

# 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](#), [vaccine research](#) and [ethical considerations for HIV trials](#).

## The search for a cure

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 how to define the different strands of HIV 'cure' research which are broadly categorised under two types - a 'functional cure' and a 'sterilising cure'.

There has been a lot of progress around the idea of finding a 'functional cure', where low levels of

HIV remains in the body by using a treatment strategy that keeps the virus under control but doesn't require any ongoing medication.<sup>2</sup> There has also been an aim among researchers to completely eradicate the virus' presence within the body with a 'sterilising cure'.

## How HIV has evaded a cure

Due to the complex nature and structure of HIV, locating and quantifying the amount of virus within a patient's body has proved to be a daunting task.

**When the HIV replicates**, it inserts its genetic code into CD4 cells, also known as T-cells or T-helper cells. These cells play a vital role in defending the body from infection, as they send signals to activate the immune response.

If left untreated, the virus will eventually develop into a chronic infection and destroy many of these protective immune cells, leaving the body exposed to opportunistic infections. Despite ART working very effectively at inhibiting the replication process and keeping the body's immune system stable, the virus is still able to persist at an undetectable level.

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>3</sup>

Unlike T-cells, these macrophage cells have been shown to persist under ART - giving them the ability harbour 'hidden HIV' in latent reservoirs despite treatment. This poses another major obstacle to virus eradication from infected individuals. If an individual's treatment stops or is interrupted, dormant HIV can re-establish itself by leaking out of these reservoirs.<sup>4</sup>

Discovery of latent HIV residing in these cells gives us new insight into why locating viral reservoirs has been so difficult. The expansive presence of macrophage cells unfortunately makes their isolation and analysis challenging. The long and resilient 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>5</sup>

Indeed, a number of critical technology gaps remain. 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>6</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>7</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 bears any risk of progressing to AIDS or transmitting the virus.

A functional cure could be more precisely described as a level of 'remission'. Some advisory bodies have further suggested that this term should 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>8</sup>

Early antiretroviral treatment (ART), which is initiated close to the 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 the HIV infection re-emerging.<sup>9</sup> Remarkably, they maintained low levels of HIV virus in their systems for an average of seven years before a recurrence of the virus emerged.<sup>10</sup>

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I am personally convinced that remission is achievable. When? I don't know. But it is feasible. We have 'proof of concept'. We have the famous Visconti patients, treated very early on. Now it is more than 10 years since they stopped their treatment and they are still doing very well, most of them.

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- Françoise Barre-Sinoussi, virologist and Director of the Regulation of Retroviral Infections, Institut Pasteur <sup>11</sup>

#### **Case study: 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>12</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>13</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 ARVs. However, it is not yet known why she has fared better than the Visconti cohort or the Mississippi baby.<sup>14</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>15</sup>

While it is still not known why these particular post-treatment controllers were able to retain a state of remission for so long without viral rebound, it is noted that these people were different from those with natural immunity - otherwise known as 'elite controllers'. Hypothesis 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>16</sup>

Although sustained viral remission is clearly possible, it is important to note that all study participants who have achieved this state have since experienced a rebound of their infection. The failure to create a state of permanent remission suggests that even a small amount of virally infected cells at an undetectable level can re-establish the active virus throughout the body.

## 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.<sup>17</sup>

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 during 2008.<sup>18</sup>

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 this co-receptor needed to inject HIV into the cell deficient.<sup>19</sup>

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 affected a successful 'sterilising cure'.

The procedure involved, however, was considered very dangerous, rendering it unfeasible beyond exceptional circumstance as an option for other people living with HIV. Several attempts to repeat this 'cure' have failed, and many of the cures currently being investigated are potentially toxic or risky, which could make clinical trials unethical.<sup>20</sup>

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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

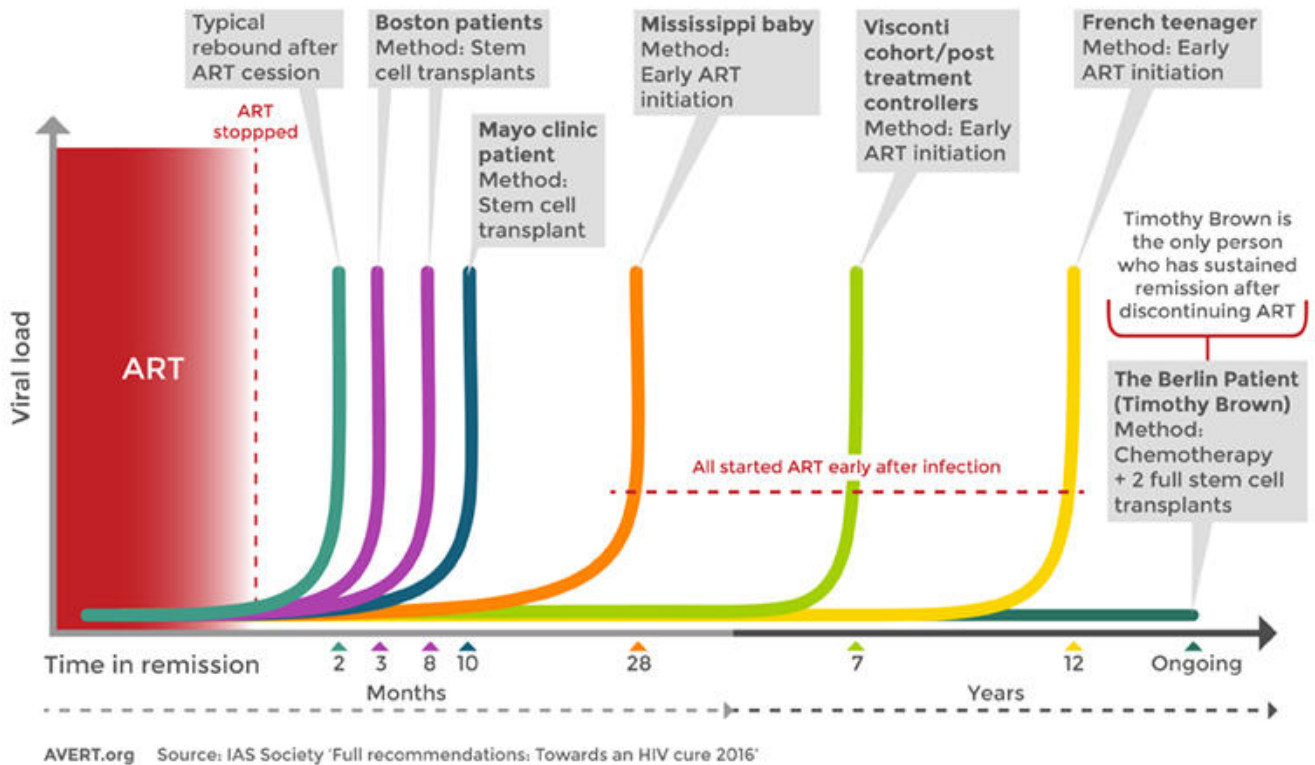
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- Dr Steven Deeks of the University of California, San Francisco<sup>21</sup>

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.<sup>22</sup>

Although Brown has since been routinely monitored, his 'cured' status has remained controversial as examined samples of plasma and tissue indicated very low levels of HIV. However, not all laboratories were able to detect this finding and this anomaly provides further evidence that more sensitive tests are needed for detecting HIV.<sup>23</sup>

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



## Existing research and development

Within these two major strands of functional and sterilising cure research, there are four broad strategies of cure therapy that are currently being investigated. Although each of these developing areas take different approaches, there is a growing overlap between areas as scientists are increasingly working together on their search for a cure.

### '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>24</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>25</sup>

There have been a number of attempts to employ this technique. Most recently, in July 2015, researchers at the University of California, [United States of America \(USA\)](#) announced that a compound called PEP005 in the anti-cancer drug Picato, is effective at waking up dormant HIV. The researchers also tested other compounds capable of reactivating dormant HIV. They found that a substance called JQ1, when used in combination with Picato, boosts the activation of HIV more than seven-fold.<sup>26</sup>

In another study published in the same journal, researchers at the Free University of Brussels reported that they had found two more drug combinations that are effective at flushing HIV out of its hiding places.<sup>27</sup>

However, so far, these drug combinations have only been shown to work on infected tissue and blood samples in the laboratory, not in people living with HIV. Moreover, these drug combinations have only been approved to prevent cancer in sun-damaged skin. Clinical trials are needed to prove that the drugs are safe and effective for people living with HIV.[28](#)

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.[29](#)

## **Stem cell transplants**

The history of stem cell transplantations 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](#)

The outcomes of such treatments were significantly improved after the introduction of HAART and ART but it wasn't until 2008 that two stem cell transplants (in addition to chemotherapy) cured Timothy Brown of his HIV infection in the Berlin patient case.

However, replications of these successful results have proven problematic for researchers. During 2014, when a similar approach was taken with two people from Boston living with HIV who received allogeneic stem cell transplants (without the CCR5 mutation) the results were less successful.

Although both patients displayed undetectable levels of the virus until 12 and 32 weeks after their ART treatment ended, their cancer treatment was not successful in permanently eradicating HIV from their immune systems and both patients experienced viral rebound.[31](#)

A slightly more successful case was discovered by researchers at the Mayo Clinic in Minnesota, United States of America (USA) in 2017. They reported that a 55-year-old man living with HIV who received a bone marrow transplant as part of cancer treatment was able to achieve just under 10 months in remission after discontinuing ART. Although the patient's viral load has since reappeared and treatment has been reinitiated, his viral reservoirs seem to have been greatly diminished.[32](#)

The results from these studies highlight that while a significant reduction in the size of the reservoir was seen after ART discontinuation, the HIV virus was still able to persist 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](#)

## **Gene editing**

Approaches to gene therapy for HIV focus on the modification of cells that are targeted by HIV (such as the CD4 cells) - in order to render them resistant to HIV. Other gene therapy strategies focus on cutting HIV from the infected cell. Currently, both of these approaches are under pre-clinical and clinical investigation.[34](#)

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.[35](#)

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. In 2014, the first human trials of this type of strategy were conducted among 12 people living with HIV, who were given these genetically modified CD4 cells, and then taken off ART.[36](#)

As expected, the HIV levels in their bodies began to rise, but as the modified cells replicated, the level of virus in the body was pushed back down.[37](#) However, the number of modified cells fell over time, halving roughly once a year. The trial has been running since 2009 and all of the participants are now back on treatment.[38](#)

A 2015 study that used a similar technique by introducing modified blood stem cells in HIV-infected mice reported an 80% to 95% decrease in HIV levels.[39](#) Once the virus was gone, the cells continued to function normally with no signs of damage, and appeared to be protected from reinfection. So far, this technique has only been used on animals or cells in the laboratory.[40,41](#)

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The next step is to increase the frequency of the modified cells in HIV-infected patients with the ultimate hope that if we do, we will achieve a `functional cure` and eliminate the need for continued HAART

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- *Dr Carl June, Director of Translational Research at the Abramson Family Cancer Research Institute at the University of Pennsylvania School of Medicine*[42](#)

Most recently, researchers reported success in using the gene editing technique to remove HIV genes completely from infected cells. There have encouraging trials investigating CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) in which researchers use 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.[43](#)

### **Case study: 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%

Incredibly, 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. Scientists now aim to propose a replicated trial in humans.[44](#)

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 in order 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 cells and, the most commonly researched, broadly neutralising antibodies (bNAbs).<sup>45</sup>

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.<sup>46</sup>

In 2014, the discovery of such antibodies were found in a South African woman (known as Caprisa 256) three years after she had become infected with HIV. Researchers were specifically interested in the 'long arms' that her antibodies possessed which are able to permeate through the virus' protective barrier - essentially reducing the lifespan of HIV.<sup>47</sup>

Unfortunately, in the case of Caprisa 256, the antibodies were not able to work quickly enough to destroy the virus and she is currently on ART. This problem is consistent for bNAbs-producing persons. Because it takes several weeks for the antibodies to develop they are unable to keep up with the rate of viral mutation - by the time the working antibodies become available, they're no longer working for the developed virus in the person's body at that time.<sup>48</sup>

Abdool Karim, one of the scientists working on the study said:

***"When a person develops broadly neutralising antibodies it actually has no benefit to the individual who develops it; [they are] not able to neutralise their own virus."***<sup>49</sup>

Although bNAbs may not be useful for the individual patient who produces them, extracting them and working on the potency of such antibodies - so that they are a step ahead of the quickly changing virus - does provide some hope for other patients who have more sensitive and less developed viruses.<sup>50</sup>

There are now several classes of bNAbs in clinical development which have the possibility to influence new gene editing strategies to benefit others living with HIV. 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.<sup>51</sup>

## Where 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.<sup>52</sup>



There has also been a developing interest in fostering collaborations with oncologists, to merge HIV cure and cancer disciplines, in order 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 tumor 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>53</sup>

Aside from the pursuit for further knowledge about HIV, there are many other hurdles for researchers to overcome on their path to discovering a cure. Cost and scalability of research proposals put pressure on scientists to set realistic expectations about how long it will be before a workable formula is discovered.<sup>54</sup>

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I can't tell you how long it will take or how much it will cost, but now we are collaborating [across fields of research], it will take a considerably shorter time

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- Rowena Johnston of AmFAR<sup>55</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>56</sup>

## What about a vaccine?

Although treatment and cure research for those already living with HIV is a predominant area of focus for scientists, a vaccine to prevent HIV infection in the first instance remains an important but challenging priority for researchers.

New HIV infections remain high and existing prevention and treatment programmes are a costly investment for many countries. The history of smallpox and polio shows that when highly effective, affordable vaccines are available, mass vaccination programmes can eradicate infectious diseases. A one-time intervention for HIV could thus be essential in establishing long-term control of the virus.<sup>57</sup>

To be effective, a vaccine would require a substance that teaches the immune system how to create protective immune responses against HIV. While scientists have discovered a great deal about the immune system's response to HIV over 30 years of research, they have not yet identified a fully

effective therapy.

The development of a vaccine to prevent HIV infection is especially challenging because:

- the diversity of [HIV subtypes](#) and the frequency with which the virus mutates means that a vaccine would need to prevent infection from multiple strains. But in general, antibodies are not effective against multiple strains
- HIV attacks and uses the same CD4 cells that are needed for an effective immune response.

One of the most promising recent attempts to create an effective vaccine came in 2014 when scientists induced sustained remission of the simian form of HIV (SIV) in infected monkeys. The vaccine worked to suppress the virus for almost two years, in some cases, and almost completely replenish key immune cells destroyed by the virus – a development unachievable with ART alone.[58](#)

Human trials have also shown some promising results. It has been estimated that even a modestly effective vaccine—one that is 50% effective—may be enough to significantly reduce new HIV infections among key populations.[59](#) In 2009, a human trial in Thailand came close to achieving this using the RV144 vaccine formulation. Results from the study showed that individuals who received a vaccine were 31% less likely to become infected with HIV than people who received a placebo.[60](#)

Another human trial (HVTN 702) is currently underway in South Africa, and hopes to build on the success of the RV144 trial by using a strengthened version of the same vaccine used in Thailand. It was modified because the strain of HIV in South Africa is not the same as the strain in Thailand and researchers are hoping that the modified vaccine will produce more effective results.[61](#)[62](#)

During the trials, participants will receive five injections of the vaccine over the course a year and will be monitored for another three years to see if the vaccine has taken effect.

Although the trial has hopes of studying 5,400 healthy, sexually active men and women, they have only so far been able to attract 500 volunteers. The duration of the trial, in addition to the personal commitment and risk taken, have been cited as reasons for the slow enrolment process.[63](#)

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There is so much stigma. I want to be part of a generation that changes this and I want my children to be proud one day of their father for getting involved in making history.

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- Mr Benenengu, Participant in the HVTN 702 trials[64](#)

If the HVTN 702 vaccine in South Africa shows sustained protective results and achieves licensing, it could mean that thousands of new infections could be averted in future. However, it is worth noting that the benefits of such a vaccine would only work as a preventative cure for those who are HIV negative and will not affect people living with HIV. Full results from the trial are expected to be announced in 2020.[65](#)

## **Ethical considerations for HIV trials**

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

Because the consequence of infection can mean a lifetime on ART there is substantial participant

risk associated with many HIV-vaccine trials and communicating these risks to the larger community is challenging too. As such, consenting participants who become infected with HIV in such trials should be assured that they will be referred to medical providers for care and treatment. They should also be given advice on how to reduce their risk of transmitting the virus.<sup>66</sup>

In similar vein, in studies that focus on finding a functional cure for people living with HIV, the goal of achieving HIV remission might turn out to be less exciting for people living with HIV than that of a cure. Participants might find that coming off ART for such trials, or the prospect of viral rebound after remission, distressing.<sup>67</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>68</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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