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I HIV PREVENTION

A. Truvada vs. Descovy for HIV prevention

Truvada is the brand name of a pill containing two anti-HIV drugs:

- tenofovir disoproxil fumarate (TDF)
- emtricitabine (FTC)

Generic formulations of these drugs are also available in one pill.

When used as prescribed, the medicines inside Truvada are highly effective at reducing a person's risk of getting HIV. This was the case in randomized clinical trials and in observational studies.

As mentioned, Truvada contains TDF. In some people this formulation of tenofovir is associated with an increased risk for kidney injury and, in some cases, thinner-than-normal bones. The manufacturer of Truvada, Gilead Sciences, has developed a new formulation of tenofovir called TAF (tenofovir alafenamide). TAF mostly concentrates inside cells of the immune system and is generally associated with a better safety profile than TDF. TAF is formulated with other medicines in one pill. The specific combination of TAF + FTC is sold under the brand name Descovy.

In a large randomized, placebo-controlled clinical trial sponsored by Gilead Sciences, called the Discover trial, HIV-negative participants were

produced by



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randomly assigned to receive one of the following pills taken once daily:

- Truvada
- Descovy

Participants did not know which formulation they received for the first 96 weeks. After this time, the study was unblinded and all participants were offered Descovy.

Most participants are gay or bisexual men and about 1% are transgender women.

The study is still ongoing; however, interim results have been released.

Overall, cases of HIV infection that occurred were distributed as follows:

- Truvada – 15 cases
- Descovy – seven cases

This difference between the two regimens was not statistically significant. What these results show is that when it comes to effectiveness, both regimens are similarly effective (the technical term for this is “non-inferior”) at reducing the risk for HIV infection.

It is important to note that additional analyses were done, particularly on blood samples from people who became infected during the study. These revealed that most people who became infected either were not taking the study drug exactly as directed or had become infected at the start of the study, perhaps within hours of the screening process. When these factors are taken into account (and such people are excluded from analysis), only one person on each formulation became infected.

However, safety analyses, particularly on bone thinning, show a clear difference in favour of Descovy.

Gilead Sciences plans to seek regulatory approval for using Descovy as part of a package of tools to reduce the risk of HIV infection in Canada, Australia, the European Union and the United States later this year.

Study details

The average profile of participants upon entering the study was as follows:

- age – 34 years (note that ages of people in the study were between 18 and 72)
- major ethno-racial groups: white – 60%; Hispanic – 24%; Black – 9%; Asian – 5%

Participants were required to have at least one of the following:

- condomless anal intercourse with at least two unique male partners in the past 12 weeks (partners must be either HIV positive or of unknown HIV status)
- documented history of syphilis in the past 24 weeks
- documented history of rectal gonorrhoea or chlamydia in the past 24 weeks

Overall results

After 96 weeks, the overall distribution of HIV infections was as follows:

- Truvada – 15 infections
- Descovy – seven infections

At first it appeared that Descovy reduced the risk of infection by at least 50%. However, when researchers subsequently analysed blood samples and other data they noted that most infections were likely caused by the following factors:

Poor adherence

- Truvada – 10 infections were linked to less-than-ideal levels of tenofovir in the blood; this suggests that these participants were not taking Truvada every day
- Descovy – six infections were associated with less-than-ideal levels of tenofovir in the blood; this suggests that these participants were not taking Descovy every day

Suspected infection at the start of the study (baseline)

- Truvada – four infections
- Descovy – one infection

Thus, when this information about drug levels/adherence and very early infections is taken into account and the people with these issues removed

from the analysis, the numbers of people infected on each formulation was as follows:

- Truvada – one infection
- Descovy – one infection

Safety analyses

Overall, Truvada and Descovy were well tolerated. The proportions of people who developed drug-related side effects were as follows:

- Truvada – 23%
- Descovy – 20%

As most side effects were generally mild to moderate, perhaps a better indicator of tolerance is the proportions of people who left the study prematurely due to side effects, distributed as follows:

- Truvada – 2%
- Descovy – 1%

Diarrhea appeared to be a fairly common issue in the study, with about 16% of participants who took either study pill reporting it.

Changes to bone mineral density

Overall, about 383 participants were assessed for changes in bone mineral density. In general, people taking Descovy had a small increase in their bone mineral density in their spine and hips, as assessed by low-dose X-ray scans called DEXA (dual-energy X-ray absorptiometry). In contrast, a small decrease in bone mineral density (about 1%) occurred among Truvada users.

The increase in bone density occurred among Descovy users because many participants were young men in their late teens or early 20s whose bones were still developing. Their bone density would have naturally increased. What is important to note is that Descovy did not harm their bone development.

Focus on the kidneys

Several different tests were used to assess kidney health in this study:

- eGFR – estimated glomerular filtration rate
- the ratio of retinol-binding protein to creatinine in the urine
- the ratio of beta-2-microglobulin to creatinine in the urine

There were very small changes in eGFR, about a two-point increase among Descovy users and about a two-point decline among Truvada users, suggesting minor injury to the kidney's ability to filter blood. Due to the large number of participants in the study, these small changes were statistically significant.

The ratio of retinol-binding protein to creatinine

This ratio increased during the study among participants using Truvada, suggesting very mild kidney injury. However, the increased ratios were still within the normal range. In contrast, the ratio remained stable among Descovy users. These differences in the ratios were statistically significant.

The ratio of beta-2-microglobulin to creatinine

Among Truvada users, levels of this ratio rose but remained within the normal range. Among Descovy users it remained stable. These differences in the ratios were statistically significant.

A note about tests

Both ratios involving retinol-binding protein and beta-2-microglobulin in the urine assess the ability of the kidneys to reabsorb nutrients from urine. Abnormalities in these ratios indicate that parts of the kidney called proximal tubules may be injured. However, doctors in clinics do not routinely use the ratios mentioned above when monitoring kidney health; these tests are research tools. To assess the possibility of injury to the proximal tubules, kidney specialists in the United States have suggested that doctors can use inexpensive and readily available tests such as monitoring the levels of phosphate and sugar in the urine of TDF users.

Bear in mind

The results from the Discover trial are very encouraging for Descovy; it has been shown to be similar in effectiveness to Truvada when it comes to preventing HIV infection. However, Descovy has a clear advantage when it comes to bone health: Most users had increased bone mineral density over the course of the study, while most Truvada users had a decrease. The kidney safety of Truvada over the course of the study was good, but there appear to be signals that a modest degree of kidney injury may be occurring over the long-term, so additional data from Discover is eagerly awaited.

Cost – Truvda vs. Descovy

A major issue for some people is cost. The price of a one-month supply of a generic formulation of Truvada is about \$250 Canadian per person. In contrast, a month's supply of Descovy is about \$1000–\$1200 Canadian per person. In Canada, many provincial and territorial ministries of health subsidize the cost of Truvada when it is used to reduce the risk of HIV infection. However, ministries of health will likely wait until Health Canada approves this use of Descovy to decide whether to subsidize its use for HIV prevention. Descovy is already approved in Canada as part of combination treatment for HIV infection but ministries of health have not subsidized it. The drug subsidy budgets of Canada's provinces and territories are under pressure from many new medicines (for many conditions), all of which have high prices. It will be interesting to see what these ministries do once Descovy becomes approved as part of a package of HIV risk reduction tools.

Resources

Pre-exposure prophylaxis (PrEP) resources and tools (www.catie.ca/prevp)

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II HIV CURE RESEARCH

A. Revisiting HIV co-receptors and their role in cure research

About 10 years ago the world was surprised by the news that a person with HIV had been cured. This person, Timothy Brown, had been treated for life-threatening cancer with two stem cell transplants, intensive rounds of chemotherapy and radiation, and additional suppression of his immune system. The transplant came from a donor with a rare genetic mutation, called delta-32 by scientists. Cells of the immune system from people with this mutation lack a receptor called CCR5—one of the receptors that HIV needs to infect a cell.

Know your receptors and co-receptors

HIV needs two receptors to infect cells of the immune system. These receptors act in the same way a lock functions on a door. Until the door is unlocked, no one, in this case HIV, can enter the room.

The main receptor is called CD4; this is found on many cells of the immune system such as T-cells, macrophages and related cells. After interacting with CD4, HIV then needs to interact with another receptor, usually either one called CCR5 (R5) or CXCR4 (X4). These two other receptors (R5 and X4) are called co-receptors.

In untreated HIV disease, HIV that uses X4 is relatively uncommon because researchers strongly suspect that it is easier for the immune system to find and attack HIV that uses that co-receptor. As a result, HIV that uses the R5 co-receptor is generally more common. However, when AIDS develops, the immune system has been severely injured and is no longer able to find and attack HIV that uses X4. As a result, HIV that uses X4 is more common in people that have severe immune deficiency (AIDS).

In very rare cases, there may even be other co-receptors used by HIV, such as CXCR6. However, because they are so rare, strains of HIV using co-receptors such as CXCR6 are not widely studied.

Genes and people

In general, it appears that HIV-negative people can live a healthy long life without having the R5 co-receptor. People who have the delta-32 mutation that causes this lack of R5 co-receptor are rare. Generally, this mutation is found in less than 1% of people of northern European descent, and it is even rarer in other ethno-racial groups.

The X4 co-receptor is found both within and outside of the immune system:

- in organs such as the brain and heart
- in tissues such as nerves and blood vessels

Blocking X4 co-receptors for a prolonged period of time could, in theory, lead to serious problems. About 20 years ago, researchers were testing an experimental drug that could block the X4 co-receptor in HIV-positive people. They halted further development of that drug in this population because of concerns from animal studies that it may cause liver injury. For these and other reasons, the only co-receptor that is largely the focus of HIV treatment or cure research is R5. There is a drug approved for HIV treatment that blocks the R5 co-receptor (maraviroc) but it is not commonly used. Furthermore, its use is not associated with anyone being cured of HIV infection.

Not just any stem cells

The stem cells that are used for HIV cure experiments must come from donors with the rare delta-32 mutation. However, for these transplants to avoid becoming infected with HIV after transplantation, the recipient must first be screened for the possibility of having X4-using strains of HIV. If they harbour X4-using HIV, there is the possibility that residual HIV could infect the transplanted stem cells.

Note that more than a stem cell transplant from a donor with the delta-32 mutation is needed to effect an HIV cure. So far chemotherapy appears to be needed as well. There may be other factors involved, such as something called graft vs. host

disease (GvHD)—an immunological reaction that occurs in people who have received transplanted tissue or cells. Later in this issue of *TreatmentUpdate* we briefly explore the issue of GvHD.

Key points

- HIV infects cells of the immune system using the CD4 receptor.
- HIV also needs one other co-receptor, most commonly one called CCR5 (R5) or to a lesser extent, another one called CXCR4 (X4).
- In rare cases, there is a genetic mutation called delta-32, found in less than 1% of people of northern European ancestry.
- Stem cell transplants from people with the rare delta-32 mutation are used in some HIV cure experiments.

As we went to press, a report emerged about an analysis of a large database suggesting that some people with the delta-32 mutation (the vast majority of whom are HIV-negative) may have an increased risk for long-term health complications. A future issue of *TreatmentUpdate* will review this report and its implications for HIV treatment and cure research.

Resources

The Canadian HIV Cure Enterprise (CanCURE) (www.cancurehiv.org)

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B. Will the London patient be cured of HIV?

At the annual Conference on Retroviruses and Opportunistic Infections held earlier this year in Seattle, doctors from London, England, reported details from the case of an HIV-positive man with life-threatening cancer who received a series of treatments, including complex chemotherapy and a stem cell transplant.

In particular, the man received a transplant of stem cells from a donor who had a rare genetic mutation called delta-32. People with this mutation lack a co-receptor called CCR5 (R5), which is needed by many strains of HIV to infect cells. The stem cells successfully grew in the man's bone marrow and formed a new immune system free from HIV. The man is now in remission both from cancer and HIV. In this article we will report his case details.

The London patient

Doctors in London, England, reported case details of a man of unknown age who was diagnosed with HIV in 2003. His lowest-ever CD4+ count was 290 cells/mm³ and his highest recorded viral load was about 180,000 copies/mL. He declined to initiate treatment until 2012 and this consisted of the following combination:

- efavirenz + TDF + FTC

In December 2012 he was diagnosed with life-threatening Hodgkin's lymphoma. His cancer did not respond to several different combinations of chemotherapy or to the anti-cancer antibody brentuximab. During his chemotherapy, his HIV combination therapy (ART) was changed to the following regimen:

- raltegravir (Isentress) + TDF + FTC

This raltegravir-based regimen was thought unlikely to interact with the drugs used for his chemotherapy.

For undisclosed reasons, there was a five-day interruption of ART and his viral load rose to 1,500 copies/mL. Analysis found that his HIV was now resistant to TDF and FTC, so doctors prescribed a new regimen, as follows:

- dolutegravir (Tivicay) + rilpivirine (Edurant) + 3TC

On this new regimen his viral load became suppressed.

Additional chemotherapy resulted in the man's lymphoma going into remission by March 2016, as CT and PET (positron emission tomography) found no evidence of residual cancer.

A conditioning regimen

In the meantime, doctors found a donor with the rare delta-32 mutation. To prepare the man's immune system to receive a stem cell transplant, they gave him what oncologists call a "conditioning regimen" consisting of the following drugs:

- lomustine
- cyclophosphamide
- ara-C
- etoposide

The purpose of a conditioning regimen is two-fold: to significantly weaken his immune system (so that it would not attack the stem cells) and to wipe out some of his bone marrow so that there was space for the stem cells to grow.

The man was also treated with intravenous infusions of the monoclonal antibody alemtuzumab. This antibody binds to mature T lymphocytes and targets them for destruction. Thus, residual HIV-infected cells (many of which are lymphocytes) would be destroyed. He continued to take ART.

GvHD

After the stem cell transplant, he was given low doses of drugs such as cyclosporine and methotrexate. These drugs are commonly used in transplant patients, as they weaken the recipient's new immune system and reduce the ability of this new immune system (formed from the transplanted stem cells) to attack the tissues of the recipient. These attacks are called graft vs. host disease (GvHD) and can cause serious and even life-threatening complications. However, the man was sufficiently well enough to leave the hospital a month after the stem cell transplant.

On the 77th day after transplantation, he sought care because of fever and unspecified gastrointestinal symptoms. Biopsies of his intestines revealed that he had injury arising from GvHD. However, this resolved without the need to intensify his dose of transplant medicines.

Six months after transplantation, doctors discontinued cyclosporine as they were no longer concerned about GvHD.

Immunological and other tests

One month after the transplant, tests showed that the man's new immune system was derived from the stem cell transplant. Also, his new immune system, particularly CD4+ and CD8+ cells, did not have CCR5 co-receptors. Overall, his white blood cells as well as his lymphocytes were generally within the normal range. However, his CD4+ cell count remained low, and at his last test it was about 300 cells/mm³.

His HIV viral load tests after transplantation were undetectable, using an ultrasensitive test with a lower limit of less than 1 copy/mL.

In September 2017, the man and his doctors decided to stop his use of ART.

Therapy interrupted

Upon interrupting ART, the patient underwent weekly blood tests to check his viral load. During the first three months of treatment interruption, researchers found that it was less than 1 copy/mL (the lower limit of the research assay that they used). Three months after interrupting ART, his viral load was checked once monthly. It has continued to remain less than 1 copy/mL.

Doctors also analysed the man's blood several times and did not detect any traces of ART.

Nearly 1,000 days after transplantation, technicians could not find any of HIV's genetic material in his cells. Furthermore, in one analysis using ultrasensitive methods, they received a positive signal that suggested the possible presence of HIV-infected cells. However, the doctors cautioned that such tests are research tools only and when a brief positive signal is reached at the outer limits of these assays, it requires interpretation, and they listed the possible meaning of such a test result as follows:

- the signal was incorrect; that is, it was falsely positive
- the sample being tested may have been contaminated with trace amounts of HIV from another source in the lab
- there may be an extremely low level of HIV-infected cells that produce infectious virus

However, if such HIV-infected cells exist, they are either quickly controlled by his new immune system or produce HIV that does not infect the new cells of his immune system.

Bear in mind that in their search for trace amounts of HIV, researchers will likely have screened millions of the man's cells.

Tests of his CD4+ cells in the lab found that they could become infected with HIV that uses the X4 co-receptor. Analysis of his old immune system, prior to the transplant, found that it harboured HIV that used the R5 co-receptor.

Technicians have also found that the man has gradually diminished levels of HIV antibodies in his blood. Furthermore, his T-cells have no immunological memory of encountering HIV. The researchers stated that these findings—diminishing antibody levels and lack of immunological memory—are “highly similar” to what happened with the Berlin patient after his second stem cell transplant.

Compare and contrast

There are both similarities and differences between the Berlin and London patients. Perhaps the most interesting difference is that the London patient had a less intensive (and debilitating) round of conditioning therapy than the Berlin patient. This is encouraging for potential volunteers who may undergo a similar course of therapy as the London patient in the future. Until the case of the London patient, researchers thought that an immense degree of immune suppression was necessary for a possible cure of HIV to occur in the setting of a delta-32 stem cell transplant.

The London researchers also credit the development of mild GvHD in their patient with helping to clear his immune system of residual HIV-infected cells and his prolonged remission from the virus.

Notes on a potential cure

Overall, the findings from the London patient are encouraging and further experiments with HIV-positive people who have leukemia or lymphoma and who need a stem cell transplant from a donor with delta-32 mutation will likely occur in the future. However, the preparation for stem cell

transplants (conditioning regimens, additional suppression of the immune system) can be deadly in the context of life-threatening cancer. Doctors at the Mayo Institute conducted a review of stem cell transplants done in HIV-positive people with cancer between 2002 and 2017. They found that nearly half of 49 patients died over the short- and long-term. The majority of deaths occurred because of a recurrence of cancer (60%) and other causes of death included severe infections, complications of GvHD and organ failure.

It is important to note that doctors in the UK have not judged the patient to be cured of HIV. In theory, it is possible that there still may be a few HIV-infected cells deep within his body, such as in the lymph nodes or brain. It will take several more years of assessments before they would feel confident in declaring him cured.

Resources

The Canadian HIV Cure Enterprise (CanCURE) (www.cancurehiv.org)

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C. The often-overlooked Düsseldorf patient

The London patient mentioned in this issue of *TreatmentUpdate* is not the only patient who has entered into remission from HIV. Researchers in the German city of Düsseldorf have reported interim results on a patient who has had remission from HIV after a bone marrow transplant from a donor with the rare genetic delta-32 mutation. This mutation results in a person not having the CCR5 (R5) co-receptor on their cells, making them resistant to infection by most strains of HIV.

The case of the Düsseldorf patient

In October 2010, a 42-year-old man from Düsseldorf was diagnosed with HIV infection. His doctors prescribed the following regimen of anti-HIV drugs (ART) for him:

- darunavir + ritonavir + TDF + FTC

In January 2011 the man was diagnosed with acute myeloid leukemia, a cancer of the white blood cells produced in the bone marrow. Doctors then changed his ART to the following combination:

- raltegravir (Isentress) + TDF + FTC

Isentress belongs to a class of drugs called integrase inhibitors. In general, most integrase inhibitors tend to have few interactions with other medicines, particularly compared to darunavir and ritonavir, which belong to a class of drugs called protease inhibitors. Doctors had prescribed chemotherapy and did not want any interactions with his ART, as maintaining suppression of HIV would help his immune system in its struggle against cancer. His viral load was less than 40 copies/mL.

After five courses of chemo the man went into remission, but in 2012 he relapsed. Doctors then prescribed three courses of new combinations of chemo, but these failed to kill the cancer.

Doctors then decided to wipe out his current immune system and give him a stem cell transplant from which a new immune system could arise. They found a donor with the rare delta-32 mutation who had a similar genetic makeup to the patient.

Doctors then gave him a conditioning regimen to try to destroy the leukemia as well as his bone marrow so that the stem cell transplant could take hold.

Post transplant

The stem cell transplant was successful and the man's cancer resolved. A new immune system was formed and though he always maintained good adherence to ART both before and after his stem cell transplant, his CD4+ cell count in 2014 was less than 260 cells/mm³ and his viral load continued to fall below the 40 copy/mL mark.

In mid 2014 doctors changed his ART to the following combination:

- dolutegravir + abacavir + 3TC (all three drugs are in one pill called Triumeq, taken once daily)

In 2015, his CD4+ count began to rise, reaching 400 cells/mm³ by the end of that year. By October 2018, his viral load continued to be suppressed and his CD4+ count had risen to 650 cells/mm³.

Looking for HIV

After his stem cell transplant and the subsequent creation of his new immune system, doctors at the university of Düsseldorf performed ultrasensitive tests on samples of his blood and lymph nodes and could not find any HIV. Given the limits of current technology to detect residual HIV, the only way to be sure that the virus has been eradicated would be to cease taking ART and monitor the patient for several years, while continuing to perform complex laboratory tests. So, in November 2018, the patient and his doctors decided to withhold ART.

The patient remains under intense medical surveillance and, at least initially, has had his blood drawn twice weekly so that it can be checked for any trace of HIV. Once a month, researchers conduct complex testing of his immune system, checking for HIV-infected cells and any signals that CD4+ and CD8+ cells have encountered HIV.

So far HIV has not been found and the man's immune system is healthy. It is possible that after several additional years of monitoring and continued lack of any trace of HIV that doctors in

Düsseldorf will declare this man cured. Right now, though, he is considered to be in remission. This alone is very promising.

Resources

The Canadian HIV Cure Enterprise (CanCURE) (www.cancurehiv.org)

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D. Beyond the Berlin, London and Düsseldorf patients

The results from patients in London and Düsseldorf reported in this issue of *TreatmentUpdate*, together with the well-known case of the Berlin patient, are very exciting. It is possible that in the course of the next several years, if no trace of HIV can be found in their blood and tissue samples, both patients could be declared cured. If that happens, then a total of three patients with HIV will be cured.

What about other HIV-positive people?

There have been other attempts to cure people with HIV using stem cell transplants with the rare delta-32 mutation. Immune systems that arise from these stem cells lack a co-receptor needed by HIV called CCR5 (R5) and are resistant to most strains of HIV. In the past, many of these attempts have failed, usually because people died from complications arising from cancer (HIV-positive people with cancer were enrolled in these attempts, as stem cell transplants can be dangerous). However, other experiments with delta-32 stem cell transplantation have been conducted and it is plausible that over the next five to 10 years a handful of people could be declared cured by scientists should no trace of HIV be found in their tissues and blood.

Stem cell transplants

Transplants of stem cells are dangerous as the recipient's immune system must first be significantly weakened prior to and after transplantation. Such transplants are expensive, require extensive medical care and monitoring, and donors with the delta-32 mutation are rare. In research settings where HIV cure experiments are underway, stem cell transplants with the delta-32 mutation are generally reserved only for some cases where HIV-positive people have life-threatening cancers that do not respond to several courses of chemotherapy and/or radiation. So, what can scientists learn from the experiments with the patients from Berlin, London and now Düsseldorf that can be safely applied to more people with HIV in the future? Here are some areas that could see changes:

Conditioning regimens

Conditioning regimens are used prior to receiving a stem cell transplant so that a person's immune system is greatly weakened. This is necessary so that the person's immune system does not attack the stem cells. Conditioning regimens can also help destroy residual HIV-infected cells and cancerous cells.

The combination of life-threatening cancer, chemotherapy, conditioning regimen, stem cell transplants and immune suppressive therapies that the Berlin patient received was intense and left him weakened for several years afterwards. However, it is encouraging that the London patient was given what some researchers called a “milder conditioning regimen” than the Berlin patient. This could mean that in the future, more people may be able to survive and eventually thrive after the combination of a stem cell transplant, conditioning regimen and other immune suppressive therapy.

Some researchers have suggested that instead of the traditional chemotherapy used in conditioning regimens, more targeted and safer therapies might be considered. For instance, some scientists are proposing that highly specialized antibodies be used for conditioning regimens. These antibodies have been developed in the lab and used in experiments with mice and monkeys. The antibodies target and disable key cells of the immune system, and they target a protein on cells of the immune system called CD117. Preliminary clinical trials with these antibodies are underway

in HIV-negative people with cancer. It is possible that if targeting CD117 in HIV-negative people is a safe and effective form of conditioning therapy, it will be tested in some HIV-positive people who are going to get stem cell transplants. However, there are still issues that need to be worked out with these antibodies in people, such as:

- What is the full range of effects of inhibiting CD117 on cells of the bone marrow and immune system?
- In addition to cells of the bone marrow, CD117 is found on a group of cells called mast cells, which are widely distributed in the body. Impairing their activity via the antibody that attacks CD117 may affect the tissues that such mast cells are in.
- Also, CD117 is found on a wide range of tissues, such as some cells of the central nervous system and others in the intestine, kidneys and so on. Researchers are uncertain about the effects of the CD117 antibody on these cells and tissues.

Thus, detailed results from both pilot and large studies with this antibody in HIV-negative people are awaited.

Graft vs. Host Disease (GvHD)

After a transplant of cells, tissues or an organ, it is common for some degree of GvHD to occur. In such cases, the new immune system attacks parts of the body. If left unmanaged, GvHD can have life-threatening consequences. Transplant drugs that suppress the immune system can be used to help control GvHD.

Note that some researchers think that a degree of GvHD may be useful in cases of HIV-positive people who have received a stem cell transplant. GvHD may have played a role in helping the immune system rid the body of HIV-infected cells in the cases of the Berlin, London and Düsseldorf patients. Additional research and further experiments with stem cell transplants and GvHD in HIV-positive people are needed to clarify the role of GvHD in HIV cure studies.

The delta-32 mutation and other approaches

As mentioned earlier, the delta-32 mutation results in cells that lack the co-receptor CCR5 (R5). Cells without this co-receptor are resistant to most strains of HIV.

In other cases (apart from the Berlin, London and Düsseldorf patients) of cancer where HIV-positive people have received a stem cell transplant that was from a donor who did not have the rare delta-32 mutation, sometimes a temporary remission from HIV occurred. This outcome strongly suggests that the delta-32 mutation is a critical aspect of successful long-term remission and, hopefully, an HIV cure.

However, the mutation is rare and using stem cell transplants as a routine procedure with currently used techniques is not likely. What is more likely is that different approaches to an HIV cure will be tested over the coming decade. Some of these approaches will seek to do the following:

- use gene therapies to make a person's immune system resistant to most strains of HIV by causing them to stop expressing the CCR5 co-receptor
- enhance the ability of the immune system to recognize and kill HIV-infected cells with techniques such as CART cell therapy (chimeric antigen receptor) and toll-like receptor agonists
- help the immune system with highly effective antibodies that target HIV or certain receptors on cells of the immune system, such as the alpha4beta7 receptors

What to expect from HIV cure research?

In the short-term, results from HIV cure experiments currently in progress will be available over the next five years. Some of these experiments involve stem cell transplants from donors who have the delta-32 mutation. Other experiments seek to try and effect the same result as the delta-32 mutation via gene therapy or a combination of approaches that were previously mentioned.

Hopefully all of these experiments will prove to be safe and show at least a degree of efficacy. Researchers will learn from these experiments, refine their approaches to a cure and then move

ahead with clinical trials. Thus, some progress should be made over the coming decade.

In the meantime, it is important for HIV-positive people to stay healthy so that they are in the best possible condition should they choose to enroll in some of these clinical trials. Unless people volunteer for HIV cure clinical trials, the field will not be able to move forward.

Resources

The Canadian HIV Cure Enterprise (CanCURE) (www.cancurehiv.org)

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E. The lone Miami monkey raises hope for gene transfer

There are a group of super-antibodies that have been developed that are highly effective when used in combination against HIV. The technical name for this group of antibodies is called broadly neutralizing antibodies (bNAbs). Several of these antibodies are in clinical trials. They are usually administered via intravenous infusion. However, researchers are testing alternative ways of getting bNAbs into people; one method under study is gene transfer.

About gene transfer

Instead of intravenous infusion of antibodies, one approach is to get a host (an animal or human)

to make the antibodies themselves. This approach involves encoding the information (in genetic material, DNA or RNA) for making the antibody into a harmless virus that acts as a carrier or vector and then using this vector to infect the host's cells with this virus. Once infection occurs, the vector releases the genetic information inside the target cell. The cell then incorporates this information and begins to make antibodies.

Scientists at the University of Miami have done this using a harmless virus called recombinant adeno-associated virus vector (rAAV). The information to make antibodies is encoded in DNA and inserted into the virus. In this case, researchers encoded the information to make three different antibodies into a strain of rAAV.

The scientists then infected four monkeys with a virus called SHIV. This is a combination of SIV (simian immunodeficiency virus), which causes an AIDS-like disease in susceptible monkeys, and HIV. The hybrid virus SHIV causes severe immune deficiency faster than SIV. It can therefore speed up the pace of experiments. Scientists allowed SHIV infection to persist for at least 80 weeks, then administered rAAV containing DNA with the instructions for making three bNAbs.

Commenting on the results of this experiment, other scientists stated:

“Strikingly, in one of the animals, there was a sharp decline in the amount of [SHIV in their blood] from approximately 10,000 copies/mL to less than 15 copies/mL within a few weeks of administration of rAAV. Further analysis revealed that only this animal had maintained robust [production] of more than one of the bNAbs.”

The Miami researchers found that three of the animals developed antibodies that attacked all three bNAbs. However, the immune system of one monkey, nicknamed “the Miami monkey,” only attacked one of the three bNAbs, leaving high levels of the other two antibodies. This monkey continues to have an undetectable viral load three years after first receiving rAAV therapy via intramuscular injection.

The researchers then attempted a similar experiment with 12 additional monkeys. However, the immune

systems of these monkeys also attacked the bNAbs. The experiments in gene transfer seemed safe.

In people

A team of researchers in New York and Surrey, UK, conducted a randomized, placebo-controlled study of rAAV that encoded instructions for making one bNAb called PC9. There were 21 participants in this study, all of whom were healthy and HIV negative and who received different doses of rAAV injected into muscle.

The gene transfer was safe and side effects were generally mild to moderate and included the following:

- pain at the injection site
- tenderness at the injection site
- general muscle pain
- headache

All side effects were temporary and resolved without treatment. No serious side effects occurred and no one died. There were no abnormal laboratory test results.

Technicians detected evidence of PG9 production from muscle cells. However, the levels of this antibody were too low to be detected in the blood.

Scientists are not certain why antibody levels were so low. They found evidence that CD8+ cells from participants who received rAAV (but not placebo) were able to recognize and attack the AAV. Some vaccine recipients developed antibodies that attacked PG9.

For the future

It may be necessary to give higher doses of rAAV that encode more potent bNAbs than PC9. Clearly, refinements to the gene transfer experiment in this study are needed to minimize the immune system's ability to destroy bNAbs.

Different teams of researchers are trying to find ways to solve this problem of the immune system attacking bNAbs that are made via gene transfer. It is likely that there will be additional gene transfer experiments in the future.

The lone success of the Miami monkey heralds a potential approach where people could one day receive gene transfer for antibodies that attack HIV. This would be helpful both to protect HIV-negative people and also to treat HIV-positive people, perhaps freeing them from the need to take anti-HIV drugs on a regular basis.

Resources

The Canadian HIV Cure Enterprise (CanCURE)
(www.cancurehiv.org)

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Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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