BACKGROUND

Combination antiretroviral therapy (ART) is a highly effective treatment for HIV infection, preventing disease progression in the vast majority of recipients. When ART is accessible and started early in the course of infection, the lifespan of HIV-positive people is typically very close to that of comparable HIV-negative people. But ART can have side effects, is often costly, and requires strict daily pill taking that can lessen quality of life. Because of the limitations of ART, a cure for HIV infection remains a vital goal for research.

In the mid-1990s, when it was first shown that triple combinations of antiretroviral drugs could suppress HIV replication, there were hopes that long-term ART would eventually cause all HIV-infected cells in the body to die off, curing the infection. But scientists discovered that HIV persists in an inactive, latent form in long-lived immune system cells known as memory CD4 T cells, and that these latently infected cells can become active and produce infectious virus when ART is interrupted (see sidebar, “Understanding HIV Latency”).

For this reason, HIV viral load almost always returns rapidly if ART is stopped. The latent HIV that persists despite ART is described as the HIV reservoir, and it is considered the major barrier to a cure.

HIV CURE RESEARCH INFORMATION SHEET

December 2017

HIV CURE RESEARCH STATUS: QUICK SUMMARY

- One person, Timothy Ray Brown, is considered cured, and there are several other documented cases where HIV viral load did not rebound for an extended period after an ART interruption (referred to as remission)

- These outcomes remain rare and resulted from exceptional circumstances—stem cell transplants for HIV-positive people with cancers or extremely early initiation of ART—but they are providing important clues to researchers working to develop a cure

- There are more numerous—but still relatively rare—examples of individuals who have controlled HIV viral load to low levels either naturally (elite controllers) or after an ART interruption (typically after beginning treatment early), but it is uncertain how long this immune-mediated control can last and if it may come at some cost to long-term health

- While many different therapeutic approaches are being studied, so far no broadly usable interventions have led to cures or remission—the best reported results involve small reductions in the HIV reservoir and some cases of short-term control of HIV viral load to low levels after ART interruption
TIMOTHY RAY BROWN

There is one individual considered cured of HIV infection, providing evidence that the goal is achievable.

Timothy Ray Brown (initially known as the Berlin patient) had been HIV-positive since 1995 and taking ART for around four years when, in 2006, he developed acute myelogenous leukemia (AML)—a potentially life-threatening cancer. The diagnosis led to the need for a stem cell transplant, a risky treatment that essentially creates a new immune system in the recipient by transferring bone marrow cells donated by another individual. Chemotherapy drugs and radiation are used to wipe out the existing immune system and make way for the donor cells. The procedure can only be used in life-threatening cancers because it carries a risk of death of approximately 20% to 30%.

The doctor supervising Brown’s cancer treatment, Gero Hütter, decided to search for a bone marrow donor with a rare genetic mutation (designated CCR5Δ32) that causes immune system cells to be resistant to most strains of HIV. When it is inherited from both parents, the CCR5Δ32 mutation prevents immune system cells from being able to display a protein, named CCR5, that the most common forms of HIV use as a latch to gain entry into target cells. Hütter’s search was eventually successful, but required assessments of over 60 potential donors.

Brown received two stem cell transplants from the donor as part of a difficult course of treatment for the AML. The cancer was ultimately cured, and despite the fact that ART had been interrupted, tests also revealed that HIV viral load had not rebounded. Hütter first reported the case at a scientific conference in 2008, at which time Brown had remained off ART with no detectable HIV in blood or tissue samples for 285 days.

It has now been over 10 years since the stem cell transplants, with no sign of a return of HIV. While there is no technique that can survey the entire body for the presence of HIV, the continued absence of any viral load rebound is viewed as compelling evidence that Brown is cured.

The risks associated with stem cell transplants mean they are not a practical approach to curing HIV-positive people who do not have cancers, but Brown nevertheless represents a beacon of hope for the future.

There are several programs hoping to repeat the outcome observed in Brown by obtaining donors with the CCR5Δ32 mutation for HIV-positive individuals who require stem cell transplants due to cancer diagnoses. However, results to date unfortunately underscore the dangers: six cases have been described in which transplants were provided from donors with the CCR5Δ32 mutation, but all recipients died either due to the cancers or complications from the procedures.

CASES OF TEMPORARY REMISSION

Brown remains the only known example of an HIV cure, but over the past several years there have been an increasing number of reports of individuals who have experienced a transient period of remission after interrupting ART. These cases also provide some reasons for optimism that a broadly applicable cure may eventually be possible.

THE MISSISSIPPI BABY

One of the most widely publicized examples of remission is the Mississippi baby. Born to a mother whose HIV infection was not diagnosed until in labor, the neonate was started on ART within hours of delivery. Treatment was maintained for around 18 months, at which time the mother and baby temporarily stopped attending medical follow-up visits. When they returned to care, doctors learned that ART had been interrupted in the infant but, surprisingly, HIV viral load remained undetectable.
The initial theory was that rapid initiation of ART might have prevented the formation of the HIV reservoir, leading to a cure. The Mississippi baby remained off ART for a little over two years with no measurable HIV, but then experienced a rebound in viral load, requiring treatment to be restarted.

Researchers now believe that the very early start of ART greatly limited the size of the reservoir of latently infected CD4 T cells, but a few were likely present, and eventually one or more became activated leading to renewed HIV production. CD4 T cells can become activated for a number of reasons, most commonly due to encountering an infectious agent or other substance that they recognize and respond to—part of their job as immune system cells.

The outcome in the Mississippi baby highlighted that HIV can persist at levels undetectable by current technologies, and that long-term monitoring is essential even if it might at first appear that an individual has been cured.

**THE PREP DEMONSTRATION PROJECT PARTICIPANT**

The closest adult equivalent to the Mississippi baby is an individual who was diagnosed with HIV extraordinarily early (within approximately 10 days), due to acquiring the infection during a short window of time between screening for participation in a pre-exposure prophylaxis (PrEP) demonstration project and the day they were started on the first dose of the PrEP drug Truvada.

Combination ART was begun as soon as the HIV diagnosis was confirmed, and subsequent tests conducted while on treatment were unable to detect HIV. After 34 months, the individual agreed to interrupt ART, and HIV remained undetectable by any measure for 224 days. Viral load then rebounded, necessitating reinstitution of treatment.

**THE BOSTON PATIENTS**

The Boston patients are two HIV-positive men who required stem cell transplants to treat cancers. They did not receive cells from donors with the CCR5Δ32 mutation, but HIV became undetectable after the procedures nevertheless. ART was maintained throughout, leading researchers to suspect that their new donor-derived immune system cells may have been protected from the virus. Both individuals also developed a condition known as graft-versus-host disease (which involves donated cells attacking recipient tissues) after their transplants, and this was thought to have potentially contributed to the clearance of HIV-infected cells. ART was eventually interrupted, and in one case HIV remained undetectable for 12 weeks, and in the other 32 weeks, before viral load re-emerged and treatment was reinitiated.

**THE MAYO CLINIC PATIENT**

Early in 2017, researchers from the Mayo Clinic in Rochester described another HIV-positive man with similarities to the Boston patients. Also a recipient of a stem cell transplant from a donor lacking the CCR5Δ32 mutation as part of treatment for cancer, the individual continued on ART after the procedure and displayed declining levels of HIV reservoirs that ultimately became undetectable. A little over two years after the transplant, ART was interrupted, leading to a period of remission from detectable HIV that lasted 288 days. Viral load tests then revealed that HIV replication had restarted, and the individual resumed ART.
POSSIBLE LESSONS FROM REMISSION

These five cases of transient remission are connected by the fact that all appeared to result from the HIV reservoir being very small at the time of ART interruption. The size in the two Boston patients has been estimated as 290 to 2900 latently infected cells and 40 to 730 latently infected cells, respectively (an estimated reduction of more than three logs—1,000-fold—compared to the pre-transplant baseline).

This is potentially important because it suggests that a central goal of HIV cure research—shrinking the size of the HIV reservoir—can at least significantly delay the rebound of HIV when ART is interrupted.

Mathematical modeling studies conducted by the researcher Alison Hill indicate that achieving even greater reservoir reductions—perhaps on the order of over four logs (10,000-fold or >99.99%)—could lead to a lifelong cure in the majority of individuals. Reducing the HIV reservoir to this extent represents a stern challenge, but at least there is a sense of a target to aim at.

The other link between these five cases is that the period of remission appears to have been caused by the few latently infected CD4 T cells that were present remaining dormant, rather than the immune system actively controlling HIV.

No significant immune responses against HIV could be detected in any of the individuals, which was expected because of the rapidity with which ART was started in the Mississippi baby and PrEP demonstration project cases (suppressing the virus before the immune system mounted a response), and due to the fact that the Boston and Mayo Clinic patients developed new immune systems—which had not yet encountered HIV—from their HIV-negative stem cell transplant donors.

The absence of immune responses appears to make this type of remission distinct from a different form—referred to as virologic remission or post-treatment control—that has also received attention in mainstream media coverage of HIV cure research.

POST-TREATMENT CONTROL

The best-known examples of post-treatment control are the VISCONTI cohort, an unusual group of HIV-positive individuals identified by researchers in France who began ART early in infection, continued for several years, and then interrupted and have maintained viral loads at low or undetectable levels—in some instances for over a decade.

A number other individual case reports have broad similarities, including a perinatally infected French teenager and a nine-year-old South African child who have displayed control of HIV viral load for 12 and 8.75 years, respectively, after limited periods of ART.

Post-treatment controllers generally display immune responses against HIV, including antibody and CD4 and CD8 T cell responses, although there is considerable individual variability. The prevailing theory is that these cases represent some sort of active containment of HIV replication by the immune system. Based on this evidence, the possibility of inducing immunological control of HIV is an avenue being explored by cure researchers.

A potential concern about post-treatment control as a model for an HIV cure relates to the parallels with rare HIV-positive individuals known as elite controllers (the frequency is estimated to be around 1% or less). Elite controllers suppress viral replication to undetectable levels for many years without ART, and this phenomenon is associated with strong and effective immune responses targeting the virus, particularly CD4 and CD8 T cells. Certain genetic traits that influence the performance of CD8 T cells have been shown to increase the likelihood of becoming an elite controller.
The caveat is that long-term studies have found that elite control is not necessarily completely protective against disease progression. The efforts of the immune system to control HIV can be associated with increased levels of inflammation and a slow decline in CD4 T cell numbers, ultimately leading to AIDS (albeit at a far slower pace than is observed in individuals with higher viral loads). It has been reported that some post-treatment controllers in the VISCONTI cohort have experienced this type of slow progression since the time the cohort was originally described.

More optimistically, there is a subset of elite controllers who exhibit extraordinarily strong control of HIV, and they may offer cure researchers a model of immune-mediated containment with less potential for detrimental effects.

UNDERSTANDING HIV LATENCY

Every cell in the body, with the exception of red blood cells, contains a copy of the entire genome. The genome consists of DNA and can be thought of as a production line capable of manufacturing all the protein components that make up your body (this is done via an intermediate step, wherein the DNA makes RNA, which then makes proteins).

Different cells employ just the parts of the DNA production line that they need to make the proteins that allow them to do their job, e.g. kidney cells make the proteins they use in clearing waste and immune system cells, like CD4 T cells, make proteins involved in the work they do in responding to infections.

Memory CD4 T cells can be in an activated state when they are responding to something—this requires the DNA production line to be busy, making the proteins the cell needs to go about its work. But memory CD4 T cells can also de-activate into a resting state, which causes the DNA production line to largely shut down.

HIV prefers to replicate in activated memory CD4 T cells, because it hijacks the busy DNA production line to manufacture more viruses, which can then exit and infect other cells. But if HIV infects a memory CD4 T cell when the DNA production line is in the process of shutting down (or is shut down), the virus essentially becomes trapped in the machinery, and can only start making viruses if the CD4 T cell becomes activated again and the DNA production line cranks back up.

In technical terms, HIV DNA becomes integrated into the DNA genome of the resting memory CD4 T cell. While the cell remains resting, HIV stays latent and is invisible to the immune system because no virus proteins are being made.

Recent estimates suggest the total number of latently infected CD4 T cells in the body is perhaps in the range of 240 million to 400 million, with the majority residing in lymphoid tissues.

Some evidence indicates that HIV may also be able to persist in other cell types, such as macrophages, stem cells, and certain brain cells. But there is still uncertainty regarding whether HIV can become latent and then subsequently reactivate to produce infectious virus in these cells, as it can in the case of CD4 T cells. Ongoing research is attempting to definitively ascertain if cells other than CD4 T cells contribute to the HIV reservoir.
The examples of remission and post-treatment control illustrate a key difficulty facing HIV cure researchers: even if success appears to have been achieved, people will need to be followed for a long period to ensure that there is no return of viral load or any negative health consequences if some virus remains present but controlled.

CURRENT THERAPEUTIC APPROACHES

Scientists are pursuing many different approaches that may have the potential to contribute to a cure for HIV.

RESERVOIR LIMITATION

Many studies have shown that starting ART as soon as possible after HIV infection occurs greatly limits the size of the HIV reservoir that is formed. The longer the duration of untreated HIV infection, the larger the size of the HIV reservoir. For this reason, people who started ART early may be ideal candidates for interventions seeking to deplete the HIV reservoir, and many research studies aim to recruit this population. Early diagnosis of HIV can be challenging in adults because the acquisition of infection is not necessarily accompanied by symptoms, and even if symptoms occur, they are typically flu-like and nonspecific.

Newborns who have acquired HIV infection from their mothers represent a population in which early diagnosis is more feasible. The administration of ART shortly after birth appears to have played a key role in the Mississippi baby case. A large clinical trial, IMPAACT P1115, is attempting to evaluate whether early ART can lead to remissions or cures in newborns who acquired HIV because their mothers did not receive ART to prevent mother-to-child transmission (MTCT), or because MTCT was inadequate.

RESERVOIR DEPLETION

A great deal of effort is being put into understanding how HIV becomes latent and persists despite ART in order to develop methods to eliminate the long-lived reservoir of the virus.

A variety of approaches that appear able to awaken latent HIV have been identified (known as latency-reversing agents), and some have advanced into human clinical trials.

Making latent HIV active is a crucial first step toward eliminating the HIV reservoir, as it makes it possible for the immune system or immune-based therapies to recognize and target latently infected cells for destruction.

The one-two combination of activating latent HIV followed by targeting the infected cells for elimination is sometimes referred to as the “kick and kill” or “shock and kill” approach.

So far, the most studied latency-reversing agents are histone deacetylase (HDAC) inhibitors, a class of cancer therapies. Examples include vorinostat, panobinostat, and romidepsin. These drugs target enzymes involved in keeping HIV’s genetic material under lockdown in latently infected cells.

Clinical trial results to date indicate HDAC inhibitors can awaken latent HIV, but no evidence of a reduction in the size of the reservoir has been documented. The results support the idea that additional strategies are needed to help eliminate the infected cells. It is not yet known whether the entire latent HIV reservoir can be roused by HDAC inhibitors, or only a portion thereof. HDAC inhibitors can also have significant toxicities, which is a concern for many candidate latency-reversing agents.
CELL PROTECTION

The experience of the Boston and Mayo Clinic patients suggests that receipt of a stem cell transplant from a donor with the CCR5Δ32 mutation was likely key for Timothy Ray Brown’s cure. This provides a rational for researchers attempting to mimic the effects of the CCR5Δ32 mutation using gene therapies.

The main focus of these approaches is CD4 T cells, HIV’s primary target. Researchers are testing gene-editing technologies that can prevent the CCR5 receptor from being displayed on cells. CD4 T cells, in some cases together with stem cells, are extracted from HIV-positive individuals, genetically modified, and then expanded in number and reinfused. There are also gene therapies that aim to equip cells with single or multiple proteins capable of blocking HIV replication.

A significant challenge for gene therapies is modifying enough cells to provide a benefit, and studies are investigating different methods to try to maximize the number of HIV-resistant cells that are created.

For HIV-positive people with life-threatening cancers requiring treatment with stem cell transplants, several clinical trials are employing gene therapy to modify stem cells from normal donors before transplantation, in an attempt to render the cells resistant to HIV (in the absence of the natural CCR5Δ32 mutation).

IMMUNE ENHANCEMENT

For many common viral infections, the immune system is highly effective at containing or clearing the virus. But in HIV-positive people, many of the immune system cells that target the virus have been shown to be dysfunctional, in part because the virus infects CD4 T cells that would normally coordinate the immune response.

Researchers are therefore investigating whether effective immune responses to HIV can be restored or created by new therapies.

Among the candidates are therapeutic vaccines and infusions of broadly neutralizing antibodies (bNAbs) capable of inhibiting the replication of many different HIV strains. In addition to inhibiting HIV, bNAbs may also have the potential to bind to latently infected cells that have been induced to produce HIV by latency-reversing agents, flagging them for elimination by the immune system.

Both therapeutic vaccines and bNAbs are being studied in combination with latency-reversing agents, in hopes they might be able to provide the “kill” part of the “kick and kill” strategy.

A wide variety of other immune-based approaches are under investigation, including immune system signaling proteins (cytokines such as IL-15, alpha interferon and IL-2), immune stimulants called toll-like receptor (TLR) agonists, and immune checkpoint inhibitors, which have shown efficacy against cancers.

RISKS, BENEFITS, AND ETHICS

The possibility of being cured of HIV infection is obviously exciting to many HIV-positive people. This creates a strong incentive to participate in HIV cure research. But because the research is currently in an early phase, there are potentially significant risks, and little or no prospect of any study participant being cured. There are ongoing dialogues between scientists and the community of HIV-positive people and their advocates about how best to define and communicate the potential risks and benefits of participation in HIV cure research. The goal is to ensure that all studies are conducted ethically and minimize any potential risk. This is particularly important now that ART is so effective that most HIV-positive people can expect to live into old age.
RELATED LINKS

TAG maintains a regularly updated listing of clinical trials and observational studies related to the research effort to cure HIV infection: http://www.treatmentactiongroup.org/cure/trials

An annual description of approaches under investigation in HIV cure research can be found in TAG’s Pipeline Report: http://www.pipelinereport.org/home

A resource page containing articles, reports, and links to other organizations and websites relevant to cure research is available at: http://www.treatmentactiongroup.org/cure

Updates adapted in part from TAG’s contributions to the December 2017 Positively Aware special issue on HIV cure research.

Treatment Action Group (TAG) is an independent, activist and community-based research and policy think tank fighting for better treatment, prevention, a vaccine, and a cure for HIV, tuberculosis, and hepatitis C virus.

This information sheet made possible, in part, by generous support from the Elton John AIDS Foundation.