Experimental HIV Treatments

(updated May 2021)

Experimental HIV Treatments

This education packet is a curated compilation of resources on experimental HIV treatments, including cure research.

The contents of this packet are listed below:

- What Is an Investigational HIV Drug? (HIVinfo)
- ¿Qué es un Medicamento Contra el VIH en Fase de Investigación? (HIVinfo)
- Future Directions for HIV Treatment Research (National Institute of Allergy and Infectious Diseases – NIAID)
- What Is a Therapeutic HIV Vaccine? (HIVinfo)
- ¿Qué es una Vacuna Terapéutica Contra el VIH? (HIVinfo)
- HIV Cure (NIAID)
- Sustained ART-Free HIV Remission (NIAID)
- Viral Eradication (NIAID)

You may wish to customize this packet to meet the needs or interests of particular groups, such as event participants, providers, patients, clients, or the general public. So please feel free to distribute all or part of this document as either a printout or PDF.

What is an Investigational HIV Drug?

hivinfo.nih.gov/understanding-hiv/fact-sheets/what-investigational-hiv-drug

HIV Overview

Last Reviewed: September 28, 2020

Key Points

- An investigational HIV drug is an experimental drug that is being studied to see whether it is safe and effective.
- HIV investigational drugs are studied in medical research studies called clinical trials. Once an investigational HIV drug has been proven safe and effective in a clinical trial, the U.S. Food and Drug Administration (FDA) may approve the drug for general use or sale in the United States.
- Investigational HIV drugs being studied include drugs to treat or prevent HIV and vaccines to treat or prevent HIV.
- Investigational HIV drugs can only be accessed through clinical trials and expanded access programs.

What is an investigational HIV drug?

An investigational HIV drug is an experimental drug that is being studied to see whether it is safe and effective. HIV investigational drugs are studied in medical research studies called clinical trials. Once an investigational HIV drug has been proven safe and effective in a clinical trial, the U.S. Food and Drug Administration (FDA) may approve the drug for general use or sale in the United States.

What types of investigational HIV drugs are being studied?

Investigational HIV drugs being studied include drugs to treat HIV and prevent HIV. Some types of investigational HIV drugs being studied include microbicides, immune modulators, latency-reversing agents, gp120 attachment inhibitors, and rev inhibitors.

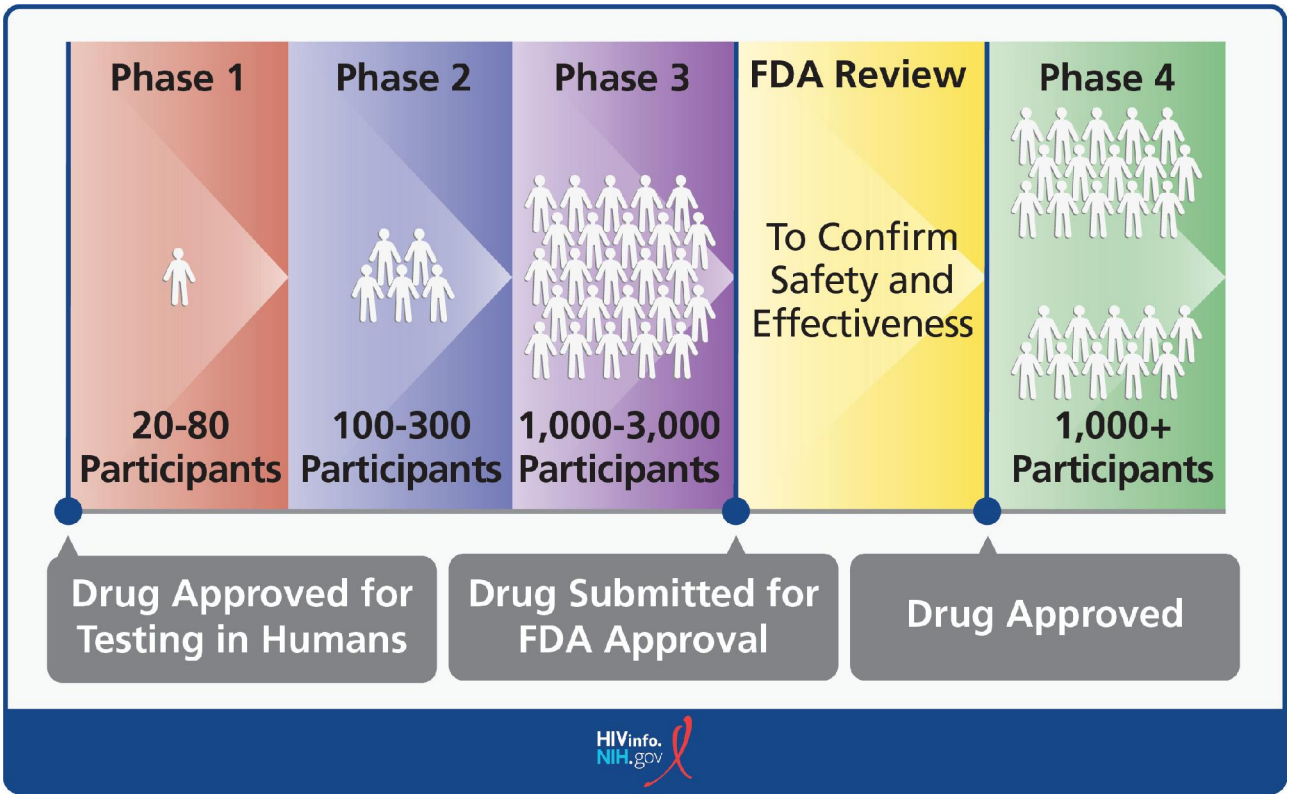
HIV researchers are also studying investigational vaccines to prevent HIV and treat HIV. The goal of a preventive HIV vaccine is to prevent HIV in people who don't have HIV but who may be exposed to the virus. A safe and effective HIV treatment vaccine (also called a therapeutic vaccine) could prevent HIV from advancing to AIDS, replace the daily use of HIV medicines, and help prevent HIV transmission. To learn more, read the ClinicalInfo What is a Preventive HIV Vaccine? and What is a Therapeutic HIV Vaccine? fact sheets.

How are clinical trials of investigational drugs conducted?

Clinical trials are conducted in phases. Each phase has a different purpose and helps researchers answer different questions about the investigational drug.

- **Phase 1 trials**: Initial testing in a small group of people (20–80) to evaluate the drug's safety and to identify side effects.
- **Phase 2 trials**: Testing in a larger group of people (100–300) to determine the drug's effectiveness and to further evaluate its safety.
- **Phase 3 trials**: Continued testing in large groups of people (1,000–3,000) to confirm the drug's effectiveness, monitor side effects, compare it with standard or equivalent treatments, and collect information to ensure that the investigational drug can be used safely. In most cases, an investigational drug must be proven effective and must show continued safety in a Phase 3 clinical trial to be considered for approval by FDA for sale in the United States. (However, some drugs go through FDA's accelerated approval process and are approved before a Phase 3 clinical trial is complete.)
- **Phase 4 trials**: Ongoing tracking that occurs after a drug is approved by FDA for sale in the United States. The purpose of the tracking is to seek more information about the drug's risks, benefits, and optimal use.

For more information, read the HIVinfo HIV/AIDS Clinical Trials fact sheet.



How can I find a clinical trial that is studying an investigational HIV drug?

To find an HIV/AIDS clinical trial that is studying an investigational HIV drug, use the clinical trial search.

For help with your search, call an ClinicalInfo health information specialist at 1-800-448-0440 or email ContactUs@HIVinfo.NIH.gov.

You can also join ResearchMatch, which is a free, secure online tool that makes it easier for the public to become involved in clinical trials.

Are investigational HIV drugs available for use outside of a clinical trial?

In some cases, an HIV investigational drug may be available through an expanded access program. Expanded access allows for the use of an investigational drug outside of a clinical trial to treat a person who has a serious or immediately life-threatening disease and who has no FDA-approved treatment options. Drug companies must have permission from FDA to make an investigational drug available for expanded access.

People seeking expanded access to an investigational HIV drug should talk to their health care provider to see if they may qualify to take part in an expanded access program.

Is it safe to use an investigational HIV drug?

One goal of HIV research is to identify safer, more effective HIV medicines. Researchers try to make clinical trials as safe as possible. However, taking an investigational HIV drug can involve both benefits and risks. Risks may include unexpected side effects from the drug, which can be unpleasant, serious, or even life-threatening.

The benefits and possible risks of participating in a clinical trial or an expanded access program are explained to people before they decide whether to participate.

How can I find more information on investigational HIV drugs?

To find more information on investigational HIV drugs, use the ClinicalInfo Drug Database, which includes up-to-date information on many investigational HIV drugs.

This fact sheet is based on information from the following sources:

Provided in collaboration with NIH's Office of Aids Research.

¿Qué es un medicamento contra el VIH en fase de investigación?

hivinfo.nih.gov/es/understanding-hiv/fact-sheets/que-es-un-medicamento-contra-el-vih-en-fase-de-investigacion

Visión general de la infección por el VIH

Última revisión: October 6, 2020

Puntos importantes

- Un medicamento contra el VIH en fase de investigación es un fármaco experimental estudiado para determinar su inocuidad (tolerabilidad) y eficacia.
- Los medicamentos contra el VIH en fase de investigación se analizan en estudios de investigación médica llamados ensayos clínicos. Una vez que se ha demostrado en un ensayo clínico que ese medicamento es inocuo y eficaz, la Administración de Alimentos y Medicamentos de los Estados Unidos (U.S. Food and Drug Administration, FDA) puede aprobarlo para uso o venta general en los Estados Unidos.
- Los medicamentos contra el VIH en fase de investigación incluyen fármacos y vacunas para tratar o prevenir dicho virus.
- Los medicamentos contra el VIH en fase de investigación se pueden obtener solamente por medio de ensayos clínicos y programas de acceso ampliado.

Un medicamento contra el VIH en fase de investigación es un fármaco experimental estudiado para determinar su inocuidad (tolerabilidad) y eficacia. Los medicamentos contra el VIH en fase de investigación se analizan en estudios de investigación médica llamados ensayos clínicos. Una vez que se ha demostrado en un ensayo clínico que ese producto es inocuo y eficaz, la Administración de Alimentos y Medicamentos de los Estados Unidos (U.S. Food and Drug Administration, FDA) puede aprobarlo para uso o venta general en los Estados Unidos.

¿Qué tipos de medicamentos contra el VIH en fase de investigación se estudian actualmente?

Los medicamentos contra el VIH en fase de investigación estudiados incluyen fármacos para tratar y prevenir la infección por ese virus. Entre los medicamentos de esta clase en fase de estudio están microbicidas, inmunomoduladores, agentes revertidores de la latencia, inhibidores de la fijación de gp120 e inhibidores de rev.

Los investigadores del VIH también estudian vacunas en fase de investigación para prevenir y tratar la infección por ese virus. La meta de una vacuna preventiva contra el VIH es evitar esa infección en personas seronegativas, pero que pueden haber estado expuestas al virus. Una vacuna inocua y eficaz para tratar la infección por el VIH (también llamada vacuna terapéutica) podría evitar que la infección por el VIH evolucione a SIDA, reemplazar el uso diario de medicamentos contra ese virus y ayudar a prevenir su transmisión. Para mayores detalles véanse las hojas informativas de Clinicalinfo tituladas ¿Qué es una vacuna preventiva contra el VIH? y ¿Qué es una vacuna preventiva contra el VIH?

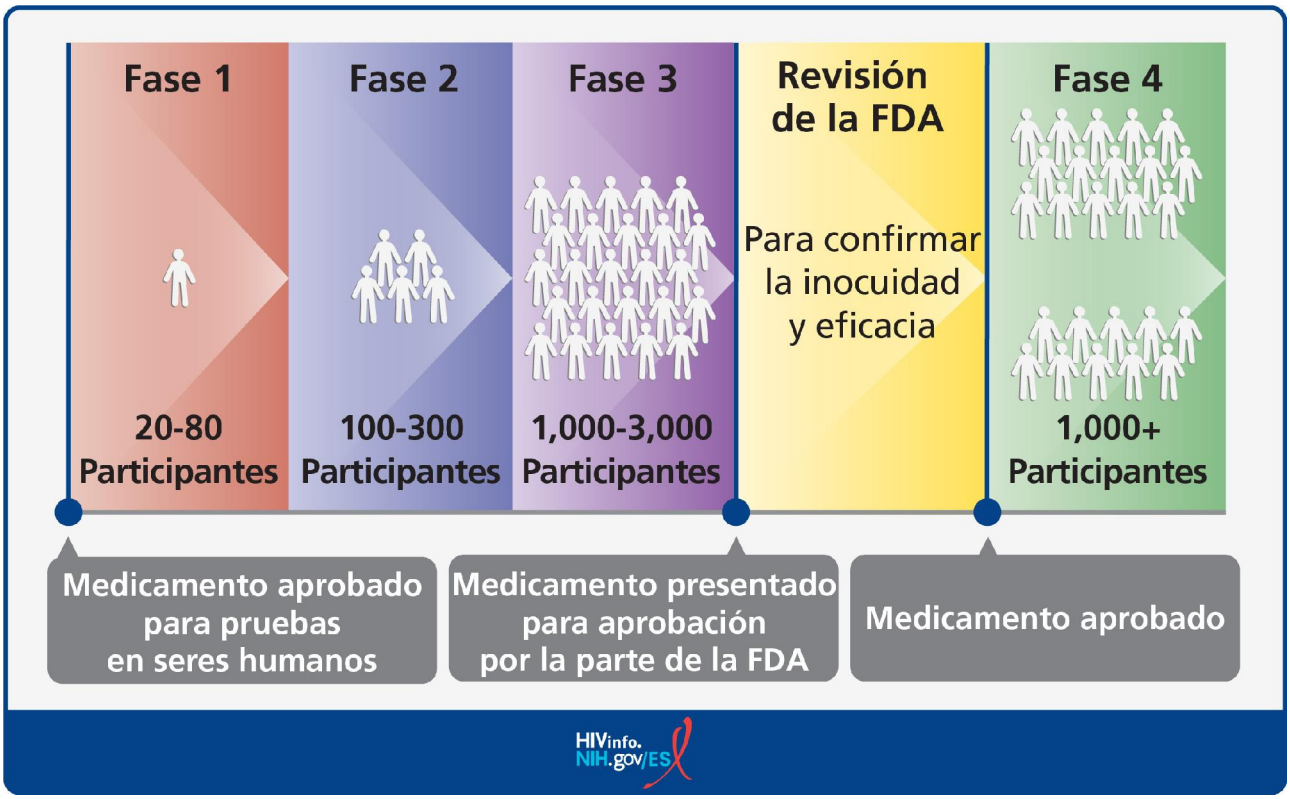
¿Cómo se llevan a cabo los ensayos clínicos de medicamentos en fase de investigación?

Los ensayos clínicos se llevan a cabo por fases. Cada fase tiene un propósito diferente y ayuda a los investigadores a responder a diferentes inquietudes acerca del medicamento en fase de investigación.

- **Ensayos de fase 1:** Prueba inicial en un pequeño grupo de (20 a 80) personas para evaluar la inocuidad del medicamento y determinar sus efectos secundarios.
- **Ensayos de fase 2:** Prueba en un grupo mayor de (100 a 300) personas para determinar la eficacia del medicamento y evaluar su inocuidad más detalladamente.
- **Ensayos de fase 3:** Prueba continua en grupos grandes de (1.000 a 3.000) personas para confirmar la eficacia del medicamento, observar sus efectos secundarios, compararlo con tratamientos estándar o equivalentes y recolectar información para asegurarse de que el medicamento en fase de investigación se pueda usar con seguridad.

  En la mayoría de los casos, se debe demostrar la eficacia de un medicamento en fase de investigación y su eficacia continua en un ensayo clínico de fase 3 para que la FDA lo considere para aprobar su venta en los Estados Unidos. (Sin embargo, algunos medicamentos pasan por un proceso acelerado de aprobación y reciben esta última antes de finalizar un ensayo clínico de fase 3.)
- **Ensayos de fase 4:** Registro continuo de la inocuidad que ocurre después de que un medicamento es aprobado por la FDA para la venta en los Estados Unidos. La finalidad de ese registro es obtener más información acerca de los riesgos, beneficios y uso óptimo del producto.

Para mayores detalles, lea la hoja informativa de HIVinfo titulada Ensayos clínicos sobre la infección por el VIH/SIDA.



¿Cómo puedo encontrar un ensayo clínico en el cual se estudia un medicamento contra el VIH en fase de investigación?

Para encontrar un ensayo clínico del VIH/SIDA en el cual se estudia un medicamento contra el VIH en fase de investigación, use la búsqueda de ensayos clínicos de ClinicalInfo.

Si necesita ayuda con su búsqueda, comuníquese con un especialista de información de salud de ClinicalInfo llamando al 1-800-448-0440 o envíe un correo electrónico a ContactUs@HIVinfo.NIH.gov.

También puede además unirse a ResearchMatch, un instrumento virtual y seguro que facilita que el público se involucre en los ensayos clínicos.

¿Hay medicamentos contra el VIH en fase de investigación disponibles para empleo fuera de un ensayo clínico?

En algunos casos, un medicamento contra el VIH en fase de investigación puede estar disponible por medio de un programa de acceso ampliado. El acceso ampliado permite emplear un medicamento en fase de investigación fuera de un ensayo clínico para tratar a una persona que tiene una enfermedad grave o potencialmente mortal en el futuro inmediato y que no tiene otras opciones de tratamiento aprobadas por la FDA. Las compañías farmacéuticas deben tener permiso de la FDA para facilitar un medicamento en fase de investigación para acceso ampliado.

Las personas que buscan acceso ampliado a un medicamento contra el VIH en fase de investigación deben hablar con su proveedor de atención de salud para ver si reúnen los requisitos para participar en un programa de esa clase.

¿Es seguro emplear un medicamento contra el VIH en fase de investigación?

Una meta de la investigación sobre el VIH consiste en identificar medicamentos más inocuos y más eficaces contra ese virus. Los investigadores tratan de que los ensayos clínicos sean lo más seguros posible. Sin embargo, el hecho de tomar un medicamento contra el VIH en fase de investigación puede acarrear riesgos y beneficios. Los riesgos pueden ser efectos secundarios imprevistos del producto, que pueden ser desagradables, graves y hasta potencialmente mortales.

Los beneficios y posibles riesgos de la participación en un ensayo clínico o en un programa de acceso ampliado se les explican a las personas antes de que decidan participar.

¿Cómo puedo encontrar más información relacionada con los medicamentos contra el VIH en fase de investigación?

Para encontrar más información relacionada con los medicamentos contra el VIH en fase de investigación, use la Base de datos de medicamentos de ClinicalInfo, que incluye información actualizada sobre muchos medicamentos de este tipo.

Proporcionado en colaboración con la Oficina de Investigación del SIDA de los NIH

Future Directions for HIV Treatment Research

niaid.nih.gov/diseases-conditions/future-hiv-treatment

A major goal of NIAID-supported research on HIV treatment today is to develop long-acting therapies that—unlike current antiretrovirals, which require daily dosing—could be taken only once a week, once a month, or even less often. Such long-acting therapies might be easier for some people to stick to than daily pills, and might also be less toxic and more cost effective. The three types of agents under study are long-acting drugs, broadly neutralizing antibodies, and therapeutic vaccines.

Long-Acting Drugs

NIAID-supported scientists aim to develop a new array of drugs for HIV treatment that include longer-acting pills as well as alternative formulations such as injections, patches, and implants. The complexity of developing such products has led NIAID to create a consortium of experts who can facilitate relationships among the many types of researchers needed to translate an idea for a long-acting HIV drug into a workable solution. Called LEAP, for Long-Acting/Extended Release Antiretroviral Resource Program, the consortium includes scientists and clinicians from academia, industry, and government, as well as patient advocates. Read more about LEAP.

NIAID also will investigate the effectiveness of two investigational long-acting HIV drugs, rilpivirine LA and cabotegravir LA, in people for whom adhering to conventional antiretroviral therapy has been a challenge. Another study is planned to test whether the combination of monthly injections of cabotegravir LA and monthly infusions of an NIAID-discovered broadly neutralizing antibody called VRC01LS can keep HIV suppressed in people whose infection was previously controlled by antiretroviral therapy.

Broadly Neutralizing Antibodies

Scientists at the NIAID Vaccine Research Center (VRC) and NIAID-supported scientists at other institutions are developing and testing multiple antibodies for the treatment of HIV. Antibodies are good candidates for treatment because they have few side effects and can be modified to ensure they last a long time in the body, suggesting that dosing could be every other month or even less often. Importantly, the antibodies under investigation can powerfully stop a wide range of HIV strains from infecting human cells in the laboratory and thus are known as broadly neutralizing antibodies, or bNAbs.

In the context of treatment, bNAbs can potentially thwart HIV in three ways:

- By binding directly to the virus, preventing it from entering a cell and accelerating its elimination.

- By binding to an HIV-infected cell, recruiting immune-system components that facilitate cell killing.
- By binding to a key fragment of HIV, forming a complex that may lead to the stimulation of immune cells in a manner similar to a vaccine, thereby preparing the immune system for future encounters with the virus.

Clinical studies have established that giving infusions of certain bNAbs to people living with HIV can suppress the virus, albeit to a limited degree. Further studies have shown that treating people living with HIV with just one bNAb fosters the emergence of HIV strains that are resistant to the antibody. Thus, just as antiretroviral therapy requires a combination of drugs to effectively suppress HIV, it appears that antibody-based therapy will require a combination of either multiple bNAbs or bNAbs and long-acting drugs to suppress the virus. Studies in monkeys infected with a simian version of HIV have already demonstrated that combinations of complementary bNAbs powerfully suppress the virus for an extended period. NIAID is now funding and conducting clinical trials of this strategy for treating HIV in people.

In addition, scientists are engineering changes to known bNAbs to optimize them for HIV treatment and prevention applications. These changes are designed to increase the number of HIV strains an antibody can block, how long the antibody lasts in the body, how powerfully the antibody attaches to the virus, and how efficiently the antibody triggers the immune system to attack both the virus and HIV-infected cells.

Therapeutic HIV Vaccines

Perhaps the ideal treatment for HIV infection would be a therapeutic vaccine. Unlike a vaccine designed to prevent HIV infection, a therapeutic vaccine would be given to people already infected with the virus. Such a vaccine would stimulate the immune system to be ready to control any future emergence of HIV and thereby end the need for further therapy, perhaps save periodic booster shots. Such an approach could lead to sustained viral remission, meaning treatment or vaccination that would result in prolonged undetectable levels of HIV without regular antiretroviral therapy.

The presence of rare people living with HIV who can control the virus naturally either from the time of infection or after halting antiretroviral therapy is evidence that a therapeutic vaccine could theoretically alter the immune system to achieve long-term control of HIV. Nevertheless, attempts to create effective therapeutic HIV vaccines have so far been unsuccessful. To help improve results, NIAID is working to advance the underlying science—in particular, to improve understanding of immune responses that sustainably suppress HIV and to improve the potency of those responses.

Three of the NIAID-funded Martin Delaney Collaboratories are pursuing strategies that involve therapeutic vaccines to achieve long-term control of HIV or reduction of the reservoir of all virus-carrying cells. Read more about the Martin Delaney Collaboratories.

Future Directions for Developing Daily HIV Drugs

At the same time, NIAID continues to support research to develop new drugs with unique mechanisms of action for daily antiretroviral therapy. Such drugs likely would be effective against HIV strains with resistance to other drug types.

For example, basic NIAID-supported research contributed to development of the experimental drug islatravir (also known as EFdA or MK-8591), which belongs to a class of drugs known as nucleoside reverse transcriptase translocation inhibitors, or NRTTIs. NIAID research also contributed to the development of maturation inhibitors, investigational drugs that target the same stage of the HIV lifecycle as protease inhibitors but act by a different mechanism.

Researchers also are attempting to target other parts of the HIV lifecycle. For example, the experimental inhibitor fostemsavir blocks HIV from infecting immune cells by attaching to the gp120 protein on the virus' surface. Another example is development of capsid assembly inhibitors, which halt construction of the viral capsid, the protein shell that encloses HIV's genetic material.

For more information on investigational antiretroviral treatments, see the AIDS*info* Drug Database.

Content last reviewed on August 26, 2019

What is a Therapeutic HIV Vaccine?

hivinfo.nih.gov/understanding-hiv/fact-sheets/what-therapeutic-hiv-vaccine

HIV Overview

Last Reviewed: September 24, 2020

Key Points

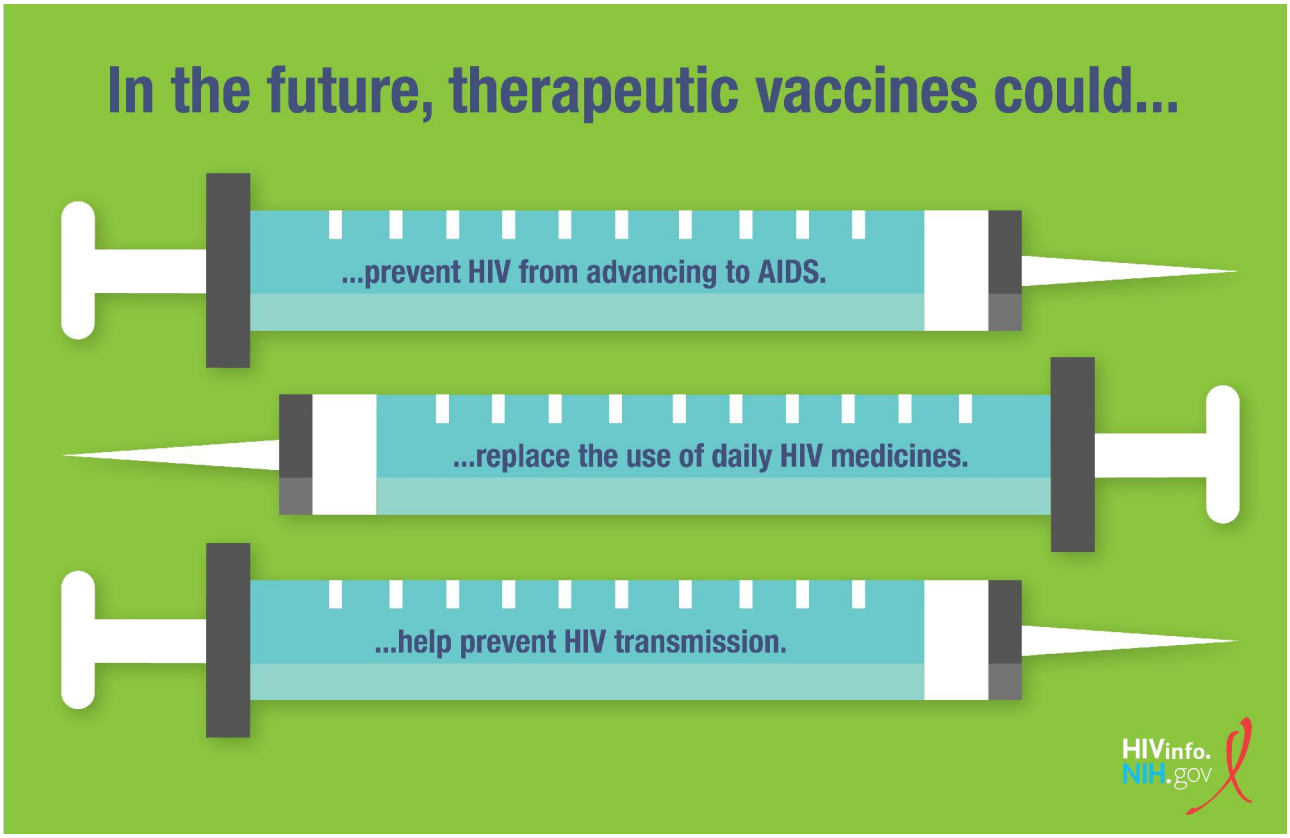
- A therapeutic HIV vaccine is a vaccine that's designed to improve the body's immune response to HIV in a person who already has HIV.
- Currently, no therapeutic HIV vaccines have been approved by the Food and Drug Administration (FDA), but research is underway. You must be enrolled in a clinical trial to receive a therapeutic HIV vaccine.
- Researchers are exploring therapeutic HIV vaccines to slow down the progression of HIV infection, and to eliminate the need for antiretroviral therapy (ART) while still keeping undetectable levels of HIV.

What is a therapeutic HIV vaccine?

A therapeutic HIV vaccine is a vaccine that's designed to improve the body's immune response to HIV in a person who already has HIV.

Researchers are developing and testing therapeutic HIV vaccines to slow down the progression of HIV to AIDS, and treating people with these vaccines would ideally keep HIV at undetectable levels without the need for regular antiretroviral therapy (ART). (ART is the recommended treatment for HIV infection and involves using a combination of different HIV medicines to prevent HIV from multiplying. Currently, a person with HIV must remain on ART to keep HIV at undetectable levels.)

A therapeutic HIV vaccine may also make it less likely that a person could transmit HIV to others.



Are there any FDA-approved therapeutic HIV vaccines?

There are currently no Food and Drug Administration (FDA)-approved therapeutic HIV vaccines, but research is underway. You must be enrolled in a clinical trial to receive a therapeutic HIV vaccine.

How is a therapeutic HIV vaccine different from a preventive HIV vaccine?

A preventive HIV vaccine is given to people who do not have HIV, with the goal of preventing HIV infection in the future. The vaccine teaches the person's immune system to recognize and effectively fight HIV in case the virus ever enters the person's body. To learn more, read the ClinicalInfo What is a Preventive HIV Vaccine? fact sheet.

A therapeutic HIV vaccine is given to people who already have HIV. The goal of a therapeutic HIV vaccine is to strengthen a person's immune response to the HIV that is already in the person's body.

Where can I get more information about clinical trials studying therapeutic HIV vaccines?

A list of clinical trials on therapeutic HIV vaccines is available from the ClinicalInfo database of *ClinicalTrials.gov* study summaries. Click on the title of any trial in the list to see more information about the study.

If you are interested in participating in a vaccine study, you can also contact the National Institutes of Health Vaccine Research Center by calling 866-833-LIFE (5433) or by emailing vaccines@nih.gov.

This fact sheet is based on information from the following sources:

Provided in collaboration with NIH's Office of Aids Research.

¿Qué es una vacuna terapéutica contra el VIH?

hivinfo.nih.gov/es/understanding-hiv/fact-sheets/que-es-una-vacuna-terapeutica-contra-el-vih

Última revisión: October 6, 2020

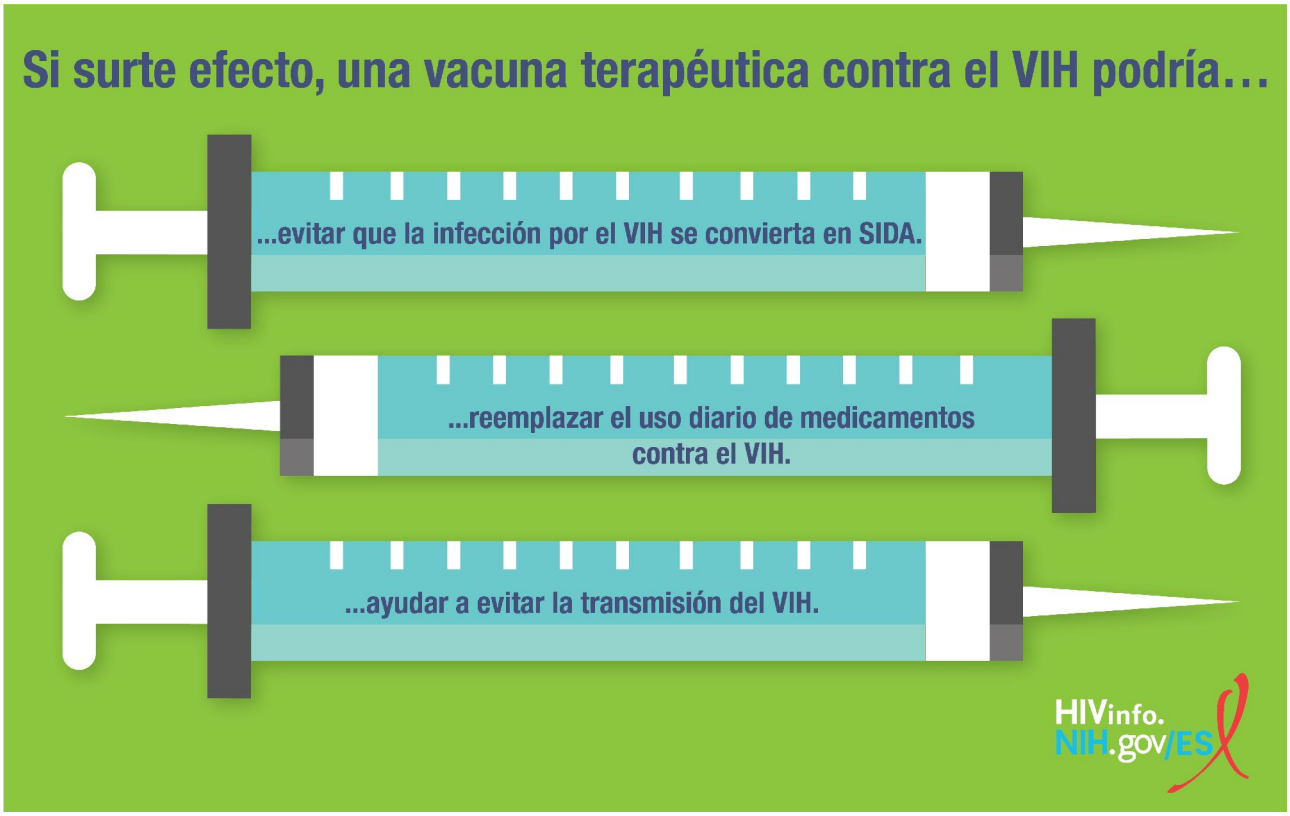
Puntos importantes

- El próposito de una vacuna terapéutica contra el VIH es mejorar la respuesta inmunitaria del cuerpo a ese virus en una persona seropositiva.
- En el momento no hay vacunas terapéuticas contra el VIH aprobadas por la Administración de Alimentos y Medicamentos (FDA), pero hay investigaciones en curso. Usted debe estar inscrito en un ensayo clínico para recibir una vacuna preventiva contra el VIH.
- Los investigadores están explorando las vacunas terapéuticas contra el VIH para desacelerar la evolución de la infección por el VIH y para eliminar la necesidad de un tratamiento antirretroviral (TAR) manteniendo al mismo tiempo concentraciones indetectables del VIH.

El próposito de una vacuna terapéutica contra el VIH es mejorar la respuesta inmunitaria del cuerpo a ese virus en una persona seropositiva.

Los investigadores están desarrollando y probando vacunas terapéuticas contra el VIH para desacelerar la evolución de la infección por el VIH a SIDA, y tratar a las persona con estas vacunas podría lograr idealmente concentraciones indetectables del virus sin necesidad de tratamiento antirretroviral (TAR) regular. (El TAR es el tratamiento recomendado para la infección por el VIH e involucra el uso de una combinación de diferentes medicamentos antirretrovirales para evitar que el VIH se multiplique. Actualmente, una persona con el VIH debe seguir con el TAR para mantener concentraciones indetectables del VIH.)

Una vacuna terapéutica contra el VIH también podría reducir la probabilidad de que una persona pueda transmitir el VIH a otros.



¿Hay vacunas terapéuticas contra el VIH aprobadas por la FDA?

Hasta el momento no hay vacunas terapéuticas contra el VIH aprobadas por la Administración de Alimentos y Medicamentos (FDA), pero hay investigaciones en curso. Usted debe estar inscrito en un ensayo clínico para recibir una vacuna preventiva contra el VIH.

¿En qué se diferencia la vacuna terapéutica contra el VIH de la vacuna preventiva contra el VIH?

Una vacuna preventiva contra el VIH se administra a personas seronegativas, con el fin de prevenir dicha infección en el futuro. La vacuna enseña al sistema inmunitario de la persona a reconocer y luchar eficazmente contra el VIH en caso que el virus entre a su cuerpo. Para más información, lea la hoja informativa de ClinicalInfo: ¿Qué es una vacuna preventiva contra el VIH?

Una vacuna terapéutica contra el VIH se administra a personas seropositivas. El objetivo de esta clase de vacuna es reforzar la respuesta inmunitaria de una persona al VIH que ya está en su cuerpo.

¿Dónde puedo obtener más información sobre los ensayos clínicos que estudien las vacunas terapéuticas contra el VIH?

Hay una lista de estudios clínicos relacionados con las vacunas terapéuticas contra el VIH en la base de datos de ClinicalInfo de los resúmenes de estudios en *ClinicalTrials.gov*. Haga clic en el título de cualquier ensayo clínico de la lista para ver más información sobre el estudio.

Si está interesado en participar en un estudio de una vacuna, también puede comunicarse con el Centro de investigación de vacunas, de los Institutos Nacionales de la Salud llamando al 866-833-LIFE (5433) o enviando un correo electrónico a vaccines@nih.gov (disponible solamente en inglés).

La hoja informativa precedente se basa en la correspondiente en inglés.

Proporcionado en colaboración con la Oficina de Investigación del SIDA de los NIH

HIV Cure

niaid.nih.gov/diseases-conditions/hiv-cure-research

While there is currently no cure for HIV, advances in treatment have made it possible for people with HIV to live long and healthy lives. We also now have more tools to halt the epidemic through treatment, prevention and education. Still, a cure would facilitate the global eradication of HIV/AIDS. For this reason, NIAID invests in basic and clinical research aimed at developing a safe, affordable and scalable cure for HIV and AIDS. Watch a video to learn about the approaches NIAID is taking to achieve a cure for HIV.

Many people involved in HIV cure research acknowledge that, much like the best treatments for HIV, a cure may consist of a combination of agents and approaches. Because of the nature of HIV infection, a cure for HIV can be defined in two ways: treatment-free remission and viral eradication.

Sustained ART-Free Remission

Many people living with HIV who adhere to regular antiretroviral therapy (ART) maintain undetectable levels of the virus in their blood. While these individuals have effectively no risk of sexually transmitting HIV and are less likely to experience most symptoms and complications of HIV infection, latent virus remains in certain cells known collectively as the HIV reservoir. If people with ART-suppressed HIV stop taking their medication, virus from the reservoir rebounds to high levels. Sustained ART-free remission, sometimes called a functional cure, would allow a person living with HIV to keep latent virus suppressed without daily medication. Read more about NIAID-supported research toward sustained ART-free remission.

Viral Eradication

In a viral eradication cure scenario, HIV would be completely absent from an individual's body. Viral eradication is generally expected to require two experimental strategies to be used in tandem. The first step would prompt latent HIV to replicate so that the cells in the HIV reservoir express HIV proteins. The second step would enhance the immune system of the person living with HIV or employ other agents to recognize and kill the cells expressing HIV proteins, thereby clearing the virus from the body. Read more about NIAID research efforts to achieve viral eradication.

Content last reviewed on March 26, 2019

Sustained ART-Free HIV Remission

niaid.nih.gov/diseases-conditions/sustained-art-free-hiv-remission

Today, people living with HIV typically must take antiretroviral therapy (ART)—a daily regimen usually of three or more antiretroviral drugs—to stay healthy and prevent transmission of the virus to others.

An HIV cure in the classic sense would require the elimination of the reservoir of all virus-carrying cells. These cells, which contain HIV DNA, have entered a resting state such that they do not produce any parts of the virus unless they become activated. HIV reservoir cells can survive in this resting state for years, even for life, while remaining invisible to the immune system and antiretroviral drugs.

An alternative to a classic cure is sustained ART-free remission. This objective would not involve eradicating the HIV reservoir, but rather would allow a person living with HIV to keep latent virus suppressed without daily medication.

Boosting the Immune System to Achieve HIV Remission

Most approaches to achieving sustained ART-free remission involve altering the immune system to induce long-term control of HIV. Researchers attempt to manipulate the immune system with interventions that target HIV and HIV-infected cells or that change the behavior of immune cells to better address the infection.

One promising intervention for achieving ART-free remission is broadly neutralizing antibodies, or bNAbs. These potent proteins can block nearly all HIV strains from infecting human cells in the laboratory and facilitate the killing of cells that have already been infected. While bNAbs develop naturally in some people with HIV, they usually do so either in amounts too small to provide a significant benefit or too late after infection to control the rapidly replicating and mutating virus. Studies are now underway in animals and people who have been taking ART to determine whether periodic infusions or injections of bNAbs can keep HIV suppressed after ART is halted. Scientists are developing bNAbs with improved attributes, including greater potency and longer duration in the body, and are testing treatment with combinations of two or three bNAbs in a manner akin to combination ART. Read about the encouraging 2018 results of a small clinical trial testing infusions of a bNAb duo for ART-free remission and about the creation and preliminary testing of a three-in-one bNAb.

Scientists also are testing whether bNAbs against the virus can produce ART-free remission by inducing long-lasting, immune-mediated control of the virus without further intervention. A study led by scientists at NIAID and Rockefeller University showed that giving infusions of

two different bNAbs to monkeys infected with the simian form of HIV enabled the immune systems of some of the animals to control the virus long after the antibodies were gone.

Another approach to ART-free remission involves antibodies that bind to parts of the immune system. One such strategy targeted a host immune cellular receptor called alpha-4 beta-7. A study giving short-term ART and infusions of an anti-alpha-4 beta-7 antibody to monkeys infected with a simian form of HIV reportedly led to prolonged control of the virus in some animals and replenishment of immune cells after all treatment stopped. An NIH study that tried to replicate this outcome did not achieve consistent results, however.

NIAID scientists conducted a small, early-phase clinical trial in which people living with HIV that was well controlled with ART received infusions of vedolizumab, an anti-alpha-4-beta-7 antibody that is FDA-approved for ulcerative colitis and Crohn's disease. These volunteers received both ART and vedolizumab at the beginning of the study, paused ART while continuing to receive the antibody, and finally stopped all treatment. The regimen was safe and well tolerated but did not generate lasting control of the virus.

In a different strategy toward ART-free remission, scientists primed killer T-cells with fragments of HIV proteins. The researchers found that these boosted cells effectively killed HIV-infected cells in petri dishes and in mice genetically modified to have human immune systems. The study suggested that a therapeutic vaccine that similarly boosts the T-cell response to HIV might be successful in achieving long-term control of the virus. NIAID scientists tested one such experimental therapeutic vaccine and found it to be safe but not effective. Other investigators have explored creating therapeutic vaccines that induce the immune system to produce bNAbs to achieve ART-free remission, but this research is still at a very early stage.

Using Very Early ART to Achieve HIV Remission

Because ART is so effective at bringing down HIV levels in the blood, some researchers have theorized that introducing medication as quickly as possible after infection may prevent HIV from building up a formidable reservoir and render therapy no longer necessary. As of 2018, three cases of sustained ART-free remission in children after early, limited ART have been reported.

The first of these cases involved a child from Mississippi born in 2010. The "Mississippi Baby" became infected with HIV from her mother at birth but began aggressive ART 30 hours later. She continued taking ART for the first 18 months of her life before stopping the medication. Although she was not seen in a clinic until 5 months after her last dose of ART, doctors found that—remarkably—she did not have a detectable viral load when she resumed receiving medical care.

The child continued to appear to be in sustained ART-free remission for two years when, in 2014, researchers announced that the child had detectable levels of HIV. While this was an unfortunate development, the case study illuminated key research questions and showed that periods of HIV quiescence in the absence of ART may be possible. Much work has been done to try to understand where the virus was “hiding” in this child and what led to its eventual rebound. In related research, NIAID is co-funding a clinical trial to explore whether giving ART soon after birth to infants who became infected with HIV in the womb leads to remission of the virus, enabling the children eventually to stop treatment for an extended time.

Since the Mississippi Baby’s case came to light, two additional cases of sustained ART-free remission in a child after early, limited ART have been reported. In 2015, researchers reported that a French child who was born with HIV in 1996, started anti-HIV therapy at age 3 months, and stopped treatment sometime between ages 5.5 and 7 years continued to control the virus without drugs more than 11 years later. Then in 2017, scientists reported that a nine-year-old South African child who was diagnosed with HIV infection at one month of age and received ART during infancy had suppressed the virus without ART drugs for 8.5 years. Learn more about the South African child.

Taken together, these three unusual cases have strengthened the hope that by treating HIV-infected children for a brief period beginning in infancy, physicians may be able to spare them the burden of life-long ART and the health consequences of long-term immune activation typically associated with HIV disease.

Developing Long-Acting ART to Aid HIV Remission Strategies

Along with testing the impact of very early ART, researchers are trying to optimize ART by developing long-acting therapeutics that can suppress HIV for extended periods. Long-acting therapeutics could offer convenience, cost savings, and ease of use to the millions of people worldwide who must otherwise take multiple drugs daily to maintain a low viral load.

Early and long-acting ART may be critical to achieving complete viral suppression and reducing the size of the HIV reservoir. These factors, in turn, could improve the success of strategies for sustained ART-free remission and HIV eradication.

Long-acting antiretroviral medication is also being tested for preventive use. View an infographic on long-acting HIV prevention research supported by NIAID.

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HIV Viral Eradication

niaid.nih.gov/diseases-conditions/hiv-viral-eradication

Viral eradication for HIV would involve the complete elimination of HIV from the body, including the destruction of cells infected with latent HIV. One strategy under study would deplete the HIV reservoir by prodding the virus out of its latent state so that an enhanced immune system or administered therapies can target and eliminate HIV-infected cells. An alternate strategy would be to use gene therapy to specifically excise or inactivate the latent HIV.

Reversing HIV Latency and Destroying the HIV Reservoir

Scientists are looking into strategies that induce latently infected cells to express HIV proteins on their outer surface so that an enhanced immune system or therapeutic agents can recognize these proteins and kill the infected cell. This strategy is sometimes called “kick and kill” or “shock and kill” —meaning latent HIV is drawn out by latency-reversing agents, allowing the latently infected cells to be targeted for destruction by the immune system or other anti-HIV therapy. Currently, several latency-reversing agents are under investigation in the laboratory and in human clinical trials.

Once the latent HIV begins to replicate after the “kick” stage, components of the immune system or therapeutic agents kill the HIV-infected cells to ensure a complete eradication of the latent HIV reservoir. In 2015, a team of researchers at NIAID developed a double-headed protein called VRC07-αCD3, which is a kind of bispecific T-cell engager, or BITE. One arm of this protein binds to a receptor on HIV-infected CD4 T-cells, prompting that cell to display HIV proteins on its outer membrane. In a separate step, the other arm of VRC07-αCD3 then binds to these HIV membrane proteins while the original arm attaches to a killer T-cell in order to activate it and bring it in proximity to the infected cell. The activated killer T cell then kills the infected cell.

Employing Stem Cell Transplantation and Gene Therapy

In the absence of ART, the vast majority of people living with HIV will eventually develop complications, including AIDS. However, some people living with HIV maintain low levels of virus in the blood—or viral load—even without therapy, indicating that their immune cells are protected from HIV. Other individuals claim to have had significant exposure to HIV but did not acquire the virus.

Beginning in the late 1990s, studies revealed that people with stronger natural protection from HIV tended to have mutations in the gene that codes for a protein called CCR5. CCR5 exists on the surface of human immune cells, and it is one of the proteins that HIV uses to enter and infect cells. When CCR5 is dysfunctional or absent, HIV can no longer infect

immune cells. If researchers induce CCR5 dysfunction or absence by mutating the *CCR5* gene in the cells of adults who do not naturally have this rare mutation, scientists may be able to help these people better control or eliminate HIV infection. Based on these findings, NIAID funds experimental genetic engineering approaches to an HIV cure.

Some clinicians have attempted to cure HIV in people who needed a bone marrow transplant to treat a life-threatening cancer by selecting a donor whose stem cells had the *CCR5* mutation. If the procedure is successful and the patient survives, it can lead to a reconstitution of the immune system with cells that are impervious to HIV. This approach has succeeded only twice in curing people of HIV, although it has been tried many other times.

One of these two successful cases was known as “the Berlin patient” for many years before revealing his identity, Timothy Brown. This American man living with HIV was diagnosed with myeloid leukemia while living in Germany. Brown’s doctors determined he needed a complete bone marrow transplant, the standard treatment for his life-threatening cancer, and selected a donor who had the *CCR5* mutation. Brown nearly died from the treatment. However, in the end, not only did the procedure cure his leukemia, but also it eliminated HIV from his body. In 2009, Brown’s physicians reported these findings in the *New England Journal of Medicine* as a case study funded by the German Research Foundation.

In 2019, researchers reported a similar case in the journal *Nature.* The anonymous “London patient” received a bone marrow transplant for Hodgkin’s lymphoma using stem cells from a donor with the *CCR5* mutation. The patient survived the transplant, and multiple subsequent analyses revealed no evidence of HIV infection. At the time of publication, the patient’s HIV had remained in remission without ART for more than 18 months. Researchers will continue to monitor the “London patient” for the reemergence of HIV, as well as long-term health effects of the transplant. The case study was supported by the United Kingdom’s National Institute for Health Research, the Oxford and Cambridge Biomedical Research Centres and amfAR (The Foundation for AIDS Research).

While these extraordinary cases are “proof of concept” that HIV can be cured, a bone marrow transplant is a highly risky, intensive and expensive procedure performed only to treat life-threatening conditions in the absence of other treatment options. It is not a realistic way to cure HIV in the millions of people around the world who are living with the virus. Moreover, attempts to cure HIV with bone marrow transplants in other individuals have not been successful, primarily because the procedure has only been performed in patients with both HIV and blood cancers, which have a high mortality rate even after bone marrow transplants.

Other recent advancements have opened up the possibility of enhancing the immune system’s ability to fight HIV through gene-editing technologies. Clinicians employing such techniques would remove immune cells from an HIV-positive patient, use gene-editing to directly alter the CCR5 gene, and then transfuse the cells back into the individual. In this

case, a donor with an advantageous CCR5 mutation is not required, and the patient does not risk life-threatening rejection of donor tissue. Some preliminary research has been done to assess gene-editing as a strategy for both HIV treatment and cure.

Some clinicians have also proposed using gene-editing technology to directly cut viral genes out of the DNA of latently infected cells. This technique would target what is called the HIV provirus. When HIV infects a cell, the virus inserts its own genome into the cell's DNA. Advances in biotechnology make it possible for scientists to potentially locate and remove these genes from latent cells using programmed DNA-slicing enzymes. Pre-clinical studies in animals have shown that such a strategy can excise proviral DNA from infected cells. However, scientists still need to understand how to efficiently deliver these gene-editing enzymes to all cells that make up the latent HIV reservoir without causing unintended consequences that may be unhealthy for the patient. Therefore, more research needs to be done to evaluate this approach in living organisms.

Content last reviewed on March 26, 2019