sterilising cure'.

The procedure is considered very dangerous, and is unfeasible as an option for other people living with HIV. Several attempts to repeat this 'cure' in people with HIV who received bone marrow transplants have failed, and many of the cures currently being investigated are potentially toxic or risky, which could make clinical trials unethical.[19](#)

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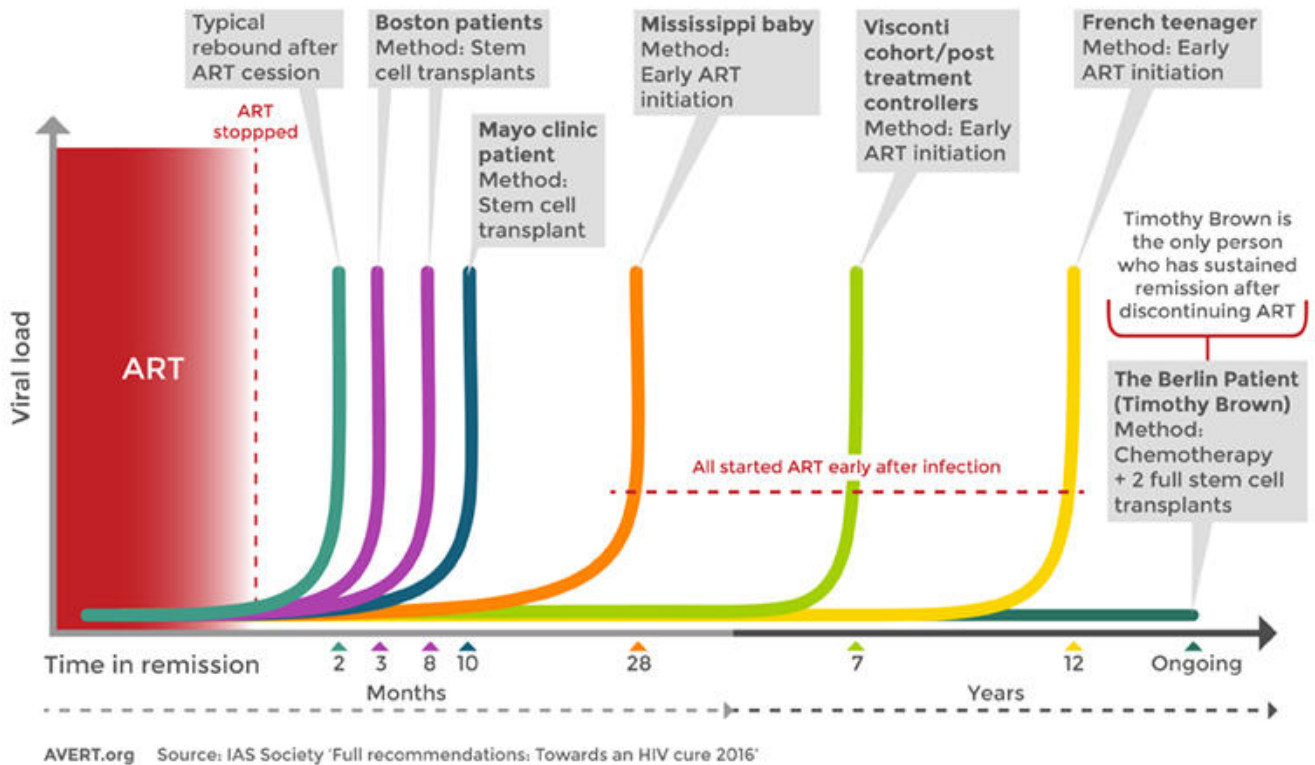
I don't think anyone would want to go through what he went through to get that cure, but it has inspired the field.

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- *Dr Steven Deeks of the University of California, San Francisco*[20](#)

The combination strategy, of chemotherapy and dual transplants, also makes replicating the results from the Berlin patient study problematic. It is not clear to scientists which specific element of the patient's treatment lead to the elimination of the virus.[21](#)

## HIV cure trials: Time in remission and viral rebound after ART cessation



## Cure research strategies

Within these two major strands of functional and sterilising cure research, there are five broad strategies of cure therapy currently being investigated. It is increasingly recognised that a combination of these strategies may be necessary for cure development.

### 'Shock and kill'

Research is currently underway to determine the extent to which viral reservoirs can be emptied by combining antiretroviral treatment with drugs that flush HIV from its hiding places.<sup>22</sup>

The idea is to force the dormant, infected cells to become active so that the body's own immune system or ARVs can destroy the last remnants of the virus. This approach has gained the name 'shock and kill'.<sup>23</sup>

So far, attempts to reduce the HIV reservoir in this way have used a group of agents called HDAC (histone deacetylase) inhibitors. These drugs, used in cancer treatment, can stimulate HIV production in latently-infected cells. Several small studies in people with HIV have found that a short course of treatment with an HDAC inhibitor had little effect on the levels of HIV DNA detectable in cells.<sup>24 25</sup>

A randomised trial which combined an HDAC inhibitor to 'kick' HIV and a vaccine to stimulate immune responses to 'kill' HIV-infected cells showed that the approach did not reduce the number of HIV-infected cells.<sup>26</sup>

But another small study which used a different type of vaccine and the HDAC inhibitor romidepsin produced a more positive result. Although HIV levels in cells did not fall, just under half of those who stopped ART were able to control HIV at very low but detectable levels. More research is needed on

what led to control of HIV in these patients, but the results are encouraging.[27](#)

Criticisms of this branch of research suggest that there may be several problems with the shock and kill strategy. Studies which have explored this approach have only activated a small amount of HIV-infected reservoir cells in their test subjects and to activate more might be damaging to the whole immune system and its natural immune response. For example, research has shown that viral reservoirs can be harboured in the many macrophages' tissues within the brain which may lead to fatal inflammation if activated through this form of treatment.[28](#)

## 'Block and lock'

There is an alternative to waking up HIV-infected cells. Instead of stimulating those cells to produce new virus, might it be better to find agents that can stop HIV replication from ever being stimulated in latently-infected cells?

Animal research reveals that an agent called dCA stops the HIV protein *Tat* from triggering the process - transcription - that sets off the production of new viruses. If *Tat* can be suppressed, latently infected cells will not produce new viruses and the HIV reservoir cannot be replenished. Scientists have called this strategy `block and lock` because it blocks the production of new viruses and locks HIV up in latently-infected cells. Human studies are needed to test whether this approach offers a viable route to long-term control of HIV without ART.[29](#)

## Stem cell transplants

The history of stem cell transplantation in people living with HIV dates back to the 1980s, when transplants were proposed as a possible way of curing the virus in the absence of treatment.[30](#)

Stem cell transplantation has been investigated because it was hoped that replacing the bone marrow cells from which all other immune system cells are derived might eventually lead to replacement of all immune system cells in the body with uninfected cells. This approach would need to be combined with eradication of infected cells from the body.

The cure of Timothy Brown is an example of a stem cell transplant, although the circumstances are unique. Subsequent attempts to replicate this cure have failed.[31](#) [32](#)

Multiple approaches have resulted in a significant reduction in the size of the reservoir after ART discontinuation, but HIV still persists in latent reservoirs within tissues that might not have been affected by the transplanted stem cells.

Similar to the criticism of 'shock and kill' treatments, it is suggested that stem cell transplants might not work as an isolated treatment approach, and that a combination of transplants and other cure strategies might be more effective.[33](#)

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## Gene editing

Approaches to gene therapy for HIV focus on the modification of cells that are targeted by HIV (such as the CD4 cells) – to render them resistant to HIV. Other gene therapy strategies focus on cutting HIV from the infected cell.<sup>34</sup>

This is a relatively new field of opportunity for cure research – with an array of tools now at the disposal of scientists to disrupt genes. These include zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and most recently, the CRISPR/Cas9 system.<sup>35</sup>

Based on the experience of the Berlin patient, most gene editing techniques target the CCR5 co-receptor, and other co-receptors, so to eliminate viral entry to a large majority of CD4 cells.

Targeted gene editing technique, ZFN, has been used to destroy the CCR5 gene in the CD4 cell, and then to reintroduce it into the person living with HIV. A proof-of-concept human trial has shown that HIV levels can be suppressed temporarily but the levels of modified CD4 cells falls over time.<sup>36 37 38</sup>

Most recently, researchers reported success in using the gene editing technique CRISPR to remove HIV genes completely from infected cells. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) uses the enzymes in CRISPR-Cas9 to act as “scissors” to cut DNA in a very specific way – by either removing a certain gene that assists the virus replicating or by inserting genes which help build the immune cells’ defence against infection.<sup>39</sup>

### CRISPR studies show success in EcoHIV mice study

In 2017, the powerful gene-editing technology known as CRISPR-Cas9 was used to genetically inactivate the virus in transgenic EcoHIV mice by targeting HIV-1 from the genome in most tissues.

The study was the first to demonstrate that virus replication within cells could be completely shut down and that the virus could be eliminated from infected cells in animals with the infection, with findings demonstrating a reduction of viral genes by roughly 60% to 95%.

The study also found that a treatment with the CRISPR-Cas9 enzyme could also affect latent reservoirs – with evidence for viral fragments successfully excised from latently infected human cells embedded in mouse tissues and organs. <sup>40</sup>

Despite promising trials, it isn't yet clear whether gene therapy could be an effective treatment for HIV as more in vivo trials with humans are needed to examine the treatment's full potential for success.

In addition, it is likely that a combination of gene therapy strategies that target different stages

of the HIV lifecycle will need to be employed to ensure all HIV in the body can be eradicated.

## Immune modulation

Immune modulation researchers focus their attentions towards drugs or procedures that can cause some type of sustained change in the immune system to better fight off HIV. Natural killers that have been found in the body include CD8+ T cells, NK (natural killer) cells and, the most commonly researched, broadly neutralising antibodies (bNAbs).[41](#)

All people living with HIV naturally respond to the virus by producing antibodies. While most people's antibodies are unable to kill HIV, the immune systems of a small minority (roughly 10-20% of people living with HIV) who have shown resilience against infection produce bNAbs, which can kill or neutralise a wide range of HIV strains.[42](#)

Antibodies which act against the sites on the virus which change least – so-called `conserved` regions – are likely to be more effective.

Several studies have now shown that bNAbs can suppress viral rebound for a period when antiretroviral treatment is interrupted. One study showed that viral rebound could be delayed for up to 19 weeks after an infusion of bNAbs, while another study using a combination of bNAbs showed that viral rebound could be delayed for up to 30 weeks after stopping ART.[43](#) [44](#)

So far, bNAb studies have used infusions of antibodies. Animal studies are now looking at whether it is possible to give a vaccine containing modified genes that stimulate the immune system to produce the bNAbs.

There are now several classes of bNAbs in clinical development and further evidence on the potential of this approach is likely to emerge within the next few years. In a similar vein, researchers in the field of vaccine development are also attempting to extract and manufacture bNAbs to see whether their neutralising ability on HIV has the potential to protect HIV-negative people from infection.[45](#)

## What next for cure research?

Through HIV cure research, much has been learnt about the virus and the ability of the human immune system to naturally or synthetically defend itself. Despite these learnings, researchers agree that a cure, functional or otherwise, will probably occur as a result of a combination of approaches rather than one isolated treatment.[46](#)

There has also been a developing interest in fostering collaborations with oncologists, to merge HIV cure and cancer disciplines, to create new ways of advancing sustained remission in people living with HIV.

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The parallels between HIV persistence and cancer are striking. In both cases, the immune response is unable to target and clear HIV-infected cells and tumour cells. Both fields also face similar



challenges in quantifying the size and distribution of those cells, which can reside in tissues that are difficult to access.

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- Nobel Laureate Françoise Barré-Sinoussi<sup>47</sup>

Cure strategists from all strands of research are also focused on the need for more human trials in order to investigate the full potential of treatments. So far, the few human trials that exist have focused largely on Caucasian middle-aged and older men in resource-rich regions, suggesting that there is still much to be learned about viral activity in people of different ages, genders, ethnicities, and other vulnerable populations.<sup>48</sup>

## Ethical considerations for HIV cure research

The ethical principles that underpin trials exploring a cure for HIV infection, naturally pose another challenging requirement for scientists to meet.

Antiretroviral treatment is highly effective if taken consistently and side-effects of modern ART are limited. Treatment prevents onward transmission when taken consistently. People who started treatment fairly soon after infection are likely to have a near-normal life expectancy.

Against these well-established facts, participants in cure research trials – especially those involving interruptions in ART – need to be informed of the potential risks. Prolonged interruptions in treatment are associated with a higher risk of serious non-AIDS-defining illnesses such as heart disease in people with high viral load. The health implication of treatment interruptions in people who appear to be in remission are unknown. A treatment interruption may pose a risk of onward transmission if viral load rebounds suddenly. Potential treatments to clear the HIV reservoir or boost the immune system may have serious or unpredictable side-effects.

Participating in cure research may have psychological uncertainties, such as a concern about the risk of onward transmission to partners. Coming off ART in such trials may cause anxiety. Although a functional cure may deliver a remission from HIV treatment, people are still likely to test positive for HIV antibodies, so people would not consider themselves fully cured.<sup>49</sup>

In order to prevent such risks in human trials, an ethical review committee that is independent of the government or pharmaceutical sponsors should evaluate all HIV cure research prior to starting the research.<sup>50</sup>

In any case, the potential scientific gains from future HIV cure and vaccine studies should be balanced against any potentially risky interventions that affect the participant's future health and wellbeing.

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