HIV CURE RESEARCH FACT SHEET

TAG Treatment Action Group

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Background

Combination antiretroviral therapy (ART) is a highly effective treatment for HIV infection, preventing progression of the disease 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 toxicities, 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 lead to the clearance of all HIV-infected cells from the body. But scientists discovered that HIV persists in an inactive, latent form in certain long-lived immune system cells (memory CD4 T cells), and that at least some of these cells can become active and produce infectious virus when ART is interrupted. 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 achieving a cure.

Over the last decade, there has been a renewed scientific focus on curing HIV infection. In 2008, evidence was presented that an individual, Timothy Brown (initially known as the Berlin patient), had been cured. Brown has since remained free of any sign of active HIV infection. Brown's cure resulted from a complicated, high-risk stem cell transplantation procedure that was needed as part of treatment for a life-threatening cancer. Although this procedure is too dangerous to be used in HIV-positive people without life-threatening cancers, Brown's case has helped restore hope that a cure for HIV is possible.

Brown is currently the only person considered cured of HIV, but there are other rare examples of individuals who have been able to stop ART and maintain undetectable or low levels of HIV viral load for extended periods of time. A term that has been applied to these cases is *functional cure*, intended to mean that HIV is still present in the body but not causing harm. However, it has been proposed that *remission* is a better description, because in some of these cases HIV viral load has rebounded to high levels after a long period of being undetectable. The most well known example is the "Mississippi baby," a child initially thought cured of HIV infection who experienced a rebound of viral load after 27 months off ART.

Another reason to use the term *remission* is that it is difficult to know for sure whether even very low levels of HIV might eventually damage the immune system and cause illness. The basis for this concern is that there are some HIV-positive individuals, known as elite controllers, who naturally control HIV to low levels, but long-term research has found that progression to AIDS can still sometimes occur in elite controllers even after decades.

One of the challenges for HIV cure research is that 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. Currently, they can be broken down into several broad categories:

Reservoir-limiting: approaches that use ART (or other interventions) as soon as possible after the acquisition of HIV infection to limit the size of the HIV reservoir

Reservoir-depleting: approaches that aim to reduce the amount of HIV that persists after ART suppresses viral replication

Cell-protecting: approaches designed to protect potential target cells from HIV infection

Immune-enhancing: approaches to strengthen the immune response against HIV in the hope of enabling the body to control or even gradually eliminate HIV reservoirs

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 study plans 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 (PMTCT), 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 virus. A variety of approaches that appear able to awaken latent HIV have been identified (described as "latency-reversing agents" or LRAs), and some have already 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 other therapies to target latently infected cells for destruction. This 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. 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 if the entire latent HIV reservoir can be roused by HDAC inhibitors, or only a portion. HDAC inhibitors can also have significant toxicities, which is a concern for many candidate latency-reversing agents.

Cell Protection

A key element of the cure achieved in Timothy Brown was the receipt of a stem cell transplant from a donor lacking a receptor used by HIV to gain entry into target cells. The receptor is CCR5, and the rare genetic mutation that affects whether it is present on cells is called the CCR5Δ32 mutation. People who inherit the CCR5Δ32 mutation from one parent are known as heterozygotes, and they have reduced levels of the CCR5 receptor on their cells. People who inherit the CCR5Δ32 mutation from both parents are known as homozygotes, and their cells completely lack the CCR5 receptor. Brown's donor was a CCR5Δ32 homozygote. Stem cell transplants lead to the development of an immune system entirely composed of cells derived from the donor, so in Brown's case his newly transplanted immune system lacks CCR5 receptors and is resistant to most strains of HIV. There are some strains of HIV that can enter cells via an alternative receptor, CXCR4, but it appears that Brown did not harbor any of these HIV variants. Brown's case suggests that protecting cells from HIV could be a viable approach to a cure.

Because stem cell transplants are so risky (the mortality rate associated with the procedure is around 20–30%), researchers are investigating alternative ways of making immune system cells resistant to HIV. The main focus of these approaches is CD4 T cells, which are HIV's primary target. The leading candidates are gene therapies designed to mimic the effects of the CCR5Δ32 mutation by preventing the CCR5 receptor being displayed on cells. There are also gene therapies that aim to equip cells with 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, studies are looking at whether the success achieved in Timothy Brown can be repeated. There are research programs in both the United States and Europe that will attempt to identify potential stem cell donors that are CCR5Δ32 homozygotes. Additionally, there are several trials using gene therapy to modify stem cells from normal donors before transplantation, in an attempt to render the cells resistant to HIV.

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 HIV 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 antibodies capable of inhibiting many different HIV strains (broadly neutralizing antibodies). Additionally there are studies of therapies that may be able to restore the function of defective immune responses against HIV.

Combinations

The above categories capture the main current approaches in HIV cure research, but there is also strong interest in the possibility of combining them. For example, clinical trials are evaluating the combination of HDAC inhibitors and therapeutic HIV vaccines in the hope of awakening latent HIV and then promoting the clearance of the infected cells by boosting the immune response to the virus.

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 many unknowns, potentially significant risks, and little prospect of any study participant's 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.

The Mississippi Baby Case and Pediatric HIV Cure Research

In March of 2013, there was widespread media coverage of a report that an infant in Mississippi might have been cured of HIV; an article describing the case was published in a scientific journal later that year.

The mother of the infant was not diagnosed with HIV infection until in labor, and there was no opportunity to administer ART to reduce the risk of mother-to-child transmission. This situation is rare in the United States, where the widespread use of ART to prevent mother-to-child transmission has almost completely prevented new cases of HIV in newborns.

The newborn was therefore considered to be at a very high risk of acquiring HIV, and the doctor chose to start treatment with ART while waiting for the results of diagnostic tests. Some of the media coverage of the case has characterized the decision to start the newborn on ART as unusually aggressive. This is because current U.S. guidelines generally recommend a preventive ART regimen in this situation, which involves fewer doses compared with regimens used for treatment. However, recommendations change based on new research findings, and some countries—including the United Kingdom and Canada—already recommend considering a treatment regimen under these circumstances.

When the results of diagnostic testing became available, they confirmed that the infant had HIV. The criteria for the diagnosis are two independent tests for HIV genetic material, and in this instance HIV DNA and HIV RNA were detected in samples taken at 30 and 31 hours after birth. ART was continued, and subsequent HIV viral-load measurements showed an expected decline to undetectable levels in response to the treatment.

ART was maintained for around 18 months until the mother and infant stopped attending doctor visits, for reasons that are unknown. When they returned to care about five months later, the doctor learned that ART was no longer being administered to the infant.

The excitement about the case was due to the test results obtained after the infant returned to the doctor: HIV viral load remained undetectable despite the five-month period off ART. There have been many prior studies of ART interruptions in children, and all have demonstrated that viral-load rebound occurs rapidly—typically to very high levels.

The surprising outcome led the doctor to bring in outside researchers with expertise in measuring HIV reservoirs and searching for trace amounts of the virus. Additional testing could only rarely detect extremely low levels of viral genetic material, and no HIV capable of replicating could be found. These results suggested to the researchers that the immediate use of ART may have prevented the formation of long-lived HIV reservoirs and cured the infant.

The Mississippi baby case inspired the hope that perhaps other babies born to mothers who had not received adequate prevention of mother-to-child HIV transmission could be cured. A clinical trial was designed to test this possibility. But in July 2014 it was announced that, after 27 months off ART with no detectable HIV, viral load had rebounded. The child has been restarted on ART and remains in good health. Efforts are now focused on trying to understand the reason for the long period of remission in order to figure out how to extend the period further. The ultimate goal is to make the remission permanent. The clinical trial based on the case is going ahead, with the aim of assessing the benefits of immediate ART and whether similar or longer remissions can be obtained in other infants.

Who Has Been Cured?

Timothy Brown has been off ART with no sign of active HIV infection for over six years and is the only person whom scientists currently consider cured. Trace amounts of HIV genetic material have been detected in a small minority of tissue samples, but the levels were so low that these results may have represented false positives. Attempts to try and repeat the cure achieved in Brown in other HIV-positive individuals with cancers requiring stem cell transplantation have so far not met with success; in all reported cases to date, the individuals have died due to the cancer or complications of the transplantation procedure. One individual appears to have harbored HIV strains capable of using the CXCR4 receptor prior to stem cell transplantation, and this virus rebounded to high levels afterward.

Although Brown is the only person thought cured, more instances of potential HIV remission have been reported; in these cases, control of HIV to very low or undetectable levels has been maintained over years of ART interruption. The VISCONTI cohort in France represents the most famous example; at the last published report, the cohort consisted of 14 individuals treated very early after acquiring HIV who stayed on ART for several years before interrupting. Control of HIV has been maintained for over 10 years in some participants. Researchers are conducting extensive studies to try to ascertain the mechanisms of HIV control in these and other similar cases in order to inform the development of cure strategies.

TAG Resource Links

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

TAG's Cure Research Media Monitor offers commentary and background on HIV cure research stories in the news: http://www.treatmentactiongroup.org/cure/media-monitor.

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

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