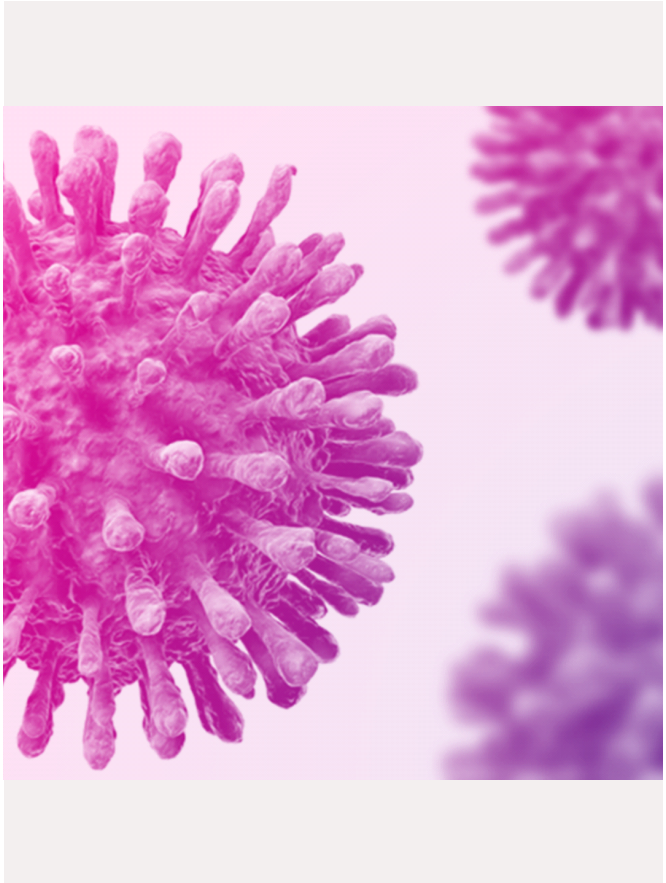
Factsheet The search for an HIV cure

Key points

- Only one person has been cured of HIV. Another possible cure was reported in 2019 but it is too early to say if HIV has been completely cleared in this case.
- HIV becomes part of the cells it infects and cannot be removed without killing the infected cells or using novel therapies to remove the HIV inside them.
- "Eradication" or a "sterilising cure" would remove HIV from the body completely, generally by killing all infected cells.
- A "functional cure" would not eradicate all HIV, but would enable the body to stop HIV proliferating and causing harm, without the need for any further treatment.
- Various approaches are being explored to achieve eradication or a functional cure. A combination of approaches is likely to be needed.



So far, HIV has proved almost impossible to eradicate from the human body because the virus integrates into long-lived immune system cells and remains dormant in those cells for many years. In most viral infections the immune system recognises infected cells and kills those cells. In a few viral infections, such as herpes simplex (the cause of genital herpes), hepatitis B and HIV, a virus infects cells that are difficult for the immune system to reach or integrates itself into the genetic material of a cell in such a way that it cannot be removed.

The HIV reservoir

HIV mainly infects CD4+ T-lymphocytes, dendritic cells and macrophages. These are immune system cells responsible for recognising pathogens and clearing them. HIV integrates into the DNA of these cells. Most infected cells are short-lived, and if antiretroviral therapy stops HIV replication they soon die.

Some immune system cells, however, become dormant until they are activated to respond to a

pathogen they have already seen and are sensitised to. These are central memory CD4 cells. They are especially long-lasting and may survive into advanced old age.

When a central memory CD4 cell is activated, new copies of HIV are produced, which in turn activate other cells. This is what happens in most cases if people stop taking their antiretroviral therapy (ART), and leads to HIV rapidly rebounding to pre-treatment levels.

These cells are described as latently infected and form what is known as the HIV reservoir. Reservoir cells are concentrated in the lymph nodes, the gut and the spleen but may also be found in the brain, the kidneys and in other tissues.

Scientists are working on tests to identify and count all HIV-infected cells in the body, as one of the barriers to an HIV cure is that scientists are unsure about which tissues in the body contain HIV-infected cells and so do not know if they are checking for eradication of the virus in all the right places. More reliable tests are needed too. For instance, although many cells may contain HIV DNA, it's not clear that this DNA always forms an intact viral sequence able to trigger production of new HIV.

Recent estimates suggest that between 100,000 and 10 million CD4 T-cells out of 200 billion CD4 cells are latently infected and form the reservoir of HIV in the body. But HIV DNA that can give rise to new virions may also be found in other cells and scientists are working on tests to identify and count all HIV-infected cells in the body.

The reservoir of HIV-infected cells becomes established within weeks of HIV entering the body. There is some evidence that treatment started very soon after infection can limit the size of the reservoir, especially in infants, and this may improve the chances of curing HIV in the future.

Latently infected cells are only detectable by testing for HIV DNA and are not detected by viral load tests used to monitor treatment.

Potential cure strategies

Several strategies are being explored to cure HIV.

One strategy is to seek complete **eradication** of HIV from the body, sometimes called a **sterilising cure**. This goal may be difficult to achieve without a better understanding of how HIV persists in the body undetected and untouched by the immune system.

Eradication of HIV from the body is likely to require a combination of:

- Safe agents that can 'wake up' HIV in a wide range of cell types without causing dangerous inflammation (latency-reversing agents such as HDAC inhibitors).
- Agents that can kill HIV-infected cells.
- Techniques that can engineer the production of cells that are resistant to infection, such as gene therapy (Zinc finger nucleases or CRISPR).

Another strategy is to achieve a **functional cure**, where HIV is not eliminated from the body but

is kept under control by the immune system without the need for antiretroviral treatment or other ongoing medication. This goal is sometimes called **remission**, a term borrowed from cancer treatment. In this context, remission means freedom from HIV replication, as there will always be uncertainty about whether HIV levels might rebound.

A "partial remission" refers to a prolonged period without HIV replication before HIV rebounds. It would be a functional cure that enabled people to stay off HIV treatment for long periods, but not for the rest of their lives. Booster doses would probably be needed.

To achieve a functional cure, it is likely that a combination of approaches will be needed:

- Reduction of the size of the HIV reservoir using drugs that 'wake up' HIV in latently infected cells.
- Alternatively, identification of agents that could make latent infection a permanent state, so that cells containing HIV would never 'wake up'.
- Improvement of HIV-specific immune responses by a therapeutic vaccine that would 'mop up' any residual HIV replication or stimulate the production of antibodies designed to suppress the widest-possible range of HIV (known as 'broadly neutralising antibodies').
- Periodic infusions of broadly neutralising antibodies or infusions of cells genetically modified to produce broadly neutralising antibodies.
- Protection of cells from infection by engineering resistance.

Both approaches will require similar techniques, so efforts to eradicate HIV or achieve remission will support each other. Eradication might be achievable for a minority of people, but remission might be feasible for a much broader population.

Reported cases of HIV cure or remission

The first rigorously investigated case of a cure was Timothy Ray Brown, who underwent a stem cell transplant to treat leukaemia in 2006, stopped antiretroviral treatment during cancer treatment and has subsequently shown no trace of HIV on numerous highly sensitive tests. Researchers think he cleared HIV because the cancer treatment eliminated HIV-infected T-cells and the stem cell transplant repopulated his body with cells resistant to HIV infection. The stem cell donor had naturally occurring resistance to HIV infection due to the lack of CCR5 receptors on their immune system cells.

A second case, in which a patient received a stem cell transplant from a donor with natural resistance to infection as part of treatment for Hodgkin lymphoma, was reported in 2019. The patient stopped antiretroviral treatment 16 months after the transplant, by which time all their CD4 cells lacked CCR5 receptors and had not experienced viral rebound at least 18 months after stopping treatment. We will need to wait longer before being able to say, as definitely as we can with Timothy Ray Brown, that this person is cured.

Researchers stress that these are unusual cases and attempts to replicate them in other people undergoing cancer treatment have failed to date. Stem cell transplants are risky for the recipient and not a suitable form of treatment for people without cancer.

Several other cases have been reported in which HIV DNA was not detectable on any tests, but HIV subsequently rebounded. The most widely reported was the case of a baby in the United States, who received antiretroviral treatment from very soon after birth. Treatment stopped after 18 months as the mother and baby stopped attending the clinic. HIV DNA was undetectable five months later when the mother and baby returned to the clinic and HIV remained undetectable for 27 months before viral load rebound occurred.

A small number of adults have also been found to control HIV off treatment, after starting antiretroviral treatment very soon after infection. A number of people in France have now been off treatment for an average of eight years without viral rebound, although they still have very low levels of HIV DNA. A review of several studies suggests that around one person in nine treated very soon after infection may be able to control HIV for at least a year without treatment, while another suggested the proportion might be less than one in 20.

The reasons for viral control off treatment are still not fully understood. Learning how to reproduce this state in a much larger proportion of people, and in those who didn't start treatment soon after infection, is a major goal of cure research.

Potential risks for participants in cure research trials

Eventually, HIV cure trials may result in individuals being cured of HIV or prolonged remission. But these outcomes are likely only after many trials have taken place in which participants are not cured or do not enjoy prolonged remission.

Taking part in a trial may expose people to risks. At the moment, because we lack sensitive tests that can detect tiny numbers of reservoir cells that harbour viable HIV, the only way to definitively test someone for a cure is to take them off ART. But nearly all such 'analytic treatment interruptions' (ATIs) designed to test the effect of stopping treatment will lead to viral rebound, resulting in a larger HIV reservoir and exposing people to the negative effects of uncontrolled HIV. These include inflammation, a higher risk of heart disease, immune suppression, and being infectious to sexual partners. It is not even known if prolonged HIV suppression without antiretroviral drugs is less or more harmful than antiretroviral treatment. Studies of "elite controllers" who maintain undetectable viral loads without starting ART suggest that some still suffer from inflammation and subtle immune damage, but this may not be the case with post-treatment controllers.

For most people, the main benefit of participating in HIV cure research is the knowledge that they are contributing to scientific research. In the meantime, antiretroviral treatment is highly effective in controlling HIV and will allow people to enjoy a near-normal life expectancy.

Find out more

HIV lifecycle Simple factsheet

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