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I HIV PREVENTION

A. The coming of lenacapavir for HIV prevention

The drug lenacapavir (Sunlenca) is approved in Canada and other high-income countries for use as part of combination therapy in people who are heavily treatment experienced, who have multidrug-resistant HIV, and whose current regimen is failing. As there are many powerful options for the treatment of HIV, lenacapavir is not commonly used for HIV treatment in Canada. However, it is being studied for another use.

Many drugs used as part of HIV treatment regimens have also been used by people without HIV to prevent infection prior to possible exposure to the virus. This use of HIV medicines is called pre-exposure prophylaxis (PrEP). Drugs approved for PrEP include the following:

- Apretude – cabotegravir
- Truvada – tenofovir DF + FTC and available in generic formulations
- Descovy – tenofovir alafenamide (TAF) + FTC

Lenacapavir works by interfering with an HIV protein called the capsid. This protein is used by HIV to protect its genetic information as it enters and infects a cell. The capsid also protects HIV's genetic information when the infected cell is making new copies of HIV. Lenacapavir is classed as a capsid inhibitor. As capsid inhibitors are not in widespread use (so far lenacapavir is the only approved one), there is little likelihood of lenacapavir-resistant HIV.

The main advantage of lenacapavir is its dosing. For HIV prevention, in clinical trials, participants first received two injections of lenacapavir. These injections were given subcutaneously (just under the skin) of the abdomen. They also took oral lenacapavir (pills) for two consecutive days. After this, they subsequently received two injections every six months. No further oral doses of lenacapavir were needed unless future injection appointments were significantly delayed. This long duration between injected doses should be attractive to many potential PrEP users.

Ongoing clinical trials

One clinical trial that is still ongoing has released interim results. Researchers found that lenacapavir is highly effective at preventing HIV infection in women and adolescent girls. In this trial, called Discover 1, researchers compared lenacapavir (given by injection every six months) to daily Truvada or Descovy. Lenacapavir provided 100% protection from HIV. In contrast, tenofovir-based regimens were significantly less effective. This reduced effectiveness was likely caused by some participants not taking their pills as directed.

Lenacapavir is generally well tolerated and associated with less risk of nausea and vomiting when compared to tenofovir-based regimens.

What lies ahead?

Gilead Sciences, the developer of lenacapavir, has an extensive research program on the drug. Trials are continuing in women and adolescent girls. There are also prevention trials in gay and bisexual men, transgender women and people who use drugs.

Interim results from a trial in men who have sex with men (MSM), transgender men, transgender women and non-binary people have recently been released (detailed later in this issue of *TreatmentUpdate*). In this trial, lenacapavir was highly effective.

Complete results from these and other clinical trials will gradually become available in the months and years ahead. Gilead plans to submit a dossier on lenacapavir for prevention to regulatory authorities in the U.S. and then likely in the European Union, followed by other countries and regions. The company will likely seek accelerated approval, given that lenacapavir only needs to be taken twice yearly.

After regulatory agencies approve lenacapavir for prevention, governments will negotiate with Gilead to find a price on which they can agree. All these processes and procedures take time, which is why lenacapavir for prevention may not be approved in Canada until perhaps 2026. It will take at least another year after that before it hopefully ascends to the list of medicines that provincial and territorial governments subsidize for HIV prevention. These lists are called formularies.

In the community

Researchers have found that most people who use PrEP in Canada are gay and bisexual men. Certainly, lenacapavir needs to reach this population. Other populations that bear a disproportionate burden of HIV—such as Indigenous people; transgender and nonbinary people; African, Caribbean and Black people; women; and people who use drugs—also need equitable access to lenacapavir to help reduce their HIV risk.

Understanding the rollout

Pilot studies (demonstration projects) to implement lenacapavir for prevention in the community can be useful, as they help busy clinics understand the best way to manage the flow of patients who require subcutaneous injections. The information from demonstration projects can be used to help integrate lenacapavir into sexual health and other clinics.

Lenacapavir will become an exciting option for many people with HIV. Hopefully Gilead will price it responsibly so that governments can afford to subsidize it. The drug also needs to be equitably distributed.

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B. Lenacapavir highly effective at preventing HIV in women

Researchers in South Africa and Uganda conducted a study on pre-exposure prophylaxis (PrEP) called Purpose 1 with 5,338 adolescent girls and young women, all of whom were cisgender. At the start of the study, all participants were HIV negative.

Researchers randomly assigned participants to receive one of the following PrEP interventions:

- lenacapavir– ultimately given by subcutaneous (just under the skin) injection every six months
- Truvada – taken as a pill once daily
- Descovy – taken as a pill once daily

The trial had a rigorous but complicated design—it was double blind and placebo controlled. In this case, that meant that all participants received a placebo (fake drug). So, everyone who was taking Truvada or Descovy also received injections of fake lenacapavir every six months. And those who were receiving real lenacapavir also received fake Truvada or fake Descovy (placebos) in pill form meant for daily use. Placebo pills and solution were made to look like the real drugs. Most personnel involved in the study were not aware which participants received which drugs until the trial was unblinded.

Researchers randomly assigned people to receive the study drugs in a 2:2:1 ratio (lenacapavir: Truvada: Descovy).

Regular monitoring, visits to study clinics and consistent counselling about adherence were features of this study. Participants received condoms and lubricants, and they underwent regular screening for HIV and other sexually transmitted infections (STIs).

Women and girls who became pregnant while in the study were given additional informed consent documents to read. If they signed the documents, they could remain in the study.

The lenacapavir regimen

Participants who were assigned to receive lenacapavir (the lenacapavir group) received two subcutaneous (just under the skin) injections in the abdomen on day 1. They also took an oral form of the drug on days 1 and 2. Participants were told to return to the study clinics within 26 to 28 weeks after their last injection. If they missed this window period and wanted to resume lenacapavir, they first had to undergo HIV testing (viral load and HIV antigen). If these tests were negative, they re-initiated oral lenacapavir for two consecutive days followed by injections.

Tenofovir-based regimens

Adherence to Truvada and Descovy was assessed in a randomly selected group of people—about 10% of participants. Researchers analysed a small amount of blood from each person for this purpose.

Participants

At the start of the study, on average, participants were generally healthy, aged 21 (only 2% were younger than 18) and most (85%) were from South Africa.

Results

The current analysis largely focuses on the first year of the study. In July 2024, the study was unblinded and researchers began to tell participants which active drug they received. Researchers then offered all participants the option to either initiate lenacapavir or continue to receive the drug.

The numbers of new HIV infections were distributed as follows:

- lenacapavir – 0 infections among 2,134 participants
- Truvada – 39 infections among 2,136 participants
- Descovy – 16 infections among 1,068 participants

Lenacapavir was associated with a significantly reduced risk of getting HIV. This drug also reduced the risk of HIV infection compared to tenofovir-based regimens. Most participants who became infected had low levels of tenofovir in their blood; this strongly suggests poor adherence.

According to researchers, the difference in the level of HIV risk reduction between Truvada and Descovy was not "meaningful."

STI screening every 26 weeks uncovered high rates of chlamydia, gonorrhea and syphilis regardless of the PrEP drug used.

Remaining in the study

It is normal in all clinical trials for any condition for some people to prematurely withdraw for a variety of reasons.

In the present study, the proportions of people who remained in the study at different time points were as follows:

- week 26 – 97% remained
- week 52 – 93% remained
- week 104 – 91% remained

Retention in the study was similar regardless of the drug taken (lenacapavir, Truvada or Descovy).

Safety

The term *adverse events* is used to describe unfortunate events that occur in a clinical trial. Some adverse events may be caused by the study drugs, others by an underlying disease process, and still others may have nothing to do with the study (such as accidents).

A common adverse event was mild-to-moderate headache, distributed as follows:

- lenacapavir – 13%
- Truvada – 15%
- Descovy – 17%

In general, adverse events were similar across the study drugs, except for nausea and vomiting, which were more common in people who received tenofovir-based regimens.

Lenacapavir
- nausea – 7%
- vomiting – 6%

Truvada
- nausea – 13%
- vomiting – 10%

Descovy
- nausea – 11%
- vomiting – 11%

As mentioned, most adverse events were mild to moderate. However, some participants had more severe symptoms, distributed as follows:

- lenacapavir – 4%
- Truvada – 5%
- Descovy – 4%

The proportions of people who prematurely left the study due to adverse events were as follows:

- lenacapavir – 0.2%
- Truvada – 0
- Descovy – 0.1%

Injection site reactions

Injection site reactions were more common in people who received lenacapavir than in those who received a tenofovir-containing regimen (with injections of fake lenacapavir). However, these reactions in people who received lenacapavir were generally mild to moderate and diminished with repeated injections in the future.

The distribution of injection site reactions was as follows:

- lenacapavir – 69%
- Truvada – 35%
- Descovy – 35%

Many people who had injection site reactions developed lumps that the researchers called "nodules." These nodules occurred in 64% of people who received lenacapavir and 17% of people who received placebo injections. The nodules generally shrunk over time. There was a reduced risk of nodules with subsequent doses of lenacapavir.

Most of the injection site reactions were mild to moderate. However, four people who developed such reactions on lenacapavir prematurely left the study. No one who received placebo injections prematurely left the study due to injection site reactions.

Abnormal lab test results

At some point in the study, researchers found that 91% of participants developed an abnormal lab test result when their blood was analyzed. However, these abnormalities were generally mild to moderate. No one appeared to experience any permanent injury from more serious lab abnormalities; such abnormalities were extremely rare.

Deaths

Six people died during the study—all were taking Descovy. Three died from violence and the remainder from complications due to the following:

- traffic accident
- cardiovascular disease (confirmed with autopsy)
- ovarian cancer

None of these deaths were related to Descovy.

Pregnancy and birth defects

During the study there was a total of 510 pregnancies, distributed as follows:

- lenacapavir – 193 people
- Truvada – 98 people
- Descovy – 219 people

At the time data were analysed, limited information was available on the outcome of those pregnancies, as follows:

- 121 births
- 66 miscarriages
- 90 abortions

Although lenacapavir is approved for the treatment of HIV in high-income countries, so far it has been rarely used. It is reserved for the treatment of people with multidrug-resistant HIV. As a result, doctors have little experience with it outside of clinical trials. Its effect on the fetus and during pregnancy is poorly understood.

The present study is the first to have a large data set on many women with long-term use of lenacapavir and in pregnancy. Further analysis of this data is needed.

One woman who used lenacapavir gave birth to an infant with an extra finger or toe. However, this woman had relatives who also had this condition (and they had not used lenacapavir), so investigators ruled that the extra digit was likely due to a preexisting genetic issue and not lenacapavir.

Bear in mind

The current study in cisgender women and girls has produced exciting results. Lenacapavir taken every six months via subcutaneous injection is associated with a high degree of protection from HIV, much greater than that from daily Truvada or Descovy. According to the researchers, this difference in protection is due to "poor adherence" in people who used oral PrEP.

The researchers stated that the factors that drove poor adherence to oral PrEP may have been related to "stigma, dislike or lack of experience with daily pill-taking, and inaccurate perception of the likelihood of the acquisition of HIV infection."

Lenacapavir given twice a year may help many women experiencing these issues.

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C. Lenacapavir highly effective at preventing HIV in cisgender men, transgender women and non-binary people

Gilead Sciences has announced interim results from a clinical trial on pre-exposure prophylaxis (PrEP) called Purpose 2. In this study, injectable lenacapavir was compared to a pill taken once daily that contained two drugs (tenofovir DF + FTC). This pill is sold as Truvada and available in generic formulations.

Participants in this randomized, double-blind study were aged 16 and older and were recruited from Latin America, South Africa, Thailand and the U.S.

The 3,200 participants in Purpose 2 included gay and bisexual cisgender men, transgender men, transgender women and non-binary people. Participants had sex with partners assigned male at birth.

Participants were randomly assigned in a 2:1 ratio to receive lenacapavir or Truvada.

Researchers found that two cases of HIV infection occurred during the study, in people who were taking lenacapavir. Bear in mind that these were two cases out of 2,180 people on lenacapavir. Gilead notes that 99.9% of participants on lenacapavir did not get HIV. Compared to the background rate of HIV in people not on some form of PrEP, overall, lenacapavir reduced the risk of getting HIV by 96%. Also, lenacapavir was nearly 90% more effective than Truvada at preventing HIV infections. This finding is likely driven by easier adherence requirements for lenacapavir, which is ultimately given as two injections every six months.

Gilead will release further details about Purpose 2 at a scientific conference in the future.

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II HIV CURE RESEARCH

A. Different approaches to HIV cure research

When used as directed, modern HIV treatment (antiretroviral therapy, ART) is highly effective at controlling HIV. As ART suppresses HIV, the immune system can mostly repair itself. As a result, researchers project that many ART users will have near-normal life expectancy. What's more, large well-designed clinical trials have found that people whose HIV is suppressed with ART do not pass on the virus to their sexual partners.

However, even with ART, HIV can still hide inside cells of the immune system deep within lymph nodes, the spleen, brain and likely other tissues. Scientists refer to the pool of infected cells as the reservoir. Long-term research has found that even in highly adherent people on ART, the reservoir appears to increase in size over a period of decades. In the reservoir, HIV is largely in a quiet or latent state. What's more, the cells that carry HIV in the reservoir appear to escape notice by the immune system. All of this means that ART helps keep

people in overall good health, but the burden of the virus cannot be eradicated by ART alone.

Another concern that scientists have is that even with treated HIV infection there is an excess level of inflammation and activation of the immune system. It is likely that these two factors increase the decline of key organ systems and may make people with HIV more susceptible to developing age-associated conditions at an earlier age.

Ideally, a simple and safe therapy that could cure a person of HIV would be best. However, it is extremely difficult (and dangerous) to cure people with existing technology. Instead, most scientific teams working on HIV cure research are attempting something that is probably more feasible in the medium term. They are developing strategies to help the immune systems of people with HIV better recognize infected cells, destroy them and significantly reduce the size of the viral reservoir. The result of such strategies would hopefully be to allow people periods of time where they would not need to take ART, as their immune systems would keep the virus in check. Some scientists call such a goal a "functional cure," though perhaps a better description would be to help people achieve virological control of HIV without needing to take ART on a regular basis.

Before delving into different approaches to cure research, here is a bit of background about some of the receptors that HIV uses. Scientists have taken advantage of this knowledge to craft strategies for cure research.

Know your co-receptors

To infect a cell of the immune system, HIV uses a receptor found on T-cells and other cells of the immune system. The receptor is called CD4. After binding to CD4, HIV needs a co-receptor, either one called CCR5 or CXCR4. Most strains of HIV need the CCR5 co-receptor in order to infect a target cell. Some people have a very rare mutation in their genes, called delta-32, which is found in about 1% of people of northern European ancestry. People with the delta-32 mutation do not have CCR5 on their cells and are largely resistant to HIV infection. Some approaches to HIV cure research try to block or remove the ability of cells of the immune system to make the CCR5 co-receptor.

Now on to different approaches in cure research.

Stem cell transplants

Stem cell transplants are risky. For the purpose of attempting an HIV cure, stem cell transplants are reserved for cases where a person with HIV has a life-threatening cancer for which such a transplant would be helpful (such as leukemia and lymphoma). Doctors who think that the person can survive a stem cell transplant search for a bone marrow donor who has the delta-32 mutation and whose genes are similar to the person with HIV. Making such a match is not easy, so these transplants are uncommon in the field of HIV. What's more, researchers reserve this intervention for people with a terminal cancer diagnosis because it is dangerous.

First, the person with HIV has to undergo an intensive course of radiation and/or chemotherapy to destroy their bone marrow (and immune system). This makes them highly susceptible to severe illness from otherwise minor infections. After their bone marrow (and much of their immune system) has been destroyed, the person with HIV can receive a transplant from a suitable donor. If successful, the donated cells can repopulate their bone marrow and create a new immune system that is resistant to HIV because it came from a donor whose immune system did not have CCR5 on their cells.

Even so, sometimes the transplant does not work—transplanted cells can be attacked by surviving residual cells of the old immune system and severe inflammatory reactions can occur that can make the recipient of the transplanted stem cells quite ill.

However, in about a handful of cases, the stem cell transplants from people with the delta-32 mutation have been successful and cures of both HIV and cancer have resulted.

More recently, doctors have been attempting to cure people with HIV using donors who do not have the delta-32 mutation.

As explained earlier, stem cell transplants are dangerous and attempted only in certain cases. Because they are so risky, stem cell transplants are not practical for most people with HIV. However, they do help scientists learn more about the immune system and how it can resist HIV. For the foreseeable future, stem cell transplants that attempt to cure HIV will be a research tool.

Inhibitors of checkpoints and other proteins

The immune system has powerful mechanisms to attack infected cells and tumours. Such attacks could easily get out of control and the immune system could inadvertently attack healthy tissue. To reduce the risk of this happening, the immune system has a series of checks and balances that help keep it from getting out of control. One of the ways that excessive activity in the immune system is prevented is with some proteins called checkpoints. Examples of checkpoints are as follows:

- PD-1 (programmed cell death protein-1)
- PD-L1 (programmed death-ligand 1)
- CTLA-4 (cytotoxic T-lymphocyte associated protein 4)
- TIGIT (T-cell immunoreceptor with Ig and ITIM domains)

Tumours and some chronic viral infections (such as HIV) appear to release chemical signals that cause the immune system to over-express checkpoints. This hinders the immune system's ability to clear tumours and viruses.

Checkpoint inhibitors have been developed as part of cancer treatment. However, a side effect of checkpoint inhibitor therapy is that it can cause the immune system to attack healthy tissue.

To minimize this problem, some pharmaceutical companies, such as AbbVie, are testing low doses of checkpoint inhibitors (such as one called budigalimab) that reduce HIV's ability to weaken the immune system but also minimize attacks on healthy tissue. Budigalimab is an antibody that interferes with the checkpoint called PD-1.

AbbVie is also testing a therapy that binds to a protein on cells of the immune system. The protein is called alpha4beta7 (a4b7). Lab experiments with cells of the immune system suggest that providing antibodies that can block a4b7 helps protect cells from HIV. By covering this protein with an antibody, HIV cannot sense target cells. Another effect of blocking a4b7 is that cells of the immune system appear to better recognize HIV and therefore can attack it. AbbVie is testing an approach that combines low-dose checkpoint inhibition with antibodies that block a4b7. A preliminary trial of this approach has yielded interesting results—with some people able to remain off ART for more than a year while maintaining virological control of HIV.

Clinical trials of this approach with a large number of people will be needed to find out if it can help the immune system keep HIV under control so that long periods without ART are possible.

Latency reversing agents

As mentioned earlier, although good adherence to ART helps keep HIV suppressed, the virus remains inside a pool of cells it has infected. Inside these cells HIV is in a quiet, or latent, state. It is difficult for the immune system to sense these quietly infected cells. Therefore, some scientists propose a two-step approach to deal with this. First, HIV is brought out of latency with drugs called latency reversing agents. Second, the immune system's virus-fighting abilities are enhanced with certain treatments or vaccines being developed against HIV. Clinical trials of latency reversing agents are underway.

CAR-T cell therapy

CAR-T cell (chimeric antigen receptor T cell) therapy is based on T-cells that have been genetically engineered in the lab to attack only one target. Initially, CAR-T cell therapy was developed to treat certain forms of cancer. As this has been found to be successful, scientists want to use CAR-T cells on another target: HIV-infected cells.

For CAR-T cell therapy, scientists take a sample of a person's blood and extract T-cells. They then modify these T-cells and give them the ability to focus on attacking HIV. Furthermore, scientists can make CAR-T cells resistant to HIV infection. The cells are grown and allowed to multiply in the lab, forming billions of cells which can then be infused into a person.

A barrier that scientists have faced in initial studies of CAR-T cell therapy in HIV is that the modified cells do not persist. However, attempts are underway to address this.

Clinical trials aimed at testing variations of CAR-T cell strategies against HIV are underway.

Super antibodies

Scientists have developed what they call bNAbs (broadly neutralizing antibodies). These antibodies can attack HIV and prevent it from infecting cells. In clinical trials, bNAbs can reduce production of HIV. However, there is the possibility that if bNAbs were used on their own (without anti-HIV drugs) HIV could eventually develop resistance to these antibodies. Clinical trials are underway that combine the use of bNAbs with other therapies or that use several different bNAbs simultaneously. The U.S. National Institutes of Health (NIH) is conducting clinical trials of combinations of bNAbs. It is also facilitating the development of long-acting formulations of these antibodies.

A potential drawback of bNAbs is that they may not be able to penetrate deep within the brain and lymph nodes where HIV-infected cells can reside. It is possible that studies that combine bNAbs with the drug metformin may be useful (see below).

Metformin

Metformin is a drug that has been used for nearly 60 years to help treat people with diabetes. HIV causes changes to the metabolism of T-cells, so researchers at universities in Montreal were interested in studying metformin's effect on T-cells in people with HIV.

Experiments in people with HIV who took metformin and ART found that metformin helped certain T-cells (called CD8+ cells) better recognize HIV-infected cells. Also, lab experiments suggest that metformin could help bNAbs better recognize HIV-infected cells..

The Montreal researchers recommend a randomized, controlled clinical trial of metformin + bNAbs in people with HIV who are using ART.

The purpose of metformin would be to enhance the immune system's ability to help reduce the reservoir of HIV-infected cells and/or enhance the activity of bNAbs.

Clinical trials are important

The approaches listed above are merely some of the different angles from which scientists are trying to attack HIV so that people with HIV can hopefully have long periods off ART. It is important that people with HIV enroll in clinical trials of cure research to help move the field forward.

A completely different approach to trying to control HIV has recently been published and is detailed in the next article.

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B. Therapeutic Interfering Particles (TIPs)

A team of researchers at the University of California at San Francisco (UCSF) has developed a completely different approach to control HIV and have recently published the results of experiments with monkeys and human cells. This approach is called therapeutic interfering particles, or TIPs.

An over-simplified explanation of TIPs follows. Researchers have created highly mutated but harmless versions of HIV and its analogue SIV (simian immunodeficiency virus; this causes an AIDS-like disease in susceptible monkeys). These mutated viruses, called TIPs, are unable to cause disease because they have vital information deleted from their genetic information.

When HIV-infected cells are exposed to TIPs, their ability to produce infectious HIV is greatly diminished. The UCSF scientists say that this effect happens because TIPs reproduce faster than infectious HIV, and in the process, TIPs "steals essential viral proteins" from HIV-infected cells. The scientists also said that another way to think about TIPs is that they are a "molecular parasite" of HIV-infected cells.

Monkey research

The UCSF scientists cooperated with scientists in Oregon who work with monkeys. The team of scientists developed a hybrid virus called SHIV, using elements of HIV and SIV. The reason for using this hybrid virus is that it can cause an AIDS-like disease in monkeys within a few months after infection (rather than more than a year with SIV). This way, scientists can determine in a relatively shorter time if their intervention against SIV is working.

A single intravenous infusion of TIPs protected five out of six monkeys infected with SHIV from developing AIDS-like disease for at least six months (the length of the experiment). TIPs had this effect on the course of disease because it greatly suppressed production of SHIV in blood and lymph nodes.

Tests revealed that the immune systems of TIPs-treated monkeys were fully functional and there was no increased level of inflammation. Analysis of SHIV samples from TIPs-treated monkeys found

that the hybrid virus was unable to evade TIPs or mutate to avoid it.

TIPs reduced the amount of SHIV in monkeys by a factor of approximately 10,000. This and other effects were maintained for just over six months.

Additional research with monkeys is needed whereby SHIV-infected monkeys are treated with HIV treatment (antiretroviral therapy, ART) to suppress the virus. They can then be given TIPs and ART can be withheld. This research is important because it might mimic what some humans would like to do if they were given TIPs.

Potential in humans with just one dose

Based on results in monkeys with SHIV, the researchers developed computer simulations of the effect of one dose of TIPs in people with HIV.

The simulations predicted that TIPs could reduce the HIV viral load in the blood to less than 1,000 copies/mL. At this level of viral load, previous research suggests that people would be extremely unlikely to pass on HIV via sex.

Human research needed

Based on promising experiments with monkeys and T-cells in the lab, the scientists developing TIPs hope to enroll people with HIV to test the effect of an infusion of TIPs. Although there is no evidence of harm in monkeys that have received TIPs, scientists are unsure about its safety in people and its potential to cause unwanted effects, perhaps even cancer (though so far there is no evidence of cancer-causing potential from TIPs in lab experiments with cells and in monkeys). So, the scientists want to recruit people with HIV who have a diagnosis of terminal cancer for the first infusion of TIPs. After the participants die from complications caused by cancer, the researchers hope to conduct autopsies to assess the impact of TIPs on their organs and immune system.

In the future, if TIPs is found to be safe, it is possible that some people given TIPs could pass on the particles the same way that HIV is most commonly transmitted—through condomless intercourse. This possibility needs to be better understood. Professor Leor Weinberg, the scientist behind TIPs, has mused that the transmission of TIPs from one person to another could be seen as a public health benefit, as it would block the spread of HIV. However, this issue needs to be examined by ethicists. Also, much more information about the long-term safety of TIPs is needed.

Bear in mind

It is still early days with TIPs. Much research lies ahead, and it will be several years before large studies in healthy people with HIV can begin.

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Cohen J. Fire-against-fire HIV therapy passes key test in monkeys. *Science*. 2024 Aug 9;385(6709):586-587.

C. A second person in Berlin is cured

In June 2009, doctors published details on the first patient that would later become cured of HIV. His cure was effected through a stem cell transplant with a rare mutation, as well as a complex and at times toxic mix of chemotherapy, radiation and other interventions. The reason this patient was cured was likely because he received a stem cell transplant from a donor who lacked a co-receptor that is used by most strains of HIV to infect cells. This co-receptor is called CCR5. Such donors have a very rare mutation that allows them to live without having cells with this co-receptor. Scientists call this rare mutation delta-32. People with both copies of a gene with the delta-32 mutation are rare; it is found in about 1% of people of northern European descent. People with only one copy of a gene with the delta-32 mutation are a bit more common—about 10% of European populations have this. Some parts of the world, such as South Africa and Chile, have small populations with this gene because of migration. (For more about HIV co-receptors, see the earlier article "Different approaches to HIV cure research.")

Subsequently, five out of seven people who have received a stem cell transplant from a donor with genes that have both copies of the delta-32 mutation (along with an intensive course of radiation and chemotherapy) have also been cured of HIV. In the long history of attempts at curing HIV, giving a

person a stem cell transplant without both copies of the delta-32 mutation has not worked.

Note that attempts at cure are difficult and dangerous, as they involve destroying a person's bone marrow (the source of the cells that ultimately form one's immune system). Not only that, but the donor of the stem cells must be genetically similar to the recipient. This genetic relatedness is necessary to reduce the risk of the recipient's immune system destroying the transplanted cells. Doctors usually only attempt stem cell transplants to try to cure HIV in people who have a life-threatening cancer (whereby the cancer can also be cured with a stem cell transplant, such as cases of leukemia and lymphoma).

Prospective recipients of a stem cell transplant must first undergo the destruction of their bone marrow (with radiation and/or chemotherapy). The loss of their immune system places them at risk for serious infections. They can then be given the stem cell transplant. But it takes time to recreate their new immune system. To prevent the residue of their old immune system from attacking the donated stem cells, their immune systems are temporarily suppressed. HIV treatment (antiretroviral therapy, ART) is taken during these procedures to minimize the risk of the virus infecting their new immune system. Several years after the transplant, when doctors can no longer detect HIV in the blood and from biopsy samples, ART is withheld to see if any HIV becomes detectable.

As mentioned earlier, a handful of people have been cured with stem cell transplants from donors with genes that have both copies of the delta-32 mutation.

Last year there was a report of a patient in Geneva being in what scientists call "remission" from HIV. After the stem cell transplant and associated procedures, doctors were unable to find HIV after they withheld ART. What makes the Geneva patient interesting is that he received a stem cell transplant from a donor who did not have the delta-32 mutation. This mutation largely renders a person's immune system resistant to HIV infection. The new immune system of the Geneva patient does not have the delta-32 mutation; therefore, it is still susceptible to HIV, but researchers are unable to find any virus in his blood and tissue samples.

The researchers theorize that the reaction between the remnants of his old immune system and the donated stem cells—a reaction called graft vs. host disease—probably helped to kill HIV-infected cells.

In Berlin

Doctors in Berlin recently reported details on a patient who was diagnosed with HIV in 2009. He began ART in 2015 with a combination of raltegravir, abacavir and 3TC, and his viral load was subsequently less than 50 copies/mL. In April of that year he was diagnosed with a form of leukemia that would prove lethal if left untreated. Analysis of the HIV in his blood samples revealed that 99.7% of viruses used CCR5. This suggested to the doctors that he would benefit from a stem cell transplant from a donor whose cells lacked CCR5 (that is, someone with the delta-32 mutation).

Doctors sought a donor who was genetically similar to the patient and whose cells had both genes with the delta-32 mutation. They were unable to find such a donor. However, they did find someone whose genes had one copy of the delta-32 mutation (the previous successful stem cell transplants that led to HIV cures were with donated stem cells that had two copies of the mutated gene).

The patient developed what doctors described as mild complications from the transplant. Within 28 days, the transplanted stem cells began to repopulate his immune system. His leukemia was cured, as usually happens with a stem cell transplant.

Over time, doctors could not find HIV in his blood after the transplant, so in September 2018 he stopped taking ART. Subsequently, doctors were not able to find HIV in his blood samples and biopsies of lymph nodes. What's more, the patient's T-cells did not recognize HIV when exposed to the virus in lab experiments. This suggests that his T-cells did not encounter the virus since the stem cell transplant.

It has been six years since the patient stopped taking ART, and researchers have not been able to find HIV in his body. They think that he is potentially cured of HIV.

Bear in mind

Researchers are not certain why the patient was cured, as the stem cell transplant lacked cells with both copies of the delta-32 mutation in their genes. However, research on this patient and his blood samples is promising and may yield clues for new therapies and interventions that are simpler and safer for curing HIV.

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Claireaux M, Robinot R, Kervevan J, et al. Low CCR5 expression protects HIV-specific CD4+ T cells of elite controllers from viral entry. *Nature Communications*. 2022 Jan 26;13(1):521.

III COMORBIDITIES

A. Frailty in Indigenous people with HIV

As people with HIV live longer thanks to HIV treatment (antiretroviral therapy, ART), they become at risk for complications related to aging. In Canada, estimates are that at least 50% of people with HIV are over the age of 50, so research on aging in this population is important. One complication of aging is that people can accumulate comorbidities, which increases their risk for frailty.

The Ontario HIV Treatment Network (OHTN) collects data from many HIV clinics in Ontario and analyzes it from time to time. Its most recent analysis involved 6,582 participants, of whom 330 (5%) were Indigenous.

For the purposes of this analysis, the researchers made the following definitions:

- the presence of one or two comorbidities resulted in participants being classed as pre-frail
- the presence of three or four comorbidities meant that participants were classed as frail

Results

Overall, pre-frailty and frailty were more common in Indigenous people, as follows:

Pre-frailty
- Indigenous people – 50%
- non-Indigenous people – 41%

Frailty
- Indigenous people – 9%
- non-Indigenous people – 6%

What's more, the research team found that, on average, Indigenous people became pre-frail four years earlier than non-Indigenous people, and they became frail five years earlier than non-Indigenous people.

In the OHTN study, females were over-represented and were more likely to become frail than males.

The researchers found that a history of injecting drugs was three times more common among Indigenous people (45%) than non-Indigenous people (16%). Furthermore, Indigenous people who injected drugs were more likely to be frail (13%) than non-Indigenous people who injected drugs (7%).

History of AIDS

Indigenous people were more likely than non-Indigenous people to have experienced AIDS at some point in the past (64% vs. 56%). Indigenous people who had experienced AIDS were more likely to experience pre-frailty and frailty than non-Indigenous people who had a history of AIDS.

Causes and underlying factors

Statistical analysis found that injection drug use increased the risk of frailty twofold. However, being Indigenous also carried a risk of frailty independently of drug use.

The OHTN researchers noted that Canada's history of colonialism and ongoing racism against Indigenous people very likely has led to greater frailty at a younger age among this population.

Researchers called for making models of care evolve to meet the needs of Indigenous people with HIV to "both address their needs at younger ages and in culturally responsive ways that work for them."

The researchers need to do further analyses to understand the impact of other factors, such as smoking, on frailty risk, as many participants appeared to have a history of smoking.

REFERENCE:

Bauer N, O'Brien KO, Light L, et al. Time is of the essence: clinical frailty among a cohort of Indigenous peoples aging with HIV in Ontario, Canada. *25th International Conference on AIDS,* Munich, Germany, 22-26 July 2024. Abstract OAB3602.

B. Does changing integrase inhibitors help reduce sleeping problems?

Integrase inhibitors are a cornerstone of HIV treatment (antiretroviral therapy, ART) in the current era. Examples of integrase inhibitors that are used today include the following:

- bictegravir (in Biktarvy)
- dolutegravir (in Dovato, Juluca and Triumeq)
- raltegravir

Most people tolerate integrase inhibitors well. However, there are reports that a small minority of people develop sleeping problems when they use this class of anti-HIV drugs.

A team of researchers in the UK used MRI scans of the brain (functional MRI) to get a sense of oxygenation of different parts of the brain and how they were communicating with each other.

For their study, the researchers sought to enroll at least 40 people who were taking dolutegravir-containing regimens and who had undetectable viral loads. They assessed sleep behaviours, quality of life, craving for food, insomnia, fatigue and sleep quality with validated questionnaires. Participants also underwent functional MRI at the start of the study and 120 days later. Researchers also took blood samples to analyze proteins linked to inflammation, such as IL-6 (interleukin-6) and neopterin.

Due to the COVID-19 pandemic, researchers were only able to enroll 19 participants, all men who had insomnia and were taking a dolutegravir-based regimen. Participants were then divided into two groups as follows:

- 7 participants were assigned to switch to a bictegravir-based regimen (in practice this would entail taking Biktarvy—a combination of bictegravir, TAF + FTC in one pill)
- 12 participants were to remain on dolutegravir-based HIV treatment

A brief average profile of the men at the time they entered the study was as follows:

- age – 55 years
- length of HIV diagnosis – 11 years
- CD4+ count – 600 cells/mm^3
- duration of pre-study ART – 41 months
- commonly used pre-study regimens: Triumeq (dolutegravir + abacavir + 3TC); dolutegravir + Truvada; dolutegravir + 3TC (Dovato)

All participants had high levels of insomnia.

Results

Researchers found that self-reported sleep quality improved in people who were switched to bictegravir. MRI scans confirmed that their brain activity resembled that of people who had restful sleep.

The switch in treatment had no impact on blood proteins associated with inflammation.

Bear in mind

This was a very small study, and its findings are not definitive. A much larger study is required to confirm its findings. The study had several shortcomings, such as a lack of placebo and no female participants.

There is also an issue that could have inadvertently biased the study results. Many participants (12) were taking a regimen that contained abacavir. This drug was developed in the early to mid-1990s and was designed to enter the brain to suppress HIV

there. In that era, before effective HIV therapy was available, many people experienced brain-related complications such as HIV-related brain injury and reduced memory and cognitive functioning. Unfortunately, reports suggest that some people can experience sleeping problems when using abacavir. Future insomnia studies need to take this into account.

REFERENCE:

Henderson M, Alford K, Doyle N, et al. A pilot study assessing changes in cerebral function parameters in persons with insomnia switching integrase inhibitors. *25th International Conference on AIDS*, Munich, Germany, 22-26 July 2024. Abstract OAB3605.

IV ANTI-HIV AGENTS

A. Bictegravir + lenacapavir – an emerging duo

Bictegravir is an integrase inhibitor and is available in a pill called Biktarvy, which also contains TAF + FTC. Biktarvy is taken once daily and is generally well tolerated and highly effective against HIV.

Lenacapavir impairs the activity of an HIV protein called the capsid. It is classed as a capsid inhibitor. Currently, lenacapavir is reserved for people with multidrug-resistant HIV. It is also being developed for HIV prevention.

Gilead Sciences, the manufacturer of both drugs, is testing a combination of bictegravir + lenacapavir, both drugs taken once daily. The idea behind this is to offer a simplified regimen for some people with HIV.

In a clinical trial, researchers enrolled participants who were on a complex HIV treatment (antiretroviral therapy, ART) regimen and randomly assigned them to one of the following combinations:

- bictegravir 75 mg + lenacapavir 25 mg – 51 people
- bictegravir 75 mg + lenacapavir 50 mg – 52 people

The remaining 25 participants stayed on their complex ART regimens.

All combinations were taken in pill form once daily.

Study details

The average profile of participants at the start of the study was as follows:

- age – 60 years
- 24% were female at birth and 76% were male at birth
- major ethno-racial groups: White – 65%; Black – 31%; Asian – 4%
- CD4+ count – 610 cells/mm^3
- length of time on ART – 27 years
- presence of HIV that had some degree of resistance to previous treatments – 81%

Prior to the study, participants were all on complex ART regimens, as follows:

- 41% were taking regimens that required twice-daily dosing
- 27% were taking at least five pills of HIV medicines daily

Examples of complex regimens that some participants took included the following:

- darunavir + cobicistat + dolutegravir + TAF + FTC
- darunavir + cobicistat + dolutegravir + etravirine or rilpivirine

Results

After one year, the following proportions of participants had a suppressed viral load:

- bictegravir 75 mg + lenacapavir 25 mg – 92%
- bictegravir 75 mg + lenacapavir 50 mg – 90%
- complex ART – 100%

CD4+ cell counts increased modestly over the course of the study and were similar among the three groups.

Two people taking bictegravir + lenacapavir 25 mg had temporarily detectable viral loads, but they resuppressed while remaining on this combination.

Adverse events

Adverse events that led to premature study discontinuation:

- bictegravir + lenacapavir 25 mg – mild but persistent nausea
- bictegravir + lenacapavir 50 mg – severe nausea due to a pre-existing condition

One person who was taking lenacapavir at the 50 mg dose died from cardiovascular disease; this was unrelated to the study medicines.

Diarrhea seemed to be the most common adverse effect and was distributed as follows:

- bictegravir + lenacapavir 25 mg – 10% had diarrhea
- bictegravir + lenacapavir 50 mg – 4% had diarrhea
- complex ART – 4% had diarrhea

Most cases of diarrhea were mild to moderate.

Higher doses of lenacapavir were not linked to increased side effects.

A pill containing bictegravir 75 mg and lenacapavir 50 mg has been developed and will be tested in larger clinical trials in the future. If such trials yield successful results, a pill containing both drugs could be approved for use in several years.

REFERENCE:

Mounzer K, Slim J, Ramgopal M, et al. Efficacy and safety of bictegravir plus lenacapavir: 48-week outcomes in virologically suppressed people with HIV-1 on complex antiretroviral regimens at baseline. *25th International Conference on AIDS*, Munich, Germany, 22-26 July 2024. Abstract OAB2602.

B. Exploring weight changes with different integrase inhibitors

Researchers from 30 clinics in Spain conducted a study called Paso Doble. In this study, participants with HIV who were taking HIV treatment (antiretroviral therapy, ART) and who had a suppressed viral load were randomly assigned to receive one of the following regimens:

- dolutegravir + 3TC (Dovato) – 277 people
- bictegravir + TAF + FTC (Biktarvy) – 276 people

Pre-study regimens included drugs such as efavirenz (85%) and tenofovir DF. No participant had previously used bictegravir- or dolutegravir-containing regimens. None had hepatitis B virus coinfection.

Researchers assessed weight changes, and future analyses will explore changes to fat cells with biopsies, scans of the liver for fat accumulation, metabolic issues and premature aging.

At the start of the study, the average profile of participants was as follows:

- age – 50
- 27% were female at birth and 73% were male at birth
- length of time on ART – 12 years
- duration with a suppressed viral load (less than 50 copies/mL) – 100 months
- CD4+ count – 700 cells/mm^3 (9% of participants had less than 300 CD4+ cells/mm^3)
- overweight or obese – 50%

Results

There have been previous clinical trials of this combination that focused on effectiveness. In such studies, Dovato was found to have similar effectiveness to Biktarvy (the technical statistical term for this is *non-inferior*).

In the present study, results were similar. The proportions of participants with a suppressed viral load (less than 50 copies/mL) at week 48 were as follows:

- Dovato – 93%
- Biktarvy – 90%

Blips

Sometimes after viral suppression is achieved, viral load will temporarily increase a small but detectable amount due to infections (such as cold,

flu, sexually transmitted infections), vaccination or seasonal allergies. After a time, viral loads generally return to undetectable. This temporary rise in viral loads is called a blip.

The proportions of participants with a blip (defined as a viral load between 50 and 199 copies/mL) were distributed as follows:

- Dovato – 6%
- Biktarvy – 9%

This difference was not statistically significant.

Only one person developed virological failure (a persistent viral load greater than 200 copies/mL) and that person was taking Biktarvy.

There were no significant changes in CD4+ cell counts.

Adverse effects

Adverse effects were reported, as follows, but they were generally mild to moderate and temporary:

Soreness of muscle/bone
- Dovato – 20%
- Biktarvy – 19%

Gastrointestinal issues
- Dovato – 14%
- Biktarvy – 9%

Neuropsychiatric issues
- Dovato – 10%
- Biktarvy – 13%

Premature departures from the study were distributed as follows:

- Dovato – 1 person experiencing general discomfort and muscle/bone soreness
- Biktarvy – 2 people with sleeping problems

Weight

Overall, participants gained weight, which was distributed as follows:

- Dovato: +1 kg
- Biktarvy: +2 kg

Readers should note that ART does not have the same effect on every person; some people can gain weight, while others can lose weight, and still others have no change in weight.

Here are the proportions of participants who gained 5% of their initial body weight by week 48:

- Dovato – 20% of participants
- Biktarvy – 30% of participants

Researchers found that people who used abacavir or TDF in their pre-study regimen and who were given Biktarvy were more likely to gain 5% or more of their pre-study body weight. This effect was not seen in people who previously used abacavir or TDF and who were given dolutegravir + 3TC.

Researchers found that the proportions of people who were overweight or obese did not change among those who were taking dolutegravir + 3TC; however, the proportions increased among people who were taking Biktarvy.

Bear in mind

Both study regimens are highly effective and generally well tolerated over time. Overall weight gain with Biktarvy was modest (2 kg) and was linked to the use of previous medicines (abacavir or TDF). On average, people taking dolutegravir + 3TC gained about 1 kg.

Researchers analyzed previous use of ART and did not find relationships between past use of efavirenz and an increased risk of weight gain when they were switched to Biktarvy.

Additional analyses are needed to assess abdominal fat accumulation, particularly around the liver. The researchers collected information from participants about diet and exercise but have not yet analyzed them.

REFERENCE:

Ryan P, Blanco JL, Masia M, et al. Non-inferior efficacy and less weight gain when switching to DTG/3TC than when switching to BIC/FTC/TAF in virologically suppressed people with HIV (PWH): the PASO-DOBLE (GeSIDA 11720) randomized clinical trial. *25th International Conference on AIDS,* Munich, Germany, 22-26 July 2024. Abstract OAB3606LB

C. A small study explores dolutegravir + 3TC in heavily treatment-experienced patients

The combination of dolutegravir + 3TC (sold as Dovato) is increasingly used as an HIV treatment option. As it contains two drugs (instead of the standard three, which has been the historical norm since 1996), doctors are cautious in their use of this combination. It is not generally used in people who have HIV that is resistant to 3TC or other drugs. Resistance to 3TC is relatively common.

The laboratory of the late McGill University scientist Mark Wainberg found that while HIV can develop resistance to 3TC, such viruses do not replicate as quickly as non-3TC-resistant virus.

In a study called Solar-3D, researchers in the U.S., independently of any pharmaceutical company, recruited consecutive participants between 2019 and 2020 for a trial. This study was initially meant to be 96 weeks long but has been extended to 144 weeks. Participants were required to have at least one of the following:

- taking ART but never achieved an undetectable level (less than 50 copies/mL)
- if they did achieve an undetectable viral load, then their viral loads subsequently rose above 200 copies/mL
- documented resistance by HIV to one or more medicines
- any CD4+ count

At the start of the study, the average profile of participants was as follows:

- age – 58 years
- length of time since HIV diagnosis – 25 years
- length of time on ART – 22 years
- number of previous regimens – 7
- duration of HIV suppression – 13 years
- lowest-ever CD4+ count – 190 cells/mm^3

The mutation code named M184V/I is associated with resistance to 3TC by HIV. At the time they entered the study, 37% of participants had this mutation detectable in their HIV reservoir. Researchers called this "historical M184V/I."

About half of the participants were taking Triumeq (a combination of dolutegravir + 3TC + abacavir) prior to entering the study. Many of the remaining participants were taking complex regimens.

About half of the participants had no historical resistance to 3TC.

Results

At week 144, 94% of participants had an undetectable (less than 50 copies/mL) viral load, as follows:

- 37 out of 39 people with historical M184V/I mutation
- 36 out of 39 people without this mutation

These results were not statistically different.

When researchers analyzed blood samples with a more sensitive threshold of 20 copies/mL, they found that the proportions of people who achieved an undetectable viral load were distributed as follows:

- with M184V/I mutation – 68% were undetectable
- without M184V/I mutation – 64% were undetectable

Among people with the M184V/I mutation, eight died because of the following complications unrelated to the study medicines:

- deterioration of the heart muscle in a person who was 69 years old
- cardio-respiratory arrest in a person who was 52
- stroke in a person who was 72
- anal cancer in a person who was 59
- congestive heart failure in a person who was 74
- overdose on methamphetamine in a person who was 48
- chronic kidney disease in a person who was 73
- abnormal heart rhythms and congestive heart failure in a person who was 62

In people without M184V/I there were two deaths: one from suicide and one possibly from suicide.

More people without M184V/I left the study and changed regimens to injectable cabotegravir + rilpivirine (Cabenuva).

The researchers found that most adverse events were mild to moderate. There were low rates of depression (three people), headache (two people) and sleeping problems (two people).

One person prematurely left the study because of vertigo.

Bear in mind

This was not a randomized clinical trial. It was a relatively small study and, therefore, the findings are not applicable to the average person with HIV. However, it has found a signal that the presence of M184V/I mutation may not necessarily be a barrier to future successful treatment with the combination of dolutegravir + 3TC. Although these findings are promising, they need to be better explored in a large randomized clinical trial.

REFERENCE:

Blick G, Cerreta-Dial E, Mancini G, et al. No confirmed virological failures (CVF) for 144 weeks when switching 2-/3-/4-drug ART to DTG/3TC in heavily treatment-experienced PLWHA with prior M184V/I and virological failures (VF) in the prospective SOLAR-3D study. *25th International Conference on AIDS*, Munich, Germany, 22-26 July 2024. Abstract SS0403LB.

D. Studies of intermittent ART

When potent HIV treatment (antiretroviral therapy, ART) was first introduced in 1996, it saved people's lives and prevented AIDS. This was the first time combination therapy had been shown to do that on a sustained basis. However, excitement about early regimens was tempered by their complexity. Most regimens in those days required twice or even three-times daily dosing. In some cases, there were strict food and water requirements that accompanied ART. People sometimes had to take a fistful of pills several times daily. Early regimens could also cause distressing side effects, including changes in appearance and body shape. All of these issues made adherence challenging.

In France

For at least the past decade, doctors in France have been conducting studies of intermittent ART—usually taken for four or five consecutive days with two or three days off. In 2022 they published results after one year of intermittent vs. continuous therapy. In the study, called Quatuor, participants whose viral loads were suppressed, thanks to several years of daily ART, were randomly assigned to one of the following regimens:

- continued daily ART
- intermittent ART – four days on ART followed by three days off, then four days on ART and so on

An analysis of 636 participants (318 people per group) found that after one year the following proportions of participants had a suppressed viral load:

- continued daily ART – 97%
- intermittent ART – 96%

This difference was not significant. Furthermore, it indicated that, statistically, intermittent ART was no worse and no better (in its effectiveness) than daily ART. The technical term for this result is *non-inferior*.

Surveys found that people on intermittent ART had improved quality of life.

Reassuringly, there was no increase in inflammation and no excess risk of blood clot formation (seen in some earlier trials of intermittent ART). In those earlier trials, the period off ART was also longer, weeks or months.

There were 10 cases of virological failure in the study, distributed as follows:

- continued daily ART – 4 people (1%)
- intermittent ART – 6 people (2%)

Researchers found that more people in the intermittent ART group who developed virological failure were more likely to have HIV that was resistant to treatment (three out of six people vs. one of four people on continuous ART).

Reservoirs

Although good adherence helps keep ART suppressed, a small proportion of cells of the immune system still contain HIV. Scientists refer to this pool of infected cells as the "reservoir." Infected cells can be found deep within the lymph nodes

and tissues, the spleen, the brain and the testicles (to name a few places).

The French researchers analysed blood and semen samples for the level of infected cells. Overall, they found no significant differences between people on the two interventions; that is, the pool of infected cells was not different between the two groups. This finding is reassuring and suggests that the size of the HIV reservoir did not increase in people on either study regimen.

Note well

At publication time, intermittent therapy as used in the Quatuor study is not recommended by leading U.S. guidelines or guidelines produced by the European AIDS Clinical Society. Such guidelines influence the prescribing practices of doctors in Canada and other countries.

However, some doctors in France (and their patients) are enthusiastic about intermittent ART.

It is important to note that when they entered the study, participants had, on average, the following characteristics:

- highly adherent on their previous regimens
- their CD4+ count had never fallen significantly below the 300 cell/mm^3 mark
- their CD4/CD8 ratio was at least 1.0, which indicates a normalization of their immune system
- their current CD4+ count was nearly 700 cells/mm^3
- HIV in blood samples was susceptible to all the drugs in their ART regimen
- they did not have chronic or active hepatitis B virus (HBV) and/or hepatitis C virus (HCV)
- most participants (85%) were male

Thus, overall, participants in Quatuor may not be representative of the average person with HIV, and intermittent ART may not be suitable for many people.

Beyond Quatuor

People enrolled in Quatuor in 2017 and 2018 and used classes of HIV drugs that are not as commonly used today, such as protease inhibitors and non-nukes (non-nucleoside reverse transcriptase inhibitors). They also used integrase inhibitors that may not be as widely used today, such as raltegravir (Isentress) and elvitegravir (in Genvoya and Stribild).

Today, the following combinations of drugs are widely used or recommended for HIV treatment by U.S. HIV guidelines:

- bictegravir (in Biktarvy, a combination of bictegravir + TAF + FTC)
- dolutegravir (in Dovato, a combination of dolutegravir + 3TC)
- cabotegravir (in Cabenuva, cabotegravir + rilpivirine given by injection ultimately once every two months)
- doravirine (Delstrigo, Pifeltro)

These drugs are generally well tolerated and highly effective.

For doctors who have concerns about their patients taking multiple HIV drugs, perhaps some two-drug regimens (mentioned earlier) may be an option. For doctors who have patients with adherence difficulties, perhaps regimens such as Cabenuva, which ultimately require injections every two months, may be an option. Longer periods between dosing of Cabenuva are under investigation.

Pharmaceutical companies are developing other complete regimens with just two drugs, and they are also developing other long-acting regimens that require infrequent dosing. Thus, the landscape of daily oral dosing, which was the only option when intermittent ART was initially developed, has changed. Furthermore, additional options will become available in the future.

French researchers should be praised for exploring and testing patient-friendly regimens. Expect to see more results from clinical trials of intermittent ART in the future. Hopefully, there will be long-term studies of intermittent ART in hundreds of participants so that doctors can understand the potential of such regimens over the long-term.

Intermittent Biktarvy

The French studies have inspired doctors in Taiwan. A one-year pilot study there with intermittent vs. daily Biktarvy has been completed with 60 participants. Preliminary analysis of this trial—five days on ART, two days off (FOTO)—has found

that both schedules had similar effectiveness. The doctors in Taiwan stated that their results provide a foundation for designing a much larger (and hopefully longer) study.

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E. Another signal of concern with abacavir and cardiovascular risk

In 2008, some researchers reported that the use of abacavir (Ziagen, and in Kivexa, Trizivir and Triumeq) was associated with an increased risk of cardiovascular events (heart attack and so on). However, these reports were based on observational studies that cannot yield definitive results. An analysis of randomized clinical trials by the U.S. Food and Drug Administration (FDA) did not find such an association with abacavir. However, because of the possible cardiovascular risk with abacavir, HIV treatment guidelines usually recommended that it be used cautiously or not at all, particularly in people at high risk for cardiovascular disease. Over the years, use of abacavir has declined significantly, likely because of concern about the drug's cardiovascular risk.

A large randomized clinical trial of people with HIV called Reprieve has found that the cholesterol-lowering medicine pitavastatin caused a 36% reduction in the risk of heart attack/stroke, peripheral artery disease and other major cardiovascular events compared to placebo. People were enrolled in Reprieve between 2015 and 2019. At the time of enrollment, their average profile was as follows:

- age – 50 years
- 69% male, 31% female
- 95% cisgender, 2% transgender and 3% did not have a gender recorded by researchers
- CD4+ count – 621 cells/mm^3
- 88% had an undetectable viral load (thanks to ART)
- 36% had high blood pressure

Results

Researchers found that 9% of participants had used abacavir in the past, for an average of three years, and 13% were taking it at the time they enrolled in Reprieve.

Considering many factors—including traditional cardiovascular risks, sex, ethnicity, smoking, high blood pressure, substance use, CD4+ cell count, kidney health and blood sugar levels—researchers found that former and current abacavir users had about a 50% increased risk for heart attack, stroke and other major cardiovascular events.

This finding is important and reinforces previous data about the cardiovascular risk associated with abacavir. It is concerning because participants enrolled in Reprieve had what researchers called "a low-to-moderate risk" of cardiovascular disease. The findings from Reprieve will likely accelerate the shift away from using abacavir.

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