I HIV CURE RESEARCH

A. Cure research takes off

It has been 32 years since AIDS was first recognized and 30 years since the cause—a virus we now call HIV—was first isolated. In that time enormous advances have been made: There are tests that can detect HIV and treatment (commonly called ART or HAART) has transformed HIV into a chronic illness. Furthermore, the power of ART is so profound that a young HIV-positive adult who begins treatment shortly after diagnosis today, who takes his/her medicines every day exactly as directed and who has no or limited co-existing health conditions is expected to live for several decades.

Although ART has helped to transform HIV into a chronic illness—particularly in high-income countries such as Canada, Australia and the U.S. and regions such as Western Europe—there are still issues. This treatment must be taken at least once a day, every day, for the rest of a person’s life. Such high levels of adherence may be difficult to sustain for many years. Furthermore, medicines to treat HIV, particularly the newest and most tolerable drugs, are relatively expensive. As the vast majority of HIV-positive people live in low- and middle-income countries, some researchers have wondered whether it is possible to provide care and treatment for all HIV-positive people in those places. At present, not every HIV-positive person in those countries can access care and treatment. Thus, a cure would be very desirable for many reasons.
Know your co-receptors

HIV needs at least two receptors to enter and infect a cell. The first receptor is CD4+, which is found on many immune system cells. HIV usually then needs one of two other co-receptors, either CCR5 or CXCR4.

Some strains of HIV prefer to use CCR5, others CXCR4, and still others use both co-receptors.

Back to the cure

Since the late 1980s, researchers have attempted to cure HIV infection. However, in the first two decades of the AIDS epidemic, such efforts were largely dangerous and unsuccessful.

Then, in 2008, a major development occurred. Doctors in Berlin appeared to have cured an HIV-positive man, who was suffering from leukemia, of both cancer and HIV. The “Berlin patient” had been taking ART for several years prior to his cancer treatment and received chemotherapy, radiation and transplants of stem cells. What was unique in this case was that the donor of the stem cells had a rare mutation (called a delta-32 mutation by researchers) that resulted in his cells having no CCR5 co-receptors. This made the cells somewhat resistant to HIV infection. After intensive chemotherapy and radiation, ART was withheld and the stem cells were transplanted and took hold in his bone marrow, helping to create his new immune system. However, the man’s new immune system attacked parts of his body, a complication called GvHD (graft vs. host disease), and doctors had to prescribe a mix of powerful immune-suppressing drugs to manage this complication. His cancer returned and he had to undergo intensive chemotherapy again as well as another stem cell transplant.

The Berlin patient survived all of these interventions and recurrent cancer. He has not needed to resume ART and sophisticated tests have revealed that either he has no HIV or he has extremely low levels of this virus deep within his body from time to time.

Why the cure?

Researchers are divided about why the Berlin patient was apparently cured. Research teams have proposed different possible reasons for his apparent cure, as follows:

- the intensive bouts of chemotherapy and radiation
- the bone marrow transplant from a donor with a delta-32 mutation
- the intensive stimulation of his immune system arising from GvHD
- the use of transplant medicines, which dampen inflammation and reduce HIV’s ability to infect cells

It is likely that more than one of these factors played a role in his recovery from HIV.

Excitement

The apparent cure of the Berlin patient has excited the imaginations of many researchers and doctors around the world. Clinical trials are underway, mostly in the U.S and Western Europe, assessing different methods for attempting to cure HIV infection. Eventually some of these trials will occur in Canada.

Caution needed

Some of the attempts at a cure, such as genetic therapy, have been relatively safe. However, in attempting to replicate the success of the Berlin patient, other HIV-positive people have died. This is not surprising, as intense chemotherapy and radiation with or without transplant drugs are very debilitating.

Researchers at Harvard University have attempted a variation of the protocol used with the Berlin patient. Although two HIV-positive patients with cancer have volunteered for this experiment and have survived for several years, they remain weak, both physically and immunologically. A major difference between these patients and the Berlin patient is that they have not stopped taking ART. Due to their poor state of health, their doctors have been reluctant to withhold ART, so it is not yet clear if they have been cured.

These experiments with stem cell transplants and chemotherapy and subsequent transplant drugs are dangerous and will not be done on a large scale because among HIV-negative cancer patients such procedures carry a death rate of about 15%. No one is certain about the death rate for HIV-positive people, but it is likely to be at least as high.
Much caution with intense monitoring and hospitalizations will be needed for attempts at a cure. This will particularly be the case as researchers use multiple methods on the same person to attempt a cure.

Still, researchers should be praised for showing imagination and embracing cure research. Such encouragement is necessary because many of the complex ways that HIV interacts with the immune system are not fully understood. Therefore, much research on monkeys infected with SIV (simian immunodeficiency virus), mice transplanted with human immune systems, and HIV-positive people will be needed to gain such an understanding.

The journey toward a cure will not be easy and many challenges lie ahead. Some of the challenges are known, others may only become known as experiments proceed. As with any great scientific endeavour, there will be setbacks. This means that research funding agencies and the public need to be patient. The initial wave of cure research experiments over the next five years should be viewed as exploratory and their results preliminary. This research will seek to answer important scientific questions that can then be used to build a foundation as researchers work toward a cure.

To assist researchers in developing new ideas for cure research, Canada’s premier scientific agency, the Canadian Institutes for Health Research (CIHR), will be seeking proposals from research teams across the country. These proposals will be reviewed by scientists and the most promising proposal(s) funded for five years.

Resources


REFERENCES:
infected with HIV produce copies of HIV that are defective.

In a clinical trial, five HIV-positive participants whose ART was failing received a single intravenous infusion of VRX496-treated CD4+ T cells. Researchers found that as a result of this, participants’ CD4+ counts temporarily rose and in one participant viral load fell by as much as 100-fold. Importantly, this genetic therapy was found to be safe.

Based on these promising results, researchers proposed that multiple infusions of gene-therapy-treated CD4+ cells would likely be more effective.

The latest study

The most recent report of VRX496 involved 17 HIV-positive participants, all of whom were taking ART. Therapy with VRX496 was generally safe. When ART was interrupted, viral load rose and then fell modestly. Side effects related to the infusion of T cells included temporary fever and chills.

For the most part, the infused T cells disappeared from the body within weeks. However, in some participants the genetically fortified T cells were still present, albeit in very small amounts, up to five years after their infusion. The reason for their disappearance is not known.

Making the cells last

Giving participants more than three infusions of these treated cells did not make the cells last any longer in the body. The research team involved with this study suggests that “conditioning agents” may be a remedy for helping the body to retain the modified T cells. Conditioning agents is coded language for intensive chemotherapy and radiation. However, such therapies would be accompanied by greatly increased toxicity. Long before researchers can consider this approach much more potent and sophisticated gene therapy would be required.

Hitting several spots at once

Led by France’s premier scientific research agency, the ANRS (Agence nationale de recherches sur le sida et les hépatites virales), researchers in France, Austria, Germany, Italy and the U.S. are planning to conduct clinical trials of a gene therapy.
therapy that has the potential to interfere with key HIV proteins (called Tat, Rev and Vif) and to also block the CCR5 receptor of cells. Such a multifaceted approach carries the possibility of not only protecting cells from the entry of HIV but also helping the immune system overcome the toxic effect of HIV’s proteins.

REFERENCES:

C. HDAC inhibitors – pushing HIV out of hiding

In people who have been taking ART for several years and who have no other co-infections, HIV-infected cells produce very few copies of HIV and appear to infect other cells at a relatively low rate. In many of these cases, HIV can lie dormant (latent) in cells that are resting, until stimulated from time to time. As part of an attempt at curing HIV, it would be important to rid the body of these infected cells. Driving HIV out of hiding in these cells is sometimes called “purging latently infected cells” by researchers.

Several years ago Canadian researchers attempted to cure HIV by giving ART users the anti-seizure drug valproic acid in addition to ART. However, this did not work.

Introducing...

Valproic acid belongs to a class of drugs called HDAC (histone deacetylase) inhibitors. Since that Canadian trial, researchers have pondered using more potent HDAC inhibitors, such as the following:

- panobinostat
- romidepsin
- vorinostat

Clinical trials with these drugs are underway in Australia, Western Europe and the U.S. in HIV-positive people to assess their impact.

The return of Antabuse

The drug Antabuse (disulfiram) is used to treat some people with alcohol addiction, as it causes highly unpleasant reactions when they drink alcohol. In the body, disulfiram is converted into another compound called di thiocarb (Imuthiol, diethylthiocarbamate). Results of laboratory experiments with cells suggest that this compound has antifungal and anti-parasite and possibly anti-HIV activity. Clinical trials in the late 1980s and early ‘90s led to mixed results, and the drug was never approved by regulatory authorities for use as an HIV treatment.

At present, researchers are having another look at disulfiram because in laboratory experiments with cells it appears to activate latent HIV.

Bryostatin

An even older drug, bryostatin, was also studied in the 1980s for its impact on HIV-infected cells. In recent years, researchers have found that bryostatin and closely related compounds can have beneficial effects that may make them useful for cure research. In particular, bryostatin appears to be able to coax HIV from latency in different types of cells of the immune system.

For the future

It is likely that future attempts at curing HIV will require multiple and perhaps novel therapies. Just what those therapies ought to be is still being debated by scientists. In this issue of Treatment Update, we explore several attempts at bringing HIV out of latency in ART users with HDAC inhibitors.
REFERENCES:


D. HDAC inhibitors and their possible consequences

When HIV infects a cell of the immune system, a number of possibilities can occur. One pathway is that HIV takes over the cell and redirects the cell to make more copies of HIV. In other cases, HIV can infect a cell but stay dormant until the cell is activated and virus production ensues. Trying to eliminate this dormant HIV will be critical in effecting a cure.

Researchers in the U.S. have proposed using the anti-cancer drug vorinostat (SAHA, Zolinza), which is an inhibitor of the enzyme HDAC (histone deacetylase). In HIV-positive people, this enzyme helps to keep HIV in a latent state in resting cells. By inhibiting HDAC, researchers hope to activate HIV-infected cells in ART users. Even though new copies of HIV will be created from the use of HDAC inhibitors, researchers hope that newly produced HIV should not be able to infect many cells because study volunteers will be using ART. In theory, after prolonged exposure to vorinostat and related drugs, researchers hope that they will be able to reduce the number of HIV-infected cells in the body, either to extremely low levels or altogether. However, this reduction in the burden of HIV-infected cells in the body arising from the use of HDAC inhibitors has not yet been proven. Moreover, the long-term safety and effectiveness of potent HDAC inhibitors such as vorinostat must be assessed in HIV-positive people. These drugs are generally used for the treatment of cancers and have side effects, some mild, others serious.

An unknown future

Although HDAC inhibitors are supposed to affect the enzyme that keeps HIV in a latent state, it is possible that the same enzyme keeps other, perhaps poorly understood, retroviruses also in a latent state. Specifically: Humans carry within their DNA traces of retroviruses other than HIV, which have evolved with us over millions of years. These traces are not sufficient to cause new infections; however, there is the theoretical possibility that by unleashing histone deacetylase with HDAC inhibitors these traces of old retroviruses may
combine with HIV, forming new retroviruses. The consequences of this for a person’s health are not known. However, there have not been reports, at least so far, of new viruses arising from HIV-positive people treated with HDAC inhibitors.

In this issue of TreatmentUpdate, we report on clinical trials of vorinostat, a relatively potent inhibitor of HDAC.

REFERENCES:

E. Two studies of vorinostat

In an attempt to bring HIV out of latency in ART users, researchers first conducted a limited study of vorinostat. Initially the drug was given in a single oral dose of 200 mg. Four weeks later participants received a dose of 400 mg, followed four weeks later by another single dose of 400 mg. Participants had their blood drawn before and after each dose of vorinostat for analysis. Specifically, participants underwent a procedure called leukapheresis after they received vorinostat. For this procedure, each participant’s blood was removed, filtered of white blood cells and then reinfused into them. The white blood cells were intensely studied in the lab.

Tests revealed that a dose of 400 mg of vorinostat significantly increased production of HIV in resting CD4+ cells that were infected with this virus.

The second study

Spurred by these positive results and the need to give a longer duration of vorinostat, researchers in Australia conducted a two-week study with this anti-cancer drug given at a dose of 400 mg once daily.

Researchers recruited 20 HIV-positive participants who had been using ART for at least the past three years and whose CD4+ counts were greater than 500 cells and viral load less than 50 copies/ml.

The average profile of participants was as follows:
- age – 48 years
- gender – 19 men, 1 woman
- CD4+ count – 721 cells
- duration of virologic suppression on ART – between three and 14 years
- 14 participants were using regimens based on nevirapine (Viramune) or efavirenz (Sustiva and in Atripla); the remaining were taking boosted protease-inhibitor-based regimens

Although participants only took vorinostat for 14 days, they were monitored for up to three months.

Results

Ninety percent of participants had a significant increase in HIV production from formerly latently infected cells.

There were no significant changes in the proportion of HIV-infected cells in the blood or in the rectal tissue (where there are many lymph tissues rich in CD4+ cells).

In most cases (17 out of 20 participants), viral load in the blood remained below the 20 copies/ml mark.

Two participants developed detectable viral loads (around 40 copies/ml)—in one case on the first day of vorinostat exposure and the other on the 20th day of the study when vorinostat was no longer being used.

The third participant was taking the following regimen:
- lopinavir-ritonavir (Kaletra) + AZT (Retrovir, zidovudine) + tenofovir (Viread)

On the 7th day of the study, his viral load rose to above 150 copies/ml and then fell. Two months later, it was less than 20 copies/ml.

No participants developed significant levels of T-cell activation because of exposure to vorinostat.
Results – Side effects

According to the researchers, most side effects experienced were of mild intensity. Common side effects included the following:

- diarrhea
- altered sense of taste
- nausea
- lethargy

Less common side effects included the following:

- nausea and/or vomiting
- headache
- dry mouth

Laboratory analyses of blood revealed that some participants developed reduced levels of platelets and elevated levels of some liver enzymes (GGT and ALP).

Generally the side effects quickly appeared once participants initiated therapy with vorinostat and quickly resolved once they stopped taking it.

Making sense of the findings

The two vorinostat studies prove that this drug can bring HIV out of hiding in resting T cells. Furthermore, exposure to the drug seemed generally safe. However, longer studies are needed to assess its impact on the reservoir of latently infected cells. Moreover, further safety studies are needed. This is because in tests with bacteria, vorinostat has the potential to cause mutations. Supposedly healthy human cells can repair damage caused by vorinostat but this needs to be investigated in HIV-positive people.

Limited exposure to vorinostat did not cure HIV; so much more work is needed. Will future clinical trials use higher doses of the drug or the same 400-mg dose for longer periods?

For the future

San Francisco-based researcher Steven Deeks, MD, raised the following questions about the first vorinostat study and they are applicable to other similar studies:

- “How should the field balance the ethical concerns about administering potentially toxic drugs to HIV-infected people who are otherwise healthy? The ideal population for these studies are those who have been doing well on long-term therapy, but this just happens to be the group with the lowest apparent need for a cure.”
- “Will future studies of anti-latency drugs require a costly and inconvenient leukapheresis before and after drug exposure? In San Francisco the cost for such a procedure is over US $2,500. Therefore a sensitive assay that can be easily used when [assessing millions of cells for the presence of latent HIV] is clearly needed.”
- “How much of the viral reservoir might be eliminated by HDAC inhibition?” In the case of the Australian study, data about this point was not presented.
- “Which assays will we use in the future to screen potential drug candidates for anti-latency activity? Vorinostat has demonstrated [anti-latency] activity in most tests, but not all.”
- “What is the fate of virus-producing cells after HDAC inhibition? Although many investigators have assumed that either the virus or host immune system would destroy such cells and therefore clear the virus, recent data suggests that this might not be true.”

REFERENCES:

5. McIlroy D. Do HIV-specific CTL continue to have an antiviral function during antiretroviral therapy? If not, why not, and what can be done about it? Frontiers in Immunology. 2013;4:52.
F. The promise of Romidepsin

As mentioned earlier in this issue of TreatmentUpdate, the anti-cancer drug romidepsin (Istodax) can also inhibit the activity of HDAC (histone deacetylase), an enzyme that can help keep HIV infection latent.

Researchers with the pharmaceutical company Gilead Sciences performed laboratory experiments with cells extracted from 46 HIV-positive ART users whose CD4+ counts were above 350 cells and viral load less than 50 copies/ml. Specifically the researchers tested the following HDAC inhibitors:

- romidepsin
- panobinostat
- givinostat
- vorinostat
- mocetinostat

Romidepsin appeared to be the most potent HDAC inhibitor in these test-tube studies. Its ability to bring HIV out of latency was consistent over time with cells from the same or different donors.

Regulatory authorities in the U.S. have approved the use of romidepsin, given intravenously at a dose of 15 mg per square metre of skin surface, for the treatment of certain cancers. However, according to the Gilead experiments, much lower doses can be used when attempting to bring HIV out of latency. These lower doses range between 2 and 5 mg/m².

Based on these promising but preliminary experiments, expect a clinical trial of romidepsin in the future.

REFERENCES:

G. Assessing the impact of chemo and stem cell transplantation on HIV

The success of doctors in Berlin apparently curing a person (the “Berlin patient”) of HIV has stimulated scientists in high-income countries to attempt to do the same. It should be noted that the apparent success of the Berlin researchers might have rested on one or more of the following factors:

- multiple stem cell transplants from a donor whose cells did not have the co-receptor called CCR5, which is needed by HIV to infect cells
- intensive doses of chemotherapy and radiation
- post-transplant the man developed an intense immunologic reaction whereby the transplanted cells attacked his tissues. This type of reaction is called GvHD (graft vs. host disease) and was ultimately controlled with the use of immune-suppressive transplant drugs. However, some researchers suspect that GvHD may have also helped to destroy residual HIV-infected cells.
- the use of transplant drugs may also have played a role by suppressing inflammation and reducing HIV’s ability to infect cells.

Since the beginning of the HIV epidemic, researchers have conducted clinical trials of transplant drugs and corticosteroids. Although these drugs are immunosuppressive and it seems counter-intuitive to use them in HIV infection, clinical trials of low doses of these drugs in HIV-positive people suggest the possibility that there may be a benefit to the immune system. This may occur because these drugs reduce excessive inflammation and other immunologic dysfunction incited by the virus.

The protocol used by the Berlin doctors is toxic and caused complications that persisted for several years. Subsequent attempts to replicate their protocol have initially led to several deaths. However, with much caution, researchers are still attempting to effect a cure by making some modifications to the Berlin protocol.

Researchers in Pennsylvania and California have evaluated 10 HIV-positive participants before and after they received intensive chemotherapy for cancer (lymphoma) followed by a transplant of stem cells. Each participant had some stem cells removed prior to chemotherapy and then had them transplanted after their course of chemo was over. These cells were not modified to resist
HIV. Participants were taking ART and generally tolerated it during chemo. However, three of them had to interrupt ART because of severe chemo-related side effects.

Technicians developed an in-house viral load test that could detect as little as one copy of HIV RNA in the blood. Using this tool they found that after transplantation, participants had a viral load of about 2 copies/ml.

In one patient, researchers could not detect HIV replication with their ultra-sensitive assay. However, when they analysed his blood with other assays, they found that he had HIV-infected cells (as did all the other participants). Despite being monitored for up to 10 years, the proportion of infected cells in all of the participants did not decline after their transplant.

Why did HIV persist?

Chemotherapy is designed to wipe out rapidly dividing tumour cells. The cells of the immune system that contain latent HIV include a group of cells called “resting CD4+ T cells” by researchers. These cells are not active and chemotherapy might not kill them.

Another possibility is that the stem cells used for transplantation contained some cells that were infected with HIV. Therefore, the transplant could have helped to re-establish HIV.

Based on these results, stem cells harvested from ART users whose viral load is less than 50 copies/ml and then transplanted after chemo are not going to reduce the burden of HIV-infected cells or cure HIV.

REFERENCES:


H. A role for immunity

In this issue of *TreatmentUpdate*, we have mentioned some of the proposed and existing experiments to awaken HIV inside resting CD4+ T cells in ART users so that the proportion of HIV-infected cells in the body can be reduced. However, once HIV is activated in such cells, the fate of the cell is unknown. For instance, an HIV-infected cell that has been stimulated from rest into activity could do the following:

- produce many copies of HIV and then die
- because it has started to produce HIV, the immune system can recognize that it has been infected and killer T cells (CD8+ cells) can attack and destroy it
- it can briefly produce a small number of copies of HIV and then go back into a state of rest, evading the immune system and harbouring the capacity to produce HIV in the future

The latter result is concerning because laboratory experiments with latently infected cells and the HDAC inhibitor vorinostat have uncovered a weakness of the immune systems of many HIV-positive ART users: Their immune systems appear unable to mount or sustain an effective response against HIV.

Therapeutic vaccines

Most vaccines are licensed to prevent infections—including measles, mumps and polio—that were once generally widespread in high-income countries. However, researchers have become intrigued with the potential for therapeutic vaccines for HIV-positive people. Such vaccines would be used to stimulate the immune system, particularly CD8+ cells, to help them better recognize and attack HIV-infected cells. Stimulating the immune system with a therapeutic vaccine is likely to become necessary before volunteers are exposed to some of the drugs mentioned earlier in this issue of *TreatmentUpdate* that can bring HIV out of hiding.
Enabling immunity

In the 1980s, when doctors were struck by the sudden outbreak of AIDS-related infections in young, previously healthy adults, they assessed the immune systems of their patients. Tests revealed a severe degree of immunologic impairment. Later, immunologists would uncover a strange finding: Cells of the immune systems of people with HIV would behave as if they were exhausted. Such cells expressed proteins or markers on their surface suggesting that they would shortly self-destruct, a process called programmed cell death, or apoptosis. A large proportion of the immune system’s cells, particularly T cells, even if they are not infected with HIV are very susceptible to apoptosis. This has been confirmed in laboratory experiments with fresh cells and HIV and the closely related virus, SIV (simian immunodeficiency virus). Together, these findings suggest that viruses such as HIV and SIV have evolved to subvert the immune system without having to infect every one of its cells. These viruses can do this by causing the immune system to display proteins or markers on their surface that researchers call death receptors.

Although ART significantly reduces HIV’s ability to infect new cells and allows the immune system to partially repair itself, such repairs are incomplete. Analyses of cells of the immune system from SIV-infected monkeys and HIV-positive humans taking ART suggest that within the lymph nodes and lymph tissues, cells of the immune system still display death receptors, albeit at a reduced level compared to SIV-infected monkeys and HIV-positive humans who are not taking ART.

Rejuvenating the immune system by reversing the impact of death receptors on cells may be one avenue for researchers to pursue. In experiments with monkeys infected with SIV and in separate preliminary studies in HIV-negative people with cancer, researchers have used specialized antibodies to attempt to disable death receptors on cells of the immune system. This has enhanced the ability of such cells to attack germs and tumors. If such therapies become licensed for the treatment of cancer as some are expected to be within the next year, researchers will be able to have access to them for testing in HIV-positive people. By reversing the impact of death receptors, researchers may be able to help the immune system better recognize HIV-infected cells and destroy them.

REFERENCES:

Participants remained on ART for about three years before interrupting treatment for unknown reasons.

Following treatment interruption, eight of 14 participants maintained a very low viral load at subsequent tests; their viral loads in the blood ranged between 1 and 39 copies/ml.

In the case of the remaining six participants, viral loads in the blood ranged from less than 40 copies/ml to 400 copies/ml. In a few cases, on several occasions viral loads were greater than 400 copies/ml but usually returned to less than 400 copies/ml after some time.

The last available CD4+ counts generally were elevated, ranging from 441 cells in one participant to nearly 1,600 cells in another.

Extensive laboratory testing was done on blood samples from participants. Mostly this testing revealed unexpected results:

- **Genetics**
  Participants did not appear to carry genes that researchers associate with good virologic control of HIV. Moreover, several participants had genes associated with the rapid development of AIDS, so the fact that they were ultimately able to keep their viral loads suppressed without ART was remarkable.

- **CD8+ cells**
  These are important cells for controlling infections and are used by the body to destroy HIV-infected cells. However, the CD8+ cells taken from participants had, according to researchers, only a "poor" ability to suppress HIV.

- **Infected cells**
  In eight participants for whom the researchers had data, the proportion of HIV-infected cells in the blood remained more or less the same in two participants, increased in one and decreased in five others despite the absence of treatment. Overall, this suggests that among these five participants, the reservoir, or burden, of HIV-infected cells was "very small," according to the research team.

It is noteworthy that none of the 14 people in the Visconti study had been cured. However, for the most part they have been able to keep their viral loads relatively low without having to reinstate ART. The precise mechanism underpinning these remarkable results remains a mystery but French researchers are actively trying to find out.
Issues related to Visconti (and similar studies) appear in the next report.

REFERENCES:


J. Very early ART and treatment interruptions

The Visconti study was not the only study to find rare cases of HIV-positive people who can interrupt ART and then have prolonged very low levels of viral load. A European-Canadian-Australian observational study called Cascade also found rare cases of virological control lasting more than two years post drug interruption. Cascade researchers searched their dataset of 25,629 HIV-positive people and found that there were 259 who were treated within three months of becoming positive and who later interrupted therapy. These people became HIV positive between 1996 and 2009. Overall, only 11 of the 259 people (4%) were able to maintain their viral loads below the 50-copy mark for more than two years after interrupting therapy. There were seven men and four women, around 30 years old. ART was taken for a year before initiating an interruption.

Several well-designed clinical trials have found that interrupting ART in people who start therapy later in the course of infection has been associated with a significantly increased risk of serious illness and death. However, it is possible that initiating ART very early in the course of HIV infection (primary HIV infection), as in Visconti and other studies, and taking this therapy for at least three years and then interrupting may allow a very small group of people to control HIV.

Unfortunately, no study to date has uncovered the specific factors—genetics or otherwise—that could help doctors identify such potential patients in future cases of primary HIV infection. Additional analyses from large databases are needed to help confirm that such rare patients exist and to extend analyses of their HIV and immune systems so that clinical trials can try to replicate the findings publicized by Visconti, Cascade and other studies.

REFERENCES:


4. Katz MH. For human immunodeficiency virus disease, more treatment seems to be better: comment on “Immunovirologic control 24 months after interruption of antiretroviral therapy initiated close to HIV seroconversion.” *Archives of Internal Medicine*. 2012 Sep;172(16):1256.

K. Was a baby cured of HIV?

At the annual Conference on Retroviruses and Opportunistic Infections (CROI) held in the U.S. in March 2013, researchers presented details of the case of a baby that was apparently cured of HIV infection. Claims of apparent cures of HIV are rare and because of their potential importance they deserve a high level of scrutiny and critical thinking.

Case details

The research team reported on a mother in the southern U.S. who sought care because she was about to give birth. They stated that “she had not been engaged in prenatal care” and so doctors did not know that she was HIV positive until she prematurely entered labour, when they performed rapid HIV testing. Her HIV viral load was low (2,423 copies/ml) and her CD4 count was relatively high (644 cells). Analysis of her HIV suggested that it had not encountered anti-HIV drugs.
Assuming that the baby was also infected, doctors sent the infant to a major hospital for care. There, 31 hours after birth, researchers found that the baby had HIV-infected cells in its blood and its viral load was 19,812 copies/ml. Doctors immediately began anti-HIV therapy with nevirapine (Viramune), AZT (Retrovir, zidovudine) and 3TC (lamivudine). After a week, nevirapine was replaced with lopinavir-ritonavir (Kaletra). The baby responded well to treatment and a month after birth its viral load was less than 48 copies/ml.

After 18 months, hospital staff lost track of the child and its family. The reasons for this lapse were not disclosed.

When the infant was nearly two years old, researchers stated that hospital staff resumed contact with the baby and its “caretaker.” This adult disclosed to healthcare providers that they had stopped giving ART to the baby at about 18 months of age. Again, the reasons for this were not disclosed.

Extensive virologic, immunologic and genetic testing was performed on the baby’s blood. The reason for the genetic testing was to confirm that the baby was indeed the same infant that had been previously cared for at the hospital. At this point, the hospital laboratory’s experimental single copy assay confirmed that the infant’s viral load was 1 copy/ml. The baby is clinically well and at the time the results were reported at the conference has not taken ART for almost a year.

Points to consider
1. This case is stark reminder about what can happen when pregnant women are not linked to prenatal care, offered HIV testing and given ART during pregnancy. The risk of HIV transmission from mother to child in untreated HIV infection ranges between 25% and 30%. In high-income countries such as Canada and the U.S., giving HIV-positive pregnant women prenatal care, counselling and ART, along with temporary treatment of the baby with anti-HIV drugs just after birth, and using formula instead of breast milk has reduced the risk of mother-to-child transmission to less than 2%. That the baby is now apparently HIV negative is an extremely lucky outcome. Still, this case underscores serious gaps in the healthcare and social service systems in the mother’s region.

2. How a major hospital in a high-income country could lose contact for several months with a family having an HIV-positive baby seems, at best, highly unusual. This also points to another apparent gap in the healthcare system, particularly for this baby and its mother.

3. Although researchers associated with this case have suggested that early initiation of ART for nearly 18 months apparently cured the baby, talk of a cure is premature. This arises because the baby’s ART could have acted as PEP—post-exposure prophylaxis. PEP is routinely used in high-income countries in healthcare settings because of needle-stick injuries when healthcare workers inadvertently become exposed to HIV. PEP is also used to help prevent HIV infection after possible sexual exposure. Given within 72 hours after exposure, PEP has a high probability of working. The ART given to the baby within this timeframe could have acted as a form of PEP, helping to greatly restrict and limit HIV infection.

4. The virus that the mother had was a strain (or clade) that is relatively common in North America, Australia, Japan and Western Europe: subtype B. Moreover, the mother’s viral load seemed unusually low, so perhaps she was infected with a weakened strain of HIV. This would have made it easier for the baby’s immune system, fortified with ART, to control and perhaps ultimately get rid of the virus.

5. According to the research team, the mother did not breastfeed her infant. This is important because breastfeeding can transmit HIV.

6. Analyses of lymph nodes and tissues need to be done to ensure that the baby is truly free from HIV.

7. There may be other possible explanations for the baby’s ability to have low levels of HIV without continued treatment that have not yet been advanced by researchers.

Implications
It is premature to suggest that routine use of prolonged ART in HIV-infected babies born to HIV-positive mothers will cure the infants. Today most babies born to HIV-positive mothers are born in low- and middle-income countries. The reasons that some of these babies in those countries are born infected are that their mothers received limited or no prenatal care, had little or no access
to ART and breast fed the babies. International agencies, local governments and NGOs are working hard to bring the rate of mother-to-child transmissions of HIV to zero.

In Canada and other high-income countries, the vast majority of HIV-positive women who become pregnant receive prenatal care and ART and give birth to healthy babies. There are, of course, cases where mothers in high-income countries may not receive prenatal care. The reasons for this are complex and vary from one woman to another but are usually related to one or more of the following factors:

- living in a remote community
- having poor mental and emotional health
- addiction
- recent migration from a country where HIV is relatively common

By making the offer of a routine HIV test much more widely available, expanding health and addiction prevention and treatment services, prenatal care and other social services to populations in need, and engaging communities in strengthening their health, Canada, the U.S. and other high-income countries can help to bring an end to babies born with HIV.

**Resources**

Society of Obstetricians and Gynaecologists of Canada (http://www.sogc.org/index_e.asp)


*Information for Women who are Diagnosed with HIV during Pregnancy* (http://library.catie.ca/PDF/ATI-20000s/26316.pdf)

*Pregnancy Planning Information for HIV+ Men and Their Partners* (http://library.catie.ca/PDF/ATI-20000s/26314.pdf)

**REFERENCES:**


Disclaimer

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.

CATIE (Canadian AIDS Treatment Information Exchange) in good faith provides information resources to help people living with HIV/AIDS and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

We do not guarantee the accuracy or completeness of any information accessed through or published or provided by CATIE. Users relying on this information do so entirely at their own risk. Neither CATIE, nor the Public Health Agency of Canada, nor the Ontario Ministry of Health and Long-Term Care, nor any of their employees, directors, officers or volunteers may be held liable for damages of any kind that may result from the use or misuse of any such information. The views expressed herein or in any article or publication accessed or published or provided by CATIE are solely those of the authors and do not reflect the policies or opinions of CATIE or the views of the Public Health Agency of Canada, nor the Ontario Ministry of Health and Long-Term Care.

Permission to Reproduce
This document is copyrighted. It may be reprinted and distributed in its entirety for non-commercial purposes without prior permission, but permission must be obtained to edit its content. The following credit must appear on any reprint: This information was provided by CATIE (Canadian AIDS Treatment Information Exchange). For more information, contact CATIE at 1.800.263.1638 or info@catie.ca

Credits
Writer Sean Hosein
Editor RonniLyn Pustil

© CATIE, Vol. 25, No. 2
March/April 2013

What CATIE Does

CATIE, Canada’s source for HIV and hepatitis C information, is committed to improving the health and quality of life of all people living with HIV/AIDS in Canada. CATIE serves people living with HIV/AIDS, and the people and organizations that support them, by providing accessible, accurate, unbiased and timely treatment information. CATIE provides such information through a comprehensive Web site, a bilingual toll-free phone service, electronic and print publications, a national reference library and workshops and exhibits at conferences across Canada.

CATIE Publications

TreatmentUpdate
CATIE’s flagship treatment digest on cutting-edge developments in HIV/AIDS research and treatment. Subscribe to TreatmentUpdate and automatically receive an email notifying you the moment a new issue is available on-line or contact us at 1.800.263.1638 to receive a print subscription.

A Practical Guide to HIV Drug Treatment
The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

The Practical Guide series also includes:
• A Practical Guide to Nutrition
• A Practical Guide to Complementary Therapies
• A Practical Guide to Herbal Therapies

The Positive Side magazine
Holistic health information and views for PHAs.

Fact Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

pre*fix
A harm reduction booklet for HIV+ drug users.

Contact CATIE
by e-mail: info@catie.ca
on the Web: www.catie.ca
by telephone: 416.203.7122
1.800.263.1638 (toll-free)
by fax: 416.203.8284
by post: 505-555 Richmond Street W
Box 1104
Toronto, Ontario
M5V 3B1
Canada

Production of this newsletter has been made possible through a financial contribution from the Public Health Agency of Canada.