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## I HIV CURE RESEARCH

### A. Gene therapy—CRISPR starts to move forward against HIV

One approach to gene therapy that has much potential is called CRISPR (clustered regularly interspaced short palindromic repeats). CRISPR was discovered several decades ago in bacteria, where it served as part of a defence system against viruses that infect bacteria. In these bacteria, invading viruses insert key parts of their genetic material into the genetic material of the bacteria. These inserted viral genes then produce proteins and other molecules that hijack the cell and turn it into a mini-virus factory, continuing the life cycle of the invading virus and eventually destroying the bacteria.

CRISPR contains small pieces of the virus' genetic material that can be used to screen the bacteria's genes for the presence of DNA from a virus. That is, CRISPR is used to screen the bacteria's DNA for signals of a viral infection—the presence of viral DNA. Once the viral DNA is detected, CRISPR then uses an enzyme called Cas9 (CRISPR-associated protein 9) to remove or edit the unwanted viral DNA. By removing the viral DNA, the bacteria are protected from the effects of viral infection.

The combination of CRISPR-Cas has many potential applications. In particular, CRISPR-Cas has the potential to treat inherited disorders such as hemophilia and some infectious diseases such as HIV. For the rest of our reports on CRISPR-Cas, we will simply refer to it as CRISPR. Before further discussion of CRISPR, we provide some

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background on HIV's infection of a cell, the virus' distribution in the body and some effects of ART.

## Removing HIV

Like the earlier example of the virus that infected bacteria, a broadly similar process affects cells of the immune system targeted by HIV. Cells that display the receptor CD4 on their surface (as well as the co-receptors CCR5 and CXCR4) can be infected by HIV. Such cells mainly include certain T lymphocytes (T-cells) commonly called CD4 T-cells (or simply CD4+ cells), as well as cells called monocytes (in their mature form these are called macrophages) and cells related to macrophages (such as dendritic cells in the skin and mucosal tissues and microglia in the brain). After HIV inserts its genetic material into target cells, these can become activated, converting into mini virus factories and eventually dying.

## ART and the HIV reservoir

HIV treatment (ART) is highly effective when taken as directed and prescribed. As a result, scientists increasingly expect that many ART users will have near-normal life expectancy. However, ART does not cure HIV. The reasons for this are not certain but some experiments suggest that despite good adherence to ART and an undetectable viral load in the blood, small amounts of HIV remain deep within the body—in lymph nodes, the brain, parts of the gut, fatty tissue, testicles and so on. Scientists refer to these parts of the body where small amounts of HIV still lurk despite the use of ART as sanctuaries or reservoirs.

## Nano-ART

For at least a decade, researchers at the University of Nebraska have been developing what they call nano-formulations of ART—very tiny crystals of drugs surrounded by a sphere of fat. These medicine-filled fat balls have been found to penetrate a range of tissues in laboratory and animal experiments where they have good anti-HIV activity. However, short-term experiments have found that nano-ART by itself does not cure HIV infection in lab mice.

## Back to CRISPR

Experiments with mice infected with HIV have found that CRISPR can remove much of HIV's DNA from infected cells. However, CRISPR by itself does not cure HIV infection in mice.

## Combining nano-ART and CRISPR

In recent experiments, scientists at the University of Nebraska have collaborated with other scientists at Temple University in Philadelphia who have expertise with CRISPR. They performed a series of very complex and detailed experiments with HIV-infected mice that received one of the following interventions:

- nano-ART
- CRISPR
- nano-ART + CRISPR
- no intervention

The nano-ART used in these experiments was made from three widely used anti-HIV medicines as follows:

- dolutegravir + 3TC + abacavir

An immediate-release formulation of all three drugs is sold as a pill called Triumeq and is taken once daily.

CRISPR was used to search for key pieces of HIV's genetic material in cells of the immune system of the mice.

Extensive analysis of blood and tissues from the mice suggested that a combination of nano-ART and CRISPR was able to remove HIV from about 30% of the mice. There was no obvious toxicity.

The results from the combination of nano-ART and CRISPR are exciting but must be considered preliminary. They suggest that one day such a combination might be able to cure some monkeys infected with SIV (simian immunodeficiency virus)—a virus that causes an AIDS-like condition in susceptible monkeys. The results also suggest the possibility that CRISPR + nano-ART could be used to try to cure HIV infection in people. However, there are still many steps that lie ahead and issues that need to be explored before nano-ART and CRISPR are ready for use in people. Below are some of these issues.

## CRISPR—safety and other issues

When reporting on exciting news about work done in a research laboratory concerning cures for HIV or other catastrophic conditions, it must be stressed that mice are not people. That is, if every experimental therapy that did not harm mice also worked safely and effectively in people, we would have many more highly effective therapies available for different conditions.

In addition to removing HIV's genetic material from the mice, it is possible that CRISPR can inadvertently remove useful DNA from cells. This has happened in some experiments done by other scientists but not in the current collaboration. Removal of useful DNA by CRISPR is called an "off-target" effect by scientists. So far, the team collaborating on the use of nano-ART and CRISPR with mice has found no off-target effects.

CRISPR is also being used to remove SIV from some infected monkeys. The preliminary results of these experiments appear promising. However, as some species of monkey are more genetically similar to people than mice, long-term observation and close clinical monitoring of monkeys that have been treated with CRISPR (and nano-ART) are needed to assess the potential for any long-term side effects. Long-term studies are important because the off-target consequences of CRISPR may not become apparent for some time—perhaps years. Such monitoring is also essential because it is currently impossible to assess every cell in the body to find out if its DNA has been inadvertently injured by CRISPR.

It is not clear how CRISPR can be turned off in people who receive it. It may not be safe to leave CRISPR constantly on and activated in a living person.

In the experiments conducted by the Nebraska-Philadelphia team, it appears that mice were infected with a harmless virus that was modified to enable CRISPR. It is not clear if the same technology would work in people.

## Nano-ART—safety and other issues

The formulations of ART used by the Nebraska-Philadelphia team of scientists were developed in a lab on a small scale and meant for use in mice. If large numbers of monkey and human experiments

with such formulations are planned, scientists will have to manufacture nano-ART on a relatively large scale. They will also have to ensure that such nano-ART is free from any contaminants. Next, they will need to assess its short- and long-term safety in monkeys and people. Nano-ART will be able to penetrate and concentrate in reservoirs in the body, including the brain, gut, lymph nodes, testicles and so on. The effect of nano-ART on the health of these tissues needs to be assessed and fully understood. After it has passed initial safety experiments, nano-ART will need to be tested for both long-term safety and effectiveness at achieving viral suppression. Nano-ART by itself is unlikely to cure HIV.

Another issue with nano-ART is determining the ideal way to get this formulation into the body. Is regular intravenous infusion best? Or will other methods, such as intramuscular injection, work equally well?

## CRISPR currently in clinical trials

Clinical trials are currently underway with CRISPR in HIV-negative people in the following countries for the following conditions:

### United States

- cancer of certain white blood cells – one person
- cancer that appears near joints – one person

### China

- non-small cell lung cancer that has spread to other organs – 12 people

Preliminary results from these experiments in people suggest that, so far, CRISPR is safe. More time is needed before doctors know if CRISPR will work in these cases. However, some scientists and doctors have warned that gene editing could inadvertently enable the spread of cancerous cells in some of these people. Therefore, long-term monitoring of CRISPR-treated participants in the above studies will be necessary.

## Bear in mind

It is important to note that about 30% of the HIV-infected mice in the Nebraska-Philadelphia study were cured of HIV with the combined use of nano-ART and CRISPR. This is an incredible

scientific achievement. However, cure rates need to increase in future experiments. CRISPR and nano-ART therapy are still in their infancy and much research lies ahead before they can be tested in large numbers of HIV-positive people.

To achieve a cure rate higher than the 30% cure rate reported in the present study, it is at least plausible that in the future CRISPR may need to be refined. Intensifying CRISPR's editing capacity may inadvertently increase the risk of vital human genes being deleted.

Another possibility is that, in addition to CRISPR and nano-ART, more experimental therapies will have to be used. Using multiple experimental therapies in people living with HIV could increase potential problems, particularly side effects. This is yet another reason for close laboratory and clinical monitoring of animals and people who undergo CRISPR, both over the short- and long-term.

There is also another issue associated with CRISPR and other potential HIV cure therapies that we discuss in the next article in this issue of *TreatmentUpdate*.

## Resources

*TreatmentUpdate* 231 ([www.catie.ca/en/treatmentupdate/treatmentupdate-231/hiv-cure-research](http://www.catie.ca/en/treatmentupdate/treatmentupdate-231/hiv-cure-research))

The Canadian HIV Cure Enterprise (CanCURE) ([www.cancurehiv.org](http://www.cancurehiv.org))

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3. Wang L, Yang Y, Breton CA, et al. CRISPR/Cas9-mediated in vivo gene targeting corrects hemostasis in newborn and adult factor IX-knockout mice. *Blood*. 2019 Jun 27;133(26):2745-2752.
4. Pipe SW, Selvaraj SR. Gene editing in hemophilia: a "CRISPR" choice? *Blood*. 2019 Jun 27;133(26):2733-2734.

## B. Will gene therapy for HIV cause financial toxicity?

The technology of gene editing through CRISPR has the potential to clear people's cells of HIV's genetic material, treat some cancers and correct inherited disorders such as hemophilia.

The different teams of scientists working to apply CRISPR or other forms of gene therapy for treating diseases in humans issue press releases from time to time that are often reproduced by some media. What is not mentioned in those press releases is the cost of CRISPR treatment should it one day be approved by regulatory agencies in Canada and other high-income countries.

### The high cost of cancer treatment

CRISPR is cutting-edge technology and is likely to be expensive. To begin to form an idea of what CRISPR might cost, it may be worth looking at the cost of cutting-edge cancer treatment. The list prices for some approved immune-based therapies (so-called "checkpoint inhibitors") for cancer are between US\$100,000 and \$200,000 per person per year. The cost can vary depending on the checkpoint inhibitor used, the dose administered, and whether or not it is prescribed in combination. Some people may require at least two years of treatment.

Looking at immune-based therapies for cancer that include some degree of genetic manipulation, such as Kymriah (produced by Novartis), list prices are higher still: around US\$500,000 per person per year, not including the high cost of managing side effects. The high price of medicines, particularly the latest treatments for cancer, causes what some researchers refer to as "financial toxicity" for patients. By "financial toxicity," the researchers mean that the catastrophic expense of cancer care has the potential to "diminish quality of life and impede delivery of the highest quality care." They note that "existing data have identified both objective financial burden and subjective financial distress as key components of financial toxicity."

The issue of cost is one that will bedevil the emerging field of gene therapy.

## Gene therapy—the world’s most expensive drug?

In May 2019, the U.S. Food and Drug Administration (FDA) approved the sale and use of a gene therapy called Zolgensma. This therapy is meant to be a one-time treatment for people with spinal muscular atrophy, an inherited condition that occurs in about 1 in every 11,000 births. The pharmaceutical company Novartis has priced the gene therapy at around \$US 2.1 million per person—\$425,000 a year spread over five years. This is possibly the world’s most expensive drug. According to Novartis, the corporation is “working closely with insurers to create five-year agreements based on success of the treatment as well as other novel pay-over-time options.”

At this time, absent a major breakthrough, it is unlikely that a quick, simple and safe method of curing HIV will become widely available in the next five years. However, should regulatory agencies subsequently approve a combination of gene therapy and other technologies that can cure HIV, the cost will likely be very high.

It is possible that through public pressure on pharmaceutical companies, governments will one day obtain a substantially reduced price for gene-based or other therapies that can cure HIV. Such substantial reductions in cost are necessary if an HIV cure is to be widely distributed, particularly in low- and middle-income countries.

### Resources

*TreatmentUpdate 231* ([www.catie.ca/en/treatmentupdate/treatmentupdate-231/hiv-cure-research](http://www.catie.ca/en/treatmentupdate/treatmentupdate-231/hiv-cure-research))

The Canadian HIV Cure Enterprise (CanCURE) ([www.cancurehiv.org](http://www.cancurehiv.org))

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## II INFLAMMATION

### A. Attention on inflammation also turns to fungi

HIV infection is associated with a range of complex injuries to the immune system that, if left untreated, ultimately result in life-threatening infections, certain cancers and relentless weight loss. However, in Canada and other high-income countries, the widespread availability of HIV testing and treatment (ART) has significantly reduced AIDS-related deaths. ART does this by suppressing the production of HIV by infected cells. Once the amount of HIV in the blood falls to very low levels, the immune system begins to rebuild itself. The effect of ART is so profound that doctors and scientists expect that many ART users will have near-normal life expectancy.

However, ART does not cure HIV infection, and while it usually restores a great deal of the immune system's functions, some immunological dysfunction persists. For instance, HIV is associated with excess activation of the immune system and excess general inflammation. ART significantly reduces these effects but not back to the very low levels of immune activation and inflammation found in healthy HIV-negative people. Some scientists say that the excess inflammation and immune activation found in HIV-positive people may increase their risk of health problems in the future. For more information about these issues, see *TreatmentUpdate 223*.

The exact cause of the excess immune activation and inflammation in ART users is not clear. One theory is that HIV infection weakens intestines, allowing microbes (bacteria, fungi) and/or proteins associated with these microbes to leak through the gut into the blood. Once in the blood, these microbes and/or their proteins circulate and contribute to excess immune activation and inflammation. Clinical trials are underway with different potential interventions to address these issues. Until recently, scientists who conducted research on the movement of microbes and/or their proteins from the gut to the blood of HIV-positive people focused exclusively on one group of microbes—bacteria. They named the movement of bacteria and/or their proteins from the gut to the blood “microbial translocation” or “bacterial

translocation.” Research on minimizing bacterial translocation continues.

### Enter the fungi

Some scientists who have been working on microbial translocation have had results that directed them to look at the role of fungi in this issue. Emerging research suggests that fungi and/or fungal products in the gut likely also contribute to the excess immune activation and inflammation associated with chronic HIV infection. They have called the issue of fungi and/or fungal products moving from the gut into the blood “fungal translocation.”

A team of scientists at McGill University in Montreal has performed a series of elegant and sophisticated experiments that strongly suggest that fungal translocation occurs in the gut of HIV-positive people. Furthermore, the researchers found that when these people started ART early in the course of HIV infection, levels of fungi and/or fungal products were high. Even when these people took ART for two years, the levels of fungal translocation did not fall. Elevated levels of fungal translocation were associated with excess immune activation and inflammation.

Thanks to the work of scientists in Montreal and elsewhere on fungal translocation, teams of researchers are considering pilot studies to test potential interventions in order to try to reduce HIV-related immune activation and inflammation.

We do not report the details of the different experiments done by the scientists in Montreal, as they were complex. Instead we focus on their results and, later in this issue of *TreatmentUpdate*, potential interventions for fungal translocation.

### Results

The scientists in Montreal focused on a substance called beta-D-glucan (BDG). This substance is found in the cell wall of fungi and can also be found in the blood and spinal fluid of people with invasive fungal infections. However, the Montreal scientists took steps to rule out the presence of invasive fungal infections so the cause of elevated BDG levels in the blood of HIV-positive people was due to fungal translocation.

## Key findings

- Levels of BDG in the blood of people with early HIV infection were higher than those found in healthy HIV-negative people.
- High levels of BDG in HIV-positive people not taking ART were associated with low CD4+ cell counts, elevated viral load and a range of proteins linked to gut injury, inflammation and immune activation.
- Initiation of ART early in the course of HIV infection stabilized BDG levels in the blood of participants. That is, ART prevented BDG levels from rising further, but BDG levels did not fall even after two years of ART.
- BDG levels were not affected by age or gender.

## Other research

The findings from Montreal are supported by other research. For instance, a study by the U.S. AIDS Clinical Trials Group (ACTG) found that elevated levels of BDG were associated with a statistically increased risk for non-AIDS-related events, including the following:

- heart attack/stroke
- cancers unrelated to HIV infection
- serious bacterial infections
- death unrelated to AIDS

Other studies in the U.S. have found that elevated levels of BDG in the blood are associated with heart-lung problems (such as elevated blood pressure within the lungs) and even HIV-related neurocognitive issues.

Taken together, the research from McGill and the U.S. strongly suggests that fungal translocation, as measured by BDG levels in the blood of HIV-positive people who do not have invasive fungal infections, should now become the focus for interventions.

## Resource

*TreatmentUpdate 223* ([www.catie.ca/en/treatmentupdate/treatmentupdate-223/inflammation-and-hiv](http://www.catie.ca/en/treatmentupdate/treatmentupdate-223/inflammation-and-hiv))

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## B. Future potential interventions against fungal translocation

As mentioned earlier in this issue of *TreatmentUpdate*, research strongly suggests that in HIV-positive people fungi and/or fungal products leak across the intestine into the blood. Scientists call this transfer of fungi and/or fungal products from the gut to the blood “fungal translocation.” Once in the blood, these fungi and/or their products, such as beta-D-glucan (BDG), circulate throughout the body and may contribute to the issue of HIV-related excess immune activation and inflammation. This problem is not reduced by taking ART.

### Back to the future

Scientists in the U.S. have tested the antifungal drug fluconazole (Diflucan, Diflucan One) in a small placebo-controlled study with HIV-positive people. These people all had problems with memory and thinking clearly (collectively called neurocognitive impairment). Fluconazole did not improve their condition.

However, fluconazole only has a limited spectrum of activity against the fungi that normally live in the gut. Physician-scientist and fungus expert Martin Hoenigl, MD, from the University of California at San Diego suggests that different antifungal agents be tested for their potential to reduce excess HIV-

related immune activation and inflammation. In an editorial in the journal *Clinical Infectious Diseases*, Dr. Hoenigl states that such antifungal drugs should have the following properties:

- “be well tolerated”
- “have a broad spectrum of activity (ideally covering the whole spectrum of BDG-producing fungi [that live] in the human gut, including [species of *Aspergillus*, *Penicillium* and *Fusarium*])”
- “be easy to use in terms of frequency and application”

Although broad-spectrum antifungals such as posaconazole (Posanol, Noxafil) may be considered for future studies of fungal translocation, Dr. Hoenigl noted that emerging antifungal drugs are likely “better tolerated and/or allow for once weekly [dosing].” Such antifungal drugs are currently in phase II or phase III clinical trials and include the following:

- ibrexfungerp
- rezafungin

Fungal translocation is an emerging idea in HIV research and it may take some time before more scientists accept it. The exact cause of the excess immune activation and inflammation seen in HIV-positive people is not clear. Nevertheless, if regulatory authorities in high-income countries eventually license drugs such as ibrexfungerp and rezafungin, it is likely that at least pilot studies on fungal translocation will be done in the future. Although the evidence for fungal translocation is growing, scientists working on interfering with bacterial translocation need to continue their efforts.

## Resource

*TreatmentUpdate 223* ([www.catie.ca/en/treatmentupdate/treatmentupdate-223/inflammation-and-hiv](http://www.catie.ca/en/treatmentupdate/treatmentupdate-223/inflammation-and-hiv))

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### 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.**

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For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

CATIE provides such information through a comprehensive website ([www.catie.ca](http://www.catie.ca)), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

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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 Positive Side magazine*

Holistic health information and views written by and for people living with HIV.

#### *Fact Sheets*

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

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