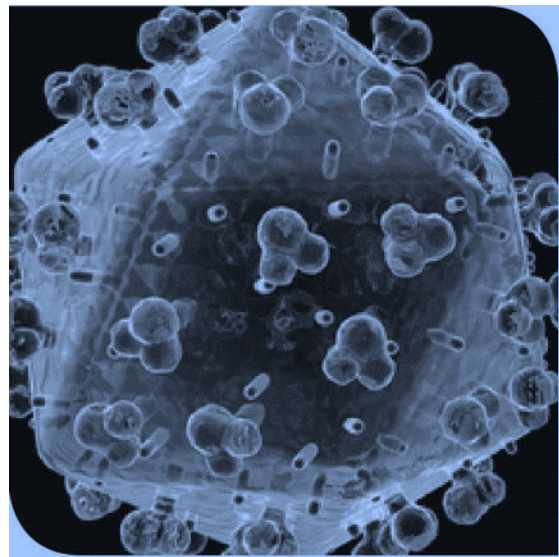
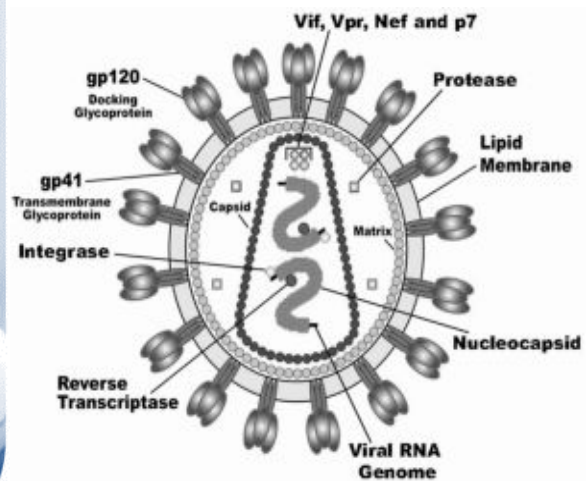


HIV/AIDS Cure Research Introduction & Resource Guide 2018



Cover Design

Upper left: Young woman looking through microscope

Upper right: Cutaway design of an HIV virion (single virus particle)

Lower left: Pipette dropping liquid into test tube

Lower right: Virion surface photomicrograph

HIV/AIDS Cure Research Introduction, Glossary & Resource Guide 2018

This document and the related web page are designed for the media and laypersons interested in understanding the issues involved in research related to curing HIV infection. It is essential to understanding most of the material to know what HIV, DNA, and a virus are, and it is quite helpful to have taken at least an introductory high school biology course.

Notes to the Reader:

1. **STRUCTURE OF THIS DOCUMENT:** This document is divided into four sections titled "Introduction to HIV/AIDS Cure Research," "Perspectives on HIV/AIDS Cure Research," "Glossary of HIV/AIDS Cure Research Terms & Phrases," and "Resource Guide" in that order.
 2. **COLOR OF HEADERS:** Introduction and Glossary entries have headers that are color coded to indicate what scientific areas they belong to, as follows:
 - Basic science and biology entries have headers that are **green**.
 - HIV background, that is, entries that aren't specifically related to cure research, and those that span categories have headers that are **blue**.
 - Gene-editing- and transplant-related entries have headers that are **violet**.
 - Entries related to HIV reservoirs, latency reversal, shock and kill, and latency silencing have headers that are **red**.
 - Entries related to individuals and groups of individuals have headers that are **orange**.
 - Entries related to social issues and practical considerations have headers that are **brown**.
 - All other entries have headers that are **black**.
- Items are arranged in each of the four parts alphabetically by the first nontrivial word; thus, for example, the Resource Guide entry **THE BODY** is under "B", not "T".
3. **Introduction to HIV/AIDS Cure Research and the Glossary of HIV Cure Terms and Phrases:** Almost all the entries that occur in the Introduction are also in the Glossary, nearly always with the same header, but occasionally, as for the second Introduction entry, with similar headers—in this case Alleles and Mutations and Allele. The difference between the two is that the Introduction entries are designed to provide introductions to their topics, while those in the Glossary provide the details.
 4. **CROSSREFERENCES:** Terms that are underlined are defined elsewhere in this document. To reduce clutter, for cross-referenced terms that occur more than once in an entry only the first occurrence is underlined. Note that entries in the Introduction may refer to entries there or in the Glossary. There are also URLs for external resources.
 5. **HIV, HIV-1 & HIV-2:** References to HIV are to what is more specifically named HIV-1, which is responsible for the pandemic. There is also a variety named HIV-2 that is confined to parts of West Africa and a few small pockets in Europe of immigrants from West Africa. See the HIV-2 Glossary entry for an explanation of why there is so little attention to it here.
 6. **RESPONSIBILITY:** This document is a project of the Delaney AIDS Research Enterprise (DARE) to Find a Cure Community Advisory Board (CAB)—which is responsible for its content—with some input from members of some of the other Martin Delaney Collaboratories for HIV Cure Research CABs and several DARE researchers.
 7. **INTRODUCTION IN SPANISH:** The Introduction section has been transformed to a self-contained version that has been translated to Spanish. It is available as a PDF and as a hyperlinked web page on this website by selecting the "Community Engagement" item and "Recursos ..." in the list of items in the resulting dropdown menu.
 8. **CONTACTING THE AUTHOR:** You are welcome to send suggestions for edits and additions to this document's author at hivcureglossary@gmail.com. You may also send questions to the author about items in this document. However, please note that, while an attempt will be made to answer all relevant questions, not all of them will be answered quickly because of time limitations.

Introduction to HIV/AIDS Cure Research

Overview

While effective treatment is available that turns living with HIV from an almost certain death sentence to a relatively normal lifespan on treatment, there are several reasons why curing it is essential, as follows:

1. Despite treatment that reduces HIV viral load to an undetectable level in almost everyone who can stand that treatment and stick to taking it daily, everyone—including almost all elite controllers, who achieve un-detectability without treatment—suffers from the effects of chronic systemic inflammation that is a factor in the development of diabetes, cancer, and other diseases that shorten lifespan. Long-term HIV infection makes older people effectively about ten years older biologically than they are chronologically.
2. Despite having undetectable viral load, one still has a tiny possibility of passing HIV on to a sexual partner.

Note that these reasons make it essential to cure HIV as soon as possible after one becomes infected.

There are two types of cures that are the subject of research. The more ambitious is sterilizing, which removes all HIV from the body, or at least all HIV that can replicate. This is the kind of cure that is achieved for most diseases. It is increasingly being realized that sterilizing cure is likely not to be achievable for HIV, or at least not in the foreseeable future. The more realistic is functional cure, also known as remission, whose goal is to make the body able to control the disease without needing antiretroviral treatment (ART) for some period of time, preferably measured in years, and to have remission be repeatable.

There are five approaches to curing HIV infection being explored in research, namely:

- **Hematopoietic stem cell transplant:** Transplantation of hematopoietic (that is, blood-cell-producing) stem cells that lack a factor essential to most HIV infections is the approach used to cure the one person who has been cured so far, namely, the Berlin patient (Timothy Ray Brown). However, this approach is very impractical. It requires conditioning of the body—wiping out its immune system—so the transplant is not rejected, which makes one open to a wide range of infections until the transplant

repopulates the immune system. In fact, Timothy nearly died in the process of his cure. The conditioning and the series of other medical interventions make this approach very time consuming, expensive, and risky. As a result, despite its being effective, this approach is simply not anywhere near generalizable to everyone living with HIV either now or in the near future, though there are researchers working on “transplant in a box.”

- **Gene editing:** One reason HIV is so difficult to cure is that, unlike almost all other viruses, it integrates many copies of its genetic material into the DNA of the human cells it infects. Gene editing is a strategy for modifying the HIV DNA in the host's cells, such as removing it entirely or altering one or more of the factors that make those cells susceptible to HIV infection. There are numerous experimental gene editing techniques being investigated. However, the most precise and effective one is named CRISPR or CRISPR/Cas9. A recent mathematical modeling study of gene editing strategies for HIV cure has shown that achieving positive results requires major improvement of some key components of the strategy.
 - **Shock and kill:** Shock and kill is focused on a type of immune-system cells called helper T cells or CD4+ T cells, which are the cells that are the primary focus of HIV infection. In fact, one would not be far wrong to say that HIV *is* a disease of helper T cells because it preferentially infects them and in the process of reproducing HIV virions (single virus particles) it destroys them. After becoming infected, CD4+ T cells go into a state called latency in some bodily organs, particularly lymph nodes. In that state they are not producing new virions, are out of the blood, and are inaccessible to anti-HIV drugs.
- Shock and kill's goal is to reactivate latent infected helper T cells and kill them. It is—obviously—a two-step process. The shock step uses drugs called latency-reversal agents (mostly ones developed for treating cancers) to reactivate the latent infected T cells. The

second step uses other drugs to kill them. There are currently two very significant problems with shock and kill: (1) there is no solid way to measure the number of latent infected cells in the body; there are several methods, but they provide vastly different numbers; and (2) despite the variation in measurements, it is clear that all the approaches to reactivation come nowhere near reactivating all the latently infected helper T cells, and there are several cases of people who were thought to be cured turning out to have viral rebound either quickly or eventually.

Shock and kill is also known as kick and kill.

- **Latency Silencing:** Latency silencing is the opposite of shock and kill. Instead of reactivating latent cells to kill them, its goal is to keep latent infected helper T cells and other infected cells from ever being activated. It is particularly important in the central nervous

AIDS (Acquired Immune Deficiency Syndrome)

AIDS (Acquired Immune Deficiency Syndrome) is the final stage of HIV infection. While AIDS and death ended in death for most HIV-positive people before 1996, with the advent of highly active antiretroviral therapy (HAART) that year it retreated into the background in the developed world, though it remains a serious problem in some areas.

Alleles and Mutations

An allele is a variant of a gene at a particular position on a chromosome. Humans and all other living organisms have two mirror images of each gene linked together on the two strands making up the double helix of DNA. The linkage of the genes across the strands provides a checking mechanism that greatly decreases the occurrence of errors (called mutations) that may cause diseases and particularly the runaway replication that characterizes cancer.

HIV has two strands of RNA as its genetic material, but the strands are not linked together unlike in the DNA double helix. The two occurrences of a gene are one on each strand. Because the strands are not connected there is no error checking, which makes the occurrence of mutations very much more common than in living things. This can result in virions (single virus particles) that are not infective, but it can also lead to so-called escape variants of HIV that are not susceptible to one's current antiretroviral therapy (ART).

system (the brain and spinal cord) where reactivation could cause a storm of disastrous effects. Several approaches are being explored including using gene editing to make the HIV neither dangerous nor infective, using drugs to inhibit important HIV proteins, and using a protein to block integration of HIV into cellular DNA.

- **Immune-Based Therapies:** Immune-based therapies use drugs to alter some part of HIV's replication process or enhance the effects of other approaches. An example is the use of drugs called TLR7 agonists (drugs that cause another substance to perform an action) to suppress HIV replication. Other immune-based therapies include therapeutic vaccines that boost immune system responses to HIV in infected persons, natural killer (NK) cells, and immune-system-related drugs that enhance shock and kill.

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Allogeneic Transplant

An allogeneic transplant, in the context of curing HIV infection, involves transplanting hematopoietic stem cells from a donor other than the transplant recipient.

As described above, this is being studied as a possible way to perform a sterilizing cure of HIV infection. See autologous transplant below for an alternative.

Allogeneic transplants, so far (and this is shared with autologous transplants), are very expensive and require intensive medical monitoring, making this approach simply technologically infeasible. What is needed has been called "transplant in a box" technology, analogous to what has been achieved by home HIV testing, and there are researchers working on this, though achieving the goal is still far in the future.

Analytical Treatment Interruption (ATI)

An analytical treatment interruption (ATI) is a medically monitored interruption of antiretroviral therapy (ART) as part of a research study. It is essential to test the effectiveness of a cure strategy, but it is also the subject of considerable concern for the reasons mentioned here and discussed in detail the reference below.

The monitoring is almost always done by the researchers performing the study or by clinicians working with them. The purpose of the interruption is

to determine the effect of the intervention used in the study on one or more measures of, for example, latent reservoir reactivation or the CD4+ T cell population. Analytical treatment interruptions pose important ethical issues, such as the possibility that the participant's viral load becomes high enough that he or she infects one or more other persons or that her or his virus population becomes resistant to all available antiretrovirals (ARV); for a discussion of the ethical issues see the article that the Ethics of ART interruption after stem-cell transplantation Resource Guide entry concerns.

Animal Models

Animal models, such as macaque monkeys, are particularly useful in HIV cure research because

- They make it possible for the researcher to do what he or she wants;
- The ethical issues concerning them are simpler than those for people;
- They *may* be quite faithful models of what occurs in humans; and
- They may be “sacrificed” as the final step in the research and their tissues analyzed in ways that are obviously not possible in human clinical trials.

Numerous studies have been done in monkeys using simian immunodeficiency virus (SIV), a variety of which is the virus HIV developed from, or simian-human immunodeficiency virus (SHIV), a genetic combination of SIV and HIV created in a laboratory, before they were tried in human clinical trials. Unfortunately neither of these models is as faithful to HIV and humans as would be preferred.

Another quite useful animal model is bone marrow-liver-thymus mice with HIV.

Antigens and Antibodies

An antigen is an invading bacterium, virus, or foreign substance that induces an immune response in the body, particularly the production of an antibody. An antibody is a mechanism the body has for fighting infections and other foreign substances. It is a specific protein produced by a B cell in the blood in response to and to counteract an antigen. It forms a chemical combination with the foreign substance that makes it inert.

Antiretroviral Therapy (ART)

Antiretroviral therapy (ART) involves the use of several (usually three) anti-HIV drugs to halt or greatly decrease viral replication. ART drugs may target any of several viral enzymes, such as reverse transcriptase, protease, or integrase, or entry of HIV into cells. Some

drugs may instead target essential parts of the infected cell, as the CCR5-blocking drugs do. Some researchers believe that ART will be needed in shock and kill cure strategies to halt HIV reproduction as part of killing them in cells that have been reactivated by latency reversal.

Autologous Transplant

An autologous transplant is, specifically for curing HIV, a transplant of hematopoietic stem cells that have been provided by the transplant recipient and been modified to remove the DNA that encodes HIV, or, for example, the gene that encodes the CCR5 co-receptor for HIV. This is being studied as a possible way of performing a sterilizing cure of HIV infection. It has been argued that autologous transplantation is much more likely to be easily scalable to larger patient populations than allogeneic transplant for at least two reasons, namely, (1) it avoids the issue of having to find a very well-matched donor, since the recipient *is* the donor; and (2) it greatly reduces the risk of graft-versus-host disease (GVHD), again because the donor is the recipient.

However, autologous transplants have issues of their own, the most important of which are

1. The cells to be transplanted (presumably hematopoietic stem cells) must be modified by some method to make them resistant to HIV infection (rather than being selected to be resistant, for example, by having the CCR5Δ32/Δ32 mutation—see the Zinc-Finger Nuclease (ZFN) item under the Gene Editing Glossary header for an example of a clinical trial with this goal);
2. There is not yet a safe and effective method for selecting the gene-modified cells, though several have been tried;
3. There must be sufficient numbers of transplanted cells to swamp the already infected blood stem cells.

Autologous transplants, so far (and this is shared with allogeneic transplants), are very expensive and require intensive medical monitoring, making this approach simply technologically infeasible. What is needed has been called “transplant in a box” technology, analogous to what has been achieved by home HIV testing; there are researchers working on this, though the goal is still far in the future.

B Cell

A B cell is a variety of immune-system cell that originates in the bone marrow (hence the “B”). It produces antibodies in response to an antigen presented by an antigen-presenting cell, such as a

dendritic cell.

Berlin Patient (Timothy Ray Brown)

The Berlin Patient (Timothy Ray Brown) is the only person to have achieved a sterilizing cure of his HIV infection so far. His cure occurred after he had been diagnosed with an acute leukemia that affects a type of white blood cells essential for fighting infections. The leukemia would almost certainly have been fatal, so he had nothing to lose by trying a CCR5Δ32/Δ32 allogeneic transplant of hematopoietic stem cells in his bone marrow that would make him insusceptible to

infection by most types of HIV. He actually required two transplants (in 2006 and 2007) for the cure to be successful. A very serious infection after the second transplant nearly killed him, but he bounced back from it, and he remains HIV free by the most sensitive tests available. Replicating such a cure remains a very high priority of cure research, preferably without requiring the chemotherapy (called conditioning) that Timothy required to wipe out his leukemia and prepare his bone marrow for the transplants.

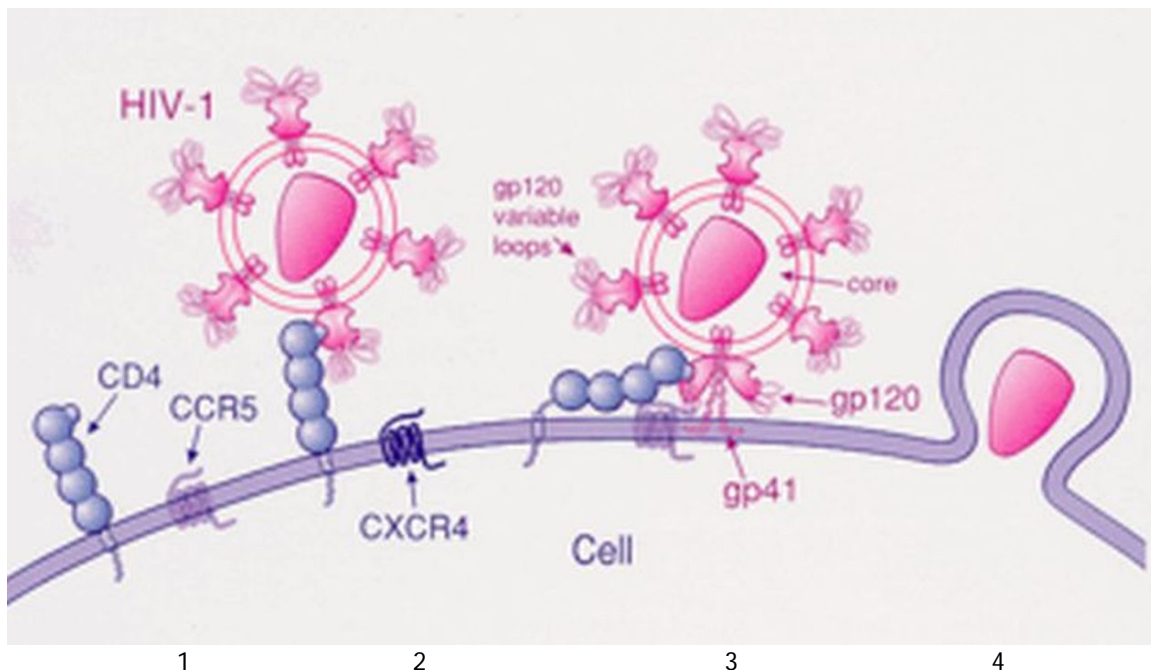


Figure 1. This sequence shows HIV binding to the CD4 receptor, then to the CCR5 co-receptor, and finally having released its genetic material into a CD4+ T cell in four steps: (1) the CD4 receptor and CCR5 co-receptor on the cell surface; (2) HIV glycoprotein gp120 binds to CD4; (3) gp120 binds to CCR5 and releases gp41, which pierces the cell surface releasing the infective part of the virion into the cell; (4) the capsid (see HIV Structure and Function in the Glossary) enters the CD4+ T cell through the pore in the cell wall created in (3).

CCR5

CCR5 is a co-receptor on the surface of CD4+ T cells and some other cells that, during most of the course of HIV infection, is essential to entry of HIV into these cells. HIV attaches to both CD4 and CCR5 to achieve entry. (Some variants of HIV use a co-receptor called CXCR4 rather than CCR5; these variants almost always occur only late in untreated HIV infection; HIV transmitted from one person to another almost always uses the CCR5 co-receptor. However, some rare strains of HIV use both the CCR5 and the CXCR4 co-receptors.) Figure 1 (adapted from

<https://en.wikipedia.org/wiki/CCR5>) shows (1) the CD4 receptor and the CCR5 co-receptor on the surface of a cell, (2) HIV binding to CD4, (3) then to CCR5, and finally (4) having released its genetic material into a CD4+ T cell through the pore in the cell wall created in (3). CCR5-tropic HIV is also called M-tropic because it can also infect macrophages and monocytes.

CCR5Δ32/Δ32

CCR5Δ32/Δ32 indicates a mutation that deletes 32 nucleic acid base pairs from both parents' copies of the gene that encodes the cellular co-receptor CCR5. The

absence of these base pairs eliminates the ability of CCR5 to function on CD4+ T cells; the CCR5 co-receptor is needed by almost all strains of HIV to enter and infect these cells. Notably, the allogeneic immune-system transplants that resulted in a sterilizing cure of HIV infection in the Berlin Patient (Timothy Ray Brown) had this mutation in both strands of the DNA included in the transplant. Unfortunately, only about 10 – 15% of Caucasians have this mutation and almost no one else does, which makes this approach nearly useless for curing HIV infection in all infected persons, unless gene editing can make more instances of the mutation, which is one of the focuses of HIV cure research. Note that “Δ” is the upper-case Greek letter “delta” and stands for the deletion. Further, CCR5Δ32/Δ32 is associated with increased susceptibility to West Nile virus infection and a variety of encephalitis.

CD4

CD4 is a receptor that is necessary, along with a co-receptor (CCR5 or CXCR4), to the attachment of HIV virions to CD4+ T cells. CD4 is one of hundreds of receptors known as clusters of differentiation that are found on the surfaces of various cell types and facilitate attachment of virions, chemicals, and other cells. CD8 is another. Note that, in addition to HIV-specific CD4+ T cells, CD4 is also found on other types of immune-system cells.

CD4+ T Cell

A CD4+ T cell is a primary white blood cell of the immune system; it is also known as a helper T cell. CD4+ T cells act, for the most part, as the “directors” of the immune system; they signal to other immune-system cells how and when to fight infections. CD4+ T cells are preferentially infected by HIV, which causes its own genetic material to be converted from RNA to the corresponding DNA and to be integrated into the cells’ DNA. HIV-infected CD4+ T cells, when activated, produce copies of HIV instead of reproducing or conducting immune functions.

CD4+ T cells can develop that specifically target parts of an infectious agent and such cells become activated in response to infection by that pathogen. After the infection is cleared or controlled, they can then become resting memory CD4+ T cells that lie in wait for future occurrences of the pathogen to which they then respond. Such resting memory CD4+ T cells are thought to constitute most of the latent reservoir of HIV. CD4+ T cells all have the CD4 receptor on their surfaces.

CD8

CD8 is a receptor that is necessary to the attachment of virions chemicals, and other cells to CD8+ T cells.

CD8 is one of hundreds of receptors known as clusters of differentiation that are found on the surfaces of various cell types and facilitate attachment of virions, chemicals, and other cells. CD4 is another example. Note that, in addition to responding to HIV-specific CD4+ T cells, CD8+ T cells also respond to other CD4+ T cells and CD8 is found on other types of immune system cells.

CD8+ T Cell

A CD8+ T cell is a primary white blood cell of the immune system that kills infected or disabled cells as directed by CD4+ T cells. CD8+ T cells can be created that are specific to HIV. CD8+ T cells all have the CD8 receptor on their surfaces. These cells are also known as cytotoxic T lymphocytes (CTLs).

Recent research suggests that harnessing the killing power of CD8+ T cells may be essential to both functional and sterilizing HIV cures (see the HIV Cure (Functional) and HIV Cure (Sterilizing) Glossary entries).

Central Nervous System (CNS)

The central nervous system (CNS) consists of the brain and spinal cord. It is important for curing HIV for at least four reasons:

- (1) it is a latent reservoir for HIV that is affected by chronic inflammation that begins very early in HIV infection;
- (2) it can only be reached by a small minority of HIV antiretroviral therapy (ART);
- (3) HIV’s gp120 glycoprotein impacts the function of neurons; and
- (4) since the brain is so very essential, there is concern among cure researchers that approaches other than shock and kill, such as latency silencing of reactivation entirely, will be necessary to achieve a cure in the CNS because of the seriously toxic effect reactivation is likely to have on CNS functioning.

Also, several free-floating HIV proteins have been shown to enter neurons and have pathogenic effects.

Clinical Trials

Clinical trials are the standard process for testing new medications, medical devices, and medical procedures in humans. They are typically preceded by studies done in nonhuman animals (sometimes called “Phase 0”) to weed out those that are not worth the effort and expense of clinical trials. Clinical trials have three phases, as follows (we use medication to represent all three categories below):

- Phase I: A Phase I clinical trial involves a small

number (usually not more than about 20) of healthy volunteers to test the safety of the medication and any side effects it may have. If the procedure is determined to be safe and to have only acceptable side effects, it may proceed to Phase II.

- Phase II: A Phase II clinical trial will usually involve several hundred volunteers. It continues to test for safety and side effects and also adds on determination of its effectiveness.
- Phase III: A Phase III clinical trial involves several thousand volunteers and is intended to confirm the effectiveness of the medication, monitor its side effects, compare it to commonly used drugs if there are any already, and continue to collect information to determine whether the drug is safe. Only after a successful Phase III study does a medication go before a panel of the U.S. Food and Drug Administration (FDA) or similar agency elsewhere in the world for approval for distribution.

There is also what is sometimes called "Phase IV": a post-marketing phase, in which the medication or procedure is used in diverse populations and continues to be monitored for side effects.

In some case, clinical trials have phases that are numbered with a Roman numeral followed by the letter "A" or "B" to indicate whether it is an early or late part of the phase, respectively. These letters are usually used in combinations of phase numbers to indicate that the clinical trial straddles two consecutive phases; an example of this might be a Phase IB/IIA trial.

Every clinical trial done in the United States is required to have a written trial protocol that describes at the least

- a detailed plan of what is to be done,
- why it is being done,
- justification for it based on prior research,
- known and hypothetical risks and benefits,
- criteria for inclusion and exclusion of potential participants, and
- a schedule of what will be done (for example, physical exams, blood draws, and monitoring side effects).

It also must have an informed consent form (ICF) that explains the trial to the volunteers, informs them of the above facts in lay language, tells them they may withdraw from participation at any point without giving a reason for doing so, and requires their signed and witnessed consent to participation before they begin the trial's procedures. Every clinical trial protocol and ICF is reviewed and approved by an independent

Institutional Review Board and one or more of several government agencies (which one(s) depend on the nature of the trial) before it can begin recruiting volunteers.

Clinical trials done outside the United States are required to follow the same or a very similar rigorous plan and process.

Clonal Expansion

Clonal expansion is the production of numerous daughter cells with identical genomes resulting from a parent cell. Clonal expansion of HIV-infected CD4+ T cells in circulating blood is thought by some researchers to be a significant contributor to the latent reservoir and so a barrier to HIV remission.

Co-Receptor

A co-receptor, in the context of HIV medicine (including cure research), is a chemical, such as CCR5 or CXCR4, attached to the surface of a cell such as a CD4+ T cell that facilitates attachment and entry along with a receptor, such as CD4, of an HIV virion into the cell.

CXCR4

CXCR4 is a co-receptor on the surface of CD4+ T cells that, during late stages of untreated HIV infection, is essential to entry of HIV into these cells. (Some variants of HIV use a co-receptor named CCR5 rather than CXCR4; these variants almost always occur in all but the last part of the course of HIV infection; HIV transmitted from one person to another almost always uses the CCR5 co-receptor, though rare cases with the CXCR4 co-receptor do occur.) Further, some rare strains of HIV use both the CCR5 and the CXCR4 co-receptors. Also, unlike CCR5, CXCR4 is not a good candidate for gene editing because it occurs on several cell types other than CD4+ T cells and is essential to their function. CXCR4-tropic HIV is also called T-tropic because unlike CCR5-tropic virus it can infect CD4+ T cells but not macrophages and monocytes.

Defective Virion

A defective HIV virion is one containing an RNA genome that makes it incapable of viral replication. This results from the single-stranded nature of HIV's RNA. All living organisms have linked double-stranded DNA making up the well-known double helix; the cross links in the helix provide a self-checking mechanism to prevent frequent mutations. Of course, some mutations *do* occur in living organisms, and they are one of the mechanisms that cause cancers and numerous other diseases, such as sickle-cell anemia and Huntington's disease. However, the unlinked single strands of HIV's RNA have no such self-checking mechanism, and

mutations occur in them very frequently, as we shall see.

Let's calculate how often a typical nucleic acid base is mutated each day in a person who is not on antiretroviral therapy (ART). Note that, despite the extremely high frequency of mutations, this has no chance at all of eliminating HIV from a human in a lifetime!

1. The current best estimate for the overall mutation rate is one per 34 viral replication cycles.
2. Given that roughly 10 billion new virions are created each day, roughly 300 million of the new virions will have at least one mutation.
3. With about 9,750 nucleic acid bases in each strand or 19,500 across both strands, that's an average of one mutation in each base position about 16,000 times a day!

Compared to a living organism's mutation rate, this is absolutely staggering! It doesn't require very many mutations in genes encoding critical proteins, such as reverse transcriptase or integrase (see the HIV Structure and Function Glossary entry), to render a virion incapable of infectivity, that is, make it defective. Even in persons on suppressive antiretroviral therapy (ART), the accumulation of mutations that make new virions defective is staggeringly common.

Dendritic Cell

A dendritic cell is one variety of antigen-presenting cell whose main function is presenting antigens found on external surfaces in the body to B cells or CD4+ T cells. They are found in the skin and other areas that are on the outside of the body, such as the nose, lungs, mouth, stomach, and intestines, and so in contact with the environment.

Diversity and Inclusiveness in Cure Research

It is no secret that HIV/AIDS is a pandemic disease, yet HIV-related research and cure research in particular tend very strongly to be concentrated in the developed world (particularly the United States, Canada, Western Europe, and Australia) plus a few relatively isolated outposts in Thailand and South Africa. There are issues of sex, gender, sexuality, age, race, economics, convenience, and researcher bias at the least that are responsible for this. Following are a few of the relevant facts and resources that make clear some of the issues and possible approaches to dealing with some of them; all of them are discussed in the Perspectives entry with the same header (in black).

- It is clear from numerous studies that the immune system's effectiveness decreases with increasing

age. This has effects on how well the body can deal with HIV infection among many other types of assaults and it also probably impacts the effectiveness of approaches to HIV cure, though this is currently unknown.

- Similarly, the hormonal and other developmental changes that occur during adolescence and the legal issues involved in obtaining informed consent for research very often exclude adolescents from HIV research studies. A notable positive development in this area is in South Africa, the country with the highest prevalence of HIV+ youths and young adults.
- There are barriers to including women in cure research, at the least because current approaches to cure have unknown interactions with pregnancy, both on the mother and the fetus.
- Transgender health is a developing field, but, so far, virtually nothing is known about the impact of hormonal treatment and cure strategies.

Droplet Digital Polymerase Chain Reaction (ddPCR)

Droplet digital polymerase chain reaction (ddPCR) is a type of polymerase chain reaction that is characterized by the creation under digital control of tiny droplets of highly amplified DNA resulting from an initial single molecule that are digitally measured. This technique has greatly automated the PCR technology and markedly decreased its expense.

Dual Antibody Use to Reduce the Latent Reservoir

Three studies published in late 2015 examine the use of so-called dual antibodies to achieve various aspects of reduction of the latent reservoir of HIV-infected CD4+ T cells, as follows:

1. One study discusses the use of dual-affinity re-targeting (DART) molecules to bind to both the HIV Env protein and the CD3 receptor on infected cells and "recruit" CD8+ T cells to kill the bound cells.
2. Another study used DARTs to bind to the same protein and receptor as in item 1 above to direct CD8+ T cells to kill infected CD4+ T cells.
3. The third study used what it calls bispecific antibodies that bind to the Env epitope recognized by the broadly neutralizing antibody VRC07 and the CD3 receptor to reduce HIV DNA in most of the laboratory isolates of infected cells tested. A broadly neutralizing antibody is one that is effective against a large class of antigens. "VRC" abbreviates the Vaccine Research Center at NIH that was responsible for discovering and characterizing the antibody.

One potential concern about all three of these studies is the possibility that their targeting CD3 might cause general activation of T cells, since it is the receptor that occurs on all of them, which could be disastrous. Apparently the dual nature of the targeting caused only minor, transient effects of this sort.

Elite Controllers

Elite controllers are rare individuals living with HIV who maintain undetectable viral loads in the absence of—in most cases—any antiretroviral therapy. In about 2/3 of known cases, they possess immune-system mutations that appear to enhance immune-system recognition and removal of HIV. In some elite controllers, undetectable viral loads are found in the absence of protective genes, indicating that specific genes are neither necessary nor sufficient for elite control of HIV. However there is evidence that many elite controllers suffer from chronic systemic inflammation like other people living with HIV, so they are likely to suffer from its long-term effects.

Enzyme

An enzyme is an organic molecule, in most cases a protein or peptide but in a few cases an RNA (such as a ribozyme), that acts as a catalyst: It facilitates a biochemical process without itself being modified, so it can be used again. Almost all proteins that are enzymes have names ending in “ase”.

Gene Editing

Gene editing is a cure strategy for modifying genetic information in cells, such as removing HIV proviral DNA from a person’s DNA or altering the CD4 receptor, CCR5 co-receptor, or anti-HIV restriction factors to make CD4+ T cells resistant to HIV infection. There are numerous experimental gene-editing techniques being investigated (many targeting the gene that encodes CCR5). We describe below only the most important one, namely, CRISPR. A recent mathematical modeling study of gene editing for HIV cure has shown that achieving positive results is possible only under a narrow range of conditions and that further improvements are likely necessary to improve outcomes.

CRISPR-based gene editing is a combination of two drugs, CRISPR (a DNA sequence originally derived from bacteria) and, usually, a Cas protein (CRISPR associated protein—most often Cas9), that is currently the most efficient, effective, and easy-to-use method for gene editing. A recent report discussed laboratory comparisons between older methods and uses of CRISPR/Cas9 to perform the same tasks and showed

that there were erroneous results in a significant number of cases using the older methods.

In fact, *Science*, the most prominent U.S. scientific journal, declared CRISPR to be the “Breakthrough of the Year” for 2015 because of its very wide applicability and ease of use, and *Nature*, the most prominent British scientific journal, chose it as No. 1 among its ten most important breakthroughs of 2015. Further, in early 2016, it was reported by two research teams that CRISPR technology, one using Cas9 and another using a different protein, had been used to remove entire HIV proviral DNA from latently infected CD4+ T cells in vitro and this has more recently been reported in vivo. Problems remain, however, for generally translating this technology to use in vivo—in fact another recent study about it reported that CRISPR/Cas9 resulted in an immune response to the Cas9 protein as a substance foreign to the body (a pathogen).

See also the CRISPR Perspectives entry and the first item under the Gene Editing header in the Glossary.

Genome

A genome is the collection of all the genes in a living organism or virion.

Graft-versus-Host Disease (GVHD)

Graft-versus-host disease (GVHD), also called rejection, is a natural reaction by the body’s immune system to a graft or transplant that typically results in elimination of the graft or transplant unless immunosuppressive drugs, such as cyclosporine, are administered. The reaction is predominantly carried out by CD8+ T cells. Nevertheless, in the case of the Berlin Patient (Timothy Ray Brown), graft-versus-host disease may have played a significant essential role in destroying his original HIV-infected CD4+ T cells.

Gut-Associated Lymphoid Tissue (GALT)

Gut-associated lymphoid tissue (GALT) consists of immune cells lining the gut that are a critical component of the immune response to pathogens. It is usually severely depleted very early in the course of HIV infection. It is believed that the depletion is mostly irreversible.

HIV Cure (Functional)

This type of cure allows some infected cells to persist in the body of a person living with HIV but means that antiretroviral therapy is no longer necessary, at least for a long time. With this approach, the immune system should be able to handle the virus that is still in the body. Because such individuals would typically have very low levels of HIV, they would much be less likely to transmit HIV to others than most infected people but

might themselves be vulnerable to reinfection with other strains of HIV than the one with which they are already infected. This type of cure is also commonly called HIV remission.

HIV Cure (Sterilizing)

This type of cure completely eliminates HIV from an infected person's body, which would likely require activation and killing of all infected resting memory CD4+ T cells (and probably infected macrophages), plus eliminating or silencing other cells contained in latent reservoirs. Depending on the strategy used, such individuals might or might not be resistant to reinfection with HIV. This approach results in there being no HIV capable of viral replication left in the body, so the person would not be able to transmit HIV to others. However, proving that all HIV has been eliminated from a person's body is impossible with current approaches, including in the case of the Berlin Patient (Timothy Ray Brown), though he has been HIV- for ten years.

HIV Genome

The nucleus of HIV (see the HIV Structure & Function Glossary entry) contains the two separate single strands of RNA that make up HIV's genetic material or genome. Each strand comprises nine genes and two long terminal repeats, one at each end, the right-hand one of which is crucial for beginning the production of proteins from the resulting proviral DNA. The overlapping of segments in the diagram corresponds to what are known as open reading frames. (Note that the open reading frames in the HIV genome are *never* directly transcribed and translated to proteins: The HIV genome must first be integrated into a host cell's DNA as proviral DNA that is, in turn, transcribed and translated to proteins.) In all, each strand has roughly 9,750 bases (nucleic acids), though this varies somewhat with the faulty replication of HIV RNA (see the Defective Virion Introduction and Glossary entries).

HIV Structure & Function

The cutaway diagram in Figure 4 in the Glossary shows schematically the structure and components of an HIV virion. Note that Figure 1 in this Introduction shows the capsid about to be inserted into an about-to-be infected cell. The capsid contains everything necessary to insert the HIV genome (transcribed from RNA to DNA) into the cell's DNA and to produce new virions. The components are described in detail in the Glossary entry with the same name.

HIV's Uniqueness

HIV is unique among human pathogens in several respects, as follows (adapted in part from a slide created and provided for use by Nobel Prize winner

Prof. David Baltimore, PhD, of CalTech):

- It preferentially attacks CD4+ T cells, the "directors" of the adaptive immune system.
- It eludes control by antibodies.
- Sugars cover almost its entire accessible surface. The only notable exception is the CD4 binding site, but that site is deep inside the protein coat, where it can't be reached by most antibodies.
- It employs a remarkable two-part attachment mechanism, using CCR5 or CXCR4 in addition to CD4. Entry only takes place after viral gp120 protein has bound to the CD4 site (see the CCR5 Glossary entry). As a result, very few antiviral antibodies can neutralize HIV, and fewer still are both broad and potent. Broad refers to the range of variants of HIV that the antibody is active against.
- It destroys the gut-associated lymphoid tissue (GALT) very early in infection altering the gut's bacterial community.
- It also attacks the central nervous system (CNS) very early in infection.

All of these aspects of HIV's uniqueness make it a much more difficult target for cure research than for almost all other pathogens.

Immune System

The immune system is the body's protection against disease. It consists of two major parts, the innate immune system and the adaptive immune system.

The innate immune system comprises three parts: biological barriers, natural killer (NK) cells, and killer-cell immunoglobulin-like receptors on the surfaces of natural killer cells, which are generally known by their abbreviation "KIR". Biological barriers at the surface of the body may be effective in keeping out pathogens, such as foreign substances, bacteria, and viruses that the barriers recognize as different from the body. Pathogens that make it through the biological barriers may be recognized by KIR components that are specific to them. If a KIR component recognizes a pathogen, it activates natural killer cells.

The adaptive immune system comprises B cells, T cells, antibodies produced by B cells, and the human leukocyte antigen (HLA) complex, which consists of genes that code for body surface proteins that distinguish between self and non-self and cell-surface proteins, such as CD4 and CD8, that regulate the adaptive immune system in humans. T cells, in turn, are a large family of varieties, including at least CD4+ T cells, CD8+ T cells, and at least a half dozen other types. See the entries for the underlined cell types for descriptions of their roles in immunity.

Inflammation

Inflamed immune-system cells can signal other immune-system cells to reproduce or respond to a pathogen. The key white blood cell in inflammation is the macrophage. Macrophages can assemble within themselves specialized platforms named inflammasomes that produce the substances that promote inflammation. These platforms are assembled when needed and destroyed when they are no longer needed. This is usually helpful.

However, HIV infection, even in those whose virus is either suppressed naturally (elite controllers) or by antiretroviral therapy (ART), is known to cause chronic inflammation, which can lead to heart attacks, strokes, cancers, and other serious health conditions. Activated cells can also produce scarring (also called fibrosis) in lymph nodes, a critical part of the immune system. For most purposes chronic immune activation equals chronic inflammation (that is, every state of chronic inflammation leads to chronic immune activation and vice versa).

Latency Reversal

Latency reversal is fundamental to activating the bound HIV proviral DNA in resting CD4+ T cells in latent reservoirs in the body to make it susceptible to destruction in the approach to cure known as shock and kill. This is considered by many HIV cure researchers to be fundamental to curing HIV. The Glossary entry with the same name lists many types of substances and individual substances being tested as latency-reversal agents.

Latency Silencing

Latency silencing is a term used to describe an approach to completely stop reactivation of latently infected CD4+ T cells in latent reservoirs, thus making them incapable of producing further HIV virions. Latency silencing is essential to curing HIV in areas such as the central nervous system (CNS) where latency reversal is believed to have disastrous consequences. At least five distinct approaches are currently being explored, and NIH has a request for research-grant applications for another that is active as this is being written. Latency silencing is also called block and lock.

Latent Reservoir

Latent reservoir is used in HIV cure research in two closely related senses, as follows:

- (1) A latent HIV reservoir is a tissue in a person's body that is reachable by HIV. In the context of HIV infection, it is a part of the body that, it is

generally believed, is not affected by antiretroviral therapy (ART) as effectively, if at all, as in the blood. Latent reservoirs provide long-lived homes for HIV to reemerge from if therapy is stopped. Examples of confirmed and likely latent reservoirs include a subset of CD4+ T cells named resting memory CD4+ T cells, macrophages and monocytes (white blood cells), and parts of the intestines.

A recently reported study of HIV and macrophages performed in bone marrow-liver-thymus (BLT) mice showed that HIV persists in macrophages in vivo and thus they are very likely to be a component of the latent reservoir.

- (2) The latent HIV reservoir is the totality of the individual latent reservoirs of type (1). The size of the latent reservoir is estimated to be anywhere from 1 million to over 50 million HIV-infected resting memory CD4+ T cells by the methods listed in the Measuring the Latent Reservoir Glossary entry.

A 2011 freely available survey article (Richman D "Introduction: challenges to finding a cure for HIV infection" Current Opinion in HIV and AIDS 6, January 2011, p. 1; it can be downloaded from the webpage <http://journals.lww.com/co-hivandaids/toc/2011/01000>) noted what we know about the latent reservoir as follows (lightly edited):

- a) Latently infected resting memory CD4+ T cells are the best characterized latent reservoir for HIV-1.
- b) Less than 1 cell per million of resting CD4+ T cells from persons on potent antiretroviral therapy harbors replication-competent latent provirus.
- c) Other drug-insensitive reservoirs, including brain, macrophages and hematopoietic stem cells, may also exist.
- d) The genetic information in latent proviruses does not evolve—because it is produced by a clonal expansion of a single infected cell—which suggests there is no ongoing viral replication within the cells containing them. Discontinuation of antiretroviral therapy permits the rebound of viral replication originating from the latent reservoir.
- e) Patients successfully treated with antiretroviral therapy for a decade or more exhibit no appreciable decrease in the size of the latent reservoir.

- f) The persistence of the latent reservoir precludes its elimination by antiretroviral therapy for the lifetime of the patient.
- g) Latency is likely established by numerous steps of HIV-1 replication, which potentially complicates eradication strategies.

It is generally accepted that the latent reservoir of at least HIV-infected resting memory CD4+ T cells containing proviral DNA and almost certainly other types of HIV-infected cells is established within days after infection.

Lymph Node

A lymph node is a small organ containing immune-system cells named lymphocytes that filter lymph, which is a milky fluid similar in composition to blood plasma that contains fats (responsible for its color), B cells, and T cells; the latter include CD4+ T cells and CD8+ T cells. Prominent clusters of lymph nodes are found in the underarms, the groin, and the neck. See the Lymphoid Tissues & Lymphatic System Introduction and Glossary entries for more information about them.

Lymph Node Collagen Deposition (Fibrosis)

When cells die, they are sometimes replaced by scar tissue composed of collagen, which is a protein found in numerous tissues including bones. This is called fibrosis. When lymph nodes are inflamed by HIV viral replication they can lay down scar tissue. This can begin within days of HIV infection and may be largely complete within months after infection. Experts currently believe that when lymph nodes are scarred, it may be difficult to regain their ability to respond to HIV and other infections as effectively as before the deposition had occurred, causing lasting damage to the immune system that a cure *may* not be able to reverse.

Lymphoid Tissues & Lymphatic System

A lymphoid tissue is a component of the lymphatic system. The tissues are found in lymph nodes, the thymus gland, gut-associated lymphoid tissue (GALT), Peyer's patches, the spleen, tonsils, and adenoids.

The lymphatic system is made up of the lymphatic tissues described above and lymphatic vessels, which parallel the veins and carry lymph toward the heart. The system is responsible for producing lymphocytes. The lymphatic system is essential to fighting infections.

Measuring the Latent Reservoir

Measuring the latent HIV reservoir(s) is vital to determining the effectiveness of approaches to latency reversal. It can be used to determine the number of reactivated HIV-infected CD4+ T cells, in addition to its

basic measurement role.

It is estimated that the latent reservoir typically contains anywhere from about 1 million to over 50 million HIV-infected CD4+ T cells. The ultimate goal of measuring the latent reservoir is to count all and only replication-competent provirus, which no measurement tool is yet capable of doing. There are several approaches to measuring the number of HIV-infected CD4+ T cells in the latent reservoir, and more are being designed continually.

The "gold standard" to which all other approaches are compared is the quantitative viral outgrowth assay (QVOA), which attempts to count replication-competent latent provirus. It is complex and expensive and has the added disadvantage of being *very likely to significantly underestimate the actual size of the latent reservoir*. However, some studies show a significant correlation between the results of QVOA and total HIV DNA.

Natural Killer (NK) Cells

Natural killer (NK) cells are white blood cells responsible for killing infected cells and cancer cells. They are the most ancient component of the cellular immune system. They have long been thought to be purely "natural" in the sense that they are preprogrammed to respond to particular types of infected or disabled cells, unlike CD4+ T cells and CD8+ T cells, which must be trained to respond to their target pathogens and thus can have numerous distinct targets. However, recent evidence suggests that there are memory-like subsets of natural killer cells in mice and in nonhuman primate (NHP) models, such as rhesus macaques infected with SHIV. There is ongoing research into whether such memory-like natural killer cells may play a role in curing HIV infection.

Post-Therapy Controllers

Post-therapy controllers are a small group of HIV+ individuals, so far mostly the VISCONTI (**V**iro-**I**mmunologic **S**ustained **C**ONTrol after **T**reatment Interruption) cohort in France, who started antiretroviral therapy (ART) within weeks of infection, stayed on therapy for an average of about four years, and then stopped therapy. Because there has been no large or lasting rebound of HIV, these individuals are able to stay off therapy for as long as 10 years. Unlike most elite controllers, these people mostly lack immune-system mutations that would make them less susceptible to ongoing virus replication. Natural killer (NK) cells are believed to be largely responsible for HIV control in this cohort.

Receptor

A receptor, in the context of HIV cure research, is a chemical (such as CD4 and CD8). For a CD4+ T cell, the corresponding CD4 receptor facilitates attachment and entry along with a co-receptor, namely CCR5 or CXCR4, of an HIV virion into a CD4+ T cell.

Remission

Remission is a term preferred by many researchers for HIV Cure (Functional). This is because functional cures, like cures for many types of cancers, may be short lived though they are likely to be repeatable at least for HIV.

Retrovirus

A retrovirus is a virus, such as HIV, whose genetic material is RNA rather than DNA. Retroviruses are special in that they are able to integrate their RNA into the host DNA as proviral DNA, which enables the creation of new virions.

Ribozyme

A ribozyme is a small RNA that acts as if it were an enzyme.

RNA

RNA stands for ribonucleic acid. Unlike DNA, which exists only in the well-known double helix structure found in all living things or as single strands in some viruses, there are more than 30 forms of RNA with distinct functions. One form serves as the two unconnected strands of genetic material in HIV.

Stakeholder Engagement

Stakeholder engagement refers to the involvement of essential people and organizations, including governments, foundations, research groups, companies, and *especially* individuals, in promoting understanding of HIV-related research, particularly clinical trials of both cure basic science and, potentially, curative processes; developing appropriate expectations; and sustaining involvement of persons in those trials. See also the Resource Guide entry with the same header.

Thymus Gland

The thymus gland is located in the chest just below the neck. It is the origin of all T cells (including specifically CD4+ T cells and CD8+ T cells) all of which migrate to the bone marrow. The thymus gland typically shrinks to almost nothing during adolescence.

Viral Load

HIV viral load measures the amount of HIV virions circulating in the blood. It is usually reported as copies of virus per milliliter of blood (abbreviated c/ml). It is important in HIV cure research because activating cells containing latent HIV from latent reservoirs increases viral load in a measurable way.

Virion

A virion is a single complete virus particle that consists of an RNA or DNA core with proteins, such as enzymes, and often with an external envelope. It is the extracellular infective form of a virus.

Women's Involvement in Cure Research Studies

A recent open-access viewpoint article concerning women's involvement in cure research suggests six ways to increase women's involvement. Before summarizing the points in the article, we must point the reader to the Estradiol, Estrogen, Progesterone, and Estrogen Receptors Glossary entry, which makes clear several very important biological reasons for increasing women's involvement. Current barriers and suggested ways to increase involvement are as follows:

1. The possibility of pregnancy and its unknown or not clearly understood impact on HIV-related research of all kinds is a *very* frequent barrier, especially for treatment studies. Most study designs can be modified to reduce the impact of this barrier, if not eliminate it.
2. Researcher and clinic coordinator perceptions may impact recruitment of women.
3. Engagement of women stakeholders and improving the perceptions of women held by male stakeholders can increase women's recruitment and retention in clinical trials.
4. Overcoming structural barriers, such as the lack of child care at research sites, and including women-focused community organizations in recruitment can improve involvement of women in studies.
5. Policy interventions in research funding can promote sex and gender equity.
6. The Gender, Race, and Clinical Experience (GRACE) study (a description of which can be downloaded from <http://online.liebertpub.com/doi/pdf/10.1089/apc.2013.0015>) is an excellent example that specifically included recruitment of women and can serve as a model for other studies.

Perspectives on HIV/AIDS Cure Research

This section presents several of the most important

trends, subject areas, and less than obvious reasons

for HIV cure research, with references to items in the following two sections that are related to them.

Chronic Inflammation

Chronic inflammation is a process that involves body-wide inflammation, which is very deleterious to overall health, and begins very early in the course of HIV infection. While antiretroviral therapy (ART) is highly effective at reducing or stopping HIV replication, it lessens but does not eliminate chronic inflammation, which is implicated in premature aging, heart and circulatory problems, cognitive decline, and numerous other serious medical problems. All this makes it one of the most urgent reasons for cure research.

CRISPR

CRISPR (clustered regularly interspaced short palindromic repeats) are segments of DNA in some bacteria and archaea that, combined with a protein such as Cas9 (CRISPR associate protein 9) or Cpf1 (centromere and promoter factor 1), constitutes a primitive immune system that is mostly effective against genetic sequences found in viruses, and plasmids (genetic structures in cells that reproduce independently of the DNA in the nucleus—see also the Organelle Glossary entry), two types of potentially injurious foreign material. The combination of CRISPR and either of the two proteins has been found to be the most effective and exact technique for editing DNA. It is particularly useful to HIV cure because it can be used to edit out the genes for the co-receptors CCR5 and CXCR4 and/or the entire HIV genome. In fact, CRISPR was recognized as the breakthrough of the year for 2015 by the journal *Science* and number one of the ten breakthroughs of 2015 by the journal *Nature*. It is fair to say that while there are researchers and companies still using several of the other techniques listed in the Gene Editing Glossary entry, CRISPR is very likely to eclipse them within the next few years—it already has a significant industry: as of January 2018 there were already at least seven public companies and numerous others that were still private. Several research projects that used other gene-editing techniques have recently been repeated using CRISPR/Cas9, which has shown that some of them had incorrect conclusions.

Diversity and Inclusiveness in Cure Research

It is no secret that HIV/AIDS is a pandemic, yet HIV-related research and cure research in particular tend very strongly to be concentrated in the developed world (particularly the United States, Canada, Western Europe, and Australia) plus a few isolated outposts in Thailand and South Africa. There are issues of sex, gender, sexuality, age, race, economics, convenience, and researcher bias at the least that are responsible for

this. The following are a few of the relevant facts and resources that make clear some of the issues and possible approaches to dealing with some of them:

- It is clear from numerous studies that the immune system's effectiveness decreases with increasing age (see, for example, for a very readable exposition, Chapter 2 "Things Fall Apart" in the book A Gawande **Being Mortal** pp. 25 – 54 Henry Holt and Co. New York 2014). This has effects on how well the body can deal with HIV infection among many other types of assaults and it also probably impacts the effectiveness of approaches to HIV cure, though this is currently unknown, in large part because most HIV research studies along with other HIV research have upper limits on the age of participants.
- Similarly, the hormonal and other developmental changes that occur during adolescence and the legal issues involved in obtaining informed consent for research very often exclude adolescents from HIV research studies. A notable positive development in this area is in South Africa, the country with the highest prevalence of HIV+ youths and young adults. There, for example, the Centre for the AIDS Program of Research in South Africa (CAPRISA) is enrolling not just adolescents but also children in research. An article about CAPRISA is available online at http://www.unicef.org/infobycountry/southafrica_70973.html and CAPRISA's website is <http://www.caprisa.org/Default>.
- There are barriers to including women in cure research, at the least because current approaches to cure have unknown interactions with pregnancy, both on the mother and the fetus.
- Initial research on the effects of female hormones on HIV cure research are described in the Estradiol, Estrogen, Progesterone, and Estrogen Receptors Glossary entry below and barriers to and some suggestions for increasing participation by women in cure research are discussed in the Women's Involvement in Cure Research Studies Glossary entry.
- The AIDS Malignancy Consortium (website: <https://web.emmes.com/study/amc/public/>), a clinical-trials-sponsoring network of the National Cancer Institute that supports studies of cancers in HIV+ people and their treatment, has set up a laboratory in eastern Africa because of the expense and infeasibility of getting frozen samples to laboratories in the United States. This might conceivably be shared with cure research studies.
- Transgender health is a rapidly developing field,

but so far almost nothing is known about the impact of combining hormonal treatment with cure approaches. A wonderful recent book that explores transgender health issues is the book L Erickson-Schroth **Trans Bodies, Trans Selves: A Resource for the Transgender Community** Oxford Univ. Press New York 2014. While it devotes only about a dozen pages to HIV specifically, it also provides access to other relevant resources.

The Fundamental Problems

There are two fundamental problems in HIV cure research that are somewhat different from each other, as follows:

- One is the need to very accurately measure the latent reservoir of HIV-infected cells so as to assess the effectiveness of both experimental approaches and likely the ultimate effect of clinical methods. Perhaps the most important example of both is the Mississippi Baby, who, when returned to medical care, was found to be infected. It was hypothesized that she may have had only a single HIV-infected cell at that time. It is possible that this problem has been largely solved early in 2018—see item 5 in the Measuring the Latent Reservoir Glossary item.
- The other is the need to determine, once an effective approach to cure, be it sterilizing (see HIV Cure (Sterilizing)) or functional (see HIV Cure Functional), has been developed what fraction of the infected population needs to be cured to achieve population-wide cure. This is akin to the question of achieving what's known as herd immunity—the fraction of a population that needs to be vaccinated against a disease organism to protect the entire population from infection. This may end up being 100%, but it could be fewer.

Microbiome and Microbiota

Microbiotum (the singular of microbiota) is a collection of bacteria, archaea, fungi, and viruses that colonizes a particular part of a plant or animal's body. The term microbiome was originally coined to refer to the genome of a microbiotum, but it is now increasingly used interchangeably with and more commonly than microbiota.

Our concern is with the human microbiomes; it is estimated that the genomes of all microbiomes in one person have roughly 200 times the genetic material of the human genome. Various parts of our skin have individual microbiomes, as do parts of the digestive

system, the respiratory system, and other parts of the body. Further, microbiomes vary from person to person. Particular changes in microbiomes are associated with diseases. HIV alters human microbiomes, and they are involved in all aspects of HIV disease from prevention through treatment and cure. For example, very early in infection, the gut-associated lymphoid tissue (GALT) is severely depleted, and this changes the intestinal microbiome. In HIV cure research microbiomes are just beginning to be a subject of significant study. This is definitely an area to watch.

Remission (Functional Cure)

While the term “cure research” continues to be used somewhat indiscriminately, it is recognized by most researchers that a generally applicable approach to a sterilizing cure (see the HIV Cure (Sterilizing) Glossary entry) is extremely difficult to develop and is very unlikely to be developed any time soon. Thus, almost all cure researchers use the term remission or functional cure (see the “HIV Cure (Functional)” Glossary entry) in a similar sense to how it is used in cancer treatment instead. Remission would involve being entirely *symptom* free for at least several years—and, one hopes, preferably much longer—before requiring treatment to re-achieve remission.

Shock and Kill

Shock and kill is the subject of intensive research in many laboratories, but it is increasingly recognized as likely to be insufficient to achieve a cure on its own. There are several reasons this is the case, but the most important ones are as follows:

1. Until early 2018 we lacked the capacity to measure the latent reservoir accurately, so shock-and-kill studies may impact it, but we had no way to know to what degree they do; item 5 in the Measuring the Latent Reservoir Glossary entry describes a much more promising approach. Nevertheless it is clear that current shock agents affect only a small fraction of the latent reservoir;
2. The sites of integration of the virus are very likely to affect the potency of a shock agent (latency reversal agent), and they have off-target effects—we need more powerful and more specific agents and likely ones that also attack infected cells that have the same HIV integration site in their DNA (that is, cells that are the result of clonal expansion);
3. Any shock agent *might* induce infected cells to proliferate and expand, but they have not yet been paired with powerful enough kill drugs, such as, perhaps, immunotherapeutic agents, vaccines, or other types of drugs that induce cell death in response to HIV proteins.

Glossary of HIV/AIDS Research Terms & Phrases

1-LTR and 2-LTR Circles

1-LTR and 2-LTR circles are dead-end byproducts of partial HIV viral replication: neither can make additional virions. A 1-LTR circle is distinguished from a 2-LTR circle by incorporating only a single long terminal repeat, while a 2-LTR circle has two adjacent ones. See the HIV Genome Glossary entry for a description of long terminals repeats (LTRs). In the shock and kill approach to purging latent reservoirs of HIV, the quantities of 1-LTR and 2-LTR circles resulting from the shock are measured because they are indications of the quantity of defective virions made by reactivation.

Adeno-Associated Virus (AAV)

An adeno-associated virus (AAV) is a type of virus that can be used as a vector to carry genetic material (typically DNA but occasionally RNA) or a protein into humans by injection. Adeno-associated viruses are not known to cause disease in humans, which makes them typically better candidates as vectors than adenoviruses. Adeno-associated viruses are expected to be used to deliver therapeutic vaccines in some approaches to the “kill” phase of some shock and kill strategies for reactivation and elimination of HIV-containing resting memory CD4+ T cells in latent reservoirs.

Adenovirus (AV)

An adenovirus (AV) is one of the many types of rhinoviruses, which cause the common cold. It can be used as a vector to carry genetic material (DNA or RNA) or a protein into a cell or in a vaccine. There are 57 known types of adenoviruses that are known to infect humans.

Adjuvant

An adjuvant is a substance administered with a vaccine that increases the effectiveness of the vaccine.

Adoptive Immunotherapy

Adoptive immunotherapy is transfer of immunity from a donor to a recipient (the adopter) through inoculation of modified white blood cells or antibodies into the recipient’s blood or bone marrow. This term is frequently used in gene editing studies.

Aging, HIV-Infection Effects & Cure

Even well-controlled HIV infection that has reached undetectable viral load results in a vicious circle of immune activation and chronic inflammation. The vicious circle has numerous possible effects ranging from increased susceptibility to infections and cancers

and, over the long term, adding an average of ten years to one’s chronological age to determine his or her biomedical age. The biomedical age difference makes finding an HIV cure all the more urgent. A layperson’s introduction to the aging process will be found in Chapter 2 “Things Fall Apart” of Gawande A **Being Mortal** Metropolitan Books 2014.

Agonist

An agonist is a drug or other substance that causes the action of another drug or substance. The opposite of an agonist is the much more familiar antagonist, which in biology prevents something from happening.

AIDS (Acquired Immune Deficiency Syndrome)

AIDS (Acquired Immune Deficiency Syndrome) is the final stage of HIV infection. While AIDS and death for most HIV-positive people before 1996, with the advent of highly active antiretroviral therapy (HAART) that year it slowly retreated into the background in the developed world, though it remains a serious problem in some areas.

Allele

An allele is a variant of a gene at a particular position on a chromosome. Humans and all other living organisms have two alleles for each gene, one each in a corresponding position on each of the two strands making up the double helix of DNA.

Retroviruses, such as HIV, have two strands of RNA, but the strands are not linked together unlike in the DNA double helix found in living organisms. They also have alleles, but they are single ones on each strand.

Allogeneic Transplant

An allogeneic transplant, in the context of curing HIV infection, involves transplanting hematopoietic stem cells from a donor other than the transplant recipient. This is being studied as a possible way of performing a sterilizing cure of HIV infection.

Allogeneic transplants, so far (and this is shared with autologous transplants), are very expensive making this simply technologically infeasible. What is needed has called “transplant in a box” technology, analogous to what has been achieved by home HIV testing, and, indeed, there are researchers working on this, though achieving the goal is still far in the future.

Amino Acid

An amino acid is one of twenty types of organic

compounds that make up proteins. Each amino acid has an amino group (-NH₂) at one end and an organic acid group (-COOH) at the other—it's what's in between that distinguishes one from another. Biologists and other researchers use both three-letter and single-letter abbreviations to denote them. For example, the amino acid proline is denoted both by "Pro" and by "P", cysteine by "Cys" and "C", and tyrosine is denoted by "Tyr" and "Y". Cysteine is special in that it's one of the two amino acids that contain a sulfur atom. In the co-receptor CCR5 the two C's refer to two cysteines that are linked together by their two sulfur atoms; similarly in the co-receptor CXCR4, the two C's also refer to cysteines but there's an amino acid between them denoted by the X (see the CC and CXC Chemokine Structure and Naming Glossary entry).

Analytical Treatment Interruption (ATI)

An analytical treatment interruption (ATI) is a medically monitored interruption of antiretroviral therapy (ART) as part of a research study. The monitoring is almost always done by the researchers performing the study or by clinicians working with them. The purpose of the interruption is to determine the effect of the intervention used in the study on one or more measures of, for example, latent reservoir reactivation or CD4+ T cell count. Analytical treatment interruptions pose important ethical issues, such as the possibility that the participant's viral load becomes high enough that he or she infects one or more other persons or that her or his virus population becomes resistant to all available antiretrovirals (ARV); for a discussion of the ethical issues see the article that the Ethics of ART interruption after stem-cell transplantation Resource Guide entry concerns.

Animal Models

Animal models, such as macaque monkeys, are particularly useful in HIV cure research because

- They make it possible for the researcher to do what he or she wants;
- The ethical issues concerning them are simpler than those for people;
- They *may* be quite faithful models of what occurs in humans; and
- They may be "sacrificed" as the final step in the research and their tissues analyzed in ways that are obviously not possible in human clinical trials.

Numerous studies have been done in monkeys using simian immunodeficiency virus (SIV), a variety of which is the virus HIV developed from, or simian-human immunodeficiency virus (SHIV), a genetic combination of SIV and HIV created in the laboratory, before they were tried in human clinical trials. Unfortunately

neither of these models is as faithful to HIV and humans as would be preferred.

Antigen-Presenting Cell

An antigen-presenting cell is a cell whose primary purpose is presenting antigens to B cells and CD4+ T cells.

Antigens and Antibodies

An antigen is a toxin or other foreign substance that induces an immune response in the body, particularly the production of an antibody. It is presented to a B cell (which produces antibodies) by an antigen-presenting cell, such as a dendritic cell. An antibody is a mechanism the body has for fighting infections and other foreign substances. It is a protein produced by a B cell in the blood that is produced in response to and to counteract a specific antigen. It forms a chemical combination with the foreign substance that neutralizes it.

Antiretroviral Therapy (ART)

Antiretroviral therapy (ART) involves the use of several (usually three) antiretroviral drugs to halt HIV viral replication. ART drugs may target any of several viral enzymes, such as reverse transcriptase, protease, or integrase, or entry of HIV into cells. Some drugs may instead target cellular structures, as the CCR5 blocker drugs do. Many experts believe that ART will be needed in cure strategies to halt HIV reproduction in cells that have been perturbed by latency reversal.

Antiretroviral Therapy (ART) Intensification

Antiretroviral therapy (ART) intensification involves adding drugs to an existing three-drug regimen to reduce inflammation caused by HIV and residual HIV viral replication and hence the size of HIV latent reservoirs. There is mixed data indicating whether intensifying ART will be necessary in cure strategies or not.

Apoptosis

Apoptosis is a form of cell death in which a programmed sequence of events leads to the elimination of the cell. It plays a crucial role in developing and maintaining the health of the body by eliminating old, unneeded, and unhealthy cells. Pronunciation hint: the second "p" is silent.

Auranofin

Auranofin (brand name Ridaura) is a gold-containing drug used to treat rheumatoid arthritis. It has a partially selective killing effect against central memory T cells (T_{CM}) and transitional memory T cells (T_{TM}). It has also been shown in the macaque nonhuman primate (NHP) models, when combined with

antiretroviral therapy (ART), to produce a long-term reduction in simian immunodeficiency virus (SIV) viral set point after stopping antiretroviral therapy (ART).

Australian Patients

Prof. David Cooper of the University of New South Wales, Sydney, Australia, reported in 2014 that two men with cancer and HIV infection had received bone-marrow transplants that cured their cancers (one had non-Hodgkin's lymphoma and the other leukemia—see the Cancer Glossary entry) and *may* have cured their HIV infections. They had no detectable HIV in their blood by very sensitive tests two and three years, respectively, after their transplants, but they were being kept on antiretroviral therapy (ART), so it is not clear whether they have been cured.

Autologous Transplant

An autologous transplant is, specifically for curing HIV, a transplant of hematopoietic stem cells that have been provided by the recipient and have been modified to remove the HIV proviral DNA, CCR5 gene, or something else that is relevant. This is being studied as a possible way of performing a sterilizing cure of HIV infection. It has been argued that autologous transplantation is significantly more likely to be scalable to larger patient populations than allogeneic transplants for at least two reasons, namely, (1) it avoids the issue of having to find a very well-matched donor, since the recipient is the donor; and (2) it greatly reduces the risk of graft-versus-host disease, again because the donor is the recipient.

However, autologous transplants have issues of their own, the most important of which are that

1. The cells to be transplanted (presumably hematopoietic stem cells) must be modified by some method to make them resistant to HIV infection (rather than being selected to be resistant, for example, by having the CCR5Δ32/Δ32 mutation—see the Zinc-Finger Nuclease (ZFN) item in the Gene Editing Glossary entry for an example of a clinical trial with this goal);
2. There is not yet a clearly safe and effective method for selecting the gene-modified cells, though several have been tried;
3. There must be sufficient numbers of transplanted cells to swamp the already infected stem cells in the recipient.

Finally, autologous transplants, so far (and this is shared with allogeneic transplants), are very expensive, making this simply technologically infeasible. What is needed has been called “transplant in a box” technology, analogous to what has been achieved by

home HIV testing, and, indeed, there are researchers working on this, though the goal is still far in the future.

Aviremia

Aviremia in peripheral blood, as reported, for example, for the Ethiopian Patient, refers to having no detectable virus in circulating blood.

Barcelona Patients

The Barcelona patients are five of the 13 participants in a shock-and-kill clinical trial. All 13 received romidepsin (see the Latency Reversal Glossary entry) and a therapeutic vaccine. Five of the 13 achieved the trial's definition of remission, namely, maintaining a very low viral load for up to six months. Three of the five maintained viral loads below 20 c/ml of blood; the other two have had occasional blips up to about 2,000 copies.

B Cell

A B cell is a variety of immune-system cell that originates in the bone marrow (hence the “B”). It produces antibodies in response to an antigen presented by an antigen-presenting cell, such as a dendritic cell.

B Cell Follicle

A B cell follicle is a component of a lymphoid tissue (such as a lymph node or the spleen that contains B cells) that hosts HIV production in humans and SIV production in nonhuman primate (NHP) models.

Berlin Patient (Timothy Ray Brown)

The Berlin Patient (Timothy Ray Brown) is the only person to have achieved a sterilizing cure of his HIV infection so far. His cure occurred after he had been diagnosed with acute myeloid leukemia, which affects white blood cells named granulocytes that are essential for fighting infections. The leukemia would almost certainly have been fatal, so he had nothing to lose by trying a CCR5Δ32/Δ32 allogeneic transplant of hematopoietic stem cells in his bone marrow. He actually required two transplants (one each in 2006 and 2007) for the cure to be successful. A very serious infection after the second transplant nearly killed him, but he bounced back from it, and he remains HIV free. Replicating such a cure remains a very high priority of cure research, preferably without requiring the chemotherapy (called conditioning) that Timothy required to wipe out his leukemia and prepare his bone marrow for the transplants.

See the Essen/Berlin Patient Glossary entry for another, less successful German cure attempt and the Resource Guide entry for the book CURED: How the Berlin Patients Defeated HIV and Forever Changed

Medical Science

Biomarker

A biomarker is a measurable substance in an organism whose presence is indicative of some phenomenon, such as a cell type or disease. In HIV cure research biomarkers are almost always cell-surface markers, such as CD4 and CD8.

Biomarker for the Latent Reservoir's Size and Viral Rebound

The SPARTAC (Short Pulsed Anti-Retroviral Therapy At seroConversion) clinical trial provided the first evidence (in 2013) of a biomarker for the size of the latent reservoir and viral rebound upon stopping therapy, namely, total HIV proviral DNA in CD4+ T cells as early as possible in the course of infection. Total HIV proviral DNA overestimates the size of the reservoir, as described in the Latent Reservoir Glossary entry, since it measures defective virions as well as replication-competent latent virus.

Biomarkers to Predict Time to Plasma HIV RNA Rebound

Biomarkers to Predict Time to Plasma HIV RNA Rebound is the title of AIDS Clinical Trials Group protocol A5345, which is a Phase I clinical trial with 56 participants intended to find what its title indicates. It will use an analytical treatment interruption (called an intensively monitored antiretroviral pause in the protocol description) with blood collected at specified times to attempt to determine biomarkers as indicated in the title and for how long it will take for HIV to be controlled again after therapy is restarted.

Bone Marrow-Liver-Thymus (BLT) Mouse

A bone marrow-liver-thymus (BLT) mouse, developed in the 1990s by Joseph M. McCune, MD (formerly one of the principal investigators of the Delaney AIDS Research Enterprise (DARE) to Find a Cure's first iteration) is a severely immune-depleted mouse that has been "humanized" by having human bone marrow, liver, and thymus-gland tissues grafted into it. It develops robust human bone marrow and a thymus gland roughly 12 to 16 weeks after the grafting process. BLT mice serve as a very good model for HIV research, including cure research, in animals that are much less expensive and much more manageable than nonhuman primate (NHP) models, such as rhesus and pigtail

macaques. However, they are quite susceptible to lymphoma (see the Cancer Glossary entry) of the thymus gland and tend not to live longer than about 8½ months after grafting, so they are not suitable for long-term research studies. One researcher has suggested they be called NPHs for "non-primate humans."

A NOD/SCID/γ (NSG) mouse is one that has very severe immunodeficiency, lacking all the varieties of white blood cells involved in the immune system, such as natural killer (NK) cells, macrophages, and T cells, making them good platforms for the creation of bone marrow-liver-thymus (BLT) mice. "γ" is the lower-case Greek letter gamma.

Boston Patients

The Boston patients were three men with lymphoma (see the Cancer Glossary entry) and HIV infection who underwent CCR5Δ32/Δ32 hematopoietic stem cell transplants after milder myeloablative conditioning than the Berlin Patient (Timothy Ray Brown). All three had been on long-term antiretroviral therapy (ART). One of the three died from recurrence of his lymphoma several months after the transplant. Both of the others were put back on ART, and had weekly leukapheresis to obtain samples of CD4+ T cells to apply very sensitive tests for the presence of HIV RNA and proviral DNA that were negative in both cases. In 2.6 years in one case and 4.3 years in the other, they were taken off therapy. Both had HIV viral rebound. The researchers concluded that "allogeneic hematopoietic stem cell transplantation can result in loss of detectable HIV-1 from blood and gut tissue and antiretroviral-free HIV-1 remission for variable duration," but "viral rebound occurred despite a reduction in reservoir size ... of at least a thousand-fold."

Broadly Neutralizing Antibodies (bNAbs) for Reservoir Eradication

A neutralizing antibody (NAb) is an antibody that fully defends its target cell from an antigen. A broadly neutralizing antibody (bNAb) is a neutralizing antibody that has this effect against a wide range of antigens. In recent years about two dozen broadly neutralizing antibodies have been isolated from persons living with HIV. Some of them are being studied and, in a few cases, used in clinical trials, to defend humans against HIV infection, to treat HIV infection, and to kill HIV-infected CD4+ T cells in latent reservoirs.



Figure 1. Structure of chemokines with cysteine ("C") crosslinks.

CC and CXC Chemokine Structure and Naming

CC and CXC are two chemokine varieties that are characterized by having cysteine amino acids (abbreviated "C") in them. (The "X" abbreviates some amino acid other than cysteine, and the red lines represent chains of other amino acids.) Cysteine is one of two amino acids that contain sulfur and is special in that sulfur atoms in pairs of cysteines can form cross links that form loops in the structure of a CC or CXC chemokine, as shown in Figure 1 (adapted from a figure provided by Prof. Laszlo Kohidai, MD, PhD, Semmelweis University, Budapest, Hungary). Pairs of chemokines are named, for example, CCL2 and CCR2, to denote a ligand and its receptor (a ligand is a chemical that binds to a receptor to cause a biological action).

Cancer

Several types of cancers are either associated with HIV infection (usually in its last stages) or have been serious morbidities that have encouraged researchers to attempt cure or remission of HIV infection. The latter include the following discussed here:

- Leukemia is a cancer of the bone marrow and other blood-producing organs, such as the spleen, that results in the overproduction of abnormal white blood cells (the "leuk" part of the name is from Greek and translates as "white"). The overproduction reduces creation of normal blood cells, including red cells.
- Lymphoma is a cancer of immune-system blood cells, including natural killer (NK) cells, B cells, and T cells. There are numerous types of lymphomas, and the lack of detailed descriptions makes it impossible to know which ones are present in the several cure attempts (and one success, namely, the Berlin Patient (Timothy Ray Brown)) discussed here.

- Melanoma is a cancer that results in the production of abnormal melanocytes (pigment-containing cells) that occur mostly in the skin, though they may occur in the digestive system. The first two syllables of the name come from Greek and translate as "black."

CCR5

CCR5, which abbreviates CC chemokine receptor type 5, is a co-receptor on the surface of CD4+ T cells that, during early HIV infection, is essential to entry of HIV into these cells. HIV attaches to both CD4 and CCR5 to achieve entry. (Some variants of HIV use a co-receptor called CXCR4 rather than CCR5; those variants almost always occur only late in the course of untreated HIV infection; HIV transmitted from one person to another almost always uses the CCR5 co-receptor. However, some rare strains of HIV use both the CCR5 and the CXCR4 co-receptors.) Figure 2 (adapted from <https://en.wikipedia.org/wiki/CCR5>) shows the sequence HIV binding to CD4, then to CCR5, and finally having released its genetic material into a CD4+ T cell. CCR5-tropic HIV is also called M-tropic because it can infect macrophages and monocytes. See the CC and CXC Chemokine Structure and Naming entry for a description and illustration of the CC in the name.

CD3

CD3 is a receptor found on the surface of all T cells, including natural-killer (NK) cells, CD4+ T cells, and CD8+ T cells, among others. CD3 is one of hundreds of receptors known as clusters of differentiation that are found on the surfaces of various cell types and facilitate attachment of virions, chemicals, and other cells. CD4 and CD8 are two others.

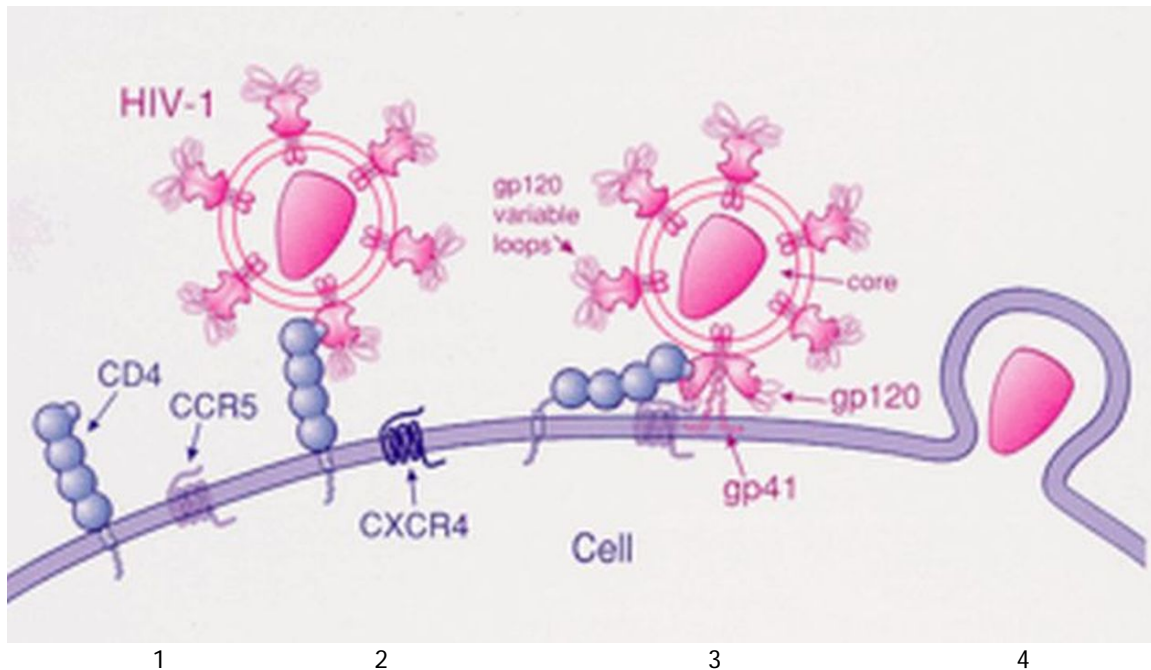


Figure 2. This sequence shows HIV binding to CD4, then to CCR5, and finally having released its genetic material into a CD4+ T cell in four steps: (1) the CD4 receptor and CCR5 co-receptor; (2) HIV glycoprotein gp120 binds to CD4; (3) gp120 binds to CCR5 and releases gp41, which pierces the cell surface opening a pore in the cell's surface; (4) the capsid (see HIV Structure & Function) enters the CD4+ T cell through the pore in the cell wall created in (3).

CD32a as a Biomarker for CD4+ T Cells in the Latent Reservoir

In late 2017, a research group proposed the cell-surface marker CD32a as an indicator of the cell's being in the latent reservoir. This has since been debunked by several researchers: in particular, CD32a occurs on several other types of cells.

CD34

CD34 is a receptor that is found on the surface of all and only hematopoietic stem cells.

CD4

CD4 is a receptor that is necessary, along with a co-receptor such as CCR5 or CXCR4, to the attachment of HIV virions to CD4+ T cells. CD4 is one of hundreds of receptors known as clusters of differentiation that are found on the surfaces of various cell types and facilitate attachment of virions, chemicals, and other cells. CD3 and CD8 are two others. Note that, in addition to HIV-specific CD4+ T cells, CD4 is also found on other types of T cells, macrophages, monocytes, and dendritic cells.

CD4+ T Cells

CD4+ T cells are primary white blood cells of the adaptive immune system that has the receptor CD4 on its surface; they are also known as helper T cells.

These cells act, in part, as the “directors” of the immune system that signal to other immune-system cells how and when to fight infections. CD4+ T cells are preferentially infected by HIV, which reverse transcribes its own genes and integrates them into the cells' DNA. HIV-infected CD4+ T cells, when activated, produce copies of HIV instead of reproducing or conducting other immune functions.

CD4+ T cells can develop that specifically target parts of an infectious agent and those T cells are activated in response to infection by that pathogen. After the infection is cleared or controlled, they can then become resting memory CD4+ T cells that lie in wait for future occurrences of the pathogen to which they then respond. These resting memory CD4+ T cells are thought to constitute most of the latent reservoir of HIV. CD4+ T cells all have the CD4 receptor on their surfaces.

CD8

CD8 is a receptor that is necessary to the attachment of virions, chemicals, and other cells to CD8+ T cells. CD8 is one of hundreds of receptors known as clusters of differentiation that are found on the surfaces of various cell types and facilitate attachment of virions, chemicals, and other cells. CD3 and CD4 are two others. Note that, in addition to responding to HIV-specific

CD4+ T cells, CD8+ T cells also respond to other CD4+ T cells and CD8 is found on natural killer (NK) cells and dendritic cells.

CD8+ T Cells

A CD8+ T cell is a primary white blood cell of the adaptive immune system that has the receptor CD4 on its surface and that is responsible for recognizing infected CD4+ T cells and macrophages, among other duties, the most important of which is killing infected or disabled cells as directed by CD4+ T cells. CD8+ T cells can be created that are specific to HIV. CD8+ T cells all have the CD8 receptor on their surfaces. These cells are also known as cytotoxic T lymphocytes (CTLs). Recent research strongly suggests that harnessing the killing power of CD8+ T cells may be essential to both functional and sterilizing HIV cures (see the "HIV Cure (Functional)" and "HIV Cure (Sterilizing)" Glossary entries).

Cell-Associated RNA (caRNA)

Cell-associated RNA (caRNA) is HIV RNA found in peripheral blood CD4+ T cells, which may be complete HIV genomes or any of nearly 40 other types of HIV-derived RNAs that are found in infected CD4+ T cells. Early in HIV infection, they are typically RNA sequences that transcribe, resulting in the production of the HIV proteins Tat, Rev, and Nef; later in untreated infection they are more likely to be sequences that result in producing the HIV proteins Gag, Pol, Env, Vif, Vpr, and Vpu. For descriptions of both types of proteins, see the HIV Structure & Function Glossary entry.

Cell-to-Cell HIV Infection

Cell-to-cell HIV infection refers to HIV infection of cells by coming in contact with already infected cells, rather than by free-floating HIV. It is believed that this type of infection is a significant factor in the overall rate of propagation of HIV, perhaps accounting for more than 50% of newly infected cells.

Central Memory CD4+ T Cell (T_{CM})

Once a CD4+ T cell responds to a pathogen, it can go into a resting state, which allows it to lie in wait for further instances of infection by that pathogen, to then replicate, producing many copies of itself, and to mount a quick immune response. Such memory cells can live for many years. In HIV infection, central memory CD4+ T cells (T_{CM}) may be infected with the virus, but are invisible to the immune system, which allows HIV to reemerge in individuals whose immune systems can't control the virus over long periods of time or who have been on successful antiretroviral therapy and then stop that therapy.

Central Nervous System (CNS)

The central nervous system (CNS) consists of the brain and spinal cord. It is important for curing HIV for at least four reasons:

- (1) it is a latent reservoir for HIV that is affected by chronic inflammation established very early in HIV infection;
- (2) it can only be reached by a small minority of HIV antiretroviral medications;
- (3) HIV gp120 glycoprotein impacts the function of neurons; and
- (4) since the brain is so very essential, there is concern among cure researchers that approaches other than shock and kill, such as latency silencing of reactivation entirely, will be necessary to achieve a cure in the CNS because of the seriously toxic effect reactivation is likely to have on CNS functioning.

At least two types of cells in the CNS are latent reservoirs for HIV as follows:

- Microglia are macrophages that maintain homeostasis (stability of internal conditions, such as pH balance) and are both the most important immune-system component and the largest latent reservoir of HIV-infected cells in the CNS; and
- Astrocytes ("star-shaped cells") are a smaller population of HIV-infected cells in the CNS than microglia that perform numerous functions, such as physically supporting the cells that constitute the blood-brain barrier (a filter composed of capillaries that carry blood to the CNS that blocks certain substances, such as nerve poisons, while allowing the passage of water, some gasses, glucose, and amino acids), providing nutrients to nerve cells, repairing the CNS after trauma, and maintaining electrolyte balance in the fluid surrounding neurons.

In addition to the cellular latent reservoirs of HIV in the CNS, several free-floating HIV proteins, including Tat, gp120, and Vpr, have been shown to enter neurons and have pathogenic functions. For descriptions of these proteins, see the HIV Structure & Function Glossary entry.

A recent development for quantifying a protein named neurofilament light-chain protein (NFL) that may be a significant biomarker for the effect of HIV on nerve cells is the Single Molecule Array (Simoa) immunoassay.

A substudy of a latency reversal clinical trial using the histone deacetylase inhibitor (HDACi) panobinostat (see the Latency Reversal Glossary entry) probed the effect of the drug on the central nervous system. It found no

panobinostat or HIV RNA in cerebrospinal fluid and no change in HIV-related biomarkers. The study report (Rasmussen TA et al. Activation of latent human immunodeficiency virus by the histone deacetylase inhibitor panobinostat: a pilot study to assess effects on the central nervous system Open Forum Infectious Diseases 30 March 2015) is freely available at <https://academic.oup.com/ofid/article-lookup/doi/10.1093/ofid/ofv037>.

Chemokine

A chemokine is a signaling protein secreted by a cell to produce a reaction in a nearby cell; the reaction is frequently chemotaxis, which is movement of the target cell in response to the chemokine. See also the [Cytokine](#) and [CC and CXC Chemokine Structure and Naming](#) Glossary entries.

Chimeric Antigen Receptor (CAR)

A chimeric [antigen receptor](#) (CAR) is an artificial T-cell receptor that usually consists of a [monoclonal antibody](#) that is recognized by the desired target cell combined with part of the typical cellular receptor to facilitate entry into the cell. Chimeric antigen receptors are mostly used to fight cancers, but they can also be designed to be HIV specific.

On August 30, 2017, the U.S. Food and Drug Administration (FDA) (website: <http://www.fda.gov>) approved Novartis's (website: <https://www.novartis.com>) gene-editing drug tisagenlecleucel (brand name: Kymriah) for the treatment of acute lymphoblastic leukemia in children and adults up to age 25, making it the first gene-editing drug approval in the U.S.

Chimerism

Chimerism, in the context of [chimeric antigen receptors](#), refers to a molecule that is made in a laboratory from two unrelated biological substances. Chimerism is also used to refer to entire (usually mythical) organisms made up of parts of two distinct organisms, such as a centaur with horse and human parts; such organisms are called chimeras

Chromatin

Chromatin is the material of which the chromosomes of organisms other than bacteria are composed. It consists of DNA and proteins called [histones](#). Chromatin is a very efficient packaging mechanism that holds DNA in a cell. Once HIV integrates into a cell's DNA, whether the HIV genes are bound in chromatin or not determines whether they are kept packaged in a latent form or are able to make more [virions](#), respectively.

Clade

A clade is, in the context of a virus, a subgroup of viruses that consists of a common ancestor and all its descendants. There are four major subtypes or groups of HIV called M, N, O, and P. "M" stands for major; "O" for outlier; and "N" for non-M, non-O. In 2009, a new subtype was reported in Cameroon that is very similar to the wild type of [simian immunodeficiency virus \(SIV\)](#) found in gorillas; it is now identified as subtype "P". In turn, subtype M is divided into 11 clades identified by the letters "A" through "K", as follows:

- Clade A is common in West Africa;
- Clade B is the dominant form in Europe, the Americas, Japan, Thailand, and Australia;
- Clade C is the dominant form in southern and eastern Africa, India, Nepal, and parts of China;
- Clade D is seen in eastern and central Africa;
- Clade E is found only in a [genetic recombinant](#) called CRF01_AE;
- Clade F is found in central Africa, South America, and Eastern Europe;
- Clade G and the genetic recombinant CRF02_AG are found in Africa and central Europe;
- Clade H is found only in central Africa;
- Clade I was formerly used as the name of what is now termed the genetic recombinant CRF04_cpx, which is understood to be a genetic recombinant of several clades (thus "cpx" for complex);
- Clade J is found primarily in northern, central, and western Africa and the Caribbean; and
- Clade K, including the recombinant CRF03_AB, is found only in the Democratic Republic of Congo and Cameroon.

Some research has shown that clade variation contributes to the magnitude of replication capacity via variations in part of the [gp41 glycoprotein](#) and other aspects of the HIV subtype.

Clinical Trials

Clinical trials are the standard process for testing new medications, medical devices, and medical procedures in humans. They are typically preceded by studies done in nonhuman animals (sometimes called "Phase 0") to weed out those that are not worth the effort and expense of clinical trials. Here we focus on medical procedures, such as the [shock and kill](#) approach to eliminating latent HIV from [latent reservoirs](#). There are three phases of clinical trials, as follows:

- Phase I: A phase I clinical trial involves a small number (usually not more than about 20) of healthy volunteers to test the safety of the medical procedure and any side effects it may have. If the procedure is determined to be safe and to have

only acceptable side effects, it may proceed to phase II.

- Phase II: A phase II clinical trial usually involves several hundred volunteers. Its goal depends on what is being tested. For a medical procedure, it continues to test for safety and side effects and adds on determination of whether it is effective.
- Phase III: A phase III clinical trial involves several thousand volunteers and is intended to confirm the effectiveness of the medical procedure, monitor its side effects, compare it to commonly used procedures if there are any yet, and continue to collect information to determine whether the procedure is safe. Only after a successful Phase III study does a medication go before a panel of the U.S. Food and Drug Administration (FDA) or similar agency elsewhere in the world for approval for distribution.

There is also what is sometimes called "Phase IV": a post-marketing phase, in which the medication or procedure is used in diverse populations and continues to be monitored for side effects.

In some case, clinical trials have phases that are numbered with a Roman numeral followed by the letter "A" or "B" to indicate whether it is an early or late part of the phase, respectively. These letters are usually used in combinations of phase numbers to indicate that the clinical trial straddles two consecutive phases.

Every clinical trial done in the United States is required to have a written trial protocol that describes at the least

- a detailed plan of what is to be done,
- why it is being done,
- justification for it based on prior research,
- known and hypothetical risks and benefits,
- criteria for inclusion and exclusion of potential participants, and
- a schedule of what will be done (for example, physical exams, blood draws, and checking for side effects).

It also must have an informed consent form (ICF) that explains the trial to the volunteers, informs them of the above facts in lay language, tells them they may withdraw from participation at any point without giving a reason for doing so, and requires their signed and witnessed consent to participation before they begin the trial's procedures. Every clinical trial protocol and ICF are reviewed and approved by an independent Institutional Review Board and one or more of several government agencies (which one(s) depend on the nature of the trial) before it can begin recruiting

volunteers. For a glossary of terms commonly used in descriptions of clinical trials, see <https://clinicaltrials.gov/ct2/about-studies/glossary> . Additional resources for understanding clinical trials and the clinical-trial process can be found on the web at <https://clinicaltrials.gov/ct2/resources> .

Clinical trials done outside the United States are required to follow the same or a very similar rigorous plan and process.

Clonal Expansion

Clonal expansion is the production of numerous daughter cells with identical genomes resulting from a parent cell. Clonal expansion of HIV-infected CD4+ T cells in circulating blood is thought by some researchers to be a significant contributor to the latent reservoir and so a barrier to HIV remission.

Co-Receptor

A co-receptor, in the context of HIV medicine (including cure research), is a chemical, such as CCR5 or CXCR4, attached to the surface of a cell, such as a CD4+ T cell, that facilitates attachment and entry along with a receptor, such as CD4, of an HIV virion into the cell.

CXCR4

CXCR4, which abbreviates CXC chemokine receptor type 4, is a co-receptor on the surface of CD4+ T cells that, late in HIV infection's course, is essential to entry of HIV into these cells. Some HIV variants attach to CD4 and CXCR4 to achieve entry. (Some variants of HIV use a co-receptor named CCR5 rather than CXCR4; these variants almost always occur early in the course of untreated HIV infection; HIV transmitted from one person to another almost always uses the CCR5 co-receptor, though rare cases with the CXCR4 co-receptor do occur.) Further, some rare strains of HIV use both the CCR5 and the CXCR4 co-receptors. Also, unlike CCR5, CXCR4 is not a good candidate for gene editing because it occurs on several cell types other than CD4+ T cells and is essential to their function. CXCR4-tropic HIV is also called T-tropic because unlike CCR5-tropic virus it can infect CD4+ T cells but not macrophages. See the CC and CXC Chemokine Structure and Naming Glossary entry for a description and illustration of the CXC in the name.

Cytokine

A cytokine is a signaling protein secreted by a cell to produce a reaction in a nearby cell. See also the Chemokine Glossary entry.

Cytomegalovirus (CMV)

Cytomegalovirus (CMV) is a common virus that infects people of all ages. In the United States, more than half

of adults have been infected with it by age 40. Once one is infected, cytomegalovirus stays in the body for life and can reactivate. Most people infected with CMV show no symptoms because a healthy person's immune system usually keeps it from causing illness. However, CMV infection can cause serious health problems for people with compromised immune systems.

Defective HIV DNA

Defective HIV DNA is the result of retrotranscription of HIV RNA to DNA and its integration into the DNA of a CD4+ T cell. The majority of such cells that go into the resting state are defective (replication incompetent) because their HIV DNA has become defective through mutation of their RNA.

Defective Virion

A defective HIV virion is one containing an RNA genome that makes it incapable of viral replication. This results from the single-stranded nature of HIV's RNA. All living organisms have linked double-stranded DNA making up the well-known double helix that provides an inherent self-checking mechanism to prevent frequent mutations; of course, mutations *do* occur in living organisms, and they are one of the mechanisms that cause cancers. However, the unlinked single strands of HIV's RNA have no such self-checking mechanism and mutations occur in them very, very frequently.

Let's calculate how often a typical nucleic acid base is mutated each day in a person who is not on antiretroviral therapy (ART). Note that, despite the extremely high frequency of mutations, this has no chance at all of eliminating HIV from the body in a human lifetime because resting memory CD4+ T cells are the largest component of the latent reservoir and not undergoing HIV mutation because they are resting!

1. The current best estimate for the overall mutation rate is one per 34 viral replication cycles.
2. Given that about 10 billion new virions are created (that is, that many viral replication cycles occur) each day, roughly 300 million of the new virions will have at least one mutation.
3. With roughly 9,750 nucleic acid bases in each strand or 19,500 across both strands, that's one mutation in each base position, on average, about 16,000 times each day!

Compared to a living organism's mutation rate, this is absolutely staggering! It's especially so with no mechanism to detect defective virions. In addition to the lack of a built-in checking mechanism for defects in viral replication, new research reported in late 2015 shows that there is a family of cellular enzymes called

A3 that contributes very heavily to the creation of defective virions; in particular, the A3 enzymes are believed to be at least partially responsible for about 98% of the mutations that occur.

It doesn't require very many mutations in genes encoding critical proteins, such as reverse transcriptase or integrase (see the HIV Structure & Function Glossary entry), to make a virion incapable of infectivity, that is, make it defective.

Even in persons on suppressive antiretroviral therapy (ART), the accumulation of mutations that render new virions defective is very common.

Furthermore, there is an extreme form of being defective named hypermutation that is defined as the accumulation of an immense number of mutations per genome. Hypermutation invariably leads to defective virions. In particular, it frequently results in mutations in the HIV proviral DNA that stop transcription in its tracks, that is, creation of a new virion is simply not even completed.

Dendritic Cell

A dendritic cell is one variety of antigen-presenting cell whose main function is presenting antigens found on external surfaces in the body to B cells or CD4+ T cells. They are found in the skin and other areas that are on the outside of the body, such as the nose, lungs, mouth, stomach, and intestines, and so in contact with the environment.

Droplet Digital Polymerase Chain Reaction (ddPCR)

Droplet digital polymerase chain reaction (ddPCR) is a type of polymerase chain reaction that is characterized by the creation under digital control of tiny droplets of highly amplified DNA resulting from an initial single molecule that are digitally measured. This technique has greatly automated the PCR technology and markedly decreased its expense.

Dual Antibody Use to Reduce the Latent Reservoir

Three studies published in late 2015 examine the use of so-called dual antibodies to achieve various aspects of reduction of the latent reservoir of HIV-infected CD4+ T cells, as follows:

1. One study discusses the use of dual-affinity re-targeting (DART) molecules to bind to both the HIV Env protein and the CD3 receptor on infected cells and "recruit" CD8+ T cells to kill the bound cells.
2. Another study used DARTs to bind to the same

protein and receptor as in item 1 above to direct CD8+ T cells to kill infected CD4+ T cells.

3. The third study used what it calls bispecific antibodies that bind to the Env epitope recognized by the broadly neutralizing antibody VRC07 and the CD3 receptor to reduce HIV DNA in most of the laboratory isolates of infected cells tested. A broadly neutralizing antibody is one that is effective against a large class of antigens. “VRC” abbreviates the Vaccine Research Center at NIH that was responsible for discovering and characterizing the antibody.

One potential concern about all three of these studies is the possibility that their targeting CD3 might cause general activation of T cells, since it is the receptor that occurs on all of them, which could be disastrous. Apparently the dual nature of the targeting caused only minor, transient effects of this sort.

Düsseldorf Patient

The Düsseldorf patient is a 41-year-old man who was diagnosed with CCR5-tropic HIV infection in 2010 and acute myeloid leukemia (see the Cancer Glossary entry) in 2011. Like the Berlin patient (Timothy Ray Brown), he required two allogeneic CCR5Δ32/ Δ32 hematopoietic stem cell transplants to possibly cure his HIV infection because his leukemia recurred. He has remained on antiretroviral therapy (ART), but shows no signs of viral rebound. He *may* be the second person to have received a sterilizing cure of his HIV infection.

Early Initiation of Antiretroviral Therapy (ART) and Remission

At least one recent study has shown that initiation of antiretroviral therapy (ART) during primary infection (Fiebig stages I and II) and continuing it for two years will, in some cases, lead to remission. In particular, it can lead to reduction of HIV DNA in central memory CD4+ T cells (T_{CM}) to levels typically found in naive T cells (T_N), transitional memory CD4+ T cells (T_{TM}) being the major reservoir of HIV, and significant restriction of HIV mutation. Further, continuing ART for a total of six years can drive reservoir size and distribution down to levels close to those seen in post-therapy controllers, such as the VISCONTI cohort.

Effector Memory CD4+ T Cell (T_{EM})

An effector memory CD4+ T cell (T_{EM}) is a CD4+ T cell that is replicating in response to a pathogen and quick mounting an immune response to the pathogen.

Elite Controllers

Elite controllers are rare individuals living with HIV who maintain undetectable viral loads in the absence of—in most cases—any antiretroviral therapy (ART). In about

2/3 of known cases, they possess immune-system mutations, such as one or both of HLA-B*5701 and HLA-B*2701, which appear to enhance recognition of HIV. In some elite controllers, undetectable viral loads are found in the absence of protective genes, indicating that specific HLA-B genes are neither necessary nor sufficient for elite control of HIV. However there is evidence that some elite controllers suffer from inflammation like other people living with HIV, so they are likely to suffer from its long-term effects. A study published in 2014 identified ten *very* divergent definitions of elite controller in previous studies, as follows—all required that an individual not have AIDS and never have used antiretroviral therapy (ART):

1. HIV-positive at least 6 months with at least 2 consecutive viral loads < 75 c/ml,
2. HIV-positive at least 1 year with at least 1 viral load < 50 c/ml,
3. HIV-positive at least 1 year with at least 1 viral load < 75 c/ml,
4. HIV-positive at least 1 year with at least 3 viral loads < 2,000 c/ml,
5. HIV-positive at least 1 year with at least 3 viral loads < 75 c/ml spanning at least one year
6. HIV-positive at least 1 year with at least 3 viral loads < 75 c/ml spanning at least one year and no viral blips $\geq 1,000$ c/ml; a blip is defined as an isolated significant increase in viral load,
7. HIV-positive at least 2 years and at least 2 viral loads < 75 c/ml,
8. HIV-positive at least 5 years and at least 5 consecutive viral loads < 500 c/ml,
9. HIV-positive at least 10 years and all measured viral loads < 50 c/ml, or
10. HIV-positive at least 10 years and at least 90% of viral loads < 400 c/ml with at least 2 viral loads measured.

The 2014 study mentioned above examined how these definitions applied to a cohort of over 25,000 HIV-positive people known as CASCADE (**C**oncerted **A**ction on **S**ero**C**onversion to **A**IDS and **D**eath in **E**urope) that, despite its name, includes participants in Australia, Canada, and Africa in addition to Europe. All the definitions determined that elite controllers were rare, in almost no case accounting for more than about 1% of the participants.

Engraftment

Engraftment is the successful incorporation of grafted tissue into the host's body.

Enzyme

An enzyme is an organic molecule, in most cases a protein or peptide but in a few cases an RNA (such as

a ribozyme described in the Gene Editing Glossary entry), that acts as a catalyst: It facilitates a biochemical process without itself being modified, so it can be used again. Almost all proteins that are enzymes have names ending in “ase”.

Epitope

An epitope (also known as an antigenic determinant) is a part of an antigen that is recognized by the immune system, specifically by an antibody, a B cell, or a T cell.

Escape Mutation

An escape mutation, in the context of HIV, is a genetic change (a mutation, also called antigenic drift) in a daughter HIV virion that makes the resulting virion impervious to clearance of latent cells infected with daughters of the resulting HIV virion that has the escape mutation.

Essen/Berlin Patient

The Essen/Berlin patient is a man who uses the pseudonym Christian Hahn (see the Resource Guide

entry for the book **CURED: How the Berlin Patients Defeated HIV and Forever Changed Medical Science**) with Non-Hodgkin's lymphoma (see the Cancer Glossary entry), CCR5-tropic HIV infection, and the HLA-B*5701 protective mutation (see the HLA-B*5701 and HLA-B*2701 Glossary entry). Because of the poor prognosis for his lymphoma, he underwent a CCR5Δ32/Δ32 bone-marrow transplant. However, following the transplant, he was found to have either CXCR4-tropic or dual CCR5- plus CXCR4-tropic HIV infection and subsequently died from a recurrence of his lymphoma. It is not well understood why the CXCR4- or dual-tropic HIV infection was not detected; it may have been simply because there were very, very few such virions. Alternately, the detection failure may have been because the patient's particular lymphoma is an AIDS-defining condition, and progress to AIDS and some biological changes that occur in parts of CD4+ T cells' gp120 spikes are the clinical factors most likely to predispose a transition from CCR5 tropism to CXCR4 tropism.

Effects of Estrogen on Immune-System Cells	
Cell Type	Effects
T cells	<ul style="list-style-type: none"> Increases expression of <u>CCR5</u> and CCR1; Lower doses enhance T_H1 cell response; Higher doses enhance T_H2 cell response; and Expands <u>Treg</u> cells
<u>B cells</u>	<ul style="list-style-type: none"> Increases survival; Decreases <u>apoptosis</u>; and Increases certain immunoglobulins
<u>NK cells</u>	<ul style="list-style-type: none"> Lower doses increase cytotoxic activity; and Higher doses decrease cytotoxic activity
<u>Dendritic cells</u>	<ul style="list-style-type: none"> Increases production of several <u>cytokines</u>; and Promotes cell differentiation
Neutrophils	Enhances anti-inflammatory activity
<u>Macrophages & Monocytes</u>	<ul style="list-style-type: none"> Lower doses promote cell differentiation and stimulate cytokine production; and Higher doses reduce expression of CD16 and decrease cytokine production

Table 1. Estrogen's impact on immune system cells.
For explanation of terms see the notes immediately below.

Notes: (1) T_H1 and T_H2 cells are varieties of CD4+ T cells; T_H1 cells act against bacteria inside cells; T_H2 cells act against parasites outside cells. (2) Monocytes are the largest white blood cells; they have multiple roles in immune function including replenishing macrophages, and responding to inflammation. (3) Dendritic cells are antigen-presenting cells of the immune system. In most cases, the antigens are acquired from outside the body. (4) Neutrophils are a component of the innate immune system; they are the first responders to infection by bacteria. Recent data has suggested they may be a significant agent to be used in the kill phase of shock-and-kill strategies. (5) CCR1 (also called CD191) is a co-receptor that affects differentiation of hematopoietic stem cells; it is also critical for the recruitment of immune-system cells to sites of inflammation. (6) CD16 is found on the surface of natural killer cells, neutrophils, monocytes, and macrophages.

Estradiol, Estrogen, Progesterone, and Estrogen Receptors

Estradiol, estrogen, and progesterone are female sex hormones. The influences of these hormones that are relevant to HIV, and particularly cure research, are as follows:

- Estradiol at peak menstrual levels is a powerful inhibitor of HIV viral replication which may explain in part the observation that women have smaller latent HIV reservoirs than men (though a more recent study suggests that this is not true), but not smaller activatable latent reservoirs than men;
- Estrogen (one of the two primary female sex hormones along with progesterone) can both increase and decrease inflammation: at low concentrations it promotes inflammation, thus increasing the chance of HIV infection, while at high concentrations it inhibits it; it has other impacts on the specific cells of the immune system as shown in Table 1 (based on Figure 1 in the article Gianella S Tsibiris A Barr L Godfrey C "Barriers to a cure for HIV in women" Journal of the International AIDS Society 18 February 2016; available at <http://www.jiassociety.org/index.php/jias/article/view/20706> ; Creative Commons Attribution 3.0 License; courtesy of first author);
- Progesterone is a component of the injectable birth-control drug medroxyprogesterone (brand name Depo-Provera) that, when administered as a drug, enhances HIV infection;
- Agonists of the estrogen receptor ESR-1 on resting memory CD4+ T cells, such as the breast cancer

drug Tamoxifen, weakly enhance latency reversal of HIV-infected cells. In contrast, ESR-1 inhibitors, such as diethylstilbestrol (brand name Stilbetin or Stilbestrol), reduce reactivation of resting memory CD4+ T cells; and

- Selective estrogen receptor modulators (SERMs) combined with histone deacetylase inhibitors (HDACi) are promising candidates for potent latency reversal (see the Latency Reversal by Combinations of Drugs Glossary entry).

Ethiopian Patient

The Ethiopian patient is a woman with clade C HIV infection who began antiretroviral therapy (ART) during acute infection, stopped treatment after six years, and maintained peripheral blood HIV aviremia and had a normal CD4+/CD8+ T-cell ratio, so far, for ten years, despite having a low-level persistent viral latent reservoir.

Fiebig Stages

Fiebig stages are used to classify the progress of HIV infection, particularly in its early stages, which is relevant to cure because numerous studies strongly suggest that eradication is easier the earlier it is undertaken. The stages are shown in Table 2 (derived from Figure 1 in "The immune response during acute HIV-1 infection: clues for vaccine development" McMichael AJ Borrow P Tomaras GD Goonetilleke N Haynes BF Nature Reviews Immunology **10** 11-23 January 2010 and Figure 1 and Table 1 in "The Detection of Acute HIV Infection" MS Cohen CL Gray MP Busch FM Hecht Journal of Infectious Diseases **202** 2010 Suppl 2: S271 & S272).

Fiebig Stage	Characterization (beginning of test)	Duration in days (Range)
Eclipse	undetectable	10 (7 – 21)
I	Viral <u>RNA</u> +	7 (5 – 10)
II	p24 <u>antigen</u> +	5 (4 – 8)
III	<u>Antibody</u> ELISA+	3 (2 – 5)
IV	Western blot+ or -	6 (4 – 8)
V	Western blot+ & integrase-	70 (40 – 122)
VI	Western blot & integrase+	Open ended

Table 2. Fiebig stages, characterizations, and durations.

Note: Western blot is typically used as a confirmatory test for HIV infection; it uses electrophoresis to separate a purified antigen mixture into bands that correspond to the gp160, gp120, p66, p55, p51, gp41, p31, p24, p17, and p15 proteins (see the HIV Genome Glossary entry for descriptions of the proteins). See the Seroconversion Glossary entry for a description of the ELISA test. Integrase is the HIV protein responsible for integrating HIV's genome converted to DNA into host DNA.

Follicular Dendritic Cell (FDC)

A follicular dendritic cell (FDC) is an immune-system

cell found in lymphoid tissue and is a type of reservoir of latent HIV infection. This type of cell has several

functions, including antigen presentation to CD4+ T cells; assisting in apoptosis; organizing the structure of lymphoid tissues, such as lymph nodes and gut-associated lymphoid tissue (GALT); and attracting B cells.

Gene Editing

Gene editing is a cure strategy for modifying the genetic information in cells, such as removing HIV proviral DNA from the cells' DNA or altering the CD4 receptor, CCR5 co-receptor, or anti-HIV restriction factors to make CD4+ T cells resistant to HIV infection. There are numerous experimental gene editing techniques being investigated (many targeting the gene that encodes CCR5—the ones listed are designed to do so unless specified as having other or more general targets). Though we list 11 approaches, CRISPR is by far the most important, and zinc-finger nucleases and TALENs are the only ones that have so far been used in significant clinical trials of gene editing intended as a step toward a functional cure of HIV infection. A recent mathematical modeling study of gene editing strategies for HIV cure has shown that achieving positive results is possible only under a narrow range of conditions and that further improvement of engraftment is likely to be necessary to improve outcomes.

1. **CRISPR:** What's known as CRISPR is actually a combination of two drugs: CRISPR (clustered regularly interspaced short palindromic repeats) and either, most frequently, a Cas protein (CRISPR associated protein—most often Cas9) or another protein. It is currently the most efficient, effective, and easy-to-use method for gene editing. *Science*, the most prominent U.S. scientific journal, declared CRISPR to be the "Breakthrough of the Year" for 2015 because of its very wide applicability and ease of use, and *Nature*, the most prominent British scientific journal, chose it as No. 1 among its ten most important breakthroughs of 2015. CRISPR is actually a primitive immune-like system found in bacteria. Further, in early 2016, it was reported by two research teams that CRISPR technology, one using Cas9 and another using a different protein, had been used to remove entire HIV proviral DNA from latently infected CD4+ T cells in vitro and this has more recently been reported in vivo. See also the CRISPR Perspectives entry.
2. **Homing Endonuclease:** A homing endonuclease is an enzyme (either a protein or a small RNA) that homes in on a specific segment of DNA or RNA and either cuts out or replaces that part of it. If a DNA segment is cut, it is then reconnected by the enzyme DNA ligase, a DNA repair mechanism

found in all human cells. It is a goal of cure research to design homing endonucleases such that the repair will make the cells unable to make new HIV virions. Meganucleases, megaTALs, transcription-activator-like effector nucleases (TALENs) and zinc finger nucleases (ZFNs) discussed below are four types of homing endonucleases.

3. **Intrabody:** An intrabody is a variety of antibody that can bind to a protein and make it dysfunctional. CCR5 intrabodies have been found to be more effective than the intrakines described immediately below.
4. **Intrakine:** An intrakine is a chemokine found inside a cell that can target newly formed CCR5 blocking its transport to the cell surface. Unfortunately this approach resulted in incomplete inhibition of CCR5, that is, only some CCR5 co-receptors were blocked from reaching the cell surface.
5. **Meganuclease:** A meganuclease is a relatively long engineered peptide that has been used to edit DNA in genes to remove HIV proviral DNA.
6. **Mega-Transcription-Activator-Like (MegaTAL):** A mega-transcription-activator-like (megaTAL) is a long peptide useful for removing HIV proviral DNA from CD4+ T cells. It consists of a meganuclease bound to part of a transcription-activator-like endonuclease (TALEN). A megaTAL has greater specificity and is more effective than either of its component parts. MegaTALs also have more general application than just CCR5 gene editing.
7. **Ribozyme:** A ribozyme is a small strand of RNA that acts as if it were an enzyme. Ribozymes have been used in several clinical trials to target HIV genes with some success. In combination with other approaches, one type of ribozyme targeted to the CCR5 co-receptor has been effective to curtail the effectiveness of CCR5 for as long as 24 months.
8. **Short Hairpin RNA (shRNA):** A short hairpin RNA (shRNA) is an artificially produced RNA molecule that has a quite small hairpin-shaped segment and that can be used to silence expression of a gene via a mechanism called RNA interference; it requires delivery by a viral vector.
9. **Short Interfering RNA (siRNA):** A short interfering RNA (siRNA) is a very short synthetic strand of RNA that can be used to edit out the gene for CCR5; however they are somewhat problematic because they tend to have off-target effects.
10. **Transcription-Activator-Like Effector Nuclease (TALEN):** A transcription-activator-like effector nuclease (TALEN) is a peptide useful for

gene editing to remove HIV proviral DNA from CD4+ T cells.

11. Zinc-Finger Nuclease (ZFN): A zinc-finger nuclease (ZFN) is a variety of homing endonuclease that cuts strands of cellular DNA into segments that must be repaired by the immune system. When a zinc-finger nuclease that cuts the gene for the cellular co-receptor CCR5 is introduced into cells, those cells' ability to produce the co-receptor is inhibited, at least to a degree. This can potentially make those cells resistant to HIV infection by virus that requires CCR5. Sangamo Biosciences has a Phase 2 clinical trial named SB-728-T using a zinc-finger nuclease to modify CCR5 genes to make the CD4+ T cells they appear on the surfaces of incapable of being infected by HIV (see <https://clinicaltrials.gov/ct2/show/NCT01543152> for a description of the trial).

Genetic Recombinant

A genetic recombinant is a virus or other organism whose genetic material (DNA or RNA) is a mosaic of two (or more) others' genetic material.

Genome

A genome is the collection of all the genes in a living organism or virion.

Glycoprotein

A glycoprotein is a complex of sugars (the "glyco" part of the word) and a protein. In particular, HIV's gp120 and gp41 are glycoproteins, though there are many others found in viruses and cells.

gp41

gp41 is a component of the HIV glycoprotein gp160 that pierces the outer membrane of the HIV virion; note that it occurs as a trimer, that is, three copies of it are bound together; see also the HIV Structure & Function Glossary entry.

gp120

gp120 is a component of the HIV glycoprotein gp160 that sticks out of the HIV virion; note that it occurs as a trimer, that is, three copies of it are bound together; see also the HIV Structure & Function Glossary entry.

Graft-versus-Host Disease (GVHD)

Graft-versus-host disease (GVHD), also called rejection, is a natural reaction by the body's immune system to a graft or transplant that typically results in elimination of the graft or transplant unless immunosuppressing drugs, such as cyclosporine, are administered. The reaction is predominantly carried out by CD8+ T cells. Nevertheless, in the case of the Berlin Patient (Timothy

Ray Brown), graft-versus-host disease may have played a significant positive role in destroying his original HIV-infected CD4+ T cells.

Gut-Associated Lymphoid Tissue (GALT)

Gut-associated lymphoid tissue (GALT) consists of immune cells lining the gut that are a critical component of the immune response to pathogens. It is usually severely depleted very early in the course of HIV infection. It is believed that the depletion is mostly irreversible.

Hematopoietic Stem Cell

A hematopoietic stem cell is a progenitor cell found in bone marrow. It can differentiate into all the types of blood cells (red cells, white cells, platelets, etc.) Hematopoietic stem cells are CD34+ (that is, they have the receptor CD34 on their surfaces).

Hematopoietic Stem Cell Transplant (HSCT)

A hematopoietic stem cell transplant (HSCT) is the type of allogeneic transplant that was used in the Berlin Patient (Timothy Ray Brown) to effect a sterilizing cure of his HIV infection.

Hepatitis C Cure

Obviously this is *not* about HIV cure research, but it is closely related to both HIV treatment and cure research. The virus that causes hepatitis C (HCV) is an enveloped, single-strand, positive-sense RNA virus. It lacks many of the qualities that make HIV unique (see the HIV's Uniqueness Glossary entry)—it doesn't have sugar-coated spikes on the outside, it doesn't attack CD4+ T cells, it's not a lentivirus, it doesn't exhaust the immune system, etc., but it does cause a vast burden of worldwide disease and it's quite common among people who are HIV+. However, the recent very successful short-treatment approaches to curing HCV infection without the often disabling side effects of a drug named interferon have become possible only because of the major progress in HIV treatment and the initial research in curing HIV. In particular, there are now regimens using protease inhibitors, such as sofosbuvir, simeprevir, and ledipasvir (brand names Sovaldi, Olysio, and Harvoni, respectively), that act directly against some of HCV's proteins and effect very high cure rates, almost always without requiring the use of interferon, which is very desirable to avoid because of its serious side effects.

Histone

A histone is a protein that combines with DNA to form chromatin, the very compact structure in which DNA is stored in cells and stops it temporarily from being replicated.

Histone Deacetylase (HDAC)

A histone deacetylase (HDAC) is an enzyme that causes chromatin to bind its DNA, stop being replicated, and become inactive in resting memory CD4+ T cells. Because of this, HIV-infected cells can have bound DNA that keeps the virus in latent form, does not lead to production of any virus proteins or RNA, and therefore leaves the cell unexposed to both CD8+ T cells and antiretroviral therapy (ART).

HIV Cure (Functional)

This type of cure allows some infected cells to persist in the body of a person living with HIV but means that antiretroviral therapy is no longer necessary, at least for a long time. With this approach, the immune system should be able to handle the virus that is still in the body. Because such people would typically have very low levels of HIV, they would be less likely to transmit HIV to others than most infected people but might be vulnerable to reinfection with other strains of HIV than the one with which they are already infected. This type of cure is also called HIV remission.

HIV Cure (Sterilizing)

This type of cure completely eliminates HIV from an infected person's body, which would likely require activation and killing of all infected CD4+ T cells (and probably infected macrophages and other cells contained in latent reservoirs). Depending on the strategy used, such people might or might not be resistant to reinfection with HIV. This approach results in there being no HIV capable of viral replication left in the body, so the person would not be able to transmit HIV to others. However, proving that all HIV has been eliminated from a person's body is impossible with current approaches, including in the case of the Berlin Patient (Timothy Ray Brown), though he has been HIV-

for ten years.

HIV DNA

HIV DNA is the result of retrotranscription of a strand of HIV RNA constituting half of the HIV genome to DNA. That is then integrated into the host cell's DNA. The HIV enzyme that does the retrotranscription is reverse transcriptase, which is the target of the HIV drugs called nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), such as AZT (Retrovir) and EFV (Efavirenz), respectively; the HIV enzyme that does the integration is integrase, which is the target of the HIV drugs named integrase strand transfer inhibitors (INSTIs), such as RAL (Raltegravir) and DTG (Dolutegravir), respectively.

HIV Genome

The nucleocapsids of HIV (see the HIV Structure & Function Glossary entry) contain the two separate single strands of RNA that comprise its genetic material or genome. The structure of each strand of RNA is shown in Figure 3 (produced by Janie Vinson Productions, San Francisco, CA, 2016). It comprises nine genes and the two long terminal repeats (LTR), the right-hand one of which in the figure is crucial for beginning the production of proteins from the resulting proviral DNA. The overlapping of segments in the diagram corresponds to what are known as open reading frames. (Note that the open reading frames in the HIV genome are *never* directly transcribed and translated to proteins: The HIV genome must first be integrated into a host cell's DNA as proviral DNA that is, in turn, transcribed and translated to proteins.) In all, each strand has roughly 9,750 bases (nucleic acids), though this varies somewhat with the faulty replication of HIV RNA (see the Defective Virion Glossary entry).

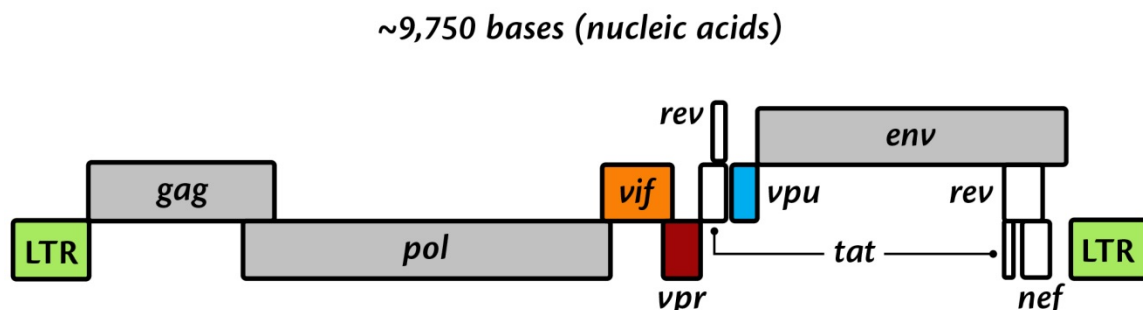


Figure 3. The genes comprising the HIV genome.

The components of the HIV RNA genome and their functions are described below; the *gag*, *pol*, and *env* genes shown in gray in Figure 3 are found in all retroviruses.

- *env* encodes the protein Env, which creates the glycoproteins gp120 and gp41 that make up the spikes shown in the HIV Structure & Function Glossary entry and that are critical for entry of virions into cells;
- *gag* (group antigen) encodes the Gag precursor protein (also called p55), whose components “orchestrate” the assembly of almost all of the resulting virion. Gag is cleaved to produce six regulatory proteins and one probably nonfunctional spacer, as follows:

- matrix polypeptide (MA), also called p17, which becomes part of the virion’s enclosing membrane,
- capsid protein (CA), also called p24, which forms the virion’s capsid,
- spacer peptide 1 (SP1), also called p2, whose function is to cause the capsid protein CA to become part of the virion’s capsid,
- nucleocapsid protein (NC), which forms the virion’s nucleocapsids, which are the membranes containing the RNA genome,
- spacer peptide 2 (SP2), also called p1, which serves as a separator between NC and p6 (described next) and *may* have an as-yet unknown additional function, and
- p6, a peptide that recruits cellular proteins essential to the budding of mature virions from the cell in which they are assembled;

- *pol* (polymerase) is reverse transcribed into proviral DNA named Pol that, in turn, encodes a polypeptide that is cleaved into four enzymes, the first three of which are targets for HIV antiretroviral therapy (ART), namely,
 - protease (PR),
 - reverse transcriptase (RT, also called p51),
 - integrase (IN, also called p31), and
 - RNase (also called p15);
- *tat* encodes the transactivator of transcription protein Tat that strongly increases the transcription of integrated proviral HIV DNA to messenger RNA (mRNA) that, in turn, is used by the cell to produce proteins; note that *tat* is composed of two separated pieces that must be spliced together to become functional;
- *rev* encodes a protein named Rev that is essential to regulating HIV protein production by causing the transition from the first to the second phase of HIV proviral DNA transcription and translation; note that *rev* is composed of two separated pieces that must be spliced together to become functional;
- *vpu* encodes the protein Vpu (viral protein unique)

that induces destruction of the CD4 receptor and may facilitate creation of Env (described above);

- *vif*, *vpr*, and *nef* encode the proteins Vif, Vpr, and Nef, respectively, which are discussed in the HIV Structure & Function Glossary entry; and
- finally, LTR is a long terminal repeat; it is a sequence of ~640 bases that are identical across the two LTRs; HIV’s right-end long terminal repeat is reverse transcribed to produce five double-stranded DNA sequences, as follows:
 - *TAR*, the transactivation response element, interacts with Tat and other HIV proteins in an unknown manner,
 - *Poly A*, which is involved in creating mature virions,
 - *PBS*, the primer binding site, is an 18-base sequence that encodes a peptide involved in initiation of retrotranscription of HIV RNA,
 - Ψ , the Psi packaging element, is involved in packing the viral genome into the capsid; it varies from ~80 to ~150 bases, depending on the strain of HIV, and
 - *DIS*, the dimer initiation site, takes part in preparing the viral RNA for packaging by Ψ .

Note that the genome in Figure 3 is a simplification: It shows only the genes in the RNA that is the actual genome. Figure 8 shows the actual structure, which comprises a backbone to which the nucleic acids are connected.

HIV Latency

Although effective antiretroviral therapy (ART) can keep a very large fraction of activated infected CD4+ T cells from reproducing HIV, it is not effective against CD4+ T cells and other types of cells that are in a resting state and not actively reproducing or producing chemical messages to cause an immune response against a pathogen. These resting memory CD4+ T cells provide a latent reservoir of virus that can be reawakened to begin producing HIV virions if antiretroviral therapy is stopped.

HIV Remission

HIV remission is an alternate term for HIV cure (functional) that is preferred by many researchers.

HIV Structure & Function

The cutaway diagram in Figure 4 (from https://commons.wikimedia.org/wiki/File:HIV_Virion-en.png) shows schematically the structure of an HIV virion. The components are as follows:

- The lipid membrane (light yellow) is a fat bi-layer that is recruited from the cell membrane of a cell

when a new virion “buds” from it; it accounts for about 30% of the total weight of the virion (Gag, described in the [HIV Genome](#) Glossary entry, accounts for about another 50%) and contains all of the virion except the [glycoprotein](#) spikes named gp160 (comprising the HIV protein Env, which forms a trimer coated with about 90 glycans (chains of sugars) containing the sugar lactose found in milk). Each gp160 spike splits to form two glycoproteins, the docking protein [gp120](#) (purple elongated ovals) on the outside of the virion's membrane and the transmembrane protein [gp41](#) (elongated green ovals) that actually pierces the viral membrane; gp160 is the part of an HIV virion that attaches it to a target cell, most often a [CD4+ T cell](#); each of gp120 and gp41 is a trimer, that is, there are three copies of each bound together; when a virion attaches to a target CD4+ T cell, the trimers open to create a mechanism that, accomplishes entry into the cell;

- Inside the membrane is a protein layer called the
 - Reverse transcriptase (RT) (black circles with red insides) is the enzyme responsible for reverse transcribing HIV RNA to HIV [proviral DNA](#);
 - Integrase (IN) (light blue open circles) is the enzyme responsible for integrating the reverse-transcribed DNA into the host cell's DNA;
 - Nef (negative regulatory factor) (one of the circles in the black bracket) is a small protein that causes numerous changes in an infected cell to adapt it to reproducing HIV;
 - Vpr (viral protein R) (another of the circles in the black bracket) is a small protein that is essential to HIV viral replication in non-dividing cells, such as [macrophages](#);
 - Vif (viral infectivity factor) (another of the circles in the black bracket) is a small protein that is essential to HIV viral replication; and
 - p7 (another of the circles in the black bracket) is a peptide that facilitates reverse transcription.

The virion also includes a [transfer RNA \(tRNA\)](#) from the cell that produced the virion that serves to prime insertion of the resulting proviral DNA into a newly infected cell.

HIV Therapeutic Vaccine

An HIV therapeutic vaccine is an [immune-system-stimulating](#) vaccine that prompts or boosts immune responses to HIV in infected individuals.

matrix (light blue) made up of matrix protein or p17, which contains essential proteins and the nucleus;

- Protease (black squares with light blue inside) is an [enzyme](#) that cleaves newly formed HIV polyproteins during [viral replication](#) into their constituent protein components;
- The capsid (dark blue) is the outer membrane of the virion's nucleus and is composed of molecules of a protein known as p24; the capsid's contents are as follows:
 - The [genome](#) (black lines sticking out of the nucleocapsids) consists of two separate strands of [RNA](#), as described in the HIV Genome Glossary entry partially encased in the nucleocapsids (grayish green);
 - The capsid also contains several proteins, namely, reverse transcriptase (RT), integrase (IN), Vif, Vpr, Nef, and p7, which are described below.

HIV's Uniqueness

HIV is unique among human pathogens in several respects, as follows (adapted in part from a slide created and provided for use by Nobel Prize winner David Baltimore, PhD):

- It preferentially attacks [CD4+ T cells](#), the “directors” of the adaptive immune system.
- It eludes control by [antibodies](#).
- Sugars cover almost its entire accessible surface. The only notable exception is the [CD4](#) binding site, but that site is deep inside the protein coat, where it can't be reached by most antibodies.
- It employs a remarkable two-part entry mechanism, using [CCR5](#) or [CXCR4](#) in addition to CD4 that only takes place after viral [gp120](#) has bound to the CD4 site (see the CCR5 Glossary entry). As a result, very few antiviral antibodies can neutralize it, and fewer still are both broadly neutralizing and potent.
- It destroys the [gut-associated lymphoid tissue \(GALT\)](#) very early in infection altering the gut's microbiome.
- It also attacks the [central nervous system \(CNS\)](#) very early,
 - can have anywhere from minor to profound consequences there,
 - can be very hard to reach by therapies there, and,
 - because of the absolutely essential maintenance of functioning of the CNS, very likely requires much more delicate approaches to cure (such as [latency silencing](#)) rather than [shock and kill](#).

All of these aspects of HIV's uniqueness make it a

much more difficult target for cure research than for almost all other pathogens.

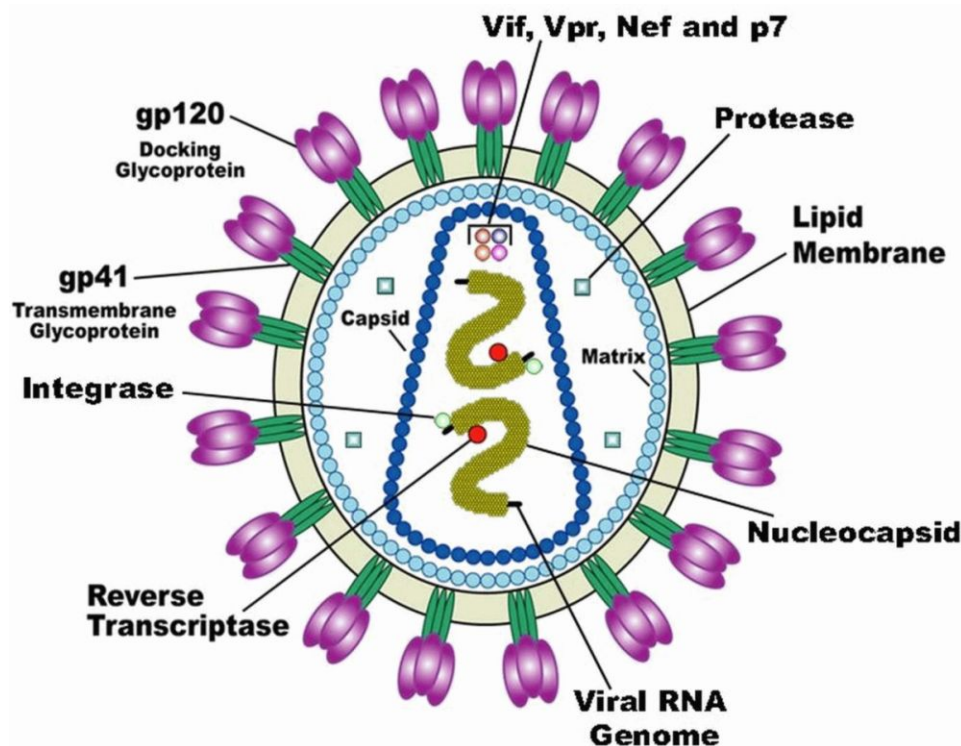


Figure 4. A cutaway schematic of the structure of an HIV virion.

HIV-2

HIV-2 is a virus distinct from but quite similar to HIV-1, which is what is referred to as simply HIV throughout this document. The reasons for paying so little attention to HIV-2 here are as follows:

- While HIV-1 is pandemic (that is, found around the world), HIV-2 is concentrated in West Africa and a few other places, most notably in parts of Europe, particularly France and Portugal, with large numbers of immigrants from West Africa.
- HIV-2's zoonotic (that is, animal) origin is distinct from HIV-1's. It resulted from consumption of "bush meat," like HIV-1, but from monkeys named sooty mangabeys, rather than chimpanzees.
- HIV-2 is much less pathogenic than HIV-1; while it causes AIDS, it progresses to AIDS much more slowly. In fact, it has been suggested that a large fraction of HIV-2-infected persons can reasonably be described as elite controllers because the asymptomatic stage of HIV-2 infection between the very early acute stage and AIDS often lasts several decades in untreated persons and the viral load is frequently undetectable except during AIDS.

- Several more varieties of HIV-2 than HIV-1 have been shown to infect cells that lack the CD4 receptor.
- Finally, but most important, approaches to curing HIV-1 disease are almost certain to be applicable to HIV-2 disease.

Recent research suggests that the typically slower progression of HIV-2 infection may be the result of a significantly higher fraction of HIV-2-infected persons naturally being elite controllers because of some unknown difference in the virus compared to HIV-1.

HLA-B*5701 and HLA-B*2701

HLA stands for Human Leukocyte Antigen and is the cellular mechanism that enables the human body to recognize non-self antigens, such as pathogens and cancer cells, and reject them. See the description of HLA in the Immune System Glossary entry. HLA-B*5701 and HLA-B*2701, in particular, are specific parts of the human leukocyte antigen that are advantageously mutated in a majority of elite controllers of HIV infection, and they are one of the mechanisms that contribute to their control of HIV

infection without antiretroviral therapy (ART).

Humanized Mouse

A humanized mouse, such as the bone marrow-liver-thymus (BLT) mouse, is a laboratory mouse that has some human genes and tissues. It serves as a very useful model for testing strategies for latency reversal and other strategies for HIV remission, such as allogeneic transplants.

Hypermutation

Hypermutation is mutation of HIV proviral DNA so extreme as to make it incapable of producing a daughter virion.

Immune Activation

Immune activation is activation of the cellular components of the immune system (primarily T cells but also B cells), which in turn leads to chronic systemic inflammation. It is associated with HIV disease progression, as well as increased morbidity and mortality in HIV-infected people, despite antiretroviral therapy (ART).

Immune Checkpoint

An immune checkpoint is a molecule in the immune system that either up-regulates a signal (co-stimulatory molecules) or down-regulates a signal. Many cancers protect themselves from the immune system by inhibiting T cell signals. Immune checkpoint inhibitors, such as PD-1, block the action of an immune checkpoint as described in the Latency Reversal Glossary entry.

Immune System

The immune system is the bodily system that protects against disease. It consists of two major parts: the innate immune system and the adaptive immune system.

The innate immune system comprises three parts: biological barriers, natural killer (NK) cells, and killer-cell immunoglobulin-like receptors on the surfaces of NK cells, which are generally known by their abbreviation “KIR”. Biological barriers at the surface of the body may be effective in keeping out pathogens, such as foreign substances, bacteria, and viruses that they recognize as different from the body. Pathogens that make it through the biological barriers may be recognized by KIR components that they are specific to. If a KIR component recognizes a pathogen, it activates natural killer cells (NK cells)—see their Glossary entry for a description of their function.

The adaptive immune system comprises B cells, T cells, antibodies produced by B cells, and the human

leukocyte antigen (HLA) complex, which consists of genes that code for body-surface proteins that distinguish between self and non-self and cell-surface proteins that regulate the adaptive immune system in humans. HLA is the human instance of a system named the major histocompatibility complex (MHC) found in all vertebrates. T cells, in turn, are a large family of varieties, including at least CD4+ T cells (and their latent varieties the central memory (T_{CM}) T cells, effector memory (T_{EM}) T cells, and stem-cell-like memory (T_{SCM}) T cells), CD8+ T cells, T follicular helper (T_{fh}) cells, T helper 17 (T_H17) cells, and at least a half dozen other types; see the entries for the underlined cell types for descriptions of their roles in immunity.

Immune-System Stimulation

Immune-system stimulation is an alternative term for latency reversal. Many HIV cure researchers believe that some form of immune-system stimulation to activate latently infected CD4+ T cells and kill them are essential to curing HIV infection.

In Vitro & In Vivo

In vitro (from Latin, literally “in glass”) is used in biological research to mean “in the laboratory”, while “in vivo” (also from Latin, literally “in life”) means in a human or animal. Both phrases are used to refer to experimental procedures.

Infant CD4+ T Cells

Recent research has shown that the CD4+ T cell populations in infants are quite different from those in adults. In particular, naïve (that is, undifferentiated) CD4+ T cells (T_N cells) constitute a significantly larger fraction than in adults. Understanding the implications of this distinction *may* provide insight into how best to cure HIV infection in infants differently from how it might be done in adults.

Inflammation

Inflamed immune-system cells can signal other immune-system cells to reproduce or respond to a pathogen. The key white blood cell in inflammation is the macrophage. Macrophages can assemble within themselves platforms named inflammasomes that produce the substances that promote inflammation. These platforms are assembled when needed and destroyed when they are no longer needed. This is usually helpful.

However, HIV infection, even in those whose virus is either suppressed naturally (elite controllers) or by antiretroviral therapy (ART), is known to cause chronic inflammation, which can lead to cardiovascular disease, cancers, and other serious health conditions. Activated cells can also produce scarring (also called fibrosis) in

lymph nodes, a critical part of the immune system. For most purposes chronic immune activation equals chronic inflammation (that is, every chronic inflammation leads to chronic immune activation and vice versa).

The *New Yorker* article “INFLAMED” Groopman J 30 November 2015, issue available at <http://www.newyorker.com/magazine/2015/11/30/inflamed> provides an excellent layperson's introduction to inflammation in its first few paragraphs.

Integrin

An integrin is a receptor that has a part outside a cell, extends through the cell wall, and has a part inside the cell. The integrin of greatest current interest in HIV cure research is a receptor named $\alpha_4\beta_7$ (alpha 4 beta 7). $\alpha_4\beta_7$ forms a complex with the CD4 receptor to produce a subset of T cells that is very susceptible to HIV infection. Such cells are found, most notably, in gut-associated lymphoid tissue (GALT).

Kick and Kill

Kick and kill is a synonym some researchers prefer for shock and kill.

Latency Reversal

Latency reversal, also called reactivation, is fundamental to activating the bound HIV proviral DNA in resting memory CD4+ T cells in latent reservoirs in the body to make it susceptible to destruction in the approach to cure known as shock and kill. This is considered by many HIV cure researchers to be fundamental to curing HIV. The following are six of the many types of substances and individual substances being tested as latency-reversal agents; most (though not all) are either experimental cancer drugs or ones already in use and are as follows:

1. **Histone Deacetylase Inhibitor (HDACi):** A histone deacetylase inhibitor (HDACi) causes chromatin to release HIV proviral DNA to be replicated and become exposed to the immune system and potentially to HIV antiretroviral therapy (ART) or other killing agents. Numerous examples that have been used in latency reversal studies are belinostat (product name Beleodaq), droxinostat, givinostat, oxamflatin (brand name Metaccept 3), panobinostat (product name Farydak), romidepsin (brand name Istodax), Scriptaid, trichostatin A, and vorinostat (formerly and still occasionally called SAHA and brand named Zolinza). Romidepsin appears to be the most effective HDACi drug for reversing latency.
2. **Immune Checkpoint Inhibitors:** Immune checkpoints, such as Programmed Cell Death 1 (PD-1) (described in item 4 below), mark T_{CM} and

T_{EM} cells. Checkpoint inhibitors, in turn, block the activity of immune checkpoints. This makes checkpoint inhibitors useful for latency reversal.

3. **Disulfiram (DSM):** Disulfiram (DSM) is a drug that was used for several decades to treat alcohol dependence because drinking alcohol while taking it causes a severe generalized physical reaction. It is rarely used for that purpose now because, in a few cases, the reaction caused the person taking it to die.
4. **Programmed Cell Death 1 (PD-1) and Programmed Cell Death Ligand 1 (PD-L1) Inhibitors:** Programmed cell death 1 (PD-1), also known as CD279, is a receptor found on the surface of some T cells. It both promotes and inhibits apoptosis, depending on the type and location of the T cells it is found on. Recently developed drugs inhibit its effect, thereby activating the immune system to fight certain types of tumors. Programmed cell death ligand 1 (PD-L1), also known as CD274, is a receptor found on the surface of some T cells. It suppresses the immune system during pregnancy so as to avoid abortion of the fetus as non-self, among other functions. Both for PD-1 and PD-L1, drugs have been developed recently that inhibit their effects, thereby reactivating HIV-infected CD4+ T cells. Because of PD-1 and its ligands' involvement in apoptosis, inhibiting them is potentially dangerous. In fact, a recent trial of a PD-L1 inhibitor resulted in one participant's developing a serious autoimmune disease (a disease in which the immune system acts against the body), with the result that the drug will not be used in future clinical trials.
5. **Sirolimus:** Sirolimus (brand name Rapamune) is a drug that is frequently used to suppress immune reactions to transplanted organs. It originated from a bacterium found on Easter Island.
6. **Toll-Like Receptors 4, 7, and 9 (TLR4, TLR7, and TLR9) Agonists:** Toll-like receptors 4, 7, and 9 (TLR4, TLR7, and TLR9) are proteins that are important to recognition of pathogens and activation of natural killer (NK) cells. A toll-like receptor agonist binds to a toll-like receptor and activates it. They may be the most promising latency-reversal agents so far. In particular, Gilead Sciences' drug candidate GS-9620 is a very potent TLR7 agonist, which, it is believed, is why Gilead Sciences is a partner in the amfAR Institute for HIV Cure Research. A trial of GS-9620 in rhesus macaques resulted in two of the nine macaques maintaining undetectable viral load for three to four months. A more recently reported study showed that repeated administration of GS-9620 can lead to remission in SIV-infected rhesus

macaques. Gilead has developed another TLR7

Some other drugs and classes of drugs that have been used as latency-reversal agents include bromodomain inhibitors, bryostatin and prostratin analogues, DNA methyltransferase inhibitors, farnesyl transferase inhibitors, histone methyltransferase inhibitors, Interleukin-7 and -15, ingenols, proteasome inhibitors, protein kinase C inhibitors, and rottlerin.

All latency-reversal agents in use in clinical trials have at least unpleasant side effects and some have serious side effects. Finding or designing ones that are both very effective and safe is a major goal.

Latency Reversal by Combinations of Drugs

Several articles published in 2015 discuss combinations of latency reversal agents tested in cell lines (that is, human cells grown in a laboratory) *outside the body* and found them to be more effective than single agents. The determination of effectiveness was made by the observation of biological signaling pathways associated with latency reversal. It is unknown whether any of the combinations will be safe when used in humans.

Latency Silencing

Latency silencing is a term used to describe an approach to completely stopping reactivation of latently infected CD4+ T cells in latent reservoirs, thus making them incapable of producing further HIV virions. It is of interest because of the potentially serious problems latency reversal would create if it were applied to the central nervous system (CNS). Several approaches are being explored, as follows:

- Using gene editing to modify the HIV tat gene (see the HIV Genome Glossary entry) so that the HIV is no longer infective,
- Inhibiting the Tat protein with didehydro-cortistatin A, an analogue of the steroid cortistatin isolated from an ocean sponge,
- Using short hairpin RNAs (shRNAs) to perform HIV gene editing,
- Using mammalian target of rapamycin (mTOR) pathway inhibitors to suppress HIV retrotranscription; rapamycin is an alternate name for sirolimus, a latency reversal agent, and
- Using a protein named lens epithelium-derived growth factor (LEDGF/p75) that plays a critical role in integrating HIV into cellular DNA.

Latent Reservoir

Latent reservoir is used in HIV cure research in two closely related senses:

agonist named GS-986.

A latent HIV reservoir is a part of a person's body that may be cells or a tissue that is reachable by HIV. Further, it is a part of the body that, it is generally believed, is not affected by antiretroviral therapy (ART) as effectively, if at all, as in the blood. Latent reservoirs provide long-lived homes for HIV to reemerge from if therapy is stopped. The only definite latent reservoir is resting memory CD4+ T cells in lymph nodes. Other tissues that contain significant amounts of infected CD4+ T cells are at least the following:

- macrophages and monocytes (white blood cells)—macrophages are a likely reservoir (see below),
- ,
- the brain,
- the innermost layer of fat (technically called the stromal vascular layer), whose cells display the CD4 receptor and both the CCR5 and CXCR4 co-receptors,
- the female and male genital tracts,
- Peyer's patches and other parts of the intestines, and
- follicular dendritic cells.

A type of T cell named V γ 9V δ 2 that does not have the CD4 receptor but that is a latent reservoir for HIV was discovered in 2015; these cells contain replication-competent latent proviral DNA. There are other types of cells that *may* be latent reservoirs, including natural killer cells (NK cells), renal (kidney) epithelial cells, mucosal epithelial cells, skin fibroblasts (cells that produce collagen—see the Lymph Node Collagen Deposition (Fibrosis) Glossary entry), and pluripotent stem cells (stem cells that can differentiate into *any* other type of cells). Epithelial cells form the outer surface of the skin and other parts of the body that are effectively outside it, such as the alimentary canal. " γ " and " δ " are the lower-case Greek letters gamma and delta, respectively.

In 2012 two researchers proposed an alternate "practical definition" of a latent reservoir as an "Infected cell population that allows persistence of replication-competent HIV-1 in patients on optimal HAART regimens on the order of years." HAART abbreviates highly active antiretroviral therapy (ART).

A recently reported study of HIV and macrophages performed in bone marrow-liver-thymus (BLT) mice showed that HIV persists in

macrophages in vivo and thus they are very likely to be a component of the latent reservoir.

(1) *The* latent HIV reservoir is the totality of all the individual latent reservoirs of type (1) above. The size of the latent reservoir is estimated to be anywhere from 1 million to over 50 million HIV-infected resting memory CD4+ T cells by the methods listed in the Measuring the Latent Reservoir Glossary entry. Richman D “Introduction: challenges to finding a cure for HIV infection” Current Opinion in HIV and AIDS 6, January 2011, p. 1 noted what we know about the latent reservoir as follows (lightly edited):

- a) Latently infected resting memory CD4+ T cells are the best characterized latent reservoir for HIV-1.
- b) Less than 1 cell per million of resting CD4+ T cells from persons on potent antiretroviral therapy harbor replication-competent latent provirus.
- c) Other drug-insensitive reservoirs, including the brain, macrophages, and hematopoietic stem cells, may also exist.
- d) The nucleotide sequences of latent proviruses do not incur mutations, so there is no ongoing viral replication within them. Discontinuation of antiretroviral therapy permits the rebound of viral replication originating from the latent reservoir.
- e) Persons successfully treated with antiretroviral therapy (ART) for a decade or more exhibit no appreciable decrease in the size of the latent reservoir.
- f) The persistence of the latently infected reservoir precludes its elimination by antiretroviral therapy for the lifetime of the person.
- g) Latency is likely established by numerous steps of HIV replication, which potentially complicates eradication strategies.

It is generally accepted that the latent reservoir of at least HIV-infected resting memory CD4+ T cells containing proviral DNA and almost certainly other types of HIV-infected cells is established within days after infection, and the existence of the latent reservoir has been known since 1995. The establishment of the latent reservoir and its reactivation are shown in Figure 5 (used with permission from “An Integrated Overview

of HIV-1 Latency” Ruelas DS Greene WC Cell **155**, 24 October 2013, p. 522). Recent research has shown that some subpopulations of replication-competent HIV-infected resting memory CD4+ T cells continue to undergo expansion in latent reservoirs.

Latency is initiated by the transactivation of transcription (Tat) protein (see the *tat* item in the HIV Genome Glossary entry) level in susceptible cells decreasing below a threshold. Resting CD4+ T cells maintain proviruses by sequestering three transcription-related proteins.

The perspective “Redefining the Viral Reservoirs that Prevent HIV-1 Eradication” Eisele E Siliciano RF is freely available from the 21 September 2012 issue of the journal Immunity. It can be downloaded from the webpage [http://www.cell.com/immunity/abstract/S1074-7613\(12\)00376-7](http://www.cell.com/immunity/abstract/S1074-7613(12)00376-7) . While the article is rather technical, as a perspective it should be accessible to a significant fraction of readers.

Latent Reservoir Establishment & Fiebig Stages

Recent research shows that latent reservoirs begin to be established as early as Fiebig stage 1. Reservoirs established in Fiebig stages 1 and 2 are characterized by HIV proviral DNA-containing CD4+ T cells, while those established in Fiebig stages 3 – 5 are characterized by both proviral DNA and RNA.

Latent Reservoir Maintenance

The latent reservoir is maintained by two mechanisms, homeostatic proliferation and clonal expansion, described below:

- Homeostatic proliferation occurs in the bone marrow when there is a low level of white blood cells, including CD4+ T cells, and it has the goal of maintaining a constant number of T cells. When the body has fewer white blood cells than needed to maintain a normal number, they proliferate in response to HLA direction. This is the major source of T cells following the withering of the thymus gland in adolescence.
- Clonal expansion is a process that generates daughter memory cells (a clone) of a single cell. If the original cell is a T or B cell, all the cells in the clone are specific to the same antigen, namely, that of the parent cell.

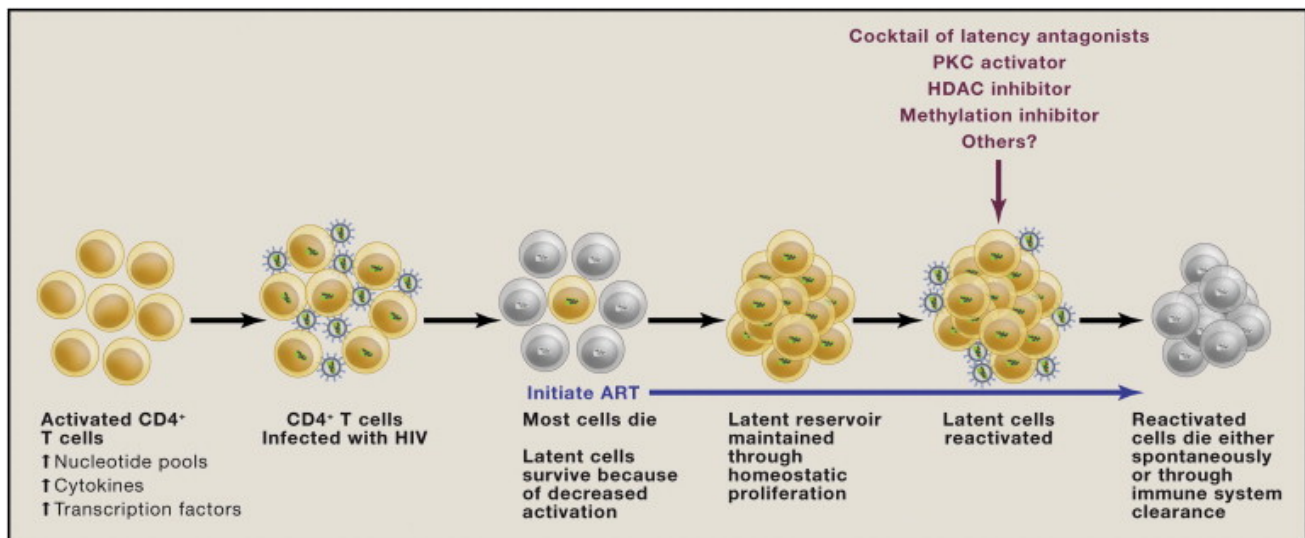


Figure 5. Establishment of the latent reservoir and its reactivation.

Latent Reservoir Reduction to Achieve HIV Cure (Functional) or Remission

Estimating latent reservoir reduction to achieve a functional HIV cure or remission is a major goal of cure research, since remission is believed to be much more easily achievable than a sterilizing cure—see the HIV Cure (Sterilizing) Glossary entry. However, the standard estimates of the reduction necessary to achieve a 30-year (essentially lifetime for many people) remission is a factor in the range of 100,000 to 1 million of the overall latent reservoir and roughly 1,000 to achieve a one-year remission.

A more recent and clearly more optimistic model suggests that only roughly a factor of 60 could achieve a one-year remission; nevertheless, while such a reduction has been realized in a few cases, it has *not* shown a yearlong remission yet.

Finally, note that this type of remission is distinct from the virologic remission found in the VISCONTI cohort (see the Post-Therapy Controllers Glossary entry): a remission of this type requires that *all* latently infected resting memory CD4+ T cells remain inactive for the period of the remission. This type of remission, further, is more like being fully healthy in that it implies no ongoing inflammation, unlike what happens in virologic remission.

Lentivirus

A lentivirus, such as HIV or simian immunodeficiency virus (SIV), is a type of retrovirus that causes a very slowly progressing infection. The prefix “lenti” comes from the Latin word meaning slow. Lentiviruses are further distinct from other retroviruses in that only they can infect cells that are latent, i.e., not dividing.

Leukapheresis

Leukapheresis is a medical procedure used in cure research to collect large numbers of white blood cells. It requires insertion of a catheter into a vein in each arm; blood is drawn out via one of them, a fraction of the white blood cells is collected by the process known as apheresis (from the Greek for “taking away”), and the remaining blood is reinserted into the body via the other catheter. The quantity of white cells collected is never enough to affect immune function. Leukapheresis is used in several areas of cure research, most prominently in some of the methods for determining the results of latency reversal.

Los Angeles Baby

The child known as the Los Angeles baby was actually born in Long Beach, CA, (in Los Angeles County) in April 2013 and was HIV+ at birth. She was treated aggressively within hours of her birth and six days later was found to have no detectable HIV in her body. She was kept on antiretroviral therapy (ART), so it is not possible to determine whether she has actually been cured.

Lymph Node

A lymph node is a small organ containing immune-system cells named lymphocytes that filter lymph, which is a fluid similar to blood plasma that contains fats that are responsible for its white milky color, B cells, and T cells; the latter include CD4+ T cells and CD8+ T cells. Prominent clusters of lymph nodes are found in the underarms, the groin, and the neck. See the Lymphoid Tissues & Lymphatic System Glossary entry for related information.

Lymph Node Collagen Deposition (Fibrosis)

When cells die in the body, they are sometimes replaced by scar tissue composed of collagen, a protein found in numerous tissues including bones—in fact it is the most common protein in a person's body. This is called fibrosis. When lymph nodes are inflamed by HIV replication they can lay down scar tissue. This can begin within days of HIV infection and may be largely complete within months. Experts believe that when lymph nodes are scarred, it may be difficult to regain their ability to respond to HIV and other infections as effectively, causing lasting damage to the immune system that a cure *may* not be able to reverse.

Lymphoid Tissues & the Lymphatic System

A lymphoid tissue is a component of the lymphatic system. The tissues are found in lymph nodes, the thymus gland, gut-associated lymphoid tissue (GALT), Peyer's patches, the spleen, tonsils, and adenoids.

The lymphatic system is made up of lymph nodes, the other lymphoid tissues described above, and lymphatic vessels, which parallel the veins and carry lymph toward the heart. It is responsible for producing lymphocytes and antibodies and is essential to fighting infections.

Macrophage

A macrophage is a type of white blood cell that may be infected with HIV. Macrophages are found in almost all organs, in addition to circulating in the blood.

Macrophage translates from Greek as “large eater.”

Macrophages perform what is known as phagocytosis—literally (from Greek) “cell-eating process”—which well describes what they do, namely, engulf cellular debris, bacteria, viruses, cancer cells, and other foreign substances—essentially anything that doesn't have the proteins found on the surfaces of healthy native cells.

In particular, macrophages devour HIV-infected CD4+ T cells. A subset of HIV virions use any of at least nine co-receptors other than CCR5 and CXCR4, some which virions attack macrophages directly. Thus, it is very likely that macrophages provide additional latent reservoirs beyond those containing resting memory CD4+ T cells.

In fact, recent research strongly suggests that HIV is the only thing that buds from macrophages. The budded HIV resulting from compartments that devoured CD4+ T cells themselves target that cell type rather than macrophages or any other.

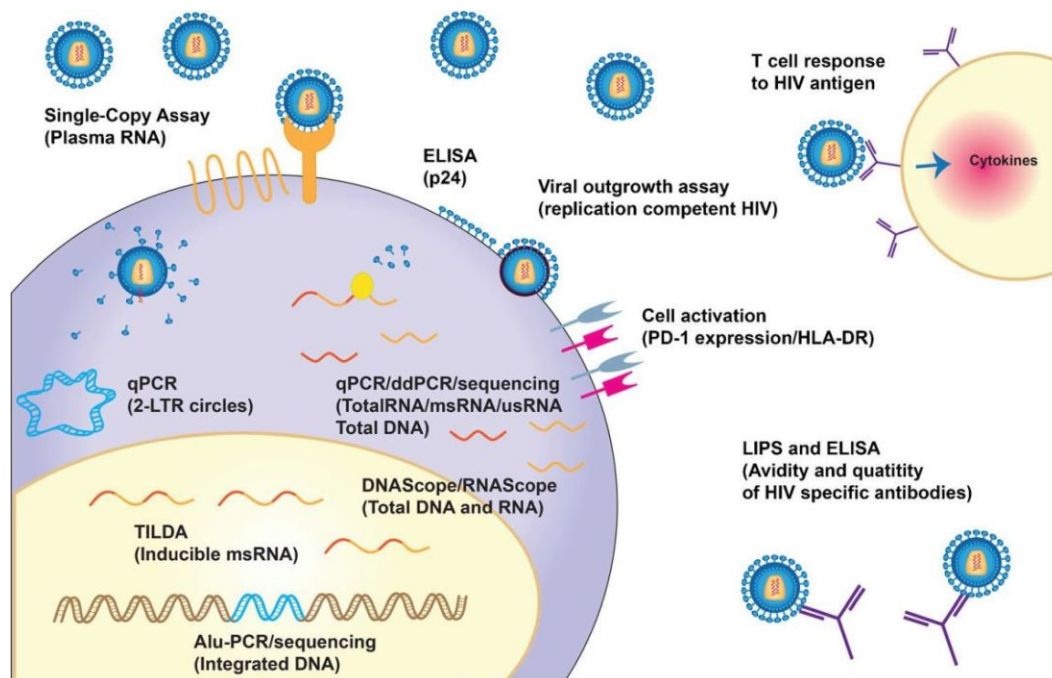


Figure 6. HIV replication cycle stages and targets of several latent reservoir measuring assays.

Measuring the Latent Reservoir

Measuring the latent HIV reservoir(s) is a vital step in

determining the effectiveness of approaches to both latency reversal and latency silencing. For latency

reversal, it could—if it were accurate— be used to determine the number of reactivated HIV-infected CD4+ T cells, in addition to its obvious basic measurement role. There are preliminary results of a development project whose result is believed to be *much* more accurate than previous methods. See item 5 below for a description of it.

It is estimated that the latent reservoir typically contains anywhere from about 1 million to over 50 million HIV-infected CD4+ T cells. The ultimate goal of measuring the latent reservoir is to count all and only replication-competent provirus, which no measurement tool is yet capable of doing (see Figure 6 from Barton KM Palmer SE “How to Define the Latent Reservoir: Tools of the Trade” Current HIV/AIDS Reports 11 February 2016, under the terms of the Creative Commons Attribution 4.0 International License <http://creativecommons.org/licenses/by/4.0/>). There are several approaches to measuring the number of HIV-infected CD4+ T cells in the latent reservoir, some of which are as follows:

1. The quantitative viral outgrowth assay (QVOA) attempts to count only replication-competent latent provirus. It begins by collecting very pure latent resting memory CD4+ T cells by leukapheresis. It then dilutes the cells in several steps and reactivates them. Then activated CD4+ T cells also collected by leukapheresis from an uninfected person or persons are added to the diluted cells and mixed with the infected CD4+ T cells to infect them and thus propagate the virus. The quantitative viral outgrowth assay is complex and expensive and has the added disadvantage of being *very likely to underestimate the actual size of the latent reservoir*. However, some recent studies show a significant correlation between the results of QVOA and total HIV DNA, suggesting that it *may* be a reasonable measure of the latent reservoir. Approaches to improving the effectiveness of QVOA are a subject of research.
2. The quantitative polymerase chain reaction (qPCR) assay measures total HIV DNA or cell-associated HIV RNA (caRNA) in a latent reservoir. This assay is most frequently used to measure persistent HIV infection, but it can be used to measure the latent reservoir. It has the disadvantage of massively overestimating the magnitude of the latent reservoir—by as much as 300 times, but on average by about 10 – 100 fold—because it does not discriminate between functional (that is, replication competent) and defective (that is, not capable of replicating HIV—see the Defective Virion Glossary entry for an explanation of this) HIV RNA. It is relatively inexpensive compared to

QVOA.

3. The single-copy assay of latent HIV RNA is an extremely sensitive method that counts as few as one HIV+ CD4+ T cell at a time. It is most often used to detect low-level viremia in people on antiretroviral therapy (ART), but it may be useful for measuring the latent reservoir. A variant named droplet digital polymerase chain reaction (ddPCR) can be used to precisely measure very low levels of HIV RNA or cell-associated RNA (caRNA). This approach (obviously) detects single copies of latent HIV RNA, and efficient counting techniques are under development to enable it to measure the magnitude of the latent reservoir. This *may* turn out to be the most effective way to perform such measurements if it can be refined to distinguish replication-competent HIV-infected resting cells from defective ones.
4. The Tat/Rev Inducible Limiting Dilution Assay (TILDA) is a polymerase-chain-reaction-based (PCR-based) assay that measures multiply spliced HIV RNA (see the Splicing of HIV RNA & Measurement of Unspliced and Multiply Spliced RNA in Cure Research Glossary entry). Studies suggest that TILDA is a more accurate predictor of actual reservoir size than other assays.
5. The Intact Proviral DNA Assay (IPDA) is the most accurate assay as of early 2018. It uses two DNA sequences to probe the HIV genome. One sequence detects deletions in the genome large enough to make the virion defective; the other detects hypermutated RNA. It uses droplet digital polymerase chain reaction (ddPCR) to perform the measurement, which is almost sufficient to detect defective provirus and separate it from replication-competent latent provirus. Early measurements using IPDA eliminate ~95% of defective proviruses. IPDA is predicted to overestimate the replication-competent latent reservoir by about 1.9 fold and so is much more accurate than any other method. In addition, it requires very much less blood than QVOA and is much faster.

Measuring the Contributions of Types of Resting Memory CD4+ T Cells to the Latent Reservoir

Measuring the contributions of types of resting memory CD4+ T cells (stem-cell-like, central, transitional, and effector) to the latent reservoir is a current topic of research.

Messenger RNA (mRNA)

Messenger RNA (mRNA) is crucial to the creation of proteins and HIV virions in cells. A messenger RNA

molecule is created by the enzyme RNase transcribing a DNA gene that encodes a protein to a complementary RNA (an RNA that mirrors a DNA sequence in the sense that, e.g., where the DNA has an adenine [A] the RNA has a guanine [G] that pairs with it in the DNA) that is used by the translation mechanism in a cell to create that protein. Detailed description of the transcription and translation processes is beyond the scope of this document.

Microbial Translocation

The gut contains bacteria that may be either helpful in digestion or harmful, but which, preferably, should not leak into the blood because parts of the bacteria can trigger severe and long-lasting inflammation. The gut-associated lymphoid tissue (GALT) in the lining of the gut contains most of the immune cells that keep these bacteria in check. In HIV disease, it can become seriously damaged very early in infection and may allow harmful bacteria to be released into the blood. Such bacteria lead to further inflammation, which leads to activation of CD4+ T cells and macrophages and more generalized inflammation leading to opportunistic infections and other conditions, such as cancers.

Mississippi Baby

The Mississippi baby is a young girl who was found to be HIV+ very soon after birth, having been infected by her HIV+ mother, and was put on intensive antiretroviral therapy (ART) within 30 hours after birth. From the time the girl was 18 months old until she was 23 months old she was lost to medical care. When she was brought back into care, she was found to have an undetectable viral load and was believed to have been only the second person in the world to have been cured. However, at age four she was found to have a detectable viral load. It is believed that she may have had only a single HIV virion left in her body that reemerged and resulted in resurgent HIV infection.

Monoclonal Antibody

A monoclonal antibody is a clone or cluster of identical antibody molecules made by identical immune-system cells that are all clones (identical copies) of a specific parent cell. Monoclonal antibodies that serve as medications are also produced industrially by bacteria that are altered to be specific to those antibodies.

Monocyte

A monocyte is a type of blood cell that accounts for 2 – 10% of the population of white cells. Like natural killer (NK) cells, monocytes are part of the innate immune system. In response to infections, they differentiate into macrophages and dendritic cells to produce inflammation. They are also believed to be a component of the HIV latent reservoir.

Myeloablative Conditioning

Myeloablative conditioning is the medical procedure that typically precedes a hematopoietic stem cell transplant. It consists of either chemotherapy or radiation sufficient to destroy the myeloid cells other than red blood cells and platelets—that is, the hematopoietic stem white blood cells in the bone marrow and usually white blood cells elsewhere in the body because it is relatively “scattershot.”

Myeloid Cell

A myeloid cell is a blood stem cell that gives rise to a granulocyte or monocyte (which are types of white blood cells), a red blood cell, or a platelet.

Naïve CD4+ T Cell (T_N Cell)

A naïve CD4+ T cell (T_N cell) is a CD4+ T cell that has developed in the thymus gland and been distributed to another bodily location— usually the bone marrow. Naïve CD4+ cells can differentiate into stem-cell-like central memory CD4+ T cells (T_{SCM}), central memory CD4+ T cells (T_{CM}), effector memory CD4+ T cells (T_{EM}), and circulating CD4+ T cells. Recent research has shown that naïve CD4+ T cells are likely a component of the latent reservoir.

Natural Killer (NK) Cells

Natural killer (NK) cells are white blood cells responsible for killing infected cells and cancer cells. They are the most ancient component of the cellular innate immune system. They have long been thought to be purely “natural” in the sense that they are preprogrammed to respond to particular types of infected or disabled cells, unlike CD4+ T cells and CD8+ T cells, which must be trained to respond to their target pathogens; however, recent evidence suggests that there are memory-like subsets of natural killer cells in mice; the clearest evidence for such memory-like properties in people is in response to cytomegalovirus (CMV) infection, which is very common in HIV+ persons. They have also been found in some nonhuman primate (NHP) models, such as rhesus macaques infected with SHIV. There is ongoing research into whether such memory-like natural killer cells may play a role in curing HIV infection. Also, some ongoing research is directed to “supercharging” natural killer cells to make them more effective at killing HIV-infected latent memory CD4+ T cells.

Nonhuman Primate (NHP) Models

Nonhuman primates (most commonly rhesus or pigtail macaques) are used in HIV research because they can be readily infected with SIV or SHIV and provide a reasonably faithful model for prevention, treatment, and cure research. The variety of SIV that infects

chimpanzees has been shown to be the zoonotic source of HIV-1 (the most common form of HIV and usually referred to as just HIV), probably as a result of humans eating so-called bush meat; “zoonotic” is the scientific term for a human disease that results from an animal disease. See also Bone Marrow-Liver-Thymus (BLT) Mouse for a description of another mammal model used in cure research.

Nucleic Acid (Base)

A nucleic acid or base is a component of DNA or RNA. Each of them has four types of nucleic acids, three of which are common to both. Triplets of consecutive bases in DNA (called codons) code for specific amino acids; there is significant redundancy among the triplets, since there are 64 distinct triplets but only 20 different amino acids.

Organelle

An organelle is, effectively, a tiny organ within a non-bacterial cell. It has its own genetic material. Two examples of organelles are chloroplasts, which conduct photosynthesis; and ribosomes, which synthesize proteins.

p and gp Numbers

p and gp numbers indicate the atomic weight in thousands of the amino acids strung together to make a protein (“p n ”) or glycoprotein (“gp n ”), where n is a numeral. For example, p24 (see the relevant item in the HIV Structure & Function entry) is a protein with roughly $24 \times 1,000 = 24,000$ atomic mass units (protons or neutrons).

Paris Patient

The Paris patient was the first reported HIV+ person with acute myeloid leukemia (see the Cancer Glossary entry) to have undergone conditioning with chemotherapy followed by a hematopoietic stem cell transplant (HSCT) in the hope of curing both of his diseases. He had serious graft-versus-host disease (GVHD) and died of multi-organ failure six months after the transplant.

Pathogen

A pathogen is a virus (such as HIV), a bacterium, a chemical foreign to the body, a fungus, a parasite, or anything else that may cause disease.

Pegylated and Pegylation

Pegylation is an organic chemical process that attaches **PolyEthylene Glycol** (hence the “peg” in the two terms) polymers to a drug to mask the drug from the host's immune system and increase its time in the body. Pegylated preceding a drug name refers to the result of pegylation of the drug.

Peyer's Patch

A Peyer's patch is a small mass of lymphatic tissue found throughout the ileum region of the small intestine. Peyer's patches are latent reservoirs for HIV-infected CD4+ T cells.

Polymerase Chain Reaction (PCR)

Polymerase chain reaction (PCR) is a molecular biology technology that revolutionized the field. It enables as little as a single molecule or part of a molecule of DNA to be magnified to millions or more copies that can be analyzed, measured, etc. In essence, it uses an enzyme name DNA polymerase that, beginning with as few as a single molecule or fragment of DNA, repeatedly doubles the number of copies of the DNA, growing them *literally* exponentially. It has become an indispensable tool in biological research and medicine. Applications range from disease diagnosis to quantification of DNA, which is, of course, the reason for HIV cure researchers' interest in it.

Positron Emission Tomography (PET)

Positron emission tomography (PET) is a nuclear medicine imaging technique used to observe metabolic processes in the body. It detects pairs of gamma rays emitted indirectly by a positron-emitting tracer compound. Three-dimensional images of tracer concentration within the body are then constructed by computer analysis in a PET scanning machine.

Post-Therapy Controllers

Post-therapy controllers are a small group of individuals living with HIV, so far mostly the VISCONTI (**V**iro-**I**mmunologic **S**ustained **C**ONTrol after **T**reatment **I**nterruption) cohort in France, who started antiretroviral therapy (ART) within weeks of infection, stayed on therapy for an average of about four years, and then, for various reasons, stopped therapy. Because there has been no large or lasting rebound of HIV, these individuals are able to stay off therapy for long periods, so far as long as 10 years. Unlike the majority of elite controllers, these post-therapy controllers mostly lack advantageous immune-system mutations (for example, HLA-B*5701 and HLA-B*2701). Natural killer (NK) cells are believed to be largely responsible for HIV control in this cohort.

Another cohort of post-therapy controllers with so far much shorter follow-up is the subgroup of participants in the RV254/SEARCH010 (a collaboration of the U.S. Military HIV Research Program and the **S**outheast **A**siatic **R**esearch **C**ollaboration with **H**awaii) who started antiretroviral therapy (ART) within two weeks of infection, all of whom later had undetectable HIV proviral DNA in central memory CD4+ T cells.

Practical Considerations in Gene Therapy for Curing HIV

A 2014 article discusses practical considerations in gene therapy for curing HIV infection using autologous transplants. The main points discussed are as follows:

1. Autologous transplants are significantly easier, though definitely still very challenging, than allogeneic transplants because there is no need to find a well-matched donor. Note by author of this document: However, it is very likely that autologous transplants need gene editing to at least make them CCR5 Δ 32/ Δ 32 and to delete proviral DNA.
2. There are several gene therapy strategies that might be used, including adoptive immunotherapy of modified messenger RNA (mRNA), RNA interference (RNAi), molecules that compete with HIV RNA, ribozymes, and several others.
3. There are several major barriers to the use of gene therapy including
 - the very large number of infected persons who would need to be treated,
 - the lack of safety of the conditioning necessary before therapy can be applied, as exemplified by the Berlin Patient (Timothy Ray Brown)'s case—though his transplants were allogeneic,
 - risk-benefit analysis for clinical trials,
 - the lack of a completely safe and effective method for identifying the cells to be modified, and
 - the very high cost so far of the therapy.

Preclinical Model

A preclinical model is an organism (usually an animal) that has sufficient similarity to humans to be useful in testing a medication or medical procedure before it enters human clinical trials. For HIV, Bone Marrow-Liver-Thymus (BLT) mice and nonhuman primate (NHP) models are common preclinical models.

Pre-Integration Complex

A pre-integration complex is a combination of genetic material and protein that can insert a viral genome into a cell's genome. With regard to HIV, it is formed after retrotranscription of HIV RNA to DNA and consists of the DNA and at least the viral proteins integrase, matrix, and Vpr (see the HIV Structure & Function entry). The complex's DNA may be integrated into the host cell's DNA as proviral DNA. HIV pre-integration complexes are important because they may lead to the creation of latent unintegrated HIV DNA. It is known that the resulting DNA can replicate HIV virions, but relatively inefficiently.

Proviral DNA

Proviral (HIV) DNA is the DNA resulting from retrotranscription of HIV RNA that is integrated into cellular DNA. It results from HIV infection and is the sine qua non of making new virions—put simply, without it there would be no transmission of HIV infection from one person to another.

Provirus

Provirus, in the context of HIV, is a synonym for proviral DNA.

Quantitative Polymerase Chain Reaction (qPCR)

Quantitative polymerase chain reaction (qPCR) is a variety of polymerase chain reaction (PCR) that is intended to count the initial number of DNA sequences that have been amplified. This is, of course, why the technology is of interest to HIV cure researchers, specifically to measure the latent reservoir of HIV-infected CD4+ T cells and the result of latency reversal. Droplet digital polymerase chain reaction (ddPCR) is the most widely used version of it.

Receptor

A receptor, in the context of HIV medicine (including cure research), is a chemical (such as CD3, CD4, CD8, CD34, CD274, or CD279) attached to the surface of a cell that indicates its function and what will attach to it. For a CD4+ T cell, the corresponding CD4 receptor enables attachment and entry along with a co-receptor, namely CCR5 or CXCR4, of an HIV virion into the cell.

Regulatory T Cells (Treg Cells)

Regulatory T cells (Treg cells) are a population of T cells that participate in distinguishing between self and non-self. In particular, they suppress the activity of the immune system to prevent auto-immune disease. They *may* be capable of infection by HIV.

Remission

Remission is a term preferred by many researchers for HIV Cure (Functional) because functional cures, like cures for many types of cancers, are much more likely to be relatively short lived than permanent, though they are also likely to be repeatable for HIV. Table 3 summarizes 32 cases of remission.

Remission in Macaques Using an Antibody to the Integrin $\alpha_4\beta_7$

It has recently been shown in a study of SIV-infected macaques that an antibody to the integrin $\alpha_4\beta_7$ can result in remission for at least 50 weeks. However this is unlikely to be a practical approach to remission from HIV infection in humans because $\alpha_4\beta_7$ has multiple uses making suppressing it potentially dangerous. See also "Anthony Fauci Explains Alpha-4 Beta-7 and HIV" in the

Resource Guide.

Replication-Competent Latent Proviral DNA

Replication-competent latent proviral DNA is HIV proviral DNA in cells (mostly CD4+ T cells) that can produce new HIV virions.

Replication-Competent Latent Provirus

A replication-competent latent provirus is a virion in the

latent reservoir that may be reactivated to circulate in the blood and infect a cell. Such proviruses contain replication-competent latent proviral DNA.

Reservoir

The term reservoir is frequently used for what is more accurately called a or the latent reservoir, i.e., both senses.

Name	No.	Sex	Length of Remission	On ART? ^b
Australian patients	2	M	2 yrs./3 yrs.	Yes
Barcelona patients	5	?	≤ 6 mos.	Yes
Boston patients	3/2 ^a	M	1 died/2.6 yrs./4.3 yrs.	Yes
Essen/Berlin patient	1	M	Died	?
Ethiopian patient	1	F	10 yrs.	?
Los Angeles baby	1	F	?	Yes
Mississippi baby	1	F	4 yrs.	No
Paris patient	1	M	Died	?
Rochester patient	1	?	288 days	No
Utrecht/EPISTEM patients	2	M	?	?
VISCONTI cohort	14	?	≤ 10 yrs.	No

Table 3. Summary of 32 cases of remission.

^aThere were originally three Boston patients, but one died after a car accident and a relapse of his leukemia (see the Cancer Glossary entry) thought to have resulted from the stress of the accident.

^bThis is an indication of whether the patients were on antiretroviral therapy (ART) after beginning their remissions.

Resting Memory CD4+ T Cells

There are at least five types of resting memory CD4+ T cells found in latent reservoirs in the body, namely T_N (naive CD4+ T cells), T_{CM} (central memory CD4+ T cells), T_{TM} (transitional memory CD4+ T cells), T_{EM} (effector memory CD4+ T cells), and T_{SCM} (stem-cell-like central memory CD4+ T cells). Memory CD4+ T cells recognize pathogens that they have been previously exposed to and target them for elimination by CD8+ T cells. Each of the types may be latently infected with HIV; the T_{SCM} cells are the smallest component, but they are thought to be very important because they serve as a source for the other types (except naive CD4+ T cells) and are very long lived. Thus, targeting HIV-infected T_{SCM} cells for activation and elimination is believed to be essential to latency reversal of HIV latent reservoirs.

Restriction Factor

An HIV restriction factor is a protein that significantly decreases HIV replication. Several examples are the APOBEC3 family, Tetherin, and SAMHD1, all of which have Wikipedia entries, in case you want to follow up on them. HIV has evolved mechanisms to counter all known restriction factors. Also, all restriction factors

are strongly related to innate immunity (see the Immune System Glossary entry for a description of innate immunity).

Retrotranscription

Retrotranscription of RNA is the process of transcribing RNA, typically from a retrovirus's nucleus, to proviral DNA that can be integrated into a host cell's DNA to make it available to produce new virions.

Retrotranscription is also called reverse transcription.

Retrovirus

A retrovirus is a virus, such as HIV, whose genetic material is RNA rather than DNA. Retroviruses are special in that they are able to integrate their genetic material by retrotranscription into a host cell's DNA (using the enzyme integrase) as proviral DNA that enables the creation of new virions. See the HIV Structure & Function Glossary entry for a description of integrase.

Ribozyme

See the Gene Editing Glossary entry.

RNA

RNA stands for ribonucleic acid. Unlike DNA, which exists only as single strands in some viruses or in the well-known double helix structure found in all living things, there are more than 40 forms of RNA with distinct functions. Several of them are described in entries in this Glossary, namely, cell-associated RNA (caRNA), messenger RNA (mRNA), multiply spliced (MS) RNA, ribozyme, short hairpin RNA (shRNA), short

interfering RNA (siRNA), transfer RNA (tRNA), and unspliced (US) RNA. For descriptions of multiply spliced (MS) RNA and unspliced (US) RNA, see the Splicing of HIV RNA & Measurement of Unspliced and Multiply Spliced RNA in Cure Research Glossary entry. The structure of RNA is shown in Figure 7 and described below it.

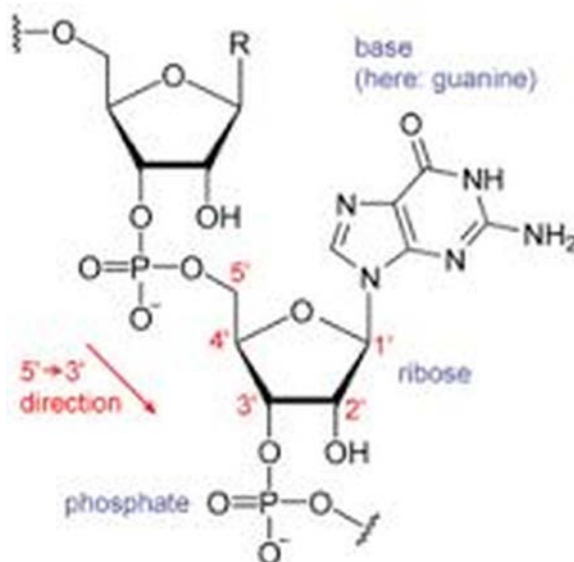


Figure 7. A pair of units comprising RNA (see note below).

RNA is composed of a chain of units of the form shown in Figure 7 (from <https://en.wikipedia.org/wiki/RNA>), which actually shows a pair of consecutive units. Each pair of units has the structure shown in the figure. The backbone consists of molecules of a sugar named ribose (hence the “ribo” part of the name), with a ring structure consisting of four carbon atoms (by convention the carbons are only shown as corners without the letter C for carbon) and an oxygen. Consecutive riboses are connected with phosphate groups. The atoms in the ribose ring are labeled 1’ through 4’, and the 3’ position of one ribose is connected to the phosphate, which is in turn connected to the 4’ position of the next ribose. Each nucleic acid or base is connected to the 1’ position of a ribose. In the example the nucleic acid base connected to the right-hand ribose is guanine and the other ribose has a base simply labeled “R”—it could be any of the four bases named adenine, cytosine, guanine, and uracil.

RNA interference (RNAi)

RNA interference (RNAi), also (more descriptively) previously known as post-transcriptional silencing, is a process in which RNA molecules inhibit gene expression, typically by causing the destruction of

specific messenger RNA molecules.

Rochester Patient

The Rochester patient is an individual (sex not disclosed) with acute lymphoblastic leukemia (see the Cancer Glossary entry) who had a hematopoietic stem cell transplant (HSCT) lacking the CCR5Δ32/Δ32 mutation. By the 56th day after the transplant, HIV proviral DNA was undetectable in the person’s blood. A leukapheresis performed at some time following day 56 showed that typical measures of the latent reservoir had significantly decreased. The person had graft-versus-host disease (GVHD) that seemed to be affecting most of his or her CD4+ T cells: They were about 1/10th of white cells on day 142 and about 13/1,000,000 on day 265. Like the third Boston patient, the patient was involved in a car accident just before viral load rebound, but while the resulting systemic inflammation may have been at least a partial cause of rebound, that is not yet clear. Research is ongoing to obtain a better understanding of the course of remission and rebound.

Seroconversion

HIV seroconversion is the period of time during which a

person goes from being HIV antibody negative to having HIV antibodies circulating in her or his blood. After seroconversion an HIV antibody test, such as the ELISA (Enzyme-Linked ImmunoSorbent Antibody) tests positive.

Set Point Viral Load

See viral set point.

Shock and Kill

The shock and kill strategy combines “shocking” latent HIV proviral DNA in CD4+ T cells in latent reservoirs out of latency and killing them by apoptosis, a monoclonal antibody, or an immune-based therapeutic agent. Shock and kill is called kick and kill by some researchers.

Shock and Kill Clinical Trials

Several small shock and kill clinical trials have been undertaken using various latency reversal agents and various approaches to killing. An example of a small (20-participant) completed shock and kill trial is the REDUC Phase IB/IIA clinical trial that administered a series of immunizations using the Vacc-4-x therapeutic vaccine and, as an adjuvant, a protein named GM-CSF that induces the creation of macrophages and another type of white blood cells named granulocytes followed by three infusions of romidepsin and killed by an HIV-specific CD8+ T cell response. REDUC is listed in the EU Clinical Trials Register as number 2013-004747-23. The company responsible for the REDUC trial announced in November 2015 a follow-on trial named BIOSKILL that is enrolling participants in several countries. It is a multicenter, randomized, double-blind, placebo-controlled Phase II clinical trial designed to confirm and expand on the results of REDUC.

Short Hairpin RNA (shRNA)

See the Gene Editing Glossary entry.

Splicing of HIV RNA & Measurement of Unspliced and Multiply Spliced RNA in Cure Research

Two concepts that are mentioned frequently by researchers studying the sizes of latent reservoirs of HIV-infected CD4+ T cells and the creation of new HIV virions are multiply spliced messenger RNA (mRNA) and unspliced RNA (see Figure 8) (Figure 3, Furtado MS Calloway DS et al. New England Journal of Medicine **340**: 27 May 1999; used by permission of the Massachusetts Medical Society).

Short Interfering RNA (siRNA)

See the Gene Editing Glossary entry.

Simian/Human Immunodeficiency Virus (SHIV)

Simian/human immunodeficiency virus (SHIV) is a series of chimeric retroviruses created in laboratories whose genetic material is a combination of simian immunodeficiency virus (SIV) genes and HIV genes. It is capable of infecting almost every type of nonhuman primate that can be infected with SIV. It serves as a model of human infection with HIV.

Simian Immunodeficiency Virus (SIV)

Simian immunodeficiency virus (SIV) is a series of retroviruses that infect nonhuman primates. The type of SIV that infects chimpanzees is the source of human infection with HIV by a species-to-species transfer that probably resulted from humans eating chimpanzee “bush meat.” It serves as a model of human infection with HIV.

Single Molecule Array (Simoa) Immunoassay

The Single Molecule Array (Simoa) immunoassay is a commercially available ultrasensitive technology that uses arrays of femtoliter-sized chambers to analyze and identify proteins. Its relevance to HIV cure research is that it has been used to detect neurofilament light-chain protein (NFL) in central nervous system (CNS) samples. Neurofilament light-chain protein is a biomarker of the progress of neurodegenerative diseases, including HIV, in the central nervous system.

Single-Copy Assay

A single-copy assay is a quantitative polymerase-chain-reaction-based tool designed to exponentially amplify a single copy of DNA or RNA that can be used to measure the HIV latent reservoir. An RNA sample must first be retrotranscribed to DNA.

The first step in the creation of new virions is transcription of the proviral HIV DNA to make short completely spliced messenger RNAs called multiply spliced mRNAs that are exported from the nucleus to the cytoplasm (that is, outside the nucleus) of an infected cell. The multiply spliced mRNAs make proteins that are essential for next making unspliced RNA. The proteins made by multiply spliced mRNAs include Tat, Rev, and Nef encoded by the *tat*, *rev*, and *nef* HIV genes, respectively (see the HIV Genome Glossary entry).

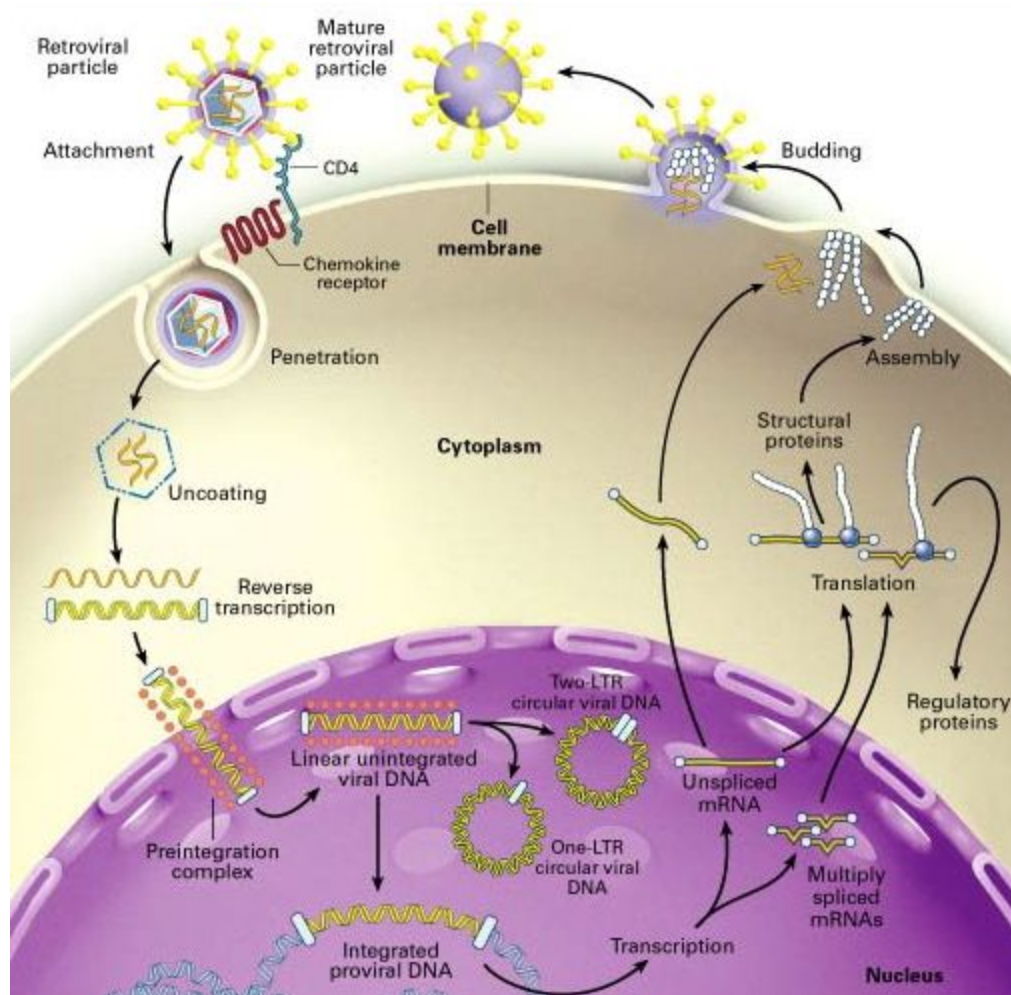


Figure 8. CD4+ T cell with multiply spliced messenger RNAs (mRNAs) and unspliced in the nucleus and cytoplasm.

The viral protein Tat is needed to boost synthesis of unspliced RNA. The viral protein Rev is needed to chaperone the unspliced RNA out of the nucleus. The unspliced RNA, in turn, makes the proteins Gag, Pol, Env, Vif, Vpu, and Vpr encoded by the HIV gag, pol, env, vif, vpu, and vpr genes, respectively, that are essential to the creation of new HIV virions (for descriptions of the genes and proteins see the [HIV Genome](#) Glossary entry). Unspliced (full-length) RNA is essential to making new virions and is also incorporated into them as the viral genome. Unspliced and multiply spliced RNA are also collectively called cell-associated RNA (caRNA) by HIV cure (and other) researchers.

Unspliced and multiply spliced mRNA are measured by cure (and other) researchers because both are markers related to whether host CD4+ T cells are actively making HIV RNA, and consequently making new virions,

and, if so, how effectively they are doing that. The detection of unspliced RNA in latently infected cells indicates that latency is not fully silent, that is, there is some (probably very inefficient) creation of new pieces of RNA going on in latent reservoirs. These cells have recently begun to be called “active” reservoirs, which some researchers consider (and probably rightly so) to be a confusing concept at best.

Stakeholder Engagement

Stakeholder engagement refers to the involvement of essential people and organizations, including governments, foundations, research groups, companies, and *especially* individuals, in promoting understanding of cure research, particularly clinical trials of both basic science and, potentially, curative processes; developing appropriate expectations; and sustaining involvement of persons in those trials. See also the Resource Guide entry with the same header.

Stem-Cell-Like Memory CD4+ T Cell (T_{SCM})

Stem-cell-like memory CD4+ T cells (T_{SCM}) are resting memory CD4+ T cells that are a very important target for elimination from the latent reservoirs they are found in because they are progenitor cells that can differentiate to produce central memory CD4+ T cells (T_{CM}), transitional memory CD4+ T cells (T_{TM}), effector memory CD4+ T cells (T_{EM}), and circulating CD4+ T cells.

Sterilizing Cure

Therapeutic Vaccine

A therapeutic vaccine is one that is administered as a therapy for a disease rather than to prevent it. One example of a therapeutic vaccine is Vacc-4x, which is discussed in the Shock and Kill Clinical Trials Glossary entry.

Thymus Gland

The thymus gland is located in the chest just below the neck. It is the origin of all T cells (including specifically CD4+ T cells and CD8+ T cells), all of which migrate to the bone marrow. The thymus gland typically shrinks to almost nothing during adolescence.

Transfer RNA (tRNA)

A transfer RNA (tRNA) is an adaptor that serves as the link between a messenger RNA (mRNA) that carries (hence “transfer”) an amino acid to the current end of a protein being assembled. It moves the amino acid from the mRNA to the organelle called the ribosome that actually builds the amino acid sequences of proteins.

Transitional Memory CD4+ T Cell (T_{TM})

A transitional memory CD4+ T cell (T_{TM}) is a type of memory CD4+ T cell that is in the process of transitioning from being a central memory CD4+ T cell (T_{CM}) to an effector memory CD4+ T cell (T_{EM}).

Tropic and Tropism

Tropism (adjective and combining form “tropic”; from Greek) means “turning toward” in general and, in the specific context of HIV co-receptors, it refers to the type of HIV (CCR5-tropic, CXCR4-tropic, or dual-tropic) that binds to a CD4+ T cell.

Utrecht/EPISTEM Patients

The two Utrecht/EPISTEM have HIV infection and two different forms of leukemia (see the Cancer Glossary entry). Both received allogeneic CCR5Δ32/Δ32 hematopoietic stem cell transplants after myeloablative conditioning. Both had significant reductions in viral load, but neither was cured. Of the two, one

See HIV Cure (Sterilizing).

T Follicular Helper Cell (T_{fh}) T follicular helper cells (T_{fh}) are found in lymph nodes and other lymphoid tissues, including the spleen and Peyer's patches, and are a minor latent reservoir for latent HIV proviral DNA.

T Helper 17 Cell (T_h17)

T helper 17 cells (T_h17) are CD4+ T cells that are very easily infected with HIV and, hence, HIV-infected ones are an important target for elimination. T_h17 cells have the co-receptor CCR6 in addition to the receptor CD4, experienced significant graft-versus-host disease (GVHD), and that seems to have contributed to his lower viral load post-transplant than the other one had. EPISTEM abbreviates “**E**uropean **P**roject to **g**uide and **I**nvestigate the potential for HIV cure by **S**TEM cell transplantation.”

Vector

A vector is typically a virus (such as an adenovirus, adeno-associated virus, or lentivirus) that can be used to carry genetic material (DNA or RNA) or protein into human cells. Vectors are used in both HIV prevention research to deliver vaccine candidates and in cure research.

Viral Load

HIV viral load measures the amount of HIV virions circulating in the blood. It is usually reported as copies of virus per milliliter of blood (abbreviated c/ml). It is important in HIV cure research because activating cells containing latent HIV from latent reservoirs increases viral load in a measurable way.

Viral Rebound and Remission

Viral rebound refers to the level of virus found in the blood after an analytical treatment interruption, possibly because it is believed one has achieved remission.

A hopeful study of delayed viral rebound and remission in SHIV-infected rhesus macaques was reported recently. Forty-four macaques were infected with a SHIV and started on antiretroviral therapy (ART) on day 7. After 96 weeks of viral suppression, each of four groups of 11 animals received one of the following: (1) broadly neutralizing antibody PGT121 for 10 weeks, (2) TLR7 agonist GS-9620 [see the Toll-Like Receptors 4, 7, and 9 (TLR4, TLR7, and TLR9) Agonists item in the Latency Reversal Glossary entry] for 20 weeks, (3) both PGT121 and GS-9620, or (4) placebo. Several weeks after the bNAbs and agonist doses were completed, antiretroviral therapy (ART) was discontinued, and time to viral rebound was measured. Only 55% or 6 of 11 animals treated with the

combination of drugs rebounded, and they did so in a median time of 112 days and with a 2.64 log reduction of peak viral load and a 1.52 log reduction in viral set point.

Viral Replication

Viral replication is the process by which HIV reproduces, making more HIV virions. To do so, it must first reverse transcribe its genetic material from ribonucleic acid (RNA) to the infected cell's deoxyribonucleic acid (DNA). The HIV DNA is then integrated into the cell's DNA. When HIV-infected CD4+ T cells are activated, they produce HIV virions, damaging the normal function of the cells and, usually, leading to cell death by apoptosis.

Viral Set Point

HIV viral set point is the viral load which stabilizes after the acute infection phase. It also applies to SIV and SHIV infection in the nonhuman primate (NHP) models.

Virion

A virion is a single complete virus particle that consists of an RNA or DNA core with proteins, such as enzymes, and often with an external envelope. It is the extracellular infective form of a virus.

Women's Involvement in Cure Research Studies

A recent open-access viewpoint article that can be downloaded as a PDF is ME Grewe Y Ma A Gilbertson et al. Women in HIV cure research: multilevel interventions to improve sex equity in recruitment from the URL http://viruseradication.com/past_articles/issue_text_se

arch/women%20in%20HIV%20cure%20research/. It suggests six ways to increase women's involvement in cure research studies. Before summarizing the points in the article, we must point the reader to the Estradiol, Estrogen, Progesterone, and Estrogen Receptors Glossary entry, which makes clear several very important biological reasons for increasing women's involvement in cure research. The existing barriers and suggested ways to increase involvement are as follows:

1. The possibility of pregnancy and its unknown or not clearly understood impact on HIV-related research of all kinds is a *very* frequent barrier, especially for treatment studies. Most study designs can be modified to ease this barrier, if not eliminate it.
2. Researcher and clinic coordinator perceptions may impact recruitment of women.
3. Engagement of women stakeholders and improving the perceptions of women held by male stakeholders can increase women's recruitment.
4. Overcoming structural barriers, such as the lack of child care at research sites, and including women-focused community organizations in recruitment can improve involvement of women in studies.
5. Policy interventions in research funding can promote sex and gender equity.
6. The **Gender, Race, and Clinical Experience** (GRACE) study (a description of which can be downloaded from <http://online.liebertpub.com/doi/pdf/10.1089/apc.2013.0015>) is an excellent example that specifically included recruitment of women and that can serve as a model for other studies.

Resource Guide

AIDS Clinical Trials Group (ACTG) HIV Reservoirs and Viral Eradication Transformative Science Group (Cure TSG)

The AIDS Clinical Trials Group (ACTG) HIV Reservoirs and Viral Eradication Translational Science Group (Cure TSG) organizes and directs clinical trials intended to test drugs that may be useful in curing HIV infection. The ACTG is funded by the U.S. National Institutes of Health. Its active trials are listed on the <https://ClinicalTrials.gov> website.

amfAR Institute for HIV Cure Research

The amfAR Institute for Cure Research, announced on 30 November 2015 and funded initially with a five-year \$20M grant, is headquartered at the University of California, San Francisco's AIDS Research Institute (website: <https://ari.ucsf.edu/>) and is a "virtual institute" composed of researchers from UCSF's Medical

School, the co-located Gladstone Institute of Virology and Immunology, the University of California, Berkeley, Blood Systems Research Institute (BSRI) (San Francisco, CA), Oregon Health and Science University (Portland, OR), Gilead Sciences (Foster City, CA), GeoVax (Atlanta, GA), the Infectious Disease Research Institute (IDRI) (Seattle, WA), Monogram Biosciences (South San Francisco, CA), and RainDance Technologies (Lexington, MA). The institute's "dream team" of researchers initially included UCSF's Steven Deeks, MD, and Joseph M. "Mike" McCune, MD, the Gladstone Institute's Warner Greene, MD, PhD, and the Blood Systems Research Institute's Satish Pillai, PhD. Dr. McCune has since left to take a position in industry.

The institute's mission is to

- Chart (pinpoint the precise locations of latent

- reservoirs of HIV),
- **Understand** (determine how the latent reservoirs are formed and persist),
- **Record** (quantify the amount of virus in them), and
- **Eliminate** (eradicating the reservoirs from the body).

Leading the research efforts are Paul Volberding, MD, director of the UCSF AIDS Research Institute; Warner Greene, MD, PhD, director, Gladstone Institute of Virology and Immunology; Satish Pillai, PhD, associate investigator, Blood Systems Research Institute; Steven Deeks, MD, professor of medicine, UCSF; Teri Liegler, PhD, director of the Virology Core Laboratory at UCSF; and Peter Hunt, MD, associate professor of medicine in the UCSF HIV/AIDS Division. The institute's home page is <http://ari.ucsf.edu/research/amfar-institute-hiv-cure-research>. The Gladstone Institute of Virology and Immunology's website is <http://gladstone.org/institutes/virology-immunology>; the Blood Systems Research Institute's website is <http://www.bsrif.org/>; Oregon Health and Science University's website is <http://www.ohsu.edu/xd/>; Gilead Sciences, Inc.'s website is <http://www.gilead.com/>; GeoVax's website is <http://www.geovax.com/>, and the Infectious Disease Research Institute's website is <http://www.idri.org/>; Monogram Biosciences' website is <http://www.monogrambio.com/>, and Raindance Technologies' website is <http://raindancetech.com/>.

Anthony Fauci Explains Alpha-4 Beta-7 and HIV

Anthony Fauci Explains Alpha-4 Beta-7 and HIV is a YouTube video in which Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases, discusses the role of the $\alpha 4\beta 7$ integrin in HIV treatment and cure in the YouTube video at <https://www.youtube.com/watch?v=nQh9knbtwo>.

Approaches to an HIV Cure

Approaches to an HIV Cure is a YouTube video produced by NIAID (the National Institute of Allergy and Infectious Diseases, an institute within the NIH that is responsible for most of NIH's research related to HIV), that uses quickly drawn cartoon-like images with a narrative to explain the process of establishing the latent reservoir and two approaches to curing HIV infection, namely gene editing and shock and kill. The video is at https://www.youtube.com/watch?v=kO_RXBAFjoI.

Assessing Factors Affecting Participation in HIV Cure-Related Research: Implications for Effective and Ethical Implementation

Assessing Factors Affecting Participation in HIV Cure-

Related Research: Implications for Effective and Ethical Implementation Dubé K (371 pp.) University of Carolina School of Public Health 2016 is a DrPH dissertation that explores the issues in its title and presages Karine Dubé's work on the CUREiculum and other projects concerning community participation in cure research cited in this Resource Guide. The dissertation may be found at https://sph.unc.edu/files/2017/05/dube_hpmdrph_abstract.pdf.

Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication (BELIEVE)

Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication (BELIEVE) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. Its principal investigator is Douglas Nixon, MD, PhD, of George Washington University in Washington, DC. Its primary purposes are

- enhancing the killing ability of HIV-specific killer T-cells;
- augmenting natural killer cell functions; and
- harnessing T-cell, natural-killer-cell, and antibody-mediated effectors in both adult and pediatric HIV infections.

BELIEVE is partnering with two companies: ALTOR Bioscience Corp. (website: <http://www.altorbioscience.com/>), whose cancer drug candidate ALT-803, a proprietary interleukin-15 superagonist, has been found to not only reverse HIV latency, but also to enhance the immune system's ability to kill the resulting cells; and Torque (website: <http://www.torquex.com/>), a biomedical engineering company with the technology to deliver drugs to CD8+ T-cells that they plan to use to clear the reservoir. It also has a Community Advisory Board (CAB). BELIEVE does not have a website at the time of this writing.

Numerous other U.S. institutions involved in BELIEVE are

- Children's National Health System (website: <http://childrensnational.org/>);
- NIH (website: <https://www.nih.gov/>);
- Howard University (website: <https://www2.howard.edu/>);
- the University of Arizona (website: <http://www.arizona.edu/>);
- the University of Pittsburgh (website: <http://www.pitt.edu/>);
- Brigham Young University (website: <https://home.byu.edu/home/>);
- the University of Minnesota (website: <http://twin->

- cities.umn.edu/);
- Johns Hopkins University (website: <https://www.jhu.edu/>);
- Seattle Children's Hospital (website: <http://www.seattlechildrens.org/>);
- Beth Israel Deaconess Medical Center, Harvard University (website: <http://www.hms.harvard.edu/hfpsq/bidmc.aspx>);
- the University of Pennsylvania (website: <http://www.upenn.edu/>);
- Georgetown University (website: <https://www.georgetown.edu/>); and
- Albert Einstein College of Medicine (website: <http://www.einstein.yu.edu/>).

Several international institutions are also involved, namely,

- the University of Toronto, Canada (website: <https://www.utoronto.ca/>);
- Simon Fraser University, British Columbia, Canada (website: <https://www.sfu.ca/>);
- Centro de Investigación en Enfermedades Infecciosas, Mexico City, Mexico (website: <http://www.cieni.org.mx/>); and
- the University of São Paulo, Brazil (website: <http://www5.usp.br/english/?lang=en>).

Studies will be conducted in concert with communities at local clinics and agencies associated with these institutions in Canada, Brazil, and Mexico plus the U.S.

THE BODY

The BODY (<http://www.thebody.com/>) is "The Complete HIV/AIDS Resource" for people who are living with HIV.

THE BODY PRO

The Body Pro (<http://www.thebodypro.com/>) is designed for health professionals, but some of its HIV cure-related topics are quite accessible for the lay reader.

California Institute of Regenerative Medicine (CIRM) HIV Cure Research Grants

The California Institute of Regenerative Medicine (CIRM/"California's Stem Cell Agency") has given out, as of this writing, 16 grants for HIV cure research. They can be found listed at [https://www.cirm.ca.gov/grants?field_public_web_disease_focus_tid\[\]=826](https://www.cirm.ca.gov/grants?field_public_web_disease_focus_tid[]=826).

CAN GENE THERAPY CURE HIV? With DAVID BALTIMORE & PAULA CANNON

"Can Gene Therapy Cure HIV? with David Baltimore & Paula Cannon" is a YouTube video of a community

event with Nobel laureate David Baltimore, PhD, and Paula Cannon, PhD, sponsored by the Delaney Cell and Genome Engineering Initiative (defeatHIV) that was recorded on 12 August 2015 as a community addition to the August 2015 Cell & Gene Therapy for HIV Cure conference that took place at the Fred Hutchinson Cancer Research Center (the "Fred Hutch") in Seattle, WA. The video can be found at https://www.youtube.com/watch?v=LVR_rUQHa0&feature=youtu.be .

CAN GENE THERAPY CURE HIV/AIDS?

"Can Gene Therapy Cure HIV/AIDS?" is a YouTube video of a community event with Paula Cannon, PhD, sponsored by the Delaney Cell and Genome Engineering Initiative (defeatHIV) that was recorded in August 2014 as a community addition to the August 2014 Cell & Gene Therapy for HIV Cure conference that took place at the Fred Hutchinson Cancer Research Center (the "Fred Hutch") in Seattle, WA. The video can be found at <https://www.youtube.com/watch?v=plvv07vd5il> .

CanCURE

CanCure is "The Canadian HIV Cure Enterprise." It has a research program with four themes, as follows:

- THEME 1 is defining the molecular, genetic, and functional characteristics of HIV/SIV persistence in human as well as in animal models, with a particular focus on myeloid cells.
- THEME 2 studies the mechanisms underlying HIV latency and persistence in myeloid cells.
- THEME 3 is seeking to identify new drug candidates and therapeutic approaches capable of eliminating persistent HIV infection and to test these in preclinical models.
- THEME 4 is establishing appropriate infrastructure to conduct HIV Cure clinical trials, through testing of immune-based therapies aimed at depleting viral reservoirs in patients undergoing antiretroviral therapy.

It lists over 90 publications as of spring 2018, and it can be found on the web at <http://www.cancurehiv.org/> .

Center for International Blood & Marrow Transplant Research (CIBMTR)

The Center for International Blood & Marrow Transplant Research (CIBMTR) does HIV-related clinical trials of bone marrow transplants, among many other kinds. Its list of clinical trials is at https://www.cibmtr.org/Studies/ClinicalTrials/BMT_CTN/Pages/ProtocolsNew.aspx .

City of Hope Clinical Studies

City of Hope in Duarte, CA, is doing clinical studies to alter hematopoietic stem cells to fight HIV/AIDS. As of early 2016, its Alpha Clinic (a project of the California Institute for Regenerative Medicine) is doing two clinical trials, as follows: (1) with the goal of “resetting” the immune system to produce T cells resistant to HIV infection (COH Protocol #13282) and (2) in cooperation with Sangamo Biosciences and the Keck School of Medicine at the University of Southern California, using a zinc-finger nuclease (see the Gene Editing Glossary entry) to edit a gene in the hematopoietic stem cells that is needed for HIV infection; the resulting T cells will then lack a key protein (CCR5) required to infect cells (COH Protocol #14017). The clinical trial has been completed and is listed on the U.S. government list of clinical trials at <http://www.clinicaltrials.gov/> ; Sangamo Biosciences’ website is <http://www.sangamo.com> .

Clinical Trials List

A list of both currently active and completed clinical trials related to curing HIV infection is maintained by the Treatment Action Group and can be found online at <http://www.treatmentactiongroup.org/cure/trials>. It can be downloaded as a PDF from that page in addition to being viewed there. Also, clicking on the trial number there will take you to the <https://clinicaltrials.gov> entry for a full description of the trial. See also the EU Clinical Trials Register Resource Guide entry.

Clinical Trials Registries

In addition to the list of HIV cure clinical trials listed by the Treatment Action Group (see Clinical Trials List) and the EU Clinical Trials Register, there are clinical trial registries maintained by Canada, Germany, the Netherlands, Switzerland, the United Kingdom, Australia, China, India, Iran, Japan, Korea, New Zealand, the Philippines, Sri Lanka, Thailand, Brazil, Cuba, Peru, Pan Africa, South Africa, and Tanzania. See <http://www.hhs.gov/ohrp/international/clinicaltrialregistriesweb.htm> for descriptions of these lists and access information for them.

Collaboratory of AIDS Researchers for Eradication (CARE)

The Collaboratory of AIDS Researchers for Eradication (CARE) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. Its principal investigator is David Margolis, MD, of the University of North Carolina. Its aim is to pursue a comprehensive collaborative search for approaches to eradicate HIV. Its primary purposes are to characterize HIV latency and develop methods for determining the size of HIV’s latent reservoirs. Its website is <http://www.delaneycare.org>. Its partners include U.C.

San Diego (website: <https://ucsd.edu>), Emory University (website: <http://www.emory.edu>) and its Yerkes National Primate Research Center (website: <http://www.yerkes.emory.edu>), the University of Southampton (website: <http://www.southampton.ac.uk>), Oregon Health & Science University (website: <http://www.ohsu.edu>), the University of Oxford (website: <http://www.ox.ac.uk>), the University of Pennsylvania (website: <http://www.upenn.edu>), Harvard University (website: <http://www.harvard.edu>), the Los Alamos National Laboratory (website: <http://www.lanl.gov>), MacroGenics (website: <https://www.macrogenics.com/>), and Merck (website: <http://www.merck.com>). It also has a Community Advisory Board (CAB).

Combined Immunologic Approaches to Cure HIV-1 (I4C)

Combined Immunologic Approaches to Cure HIV-1 (I4C) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. Its headquarters is at Beth Israel Deaconess Medical Center, Boston (website: <http://www.bidmc.org/>). Its two main focuses are to determine the “efficacy of combination immunologic approaches to target the viral reservoir” and “mechanisms and next generation strategies to target the viral reservoir.”

Countdown to a Cure for AIDS

Countdown to a Cure for AIDS is an amfAR-sponsored website that describes in lay language “Pathways to an HIV cure, namely, pharmacologic approaches, immunologic approaches, and cell therapy approaches.” The website is <http://www.curecountdown.org/pathways-to-an-hiv-cure/> .

Coursera

Coursera is a free online learning center that provides college-level courses on numerous topics. There is no course specifically devoted to HIV, but there is one titled “How Viruses Cause Disease” that provides an “introductory virology course” including several relevant topics. The Coursera website is <https://www.coursera.org/> .

A Crack in Creation

A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution Doudna JA Sternberg SH Houghton Mifflin Harcourt 2017 is a lay introduction to CRISPR and more specifically CRISPR/Cas9, whose broad and profound power was discovered in the first author’s lab among others. It traces the discovery of CRISPR, explains its mechanism of action, describes its applicability, explicates the

scientific and public policy implications of its power, and calls for a moratorium on its use in humans until these issues have been, at the least, very carefully thought out. The book has copious endnotes, most of which are references to journal articles related to its subject. Even the title on the dust jacket refers to CRISPR's use: occurrences of the letters A, C, G, and T, which abbreviate the names of the four nucleic acids making up DNA, are a different color from the others.

Critical Challenges in HIV Discovery: Cure and Vaccine

Critical Challenges in HIV Discovery: Cure and Vaccine by Anthony Fauci, MD, the Director of the National Institute of Allergy and Infectious Diseases, is a YouTube video of a plenary presentation to the 2014 International AIDS Conference. It focuses on the most important issues in the development of both a preventive vaccine for HIV and its cure. It should be accessible to any reader of this document. It can be found at <https://www.youtube.com/watch?v=DS-6oSDt3gA>.

Cure-Related Research Resources

Cure-Related Research Resources is a Treatment Action Group webpage that provides a list of web links related to curing HIV infection, as follows:

1. Trials and Research Studies,
2. TAG Publications,
3. TAG Cure Research Monitor,
4. Community-Based Articles and Reports,
5. Mainstream Media Articles,
6. Scientific Publications (Open Access),
7. Research Projects and Funding,
8. Advocacy,
9. CUREiculum,
10. Conferences, Meetings, and Events,
11. General Resources, and
12. Glossary.

The last item is currently a reference to the 2016 English edition of this document. Most of the resources are accessible to the nonscientific reader. The resources range from very accessible to the general reader (for example, nos. 4, 5, and 8) to intermediate (for example, no. 2) and very scientific (for example, 6). The list may be found on the webpage <http://www.treatmentactiongroup.org/cure>.

CURED: How the Berlin Patients Defeated HIV and Forever Changed Medical Science

CURED: How the Berlin Patients Defeated HIV and Forever Changed Medical Science N Holt Dutton 2014 is a book about the Berlin patient (Timothy Ray Brown)

and a German man named Christian Hahn (see the Essen/Berlin Patient Glossary entry). Christian Hahn (a pseudonym—he remains anonymous), a German, in fact, was another man who was treated by Heiko Jessen, MD, for HIV infection in Berlin. It's not clear in his case that he was actually cured, which is why Timothy Ray Brown is known as *the* Berlin Patient. It may be that, in Mr. Hahn's case, we have an instance of postexposure prophylaxis: a combination of factors that resulted in HIV infection never truly becoming established or post-therapy control.

CURED OF HIV: A COMMUNITY Q&A with TIMOTHY RAY BROWN & GERO HÜTTER, M.D.

CURED OF HIV: A COMMUNITY Q&A with TIMOTHY RAY BROWN & GERO HÜTTER, M.D. is a video of the Berlin Patient (Timothy Ray Brown) and Gero Hütter, M.D., the doctor who cured him, at the Seattle Public Library, Seattle, WA, February 7, 2015. The video is on YouTube at <https://www.youtube.com/watch?v=a1s7DKvHNrE>.

CURED/NOTCURED on Seattle Channel's Town Square

CURED/NOTCURED on Seattle Channel's Town Square is a YouTube video of one of the two Boston Patients, Gary Steinkohl, and his doctor Timothy Henrich, MD, discussing his case. The video was published in August 2016 and can be found at https://www.youtube.com/watch?v=-Jg_bqCGDo.

CUREiculum

The CUREiculum is a suite of modules that provides simple, accessible information on HIV cure research, organizing it into a systematic format for ongoing and/or issue-specific learning that complements this Glossary and Resource Guide. The CUREiculum was developed in a multi-collaboratory process by leading scientists, community educators, and advocates who recognized the need for increasing literacy in this area. The modules are designed for community educators, funders, the media, and other stakeholders. Sixteen key areas of HIV cure research have been developed into freestanding modules. The CUREiculum's website is <http://www.avac.org/cureiculum>. Please get in touch if there's a cure-related question or issue you'd like to have addressed. Videos of the webinars, audio recordings of them, and their PowerPoint decks are also available on the website. The modules in the CUREiculum are as follows:

1. HIV/AIDS and Cure Basics
2. Stakeholder Engagement in HIV Cure Research
3. Gene Therapy/Stem Cell Transplant
4. Shock and Kill and Latency-Reversal Agents
5. Measuring the Latent HIV Reservoir

6. Regulatory Issues in HIV Cure Research
7. Early Antiretroviral Treatment
8. Pediatric HIV "Cure"
9. Concepts in Basic Science and Translational Research
10. Therapeutic Vaccines and Immune-Based Therapies
11. Informed Consent in HIV Cure Research
12. Ethics of HIV Cure Research
13. Participation in HIV Cure Research
14. Animal Models in HIV Cure Research
15. History of Cures: Putting HIV Cure Research in Context
16. Combination Approaches and Conclusion - The Science Looking Forward

At the time of this writing the CUREiculum is being updated and will be published on the web in place of the edition described above. This item will be changed to reflect the new edition when it is available.

David Baltimore (Caltech) Part 2: Why Gene Therapy Might be a Reasonable Tool for Attacking HIV

"David Baltimore (Caltech) Part 2: Why Gene Therapy Might be a Reasonable Tool for Attacking HIV" is a YouTube video with Nobel Prize winner Prof. David Baltimore of CalTech about the subject of its title (there are also Parts 1 and 3, but they are about aspects of HIV other than cure). The video can be found at <https://www.youtube.com/watch?v=6-1JGFWodmQ&t=19s>.

Delaney AIDS Research Enterprise (DARE) to Find a Cure

The Delaney AIDS Research Enterprise (DARE) to Find a Cure is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. Its principal investigators are Steven G. Deeks, MD, from the University of California, San Francisco (website: <https://www.ucsf.edu/>); Louis J. Picker, MD, from the Vaccine & Gene Therapy Institute, Oregon Health & Science University (website: <https://www.ohsu.edu/xd/research/centers-institutes/vaccine-and-gene-therapy/index.cfm>), Portland, OR; and Sharon Lewin, FRACP, PhD, from Monash University (website: <https://www.monash.edu/>), Melbourne, Australia. It also has a Community Advisory Board (CAB), which is responsible for this web page. Its website is <http://daretofindacure.org/>.

DARE will initially

- define the role of reservoirs that enable SIV or HIV to persist during antiretroviral therapy (ART) and

use the monkey model to develop therapies to breach them;

- characterize the distribution of replication-competent latent provirus in lymphoid tissues in ART-suppressed adults and develop positron emission tomography (PET) imaging techniques to quantify the reservoir;
- define the role of immune checkpoints, such as PD-1, and their blockade on T cell function in monkeys and people; and
- define the safety, immunogenicity, and anti-HIV effectiveness of a human cytomegalovirus (HCMV)-vectored HIV vaccine in HIV-infected adults on ART.

Delaney Cell and Gene Therapy Initiative (defeatHIV)

The Delaney Cell and Gene Therapy Initiative (defeatHIV) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. It is a consortium of academic and industrial investigators working together to eradicate HIV by gene editing. Its principal investigators are Keith Jerome, MD, PhD, and Hans-Peter Kiem, MD, both from the Fred Hutchinson Cancer Research Center (known as the Fred Hutch) in Seattle, WA. In addition it includes investigators at Beckman Research Institute of the City of Hope, Duarte, CA (website: <https://www.cityofhope.org/research/beckman-research-institute>), Sangamo Biosciences, Richmond, CA (website: <http://www.sangamo.com/>), Seattle Children's Research Institute, Seattle, WA (website: seattlechildrens.org/research/), and the University of Washington, Seattle, WA (website: washington.edu). Its projects are

- hematopoietic stem cell transplant: platform for purging the latent reservoir;
- ZFN-modified stem cells for HIV eradication;
- CCR5 targeting to control HIV/SHIV in the pigtail macaque nonhuman primate model;
- targeted disruption of integrated SHIV by engineering homing endonucleases; and
- delivery of zinc finger nuclease and homing mRNA and cDNA.

It also has a Community Advisory Board (CAB). Its website is <http://defeathiv.org>.

Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy (BEAT-HIV)

The Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy (BEAT-HIV) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. It is a consortium of academic and industrial investigators

with principal investigators Luis J. Montaner, DVM, D Phil, and James L. Riley, PhD, of the Wistar Institute (website: <https://www.wistar.org/>). It has partners at

- the University of Pennsylvania (website: <http://www.med.upenn.edu/>);
- Philadelphia FIGHT (website: <https://fight.org/>);
- Rockefeller University (website: <http://www.rockefeller.edu/>);
- VA San Diego Healthcare System (website: <http://www.sandiego.va.gov/>);
- Johns Hopkins University (website: <https://www.jhu.edu/>);
- the University of Nebraska-Lincoln (website: <http://www.unl.edu/>); and
- the University of Utah (website: <http://www.utah.edu/>).

BEAT-HIV has three objectives, namely,

- to identify the locations of latent reservoirs;
- to stimulate the innate immune system with a combination of highly potent antibodies and pegylated interferon $\alpha 2b$; and
- a gene therapy strategy using CCR5 Δ 32/ Δ 32 CD8+ T cells.

It has three industry partners: Merck & Co., Inc. (website: <http://www.merck.com/>), Sangamo Biosciences, Inc. (website: <http://www.sangamo.com/>), and Inovio Pharmaceuticals (website: <http://www.inovio.com/>). Its website is <http://beat-hiv.org/>.

Differences between Women and Men in HIV Cure Research

Several groups funded by amfAR's Research Consortium on HIV Eradication (ARCHE) are studying differences in inflammation and antiretroviral therapy (ART) of HIV infection between women and men that may lead to differences in cure research between the sexes.

Ethics of ART interruption after stem-cell transplantation

"Ethics of ART interruption after stem-cell transplantation" is an article in the January 2016 issue of *The Lancet HIV* that describes five cases of HIV+ people (the Berlin patient, the two Boston patients, the Essen/Berlin patient, and the Paris patient) with cancer who received hematopoietic stem-cell transplants (HSCT) followed by interruption of antiretroviral treatment (ART). Four of the five had rebound of detectable HIV and three of the four died within several years. To quote the article, "Analytical treatment interruptions after HSCT will impose an array

of burdens on patients including the need for careful assessments before the interruption, frequent blood monitoring, invasive procedures to assess the viral reservoir, and psychosocial issues." and "Finally, it is important to emphasise that analytical treatment interruptions after HSCT are experimental and subject to careful and competent ethics review." Note that the article is *not* freely available.

EU Clinical Trials Register

The EU (European Union) Clinical Trials Register is a searchable database of all clinical trials that include EU sites or that are run by companies and research institutions located in EU countries. It also includes a "Glossary of Terms used in the EU Clinical Trials Register." Its website is <https://www.clinicaltrialsregister.eu> .

European AIDS Clinical Society (EACS)

The European AIDS Clinical Society (EACS) sponsors the European AIDS Conferences, among other activities. The 15th such conference includes six webcasts concerning "Prospects for HIV Cure and Post Treatment Remission" that are available on the society's website at <http://eacs.multilearning.com/eacs/> under its subject header.

Genome Engineering HIV and its Host

Genome Engineering HIV and its Host is a YouTube video by Paula Cannon, PhD, about what gene engineering is, how it applies to HIV and its human host, and its potential use to cure HIV. While it was designed as a presentation to a meeting of the American Society for Microbiology, much of it will be accessible to users of this document. It can be found online at <https://www.youtube.com/watch?v=dsQzEEAIMCU> .

Global Investment in HIV Cure Research and Development

AVAC, which describes its mission as "Global Advocacy for HIV Prevention" also has issued, so far, three documents titled "Global Investment in HIV Cure Research and Development" for 2012, 13, and 14. The most recent one can be downloaded from the AVAC website at <http://www.avac.org> by searching for "Global Investment in HIV Cure".

Good Manufacturing Practices (GMP)

Good manufacturing practices (GMP) refers to the practices required to conform to the guidelines recommended by agencies that control licensing for manufacture and sale of food, drug products, and other medical products and devices. The agencies include the Food and Drug Administration (FDA) in the United States and the European Medicines Agency

(EMA). The International Society for Pharmaceutical Engineering (ISPE) provides access to Australian, Canadian, European Union, Japanese, U.S. FDA, and World Health Organization GMP guidelines on the web at <http://www.ispe.org/gmp-resources/gmp-guidelines> .

Good Participatory Practice (GPP)

Good Participatory Practice (GPP) refers to the practices recommended by the United Nations AIDS Agency (UNAIDS) and AVAC, a U.S.-based organization engaged in "Global Advocacy for HIV Prevention," for stakeholder engagement in biomedical HIV prevention trials. GPP has been generalized to apply to all HIV/AIDS-related biomedical clinical trials, including cure-related trials. AVAC provides access to the GPP guidelines on the web at <http://www.avac.org/good-participatory-practice> .

HIV Cure Research Fact Sheet

The HIV Cure Research Fact Sheet is published by the Treatment Action Group and provides a brief introduction to the issues involved in HIV cure research. The most recent edition was published in November 2015. It can be found online as a webpage and a downloadable PDF at <http://www.treatmentactiongroup.org/cure/fact-sheet> .

HIV: The Quest for a Cure

HIV: The Quest for a Cure by John Mellors, MD, Is a YouTube video of a plenary presentation that was designed for the 2015 Conference on Retroviruses and Opportunistic Infections. Much of it is quite high level, but at slightly less than 22 minutes in length it is well worth the time for the reasonably accessible overview it presents of its topic. It can be found at <https://www.youtube.com/watch?v=QDupxh3T2ZA> .

The HIV Life Cycle

The HIV Life Cycle is a work in progress that was presented by its developer Janet Iwasa of the University of Utah as the introduction to the 2018 Conference on Retroviruses and Opportunistic Infections (CROI). It's a truly stunning animation of the process of HIV infection of a CD4+ T cell and its replication. An early version can be seen at http://scienceofhiv.org/wp/?page_id=20. The cutaway image of HIV in it is now the image of HIV that appears on all CROI materials from banners to booklets and lens-cleaning cloths.

I Am the Berlin Patient: A Personal Reflection

"I Am the Berlin Patient: A Personal Reflection" is an article by the Berlin Patient (Timothy Ray Brown) about his HIV cure that appeared in the January 2015 issue of *AIDS Research and Human Retroviruses*.

i-base

i-base is a United Kingdom organization that provides information about curing HIV, in addition to its more basic aim of providing information about HIV treatment. Its website is <http://i-base.info/> .

IrsiCaixa (Institut de Recerca de la Sida)

IrsiCaixa (Institut de Recerca de la Sida) is a research center located in Barcelona, Spain, that focuses on many of the issues involved in HIV/AIDS research. Its specific cure-related foci include achieving remission or eradication of HIV by combinations of therapeutic vaccines, antibodies, and latency reversal.

Is the Cure for HIV Possible in Our Lifetime?

Is the Cure for HIV Possible in Our Lifetime? is a YouTube video composed by HIV treatment and cure activist Nelson Vergel that includes presentations by Steven Deeks, MD, about the Berlin Patient's (Timothy Ray Brown) cure and the suffering involved in it that makes it so very impractical for general application, and with Timothy himself. It can be found at <https://www.youtube.com/watch?v=Sj-dFQ6Yi7k> .

Journal of Medical Ethics, vol. 43, no. 2, February 2017

The Journal of Medical Ethics is the official journal of the (British) Institute of Medical Ethics and one of the BMJ journals published by the BMJ Group, a wholly owned subsidiary of the British Medical Association. The particular issue cited here is devoted entirely to issues in curing HIV infection, and most of the articles are freely available to download from the table of contents webpage at <http://jme.bmj.com/content/43/2> and are quite accessible to lay readers. They provide an introduction to the subject, background information, articles concerning risks, benefits to clinical trial participants and nonparticipants, and an afterword.

Journal of Virus Eradication

The Journal of Virus Eradication is an open-access online and print journal devoted to cure research online at <http://www.viruseradication.com> . While much of its content is quite technical, it also includes quite accessible articles, such as "HCV cure for everyone or which challenges remain?"

Martin Delaney Collaboratories for HIV Cure Research

The Martin Delaney Collaboratories for HIV Cure Research is a group of six collaboratories (expanded from three in the initial grant cycle) that are organizations consisting of researchers devoted to studying cures for HIV infection and promoting them via clinical trials. The six collaboratories are

1. Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy (BEAT-HIV),
2. Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication (BELIEVE),
3. the Collaboratory of AIDS Researchers for Eradication (CARE),
4. the Delaney AIDS Research Enterprise to Cure HIV (DARE),
5. the Delaney Cell and Gene Therapy for HIV Cure (defeatHIV), and
6. Combined Immunologic Approaches to Cure HIV-1 (I4C).

Each of the six consists of scientists and a Community Advisory Board (CAB). The overall Collaboratory is funded by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases. The Collaboratory also has a National Community Advisory Board (NCAB) made up of two members from each of the six CABs, plus a management member from each collaboratory (total: 18 members).

Martin Delaney (1945 – 2009) was the founding director of Project Inform, one of the nation's oldest and best-known non-profit foundations working to combat HIV and AIDS by providing information and advocating for treatment. In 2009, he and five coauthors wrote "We conceive an initiative, termed here a collaboratory, in which the government contributes funding, regulatory oversight, and coordination; industry contributes funding, drug discovery, technology, and expertise; and academia contributes ideas and investigative capacity." in Richman D Margolis D Delaney M et al. The Challenge of Finding a Cure for HIV Infection *Science* 323 (5919), 1304–1307.

Note that while the current NIH grant gives DARE the name above, it continues to use the name it chose for itself in the initial grant cycle: the Delaney AIDS Research Enterprise (DARE) to Find a Cure.

NATAP/National AIDS Treatment Advocacy Project

Despite its name, NATAP does include information about curing HIV. The easiest way to find that information on its website is to go to <http://natap.org/> and search for "cure".

NIH (National Institutes of Health)

The NIH (National Institutes of Health) is the U.S. government's medicine and health research and research-funding body. It consists of 27 institutes and centers that cover the field. Its website is at <https://www.nih.gov>.

***POSITIVELY AWARE*, winter 2017/2018 "The Cure Issue"**

The Cure Issue of the magazine *Positively Aware* (winter 2017/2018) with guest Editors David Evans of Project Inform and Richard Jefferys of the Treatment Action Group includes 15 articles, mostly by the guest editors, who are also both members of the Delaney AIDS Research Enterprise (DARE) to Find a Cure Community Advisory Board. The article titles and subtitles are as follows:

1. Handle with care: Speaking the Language of an HIV cure,
2. It's important we keep hope alive: The star and co-creator of the musical *Merce* on the importance of an HIV c
3. The challenge of defining an HIV cure: Different roads to the holy grail,
4. Measuring the HIV reservoir: Current tests for sizing up viral hideouts,
5. Latent Tendencies: New strategies target dormant HIV,
6. Enhancing immunity: Manipulating the immune system to tackle HIV,
7. Collaborating on a cure: Six groups focused on the task,
8. Gene therapy in HIV cure research: Modifying immune system cells to resist, attack, or remove HIV altogether,
9. Time out: Treatment interruption: A risky but essential step in cure research,
10. Speaking the same language: Advocate Michael Louella talks about '50 shades of cure,'
11. What does a cure mean to you?: Four individuals share their hopes and fears,
12. Better late than never: Pioneering scientists prove women are essential to finding a cure,
13. Bringing HIV cure research into the real world: Looking at the need for including social science.
14. Q & A with Paula Cannon. and
15. Q & A with Susana Valente,.

The two Q & As at the end concern gene editing and block and lock (which is an alternate name for latency silencing), respectively. The two articles immediately before them, while not in question and answer format, quote extensively from Eileen Scully, MD, PhD, and Karine Dubé, Assistant Professor at the University of North Carolina.

The articles do an excellent job of covering the field of HIV cure research for the general reader. In addition to being published as a magazine, the articles are all available at the Positively Aware website at <https://www.positivelyaware.com/issues/winter-issue-2017> and, once the next issue is published, by locating it in the archive at

<https://www.positivelyaware.com/archive> .

Progress towards an HIV Cure

Progress towards an HIV Cure is a YouTube video of a presentation of a panel at the 2014 International AIDS Conference chaired by Sharon Lewin, PhD, FRACP, that focuses on issues involved in understanding where we were at that time in the search for a cure for HIV infection. It can be found at <https://www.youtube.com/watch?v=LtPZpVti-9g> .

Project Inform HIV Cure Advocacy

Project Inform's HIV cure advocacy page provides up-to-date information about a variety of cure topics. Its website is <https://www.projectinform.org/> .

Qura Therapeutics

Qura Therapeutics is a partnership between the University of North Carolina-Chapel Hill (UNC) (website: <http://www.unc.edu/>) and GlaxoSmithKline (website: <https://www.gsk.com/>) announced in May 2015 that "will focus exclusively on finding a cure for HIV/AIDS ... including a leading research approach toward an HIV cure, sometimes called "shock and kill." The announcement is available at <http://uncnews.unc.edu/2015/05/10/unc-chapel-hill-and-gsk-announce-novel-partnership-to-accelerate-search-for-hiv-cure/> . Qura's leadership is composed of David Margolis, MD, of the UNC School of Medicine, Zhi Hong of GlaxoSmithKline, and Matt Fajack, Vice Chancellor for Finance and Administration at UNC. Given that it has been more than two years since Qura Therapeutics was announced and nothing more has been heard about it, the author wonders what, if anything, is happening!

Recruitment and ethical considerations in HIV cure trials requiring treatment interruption

The *Journal of Virus Eradication* vol. 1 no. 1 includes the freely available article "Recruitment and ethical considerations in HIV cure trials requiring treatment interruption," which (obviously) discusses the subject of its title; specifically it reports the results of a late 2011 – early 2012 online survey completed by 2,094 HIV+ individuals recruited via the web. The primary goal was to measure willingness to participate in cure research clinical trials that required interruption of antiretroviral treatment (ART). The primary result was based on a four point scale that ranged from "very willing" through "not at all willing". Additional questions asked about the effects on willingness of

1. societal benefit,
2. scientific benefit,
3. perceived influence on personal health, and
4. compensation.

The sampled group was predominantly older white men with at least some college attendance and low to moderate income. More than half of the participants were motivated to take part for personal or societal benefits, compensation, or health benefits, while fewer than half were motivated by scientific benefit.

Research Toward a Cure Trials

Research Toward a Cure Trials is a collection prepared by Richard Jefferys of the Treatment Action Group and updated roughly every three months. It consists of three lists, namely, "Current Clinical Trials," "Observational Studies," and "Completed Studies," including for each one a short title, trial registry identifier(s), manufacturer/sponsor(s), phase, and either estimated completion date or published/presented data. The most recent list is dated 12 January 2018, lists about 125 studies, and can be downloaded as a PDF at <http://www.treatmentactiongroup.org/cure/trials>.

Role of Residual Viral Replication

Role of Residual Viral Replication is a YouTube video by Javier Martinez-Picado, PhD, that presents the issue of persistent low-level HIV replication in persons with very low viral loads and its implications for curing HIV. Although it was constructed to be a presentation to the American Society for Microbiology, much of it should be accessible to most readers of this document. It can be found at <https://www.youtube.com/watch?v=qjAQ5WC1TGQt> .

Scared — and brave

Scared — and brave is an article about defeatHIV Community Advisory Board member Laurie Sylla presenting at Seattle's Gay City LGBTQ (lesbian, gay, bisexual, transgender, queer) Center about the results of survey research done by a group of community members. The research was designed to ascertain what issues community members have about HIV cure research clinical trial participation. The article can be found online at <http://www.fredhutch.org/en/news/center-news/2017/06/why-volunteer-for-an-hiv-cure-study.html> . As time goes on it will be archived at <http://www.fredhutch.org/en/news.html> in the Story Archive under June 2017.

Stakeholder Engagement

An exemplary document about stakeholder engagement is the 1983 Denver Principles for involvement of civil society in every level of HIV-related decision making. See <http://www.actupny.org/documents/Denver.html> or perform a search for [gipa1983denverprinciples_en.pdf](#) .

Strategies for an HIV Cure: 2012

The meeting Strategies for an HIV Cure: 2012 was convened by the [NIH](#) in Washington, DC. The purpose of this meeting was to bring together researchers associated with each of the three NIH-funded [Martin Delaney Collaboratories](#), other researchers engaged in HIV cure research, investigators in complementary disciplines, and community members to share scientific results and engage in active discussion about the merits of various approaches under investigation. It was hoped that these discussions would stimulate new ideas for research projects and lead to new scientific collaborations. Its agenda can be downloaded by searching for Strategies for an HIV Cure, November 28 – 30, 2012, and downloading it from the resulting page.

Strategies for an HIV Cure: 2014

The meeting Strategies for an HIV Cure: 2014 was convened by the [NIH](#) on its campus in Bethesda, MD, to give the [Martin Delaney Collaboratories](#) an opportunity to present their progress and to discuss future prospects for and approaches to curing HIV infection. Its agenda can be downloaded from <https://www.blsmeetings.net/hivcuremeetin g2014/>.

Strategies for an HIV Cure: 2016

The meeting Strategies for an HIV Cure: 2016 will be convened by the [NIH](#) on its campus in Bethesda, MD, to give the [Martin Delaney Collaboratories](#) an opportunity to present their progress and to discuss future prospects for and approaches to curing HIV infection. The agenda can be downloaded as a PDF from the webpage <https://respond.niaid.nih.gov/conferences/hivcuremeetin g2016/Pages/Agenda.aspx>; the poster abstracts can be downloaded as a PDF from the page <https://respond.niaid.nih.gov/conferences/hivcuremeetin g2016/Pages/Abstract-Submission.aspx>.

A Systematic Review of the Inclusion (or Exclusion) of Women in HIV Research: From Clinical Studies of Antiretrovirals and Vaccines to Cure Strategies

The article "A Systematic Review of the Inclusion (or Exclusion) of Women in HIV Research: From Clinical Studies of Antiretrovirals and Vaccines to Cure Strategies" is freely available for download from the 1 February 2016 issue of the [Journal of Acquired Immune Deficiency Syndrome](#) (also known as JAIDS and on the web at <http://www.jaids.com>) and includes a section on cure research.

TAG HIV Basic Science, Vaccines, and Cure Project Blog

The TAG HIV Basic Science, Vaccines, and Cure Project blog, written by Richard Jefferys of the Treatment Action Group in New York City includes, among other topics—as its title says—updates and thoughts about HIV cure. It is moderated by Richard, and its website's main web page is <http://tagbasicscienceproject.typepad.com/>. To subscribe, enter your email address in the box on the right of that page, click "Subscribe", enter the displayed text in the resulting popup. You will then receive an email with a link to click on that will open a web page indicating that your subscription has been confirmed. Note that the content may be too technical for some readers.

Treatment Action Group (TAG)

The Treatment Action Group (TAG) is a New York City-based HIV information provider that was formed out of Act Up! by a group of members who believed that advocating the pharmaceutical industry to develop HIV/AIDS drugs was at least as important in the 1980s as demonstrations. Its early history is traced in the book **How to Survive a Plague** France D Penguin 2017.

Why cure, why now?

"Why cure, why now?" is a freely available article by Daniel Kuritzkes, MD, published online in the *Journal of Medical Ethics* on 7 June 2016. It includes two sections titled "RISKS OF HIV CURE RESEARCH" and "ETHICAL CHALLENGES IN HIV CURE RESEARCH." The website of the article is <http://jme.bmj.com/content/43/2/67>.

Why we need women in HIV cure research

Why we need women in HIV cure research is the header of a section on the People Living with HIV in Australia website at <http://hivcure.com.au/2018/03/08/hiv-cure-research-needs-involve-women>. The section lists four questions about potential differences between women and men that might affect HIV cure as follows:

- Is HIV latency established and maintained the same way in men and women? If not, why not?
- Are HIV reservoirs the same in men and women? Assess size, composition, location, susceptibility to reactivation etc.?
- What impact does the menstrual cycle (or other hormonal changes) have on the HIV reservoir? Do hormones affect the efficacy of interventions such as latency-reversing agents?
- How does the HIV reservoir change over a

lifetime, especially through changes associated with hormonal adjustments, e.g., adolescence, menopause?

Willingness to participate and take risks in HIV cure research: survey results from 400 people living with HIV in the US

The article "Willingness to participate and take risks in HIV cure research: survey results from 400 people living with HIV in the US" in the freely available Journal of Virus Eradication issue 3.1 at <http://viruseradication.com/> reports on a study concerning its title research. The research was performed by enrolling 400 HIV+ individuals online with diverse characteristics including women, men, and transgenders; whites, blacks, Hispanics, and a few members of other ethnic groups; a range of ages, education levels, incomes etc. Over half of the respondents were willing to take part in 14 types of cure studies ranging from surveys through allogeneic hematopoietic stem cell transplants. There are also questions regarding personal benefits (both general and clinical) and social benefits; and personal clinical risks, burdens, and societal risks.

Women and HIV Cure: A Three-Part Webinar Series

Women and HIV Cure: A Three Part Webinar Series is a project of the Women's HIV Research Collaborative (WHRC), which is a working group of the Legacy Project. The first webinar is available at <https://www.hanc.info/cp/resources/Documents/Women%20and%20HIV%20Cure%20Part%201.mp4> ; the second is at <https://www.hanc.info/cp/resources/Documents/Women%20and%20Cure%20Part%202.mp4> ; and the third is at <https://www.hanc.info/cp/resources/Documents/Women%20and%20Cure%20Part%203.mp4> . The three webinars are titled "Where are We? Women in the HIV Cure Landscape," "What Cure Means to Women, What Women Mean to Cure," and "Barriers and Facilitators to Women's Participation in HIV Cure."

The Legacy Project's mission is to build trust and collaboration between historically underrepresented communities most impacted by the domestic HIV epidemic, researchers, and research institutions; enhance cultural competence; and initiate scientific investigation to increase clinical research participation. The Legacy Project is a part of the HIV/AIDS Network Coordination (hanc), and information about may be found on the web at <https://www.hanc.info/legacy/Pages/default.aspx> .