HIV/AIDS Cure Research
Introduction, Glossary & Resource Guide 2019 (a4)

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
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. COLORS 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 in the entire document 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 all 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 hivcureresearch@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 at least the following two 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 therapy (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 definitely been cured so far, namely, the Berlin Patient (Timothy Ray Brown) and possibly one more, namely, the London Patient. However, this approach is very impractical. It requires conditioning 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,” which would greatly increase its usefulness decrease its cost.

- **Gene editing:** One reason HIV is so difficult to cure is that, unlike almost all other viruses, it integrates 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.

- **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 replicating HIV virions (single virus particles) it destroys them. After becoming infected, many 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) until very recently there has been no accurate way to measure the number of latent infected cells; 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 T cells to kill them, its goal is to keep latent T cells from ever being activated. It is particularly important in the central nervous 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 s, natural killer (NK) cells, and immune-system-related drugs that enhance shock and kill.

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**AIDS (Acquired Immune Deficiency Syndrome)**

AIDS (Acquired Immune Deficiency Syndrome) is the final stage of HIV infection. While AIDS ended in death for almost all HIV+ 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 parts of the developed world and in much of the developing world.

**Alleles and Mutations**

An allele is a variant of a gene. Humans and all other living organisms have two related 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 in HIV 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).

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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 in 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. 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 frequently as faithful to HIV and humans as would be preferred.

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

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 antigen 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 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 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 very greatly reduces the risk of graft-versus-host disease (GVHD).

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

1. The cells to be transplanted must be modified to make them resistant to HIV infection (rather than being selected to be resistant, for example, by having the CCR5A32/A32 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. The transplanted cells must totally replace 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 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 killing 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. While Timothy is the only to have been definitively cured so far, there are two people called the London Patient and the Düsseldorf Patient who may also have been cured, though it is too soon to be certain of that.

See the Berlin Patient No. 2 Glossary entry for another, less successful, German cure attempt.

**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 to another almost always uses the CCR5 co-receptor. However, some rare strains of HIV use both the CCR5 and the CXCR4 co-receptors.) 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 consecutive 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 the CCR5 co-receptor to attach most varieties of HIV to CD4+ T cells; an intact CCR5 co-receptor is needed by almost all strains of HIV to enter and infect these cells. Almost all genes in human cells are present as two copies. 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 unless gene editing can make more instances of the mutation, which is one of the major focuses of HIV cure research. Note that “Δ” is the upper-case Greek letter “delta” and stands for the deletion. Further, CCR5Δ32/Δ32 is unfortunately associated with increased susceptibility to West Nile virus infection and a variety of encephalitis.

A research group at the Affiliated Hospital to Academy of Military Medical Sciences in China is studying the use of CRISPR/Cas9 to edit genes with the goal of deleting the 32 consecutive nucleic acids to make them CCR5Δ32/Δ32. Sangamo Biosciences has a Phase 2 clinical trial using a zinc-finger nuclease (see item 3 in the Gene Editing Glossary entry) named SB-728-T to modify CCR5 genes to make the CD4+ T cells their results appear on the surfaces of incapable of being infected by HIV (see https://clinicaltrials.gov/ct2/show/NCT01543152 for a description of the trial).

**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 that are not in the latent reservoir produce copies of HIV instead of replicating or conducting immune functions.

CD4+ T cells can develop that target parts of an infectious agent, and such cells become activated in response to later infection by that infectious agent. After the infection is cleared or controlled, they can 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.

**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). 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.

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 and 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 absolutely 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 medication 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 an advisory panel of the U.S. Food and Drug Administration (FDA) or similar agency elsewhere in the world for approval for distribution.

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 cannot infect 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).

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!

Note that, despite the extremely high frequency of mutations, this has no chance at all of eliminating HIV from a human in a lifetime!

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 as this one (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 frequency 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 interaction 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 (ART). 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 (DNA) in cells, such as removing HIV proviral DNA from a ‘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. 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).

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).

An early 2019 report of a gene-editing experiment concerns using CRISPR/Cas9 (see above) delivered by adeno-associated virus 9 (AAV-9) to cut part of the proviral SIV out of macaque (see the Nonhuman Primate (NHP) Models Glossary entry) genes as a cure strategy. Two of three SIV-infected macaques were administered the AAV-9-delivered CRISPR/Cas9 and after necropsy (i.e., killing) they and the control had
potentially SIV-infected blood cells from the animals mixed with cells susceptible to SIV infection to determine whether it could be passed on from the defective DNA. The result was positive. The author modestly suggests that this supports “the potential use of CRISPR/Cas9 technology as a curative strategy that warrants further investigation.” One possible concern is that applying this technique might result in removing a segment of DNA that spans two or more copies of the proviral DNA and, thus, make the host DNA sufficiently damaged to be ineffective; this has happened but is believed to occur very infrequently.

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 an allogeneic 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. 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 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 be much 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 remission.

**HIV Cure (Sterilizing)**
This type of cure completely eliminates HIV from an infected ‘s body, which would likely require activation and killing of all infected resting memory CD4+ T cells 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 ‘s body is impossible with current approaches, including in the case of the Berlin Patient (Timothy Ray Brown), though he has been HIV- since 2009.

**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 Prof. David Baltimore of California Institute of Technology):

- 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 acive 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 the corresponding 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 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 attack, stroke, cancer, 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 several substances and types of 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:

A latent reservoir is a tissue in which resting CD4+ T cells, effectively, go to sleep. 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 and might be latent reservoirs are at least the
following: 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.

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).

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.

It is known that

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 the brain, 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 last of these includes 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 & the Lymphatic System Introduction and Glossary entries for more information about them.

**Lymph Node Collagen Deposition**

When cells die, they are sometimes replaced by scar tissue composed of collagen, which is a protein found in numerous tissues. 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 & 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 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 (see the Lymph Node entry) and 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.

However, the Intact Proviral DNA Assay (IPDA) is the most accurate assay as of 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 RNA that is so seriously mutated as to be unquestionably defective. 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.

**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 Controller**
A post-therapy controller is HIV+ individual, so far mostly members of the VISCONTI (Viro-Immunologic Sustained Control after Treatment 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 or 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, and that can integrate its 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 at least 40 types 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.

There are also several related items in the Resource Guide.

**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.

**Analytical Treatment Interruption**
An analytical treatment interruption (ATI) is a medically monitored interruption of antiretroviral therapy (ART) as part of a cure-related clinical trial. In late 2018 there were over 20 clinical trials including an ATI ranging from planned through in process and completed but no standards for how to maximize their benefit and minimize their risk. There are several different definitions of what constitutes an ATI. There are medical and ethical considerations for each and some that straddle both categories. The medical issues include the criteria for starting and stopping an ATI (usually HIV viral load and CD4+ T cell count) that vary widely from one clinical trial to another, only quite recently has there been a significantly accurate method for measuring the size of the latent reservoir, and several more technical concerns. The ethical concerns include whether it is appropriate to include a placebo arm or a continuation of previous treatment arm in an ATI for comparison purposes and whether to use the term cure in a trial independent of whether it includes an ATI or not. There are also issues that straddle the medical and the ethical categories, such as the possibility of making the participant's HIV resistant to more antiretroviral drugs and infecting a sex partner during an ATI. See the Resource Guide entry Community Recommendations for Clinical Research Involving Antiretroviral Treatment Interruptions in Adults for a discussion of community concerns and recommendations for dealing with 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), 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 protein 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-receptor CCR5 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.

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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 was believed to be cured, was lost to follow up, and, 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 the Intact Proviral DNA Assay (IPDA) item in the Measuring the Latent Reservoir Glossary entry.

- 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/AlDS Cure 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 types of adenoviruses that are known to infect humans.

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**Aging, HIV Infection Effects & Cure**
Even well-controlled HIV infection that has reached undetectable viral load results in a vicious circle of chronic 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 lay’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 were the overwhelming norm for most HIV-positive people before 1996, with the advent of highly active antiretroviral therapy (HAART) that year they slowly retreated into the background in the developed world, though they remain a serious problem in some areas.

**Allele**
An allele is a variant form of a gene resulting from mutation. Humans and all other living organisms have two mirror-image copies of each gene, one each in corresponding positions 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, which makes them 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—what’s in between 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 “Cys” and “C”, and tyrosine “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 discussions of the ethical issues see the articles the Ethics of ART interruption after stem-cell transplantation Resource Guide entries concern.

Late 2018 was a very active time for research reports, community input, and workshops on this topic. They included consideration of the current need for ATIs, their benefits, risks, inclusion and exclusion criteria, etc. The most accessible document on the subject both in its reading level and its being freely available on the Web is the Resource Guide entry Community Recommendations for Clinical Research Involving Antiretroviral Treatment Interruptions in Adults for a discussion of community concerns and recommendations for dealing with them.

Animal Models
Animal models, such as macaque monkeys and bone marrow-liver-thymus (BLT) mice, 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 humans and HIV 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 replication 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.

Apheresis
Apheresis 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—apheresis is from the Greek for “taking away”—and the remaining blood is returned to the body via the other catheter. The quantity of white cells collected is never enough to affect immune function. Apheresis is used in several areas of cure research, most prominently in some of the methods for determining the effectiveness of latency reversal.

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 (Tcm) and transitional memory T cells (TTM). It has also been shown in the macaque nonhuman primate (NHP) model, 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 totally replace or at least 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 the blood.

Barcelona Patients
The Barcelona patients are five of the 13 participants in a shock-and-kill clinical trial. All 13 received romidepsin (see item 1 in 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 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 London Patient and Düsseldorf Patient Glossary entries for descriptions of two other persons who may be the second and possibly third(s) to have been cured.

There was a second Berlin Patient (see the Berlin Patient No. 2 Glossary entry below), namely, a man who used the pseudonym Christian Hahn. See the Berlin Patient No. 2 entry below for a description of his case.

Berlin Patient No. 2
The person I’m calling Berlin Patient No. 2 was a man who used the pseudonym Christian Hahn and had 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 he 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.

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. A description of the trial can be found at https://actgnetwork.org/study/a5345.

Bone Marrow-Liver-Thymus (BLT) Mouse
A bone marrow-liver-thymus (BLT) mouse, developed in the 1990s by Joseph M. “Mike” 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.”

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, or to kill HIV-infected CD4+ T cells shocked out of latent reservoirs.

Cancer

Several types of cancers are serious enough co-morbidities with HIV infection that researchers have been encouraged to attempt cure or remission of both the HIV infection and the cancer by hematopoietic stem cell transplantation (HSCT). They are discussed here:

- Leukemia is a cancer of the bone, 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).
- 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.”

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 related chemokines are named as a ligand and its receptor, for example, CCL2 and CCR2.

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

**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 named 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 of 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.

**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 the CCR5 co-receptor to function on CD4+ T cells; the CCR5 co-receptor is needed by almost all strains of HIV to enter and infect these cells. Almost all genes in human cells are present as two copies. If one copy has the Δ32 mutation, it is called heterozygous; if both copies have it, it is called homozygous. 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 unless gene editing can make more instances of the mutation, which is one of the major focuses of HIV cure research. Note that Δ” is the upper-case Greek letter “delta” and stands for the deletion. Note that CCR5Δ32/Δ32 is sometimes described as homozygous CCR5Δ32, where homozygous means derived from both parents.

A research group at the Affiliated Hospital to the Academy of Military Medical Sciences in China is studying the use of CRISPR/Cas9 to edit genes with the goal of deleting the 32 consecutive nucleic acid pairs to make them CCR5Δ325/Δ32.

A study reported in 2018 used information about more than 400,000 people of British ancestry to determine the effect of the CCR5Δ32/Δ32 mutation on death rate. It showed an estimated 21% increase in death rate in the age range from 41 to 78. It is known that the mutation facilitates recovery from stroke, and that it may provide protection from smallpox and another less commonly known viral infection named flavivirus, but it appears to reduce protection against influenza and several other viral diseases, including West Nile virus infection and a variety of encephalitis.

**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. CD4 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 Cell**

CD4+ T cells are primary white blood cells of the adaptive immune system that have the receptor CD4 on their surfaces; 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 future infections by that pathogen. They may 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 or possibly the entire latent reservoir of HIV.

**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 Cell

A CD8+ T cell is a primary white blood cell of the adaptive immune system that has the receptor CD8 on its surface and that is responsible for recognizing infected CD4+ T cells, among other duties, the most important of which is killing infected or disabled cells as directed by CD4+ T cells. 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. 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 propagation of HIV in a, perhaps accounting for more than 50% of newly infected cells.

Central Memory CD4+ T Cell (T<sub>CM</sub>)

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<sub>CM</sub>) 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 (ART) 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 and established very early in HIV infection.
2. It can only be reached by a small minority of HIV antiretroviral medications.

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).
HIV gp120 glycoprotein impacts the function of neurons. And 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 but that blocks large molecules 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 gp120, have been shown to enter neurons and have pathogenic effects.

Neurofilament light-chain protein (NFL) is a protein found in the central nervous system that may be a significant biomarker for the effect of HIV on nerve cells.

A 2015 substudy of a latency reversal clinical trial using the histone deacetylase inhibitor (HDACi) panobinostat (see thenLatency 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.

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 specific to HIV.
- 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.

Research has shown that clade variation contributes to the magnitude of HIV's replication capacity via variations in part of the gp41 glycoprotein.

**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 for the same purpose 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 effectiveness and side effects.

In some cases, 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 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 enroll in the trial. 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. 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 (both for specialists and non-specialists) 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 from a parent cell of numerous daughter cells with identical genomes. 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 variants of HIV use a co-receptor named CCR5 rather than CXCR4; those variants almost always occur early in 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 even rarer 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 or monocytes. 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 immune system usually keeps it from causing illness. However, CMV infection can cause serious health problems for people with compromised immune systems, including those who are HIV+.

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 they are 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 15,000 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, research reported in 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, to 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 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 direct contact with the environment.

**Droplet Digital Polymerase Chain Reaction (ddPCR)**

Droplet Digital PCR (ddPCR) is a method for performing digital polymerase chain reaction that uses water-oil emulsion droplets. A sample is divided into 20,000 droplets, and PCR is performed on the molecules in individual droplets, and the results are combined digitally. 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) antibodies 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 isolating the antibody from an HIV+ person’s blood and characterizing it.

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 person born in 1973 who had HIV infection diagnosed in October 2010 and was found in January 2011 to have acute myeloid leukemia (AML) (see the Cancer Glossary entry) also. Note that the research report about the patient’s case does not indicate his or her sex; from here on, for simplicity, we assume male. He was treated with chemotherapy for his AML, and after complete remission of it had a relapse in September 2012; he was treated again with chemotherapy and achieved a complete remission again in November 2012. In February 2013 he had an autologous CCR5Δ32/Δ32 hematopoietic stem cell transplant (HSCT) in an attempt to cure both his HIV infection and AML. In May 2013 he had a second relapse and again achieved a complete remission in September. In March 2014 he began to have graft-versus-host disease (GVHD), which lasted through at least February 2015 (the last date in the timeline in the research report). In the entire period from April 2011 through February 2015 his HIV viral load was undetectable, i.e., <40 c/ml. He has remained on antiretroviral therapy (ART) and, before discontinuing it, further tests were planned as of January 2016. Since then he has been off antiretroviral therapy for 3½ years, so it is cautiously suggested that he may be the second person to be cured of HIV by the type of treatment used for the Berlin Patient (Timothy Ray Brown) (or the third if the London Patient turns out to be the second).

**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 (TEM) to levels typically found in naive CD4+ T cells (T0) 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 (TEM)**

An effector memory CD4+ T cell (TEM) is a CD4+ T cell that is replicating in response to a pathogen and quickly mounting an immune response to it.

**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 by CD4+ T cells. 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 at least 10 years and all measured viral loads < 50 copies/ml of T cells that participate in distinguishing between self and non-self. In particular, they suppress the activity of the immune system positive people known as CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) 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), 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 or a CD4+ T cell.

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### Effects of Estrogen on Immune-System Cells

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cells</td>
<td>• Increases expression of CCR5 and CCR1;</td>
</tr>
<tr>
<td></td>
<td>• Lower doses enhance Th1 cell response;</td>
</tr>
<tr>
<td></td>
<td>• Higher doses enhance Th2 cell response; and</td>
</tr>
<tr>
<td></td>
<td>• Expands Treg cells</td>
</tr>
<tr>
<td>B cells</td>
<td>• Increases survival;</td>
</tr>
<tr>
<td></td>
<td>• Decreases apoptosis; and</td>
</tr>
<tr>
<td></td>
<td>• Increases certain immunoglobulins</td>
</tr>
<tr>
<td>Natural Killer (NK) cells</td>
<td>• Lower doses increase cytotoxic activity; and</td>
</tr>
<tr>
<td></td>
<td>• Higher doses decrease cytotoxic activity</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>• Increases production of several cytokines; and</td>
</tr>
<tr>
<td></td>
<td>• Promotes cell differentiation</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Enhances anti-inflammatory activity</td>
</tr>
<tr>
<td>Macrophages &amp; Monocytes</td>
<td>• Lower doses promote cell differentiation and stimulate cytokine production; and</td>
</tr>
<tr>
<td></td>
<td>• Higher doses reduce expression of CD16 and decrease cytokine production</td>
</tr>
</tbody>
</table>

**Table 1.** Estrogen’s impact on immune system cells.

For explanation of terms see the notes immediately below.

Notes: (1) Th1 and Th2 cells are varieties of CD4+ T cells; Th1 cells act against bacteria and viruses inside cells; Th2 cells act against parasites outside cells; CCR1 is a receptor that affects differentiation of hematopoietic stem cells; it is also critical for the recruitment of immune-system cells to sites of inflammation. (2) Treg cells are regulatory T cells, 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. (3) Monocytes are the largest white blood cells; they have multiple roles in immune function including replenishing macrophages, and responding to inflammation. (4) Dendritic cells are antigen-presenting cells of the immune system. In most cases, the antigens are acquired from outside the body. (4) Dendritic cells are one type of antigen-presenting cells of the immune system. In most cases, the antigens are acquired from outside the body. (5) Neutrophils are a component of the innate immune system and 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. (6) CD16 is found on the surface of natural killer cells, neutrophils, monocytes, and macrophages.

**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.

**Estradiol, Estrogen, Progesterone, and Estrogen Receptors**
Estadiol, 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 regulates the uterus’s lining and 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 has maintained peripheral blood HIV aviremia and had a normal CD4+/CD8+ T-cell ratio, so far, for 13 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

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

Table 2. Fiebig stages, characterizations, and durations.

Notes: (1) 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). (2) After seroconversion an HIV antibody test, such as the ELISA (Enzyme-Linked ImmunoSorbent Antibody) tests positive. See the Seroconversion Glossary entry for a
description of the ELISA test. (3) 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 (DNA) in cells, e.g., removing HIV proviral DNA from the cells’ DNA or altering the CD4 receptor, CCR5 coreceptor, 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 three approaches, CRISPR is by far the most important, and the others 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.

An early 2019 report of a gene-editing experiment concerns using CRISPR/Cas9 (see item 1 below) delivered by adenovirus-associated virus 9 (AAV-9) to cut part of the proviral SIV out of macaque (see the Nonhuman Primate (NHP) Models Glossary entry) genes as a cure strategy. Two of three SIV-infected macaques were administered the AAV-9-delivered CRISPR/Cas9 and after necropsy (i.e., killing and dissection) they and the control had potentially SIV-infected blood cells from the animals mixed with cells susceptible to SIV infection to determine whether it could be passed on from the defective DNA. The result was positive. The author modestly suggests that this supports “the potential use of CRISPR/Cas9 technology as a curative strategy that warrants further investigation.” One possible concern is that applying this technique might result in removing a segment of DNA that spans two or more copies of the proviral DNA and, thus, make the host DNA sufficiently damaged to be ineffective; this has happened but is believed to occur very infrequently.

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. **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.

3. **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 using SB-728-T and 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). SB-728-T is an experimental gene-therapy product.

**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 comprises Env and 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 the Env item in the HIV Structure & Function Glossary entry.

**gp120**
gp120 is a component of the HIV glycoprotein gp160 that comprises Env and sticks out of the HIV virion; note that it occurs as a trimer, that is, three copies of it are bound together; see the Env item in 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. It 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 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 and perhaps entirely 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 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. It has also been used in the Düsseldorf and London Patients to effect what are hoped to be cures for them.

**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 that stops them from being replicated when not needed.

**Histone Deacetylase (HDAC)**
A histone deacetylase (HDAC) is an enzyme that causes chromatin to bind its DNA, stop its 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 cells 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 required, 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 strains of HIV other 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 body. It would likely require activation and killing of all infected CD4+ T cells (and probably other cells contained in latent reservoirs). Depending on the strategy used, such a 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 would not be able to transmit HIV to others. However, proving that all HIV has been eliminated from a’s body is impossible with current approaches, including in the case of the Berlin Patient (Timothy Ray Brown), though he has been HIV- for 12 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 

- rev 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 two spacers, one of the last of which is functional, 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,
  - nucleocapsid protein (NC), which forms the virion’s nucleocapsids, which are the membranes containing the RNA genome, p6, a peptide that recruits cellular proteins essential to the budding of mature virions from the cell in which they are assembled,
  - spacer peptide 1 (SP1), also called p2, whose function is to cause the capsid protein CA to become part of the virion’s capsid, and
  - 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;
- pol (polymerase) is reverse transcribed into proviral DNA named Pol that, in turn, encodes a polyprotein 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),

**HIV Genome**
The HIV nucleocapsid (see the HIV Structure & Function Glossary entry) contains the two separate single strands of RNA that comprise the virion’s 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 never directly produce proteins: The HIV genome must first be integrated into a host cell’s DNA as proviral DNA that is, in turn, used to produce 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.](image-url)
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, which abbreviates long terminal repeat and is a sequence of ~640 bases that are identical across the two LTRs; HIV's right-end long terminal repeat undergoes retrotranscription 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;
  - PolyA, 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 nucleosides 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 and by the shock step of shock and kill.

**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 matrix (light blue) made up of matrix protein or p17, which contains essential proteins and the capsid;
- 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 and a peptide, namely, reverse transcriptase (RT), integrase (IN), Vif, Vpr, Nef, and p7, which are described below.

- **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;
- **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 it 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 positive individuals.

**HIV Viremia during Suppressive Antiretroviral Therapy (ART) and Its Treatment**
HIV viremia (i.e., measurable viral load) during suppressive antiretroviral therapy (ART) occurs in roughly 10% of adherent patients and is a phenomenon that has frustrated both physicians and researchers. The well-known reason for persisting viremia is the replication and budding of new HIV virions from infected cells. But this is not the case in people with suppressive ART. Instead, the mechanism of continuing low-level viremia is virions with identical RNA at different times, called proliferation—described at the 2019 Conference on Retroviruses and Opportunistic Infections—is what are now called repliclones, i.e., clones of the same infected parent cell that continue to be replicated.

The treatment approach under consideration by at least three groups is anti-proliferation medications. One with results expected in early 2020, at the Fred Hutchinson Cancer Research Center, Seattle, WA, is using a potent anti-proliferative named Mycophenolate Mofetil (brand name CellCept); a second at UCSF is using sirolimus (see the Latency Reversal entry, item 5); and the third at the Istituto Superiore di Sanità, Rome, is using the much less toxic auranofin.

**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 (glycans) cover almost its entire 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.

**HIV-2**
HIV-2 is a virus distinct from but quite similar to HIV-1, which is what is referred to...
Figure 4. A cutaway schematic of the structure of an HIV virion.

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+ 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 their 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 certainly applicable to HIV-2 also.

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 their having relevant genetic differences or possibly 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.

**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 may serve as a very useful model for testing strategies for latency reversal and other approaches to 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 down-regulating T cell signals. For an example, see PD-1 in items 2 and 4 in the Latency Reversal Glossary entry.

**Immune System**

The innate 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 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 (Tcm) T cells, effector memory (Tem) T cells, and stem-cell-like memory (TSCM) T cells), CD8+ T cells, T follicular helper (Tfh) cells are found in lymph nodes and other lymphoid tissues, including the spleen and Peyer’s patches, and are a minor latent reservoir for HIV proviral DNA, T helper 17 (Th17) cells, and at least a half dozen other types; see the entries for the underlined cell types for descriptions of their roles in immunity.

**In Vitro, In Vivo & Ex Vivo**

In vitro (from Latin, literally “in glass”) is used in biological research to mean “in the laboratory,” “in vivo” (also from Latin, literally “in life”) means in a human or other life form, and “ex vivo” (also from Latin, literally “from life”) means extracted from life and done in a laboratory. All three 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, naive (that is, undifferentiated) CD4+ T cells (Tn) 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**

Inflammation is a process in which 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 is known to cause chronic inflammation, even in those whose virus is either suppressed naturally (elite controllers) or by antiretroviral therapy (ART), which can lead to cardiovascular disease, cancers, and other serious health conditions. Cells activated by chronic inflammation 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, 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 lay 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 α4β7 (alpha 4 beta 7) that 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 commonly, 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 the shock component of shock and kill. It 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 by the kill step. This is considered by many HIV cure researchers to be fundamental to curing HIV. The following are five 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.

1. **Histone Deacetylase Inhibitor (HDACi):** A histone deacetylase inhibitor (HDACi) causes chromatin to release its HIV proviral DNA to be replicated and become exposed to the immune system and potentially to killing agents. Numerous examples that have been used in latency reversal studies are belinostat (product name Beleodaq), droxinostat, givinostat, oxamflatin (brand name Metacept), panobinostat (product name Farydak), romidepsin (brand name Isto), Scriptaid, trichostatin A, and vorinostat (formerly and still occasionally called SAHA and brand named Zolinza). Romidepsin has appeared to be the most effective HDACi for reversing latency, but a recent clinical trial had disappointing results: essentially no infected cells emerging from latency by very sensitive assays. A brief description of the clinical trial can be found at [https://actgnetwork.org/actg-croi-2018-wrap-up](https://actgnetwork.org/actg-croi-2018-wrap-up).

2. **Immune Checkpoint Inhibitors:** Immune checkpoints, such as Programmed Cell Death 1 (PD-1) (described in item 4 below), mark TCM and TEM cells. Checkpoint inhibitors, in turn, block the activity of immune checkpoints. This makes checkpoint inhibitors useful for latency reversal. See also the Immune Checkpoint Glossary entry.

3. **Programmed Cell Death 1 (PD-1) and Programmed Cell Death Ligand 1 (PD-L1) Inhibitors:** Programmed cell death 1 (PD-1) 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) 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.

4. **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.

5. **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 agonist named GS-986 that was reported in 2017 to lead to complete remission in a group of SIV+ rhesus macaques.

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 of cure research.

**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) 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 could create if it were applied to the central nervous system (CNS). Several approaches are being explored, including at least the following:

- 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:

A definite latent HIV reservoir is resting memory CD4+ T cells in lymph nodes. Other tissues that contain significant amounts of infected CD4+ T cells and might be latent reservoirs are at least the following: monocytes (white blood cells; 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 Vγ9Vδ2 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.

The latent HIV reservoir is the totality of the types described 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. A 2011 survey article noted what is known 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, 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 latent reservoir precludes its elimination by antiretroviral therapy for the lifetime of the 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. 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 Eisele E Siliciano RF “Redefining the Viral Reservoirs that Prevent HIV-1 Eradication” is freely available from the 21 September 2012 issue of the journal Immunity. It can be downloaded from 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. A more easily readable freely available article in the open access journal Viruses on several topics related to the latent reservoir is “Cat and Mouse: HIV transcription in Latency, Immune Evasion and Cure/Remission Strategies” Delannoy A Poirier M Bell B 18 March 2019 that can be downloaded from https://www.mdpi.com/1999-4915/11/3/269. Note that this article has an incredible 301 references.

**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** is cell division occurring 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 human leukocyte antigen 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) with the same DNA as the parent cell. If the original cell is a non-latent CD4+ T cell, all the cells in the clone are specific to the same antigen, namely, that of the parent cell. A study reported in 2018 suggests that after one year on suppressive antiretroviral therapy (ART), greater than 99% of infected cells are the result of this mechanism.

**Latent Reservoir Reduction to Achieve HIV Cure (Functional) or Remission**
Estimating the amount of latent reservoir reduction necessary 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 roughly a factor of only 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.

**Lentivirus**
A lentivirus, such as HIV or simian immunodeficiency virus (SIV), is a type of retrovirus that causes delayed onset of symptoms. 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 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.

**Ligand**
A ligand is a chemical that binds to a receptor to cause a biological action. A ligand and its receptor often have closely related names, such as CCL2 and CCR2 or PD-1 and PDL-1.

**London Patient**
The London Patient is a man who may be the second (or third if the Düsseldorf Patient has been cured) to have been definitively cured of HIV infection. This man’s case was reported in March 2019 by Prof. Ravindra Gupta of the University of Cambridge while at University College London’s Division of Infection and Immunology. The man had an allogeneic hematopoietic stem cell transplant to cure his stage 4B (i.e., very serious) Hodgkin’s Lymphoma (also known as Hodgkin disease), a cancer of white blood cells. The best matched donor for the lymphoma fortuitously had the CCR5Δ32/Δ32 mutation. His conditioning was significantly less aggressive or toxic than the Berlin Patient’s (Timothy Ray Brown’s), and he required only one transplant rather than two. He had mild graft-versus-host disease in the gut and continued antiretroviral therapy (ART) for 16 months after transplant. Since stopping therapy she or he has had, by the time of the report, 18 months of no detectable HIV by the most sensitive test available (1 copy/mL of blood). Unfortunately the remission achieved is so far too short to pronounce this man definitively cured.

**Los Angeles Baby**
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 beginning four hours after 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 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 the 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 infection and may be largely complete within months. It is believed 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 uses any of at least nine co-receptors other than CCR5 and CXCR4; some such virions attack macrophages directly. Recent research strongly suggests that HIV is the only thing that buds from macrophages. The budded HIV is all defective.

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**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.

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

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**Measuring the Latent Reservoir**
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, and this 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. A new technique was reported in 2018 that is believed to be much more accurate than previous methods. See item 2 below for a description of it.

1. The quantitative viral outgrowth assay (qVOA) counts only replication-competent latent provirus and then uses a statistical approach to estimate the size of the whole reservoir. It begins by collecting very pure latent resting memory CD4+ T cells by apheresis. It then...
dilutes the cells in several steps and reactivates them. Then activated CD4+ T cells also collected by apheresis but 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 assay is complex and expensive and has the added disadvantage of being very likely to underestimate the actual size of the latent reservoir by as much as a factor of 70. 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. We mention qVOA because it is considered to be the gold standard of measurement approaches, not because of its (in)accuracy but because of its history.

2. The Intact Proviral DNA Assay (IPDA) is the most accurate assay as of 2018. It uses two DNA sequences to probe the HIV genome. One sequence detects deletions in a virion’s genome large enough to make the it 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 show that it eliminates ~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.

**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 the nucleic acids in 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 unfortunately beyond the scope of this document.

**Microbial Translocation**

The gut contains bacteria constituting the intestinal microbiome that may be either helpful 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, in turn, 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. She 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 an antibody produced industrially by bacteria with a genome that has been altered to be specific to the antibody.

**Monocyte**

A monocyte is a type of white 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 local inflammation. They may 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 chemotherapy, radiation, or both sufficient to destroy the myeloid cell products 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 (types of white blood cells), a red blood cell, or a platelet.

**Naïve CD4+ T Cell (TN Cell)**
A naïve CD4+ T cell (TN 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 (TSCM), central memory CD4+ T cells (TCM), effector memory CD4+ T cells (TEM), and circulating CD4+ T cells. Recent research has shown that naïve CD4+ T cells may be 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 the general population. 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 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 the Bone Marrow-Liver-Thymus (BLT) Mouse Glossary entry for a description of another mammalian model used in cure research.

**Nucleic Acid (Base)**
A nucleic acid or base is a component of DNA or RNA, each of which has four types of nucleic acids, including three that 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 $4 \times 4 \times 4 = 64$ distinct triplets but only 20 different amino acids. There are also codons that start and stop the transcription process to messenger RNA.

**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.

**Peptide**
A peptide is a short sequence of amino acids similar to a protein in its composition.
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. They are so far mostly the VISCONTI Viro-Immunologic Sustained CONtrol after Treatment Interruption) cohort in France, who consist of Caucasian women and men and African men and women (the largest fraction are Caucasian men who account for about 2/3 of the total) who started antiretroviral therapy (ART) within weeks of infection, stayed on therapy for an average of about three years (range: 24 – 73 months), and then, for various reasons, stopped therapy. Five of the members resumed therapy after a mean of 8.7 years (range: 2.1 – 14.3 years). Because there has been no large or lasting rebound of HIV among the others, most of these individuals have been able to stay off therapy for long periods, so far as long as a mean of 12 years.

- Fourteen of these post-therapy controllers have never had a detectable viral load, and they are the ones now known as the VISCONTI cohort.
- Four have had at least one detectable viral load (“blip”), but never higher than 400 c/ml, and remain off ART; and
- The remaining 7 have at least one blip > 400 c/ml — 2 of them are undetectable and the other 5 have resumed antiretroviral therapy.

We thank Asier Saez-Cirion of the Institut Pasteur in Paris for the preceding update. Unlike the majority of elite controllers, these individuals 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 Southeast Asian Research Collaboration with Hawaii) who started antiretroviral therapy (ART) within two weeks of infection, and 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 CCR5Δ32/Δ32 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. 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. 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.
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. The "transplant in a box" approach described in both the allogeneic and autologous transplant
Glossary entries will solve this problem some day.

**Proviral DNA**
Provir (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.

**Proviral DNA**
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**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 for this purpose.

**Receptor**
A receptor, in the context of HIV medicine (including cure research), is a chemical (such as CD3, CD4, or CD8) 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.

**Remission**
Remission is a term preferred by many researchers for HIV Cure (Functional) because functional cures, like remissions 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 33 cases of remission.

**Remission in Macaques Using an Antibody to the Integrin α4β7**
It has recently been shown in a study of SIV-infected macaques that an antibody to the integrin α4β7 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 α4β7 has multiple uses making suppressing it potentially dangerous. See also “Anthony Fauci Explains Alpha-4 Beta-7 and HIV” in the Resource Guide.

Another study of remission in rhesus macaques is discussed in the Viral Rebound Glossary entry.

**Replication-Competent Latent Proviral DNA**
Replication-competent latent proviral DNA is HIV proviral DNA in cells (probably always or almost always CD4+ T cells) that may produce new HIV virions.

<table>
<thead>
<tr>
<th>Name</th>
<th>No.</th>
<th>Sex</th>
<th>Length of Remission</th>
<th>On ART?</th>
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</thead>
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<tr>
<td>Australian Patients</td>
<td>2</td>
<td>M</td>
<td>2 yrs./3 yrs.</td>
<td>Yes</td>
</tr>
<tr>
<td>Barcelona Patients</td>
<td>5</td>
<td>?</td>
<td>≤ 6 mos.</td>
<td>Yes</td>
</tr>
<tr>
<td>Boston Patients</td>
<td>3/2</td>
<td>M</td>
<td>1 died/2.6 yrs./4.3 yrs.</td>
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</tr>
<tr>
<td>Düsseldorf Patient</td>
<td>1</td>
<td>M</td>
<td>4 mos.</td>
<td>No</td>
</tr>
<tr>
<td>Ethiopian Patient</td>
<td>1</td>
<td>M</td>
<td>10 yrs.</td>
<td>?</td>
</tr>
<tr>
<td>London Patient</td>
<td>1</td>
<td>M</td>
<td>18 mos.</td>
<td>No</td>
</tr>
<tr>
<td>Los Angeles baby</td>
<td>1</td>
<td>F</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Mississippi baby</td>
<td>1</td>
<td>F</td>
<td>4 yrs.</td>
<td>No</td>
</tr>
<tr>
<td>Paris Patient</td>
<td>1</td>
<td>M</td>
<td>Died</td>
<td>No</td>
</tr>
<tr>
<td>Rochester Patient</td>
<td>1</td>
<td>?</td>
<td>288 days</td>
<td>No</td>
</tr>
<tr>
<td>Utrecht/EPiSTEM Patients</td>
<td>2</td>
<td>M</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>VISCONTI cohort</td>
<td>14</td>
<td>B</td>
<td>≤ 10 yrs.</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 3. Summary of 33 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.

bAs noted in the London Patient and Düsseldorf Patient Glossary entries, these may be cures.

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

d“B” indicates both sexes.
**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.

**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.

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

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

1. 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.
2. 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; if only a hydrogen is attached to a carbon, it is not shown either). Note: and an oxygen.
3. Consecutive riboses are connected with phosphate groups.
4. The carbon 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.
5. 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: adenine, cytosine, guanine, and uracil.

6. The oxygen hanging off the bottoms of the phosphate groups has only one connection but its valence is two; the available connection would connect to the corresponding oxygen in a double-stranded RNA, but in a single stranded one (such as HIV’s genome) it has a hydrogen there.

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 types of RNA with distinct functions. Several of them are described in entries in this Glossary, namely, cell-associated RNA (cRNA), 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. A short interfering RNA, is a double-stranded RNA molecules, 20 – 25 base pairs in length that interferes with the expression of particular genes.

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 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 this person’s 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.

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

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 1B/IIA clinical trial that administered a series of immunizations using a therapeutic vaccine named Vacc-4-x and a biochemical named GM-CSF to increases the effectiveness of the vaccine. GM-CSF induces the creation of macrophages and another type of white blood cells named granulocytes; it's followed by three infusions of romidepsin (see item 1 in the Latency Reversal Glossary entry) and killed by an HIV-specific CD8+ T cell response. REDUC is listed in the EU Clinical Trials Register as number 2013-004747-23.

Short Hairpin RNA (shRNA)
A short hairpin RNA (shRNA) is an artificial RNA with a tight hairpin turn that can be used to silence target-gene expression via RNA interference (RNAi).

Simian/ Human Immunodeficiency Virus (SHIV)
Simian/human immunodeficiency virus (SHIV) is a series of chimeric retroviruses created in laboratories with genetic material that is a combination of simian immunodeficiency virus (SIV) genes and HIV genes. They are capable of infecting almost every type of nonhuman primate that can be infected with SIV. They serve as models of human infection with HIV.

Simian Immunodeficiency Virus (SIV)
Simian immunodeficiency virus (SIV) is a series of retroviruses that infect nonhuman primates. They serve as models of human infection with HIV. 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.
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).

The first step in the creation of new virions is transcription of the HIV proviral 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 (MsRNAs) make proteins that are essential for next making unspliced RNA (UsRNA). 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.

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 genes gag, pol, env, vif, vpu, and vpr, respectively, that are essential to the creation of new HIV virions (as for MsRNA, 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 (TSCM)**

Stem-cell-like memory CD4+ T cells (TSCM) 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 (TCM), transitional memory CD4+ T cells (TTh), effector memory CD4+ T cells (TEM), and circulating CD4+ T cells.

**Sterilizing Cure**

See HIV Cure (Sterilizing).

**T Follicular Helper Cell (Tfh)**

T follicular helper cells (Tfh) 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.

**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 hematopoietic stem cells that produce 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 or peptide being assembled. It moves the amino acid from the mRNA to the organelle called the ribosome that actually assembles the amino acid sequences of proteins and peptides.

**Transitional Memory CD4+ T Cell (TTh)**

A transitional memory CD4+ T cell (TTh) is a type of memory CD4+ T cell that is in the process of transitioning from being a central memory CD4+ T cell (TCM) to an effector memory CD4+ T cell (TEM).

**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 patients 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 experienced significant graft- versus-host disease (GVHD) that seems to have contributed to his lower viral load post-transplant than the other one had. EPISTEM abbreviates “European Project to guide and investigate the potential for HIV cure by STEM 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), protein, or a vaccine into human cells or the body as a whole. Vectors are used in both HIV prevention research to deliver a vaccine and in cure research to deliver a therapeutic vaccine.

**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**
Viral rebound refers to the level of virus found in the blood after an analytical treatment interruption.

A hopeful study of delayed viral rebound and remission in SHIV-infected rhesus macaques was reported in 2018. 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 (a neutralizing antibody is an antibody that makes an antigen ineffective; a broadly effective one neutralizes a broad range of antigens), (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 bNAb 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 437-fold reduction of peak viral load and a 33-fold 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 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, after an analytical treatment interruption etc. It also applies to SIV and SHIV infection in the nonhuman primate (NHP) models.

Viremia
Viremia is the presence of virions. Its opposite is aviremia, which (obviously) is the absence of virions.

Virion
A virion is a single complete virus particle that consists of an RNA or DNA core with proteins, such as enzymes, and usually with a containing membrane. It is the extracellular form of a virus.

Women’s Involvement in Cure Research Studies
A recent open-access viewpoint article is ME Grewe Y Ma A Gilbertson et al. Women in HIV cure research: multilevel interventions to improve sex equity in recruitment that can be read or downloaded as a PDF from the URL http://viruseradication.com/past_articles/issue_text_search/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 as a PDF from Squires K Feinberg J et al Insights on GRACE (Gender, Race, And Clinical Experience) from the Patent’s Perspective: GRACE Participant Survey AIDS Patient Care and STDs 2013 at 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.

There are also several related items in the 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 of 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 (eradicate 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.bsrisf.org/; Oregon Health and Science University’s website is http://www.ohsu.edu/; 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 α4β7 integrin in HIV treatment and cure. The YouTube video is at https://www.youtube.com/watch?v=nQh9knbmtwo .

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 abstract may be found at https://sph.unc.edu/files/2017/05/dube_hpmdrph_abstr act.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 investigators are Douglas Nixon, MD, PhD, of George Washington University in Washington, DC, and R. Brad Jones, Weill Cornell Medicine, New York, NY. 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: https://www5.usp.br/english/?lang=en);
- 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/hfpgs/bidmc.aspx);
- the University of Pennsylvania (website: https://www.upenn.edu);
- Georgetown University (website: https://www.georgetown.edu);
- 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 (http://www.thebody.com/) is “The Complete HIV/AIDS Resource” for people 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 for Regenerative Medicine (CIRM) HIV Cure Research Grants**

The California Institute for Regenerative Medicine (CIRM/“California’s Stem Cell Agency”) has given out, as of this writing, 6% of its funds in grants for HIV cure research and has three active HIV-related projects. They can be found listed at https://www.cirm.ca.gov/grants?field_public_website_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.

**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.
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 a trial number there will take you to the corresponding 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 (14C)
Combined Immunologic Approaches to Cure HIV-1 (14C) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. It’s headquarters is at Beth Israel Deaconess Medical Center, Boston (website: http://www.bidmc.org/ ). Its principal investigators are Dan Barouch of Harvard University, John Mellors of Pittsburgh University, and Nelson Michael of the U.S. Military HIV Research Program. 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.”

Community Recommendations for Clinical Research Involving Antiretroviral Treatment Interruptions in Adults
Community Recommendations for Clinical Research Involving Antiretroviral Treatment Interruptions in Adults is a compilation of material from several community events and Treatment Action Group (TAG) input on the subject of its title above. It is available on the Web at http://www.treatmentactiongroup.org/content/community-recommendations-clinical-research-involving-antiretroviral-treatment-interruptions .

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/ . amfAR is the American Foundation for AIDS Research.

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.

**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

The last item is a reference to the Delaney AIDS Research Enterprise (DARE) to Find a Cure website, which includes a link to the most recent available 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 OF HIV: A COMMUNITY Q&A with TIMOTHY RAY BROWN & GERÖ HÜTTER, M.D.**

CURED OF HIV: A COMMUNITY Q&A with TIMOTHY RAY BROWN & GERÖ 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/NOT CURED on Seattle Channel's Town Square**

CURED/NOT CURED on Seattle Channel's Town Square is a YouTube video of one of the two living 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-Reversing Agents
5. Measuring the Latent HIV Reservoir
6. Regulatory Issues in HIV Cure Trials
7. Early ART
8. Pediatric HIV Cure
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

While the CUREiculum is an excellent resource, it seems to have been abandoned. Nothing appears to have been changed on its web page in at least two years.

**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 is initially

- defining the role of reservoirs that enable SIV or HIV to persist during antiretroviral therapy (ART) and using the monkey model to develop therapies to breach them;
- characterizing the distribution of replication-competent latent provirus in lymphoid tissues in ART-suppressed adults and developing positron emission tomography (PET) imaging techniques to quantify the reservoir; defining the role of immune checkpoints, such as PD-1, and their blockade on T cell function in monkeys and people; 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;
- defining the role of immune checkpoints, such as PD-1, and their blockade on T cell function in monkeys and people; and
- defining 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 J. 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;
- zinc-finger-nuclease-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 nucleases 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, DPhil, 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 α2b. Pegylation is an organic chemical process that attaches PolyEthylene Glycol (hence the “peg” in the term) 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.. and
- a gene therapy strategy using CCR5Δ32/Δ32 CD8+ T cells.

**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 or 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. It currently provides access to over 35,000 trials of which over 1,100 are HIV related.

**Gene Therapy Researchers’ Assessments Of Risks And Perceptions Of Risk Acceptability In Clinical Trials**
Gene Therapy Researchers’ Assessments Of Risks And Perceptions Of Risk Acceptability In Clinical Trials is an article that discusses what its title describes. In particular, it focuses on the responses of 156 researchers to a survey and concludes that “researchers' perceptions of clinical context and the strength of preclinical evidence strongly influenced risk assessments and judgments of acceptable risk levels.” It helps to get full benefit from this article to know some statistics, but even readers who do not are likely to get some benefit from it. One further caveat is that the article is from 2013, so it is not truly up to date. The article can be read online and downloaded at https://www.sciencedirect.com/science/article/pii/S1525001616306542.

**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 at https://www.youtube.com/watch?v=dsQzEEAIUMCU.

**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 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 and it is somewhat dated, 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 at a conference by its developer Janet Iwasa of the University of Utah in 2018. 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 https://www.sciedirect.com/science/article/pii/S152500161306542. The narrated version can be downloaded from http://scienceofhiv.org/downloads/HIV_narrated.mov.

**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.

**International Clinical Trials Registry**
The International Clinical Trials Registry is a list of clinical trials maintained by the World Health Organization (WHO). Its English access point is https://www.who.int/ictrp/en/, and the list itself can be searched by selecting “Search portal” on the left of that page and “Access the ICTRP Search Portal” in the first line of the resulting page. As is appropriate for an international list it can also be accessed in Arabic, Chinese, French, Russian, and Spanish by selecting a language at the top of that page.
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. Its website is "http://www.irsicaixa.es/en.

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. It’s 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. Project Inform, unfortunately, closed its doors in spring 2019.

In 2009, Martin 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”.

National Association of People with HIV Australia’s HIV CURE
The National Association of People with HIV Australia’s HIV CURE website includes information about cure science, clinical trials, community, cure-related media resources and video. Its website’s URL is http://hivcure.com.au. It includes an archive of resources from previous years.

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

Perceptions of HIV cure research among people living with HIV in Australia

Perceptions of HIV cure research among people living with HIV in Australia is an article in the Public Library of Science journal PLoS ONE that explores what its title describes. It includes general descriptions of the 20 participants (18 men and 2 women; ages; sexuality; time since diagnosis ranging from < 12 months through 30 – 40 years; and degree of willingness to participate in cure clinical trials); the complete interview guide; quotations from the participants concerning attitudes about cure research and willingness to participate; and an extensive series of references. The article can be viewed or downloaded from http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0202647.

POSITIVELY AWARE, winter 2017/ 2018 “The Cure Issue”

The Cure Issue of the magazine Positively Aware (winter 2017/2018) with guest editors David Evans (formerly 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 cure,
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.
15. Q & A with Susana Valente.

The two Q & As at the end concern gene editing and block and lock (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 in the Positively Aware archive, whose website is https://www.positivelyaware.com/archive.

Primer on Cure

Primer on Cure is the slide deck for a presentation by Carl Dieffenbach, PhD, the Director of the NIH Division of AIDS, about the subject of its title. Note that “TRB” on slide 17 are the initials of the Berlin Patient (Timothy Ray Brown). It can be downloaded from the webpage http://www.treatmentactiongroup.org/content/pre-crocio-community-hiv-cure-research-workshop-2019 by selecting the 2:05-2:45pm item in orange. The link “video” in parentheses will take you to a YouTube video of Dr. Dieffenbach’s presentation.

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 therapy (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 al 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 altruistic 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 that is 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 date. The most recent list is dated 18 April 2019, 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=qjAQSWC1TGQ

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.

In Search to Repeat “Berlin Patient” HIV Cure, Questions About How It Worked
In Search to Repeat “Berlin Patient” HIV Cure, Questions About How It Worked is a 17 October 2018 POZ magazine article derived from an early version of an article in the 20 November 2018 issue of the journal Annals of Internal Medicine titled “Mechanisms That Contribute to a Profound Reduction of the HIV-1 Reservoir After Allogeneic Stem Cell Transplant” that reports a study with six participants who survived more than two years after allogeneic transplant with hematopoietic stem cells and wild type CCR5 co-receptor, five of whom achieved sustained undetectable HIV viral load, undetectable replication-competent latent provirus, and undetectable proviral HIV DNA in both blood and tissue. The POZ article is available online at https://www.poz.com/article/search-repeat-berlin-patient-hiv-cure-questions-worked

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
The Strategies for an HIV Cure meetings (so far for 2012, 2014, 2016, and 2018) were convened by the NIH various locations in and near Washington, DC. The purpose of the first two meetings was to bring together researchers associated with each of the three original 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. The 2012 agenda can be downloaded by searching for “Strategies for an HIV Cure, November 28 - 30, 2012” on Google, and downloading it from the resulting page. The 2014 agenda can be downloaded from https://www.blsmeetings.net/hivcuremeeting2014/ and a videocast of Day 2 can be downloaded from https://videocast.nih.gov/summary.asp?Live=20242&hcp=1.. In 2016 the three original collaboratories were joined by three more. The 2016 agenda can be downloaded as a PDF from the webpage https://respond.nih.gov/conferences/hivcuremeeting2016/Pages/Agenda.aspx. The event page for the 2018 meeting is http://www.cvent.com/events/strategies-for-an-hiv-cure-2018/event-summary-67d64ae8621247079e009b4757f45c9e.aspx and videocasts of the three days’ sessions can be downloaded from that page.

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/](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.

"We Need to Deploy Them Very Thoughtfully and Carefully": Perceptions of Analytical Treatment Interruptions in HIV Cure Research in the United States—A Qualitative Inquiry
"We Need to Deploy Them Very Thoughtfully and Carefully": Perceptions of Analytical Treatment Interruptions in HIV Cure Research in the United States—A Qualitative Inquiry is an article in the January 2018 issue of AIDS Research and Human Retroviruses (vol. 34, issue 1) that presents and analyzes the results of 36 standardized stakeholder interviews with people living with HIV (12), clinician-researchers (11), and policy makers and bioethicists (13) concerning the need for analytical treatment interruptions (ATI), concerns about their impact, and the ethical issues they raise. The article raises three primary themes, as follows: (1) there was little consensus on when ATIs would be ethically warranted, (2) the commonest perceived hypothetical motivators for taking part in research including ATIs were scientific advances and altruism, and (3) the most prevalent concerns were risks related to viral rebounds. Unfortunately there is a significant charge for access to the full article.

What risk of death would people take to be cured of HIV and why? A survey of people living with HIV "What risk of death would people take to be cured of HIV and why? A survey of people living with HIV" is an article that reports the results of a survey as follows (1) it surveyed 200 people living with HIV getting care from physicians at clinics associated with two major hospitals in Boston, MA; (2) they were on stable antiretroviral therapy (ART); (3) the goal was to determine associations between benefits anticipated from a cure with risk tolerance for cure interventions; (4) Two-thirds expected their health to improve if they were cured; (5) about 40% predicted HIV medications would become ineffective in the next 20 years and more than 50% predicted they would have serious side effects from meds in the same period (6) willingness to risk death for a cure varied very strongly from one person to the next: the median was 10% but the 75th percentile was 50%). The article is accessible from the Journal of Virus Eradication page for the current issue at [http://viruseradication.com/current_articles](http://viruseradication.com/current_articles) as the fifth item on the page. That page will be archived when the next issue is published; the archived copy of the issue will be accessible from the “READ” dropdown menu’s “PAST ISSUES” item as “Volume 4, Issue 2.”

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](http://jme.bmj.com/content/43/2/67).

Why HIV cure research needs to involve more women Why HIV cure research needs to involve more women 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](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 study 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 all benefits (both general and clinical) and social benefits; and all 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%HIV%20Cure%20Part%201.mp4; the second is at https://www.hanc.info/cp/resources/Documents/Women%20and%HIV%20Cure%20Part%202.mp4; and the third is at https://www.hanc.info/cp/resources/Documents/Women%20and%HIV%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 hanc and the Legacy Project may be found on the web at https://www.hanc.info/legacy/Pages/default.aspx.

**Women’s views about contraception requirements for biomedical research participation**

“Women’s views about contraception requirements for biomedical research participation” is obviously an article with much wider scope than HIV/AIDS cure research. Nevertheless the findings are applicable, and the article is available free from the Public Library of Science (PLOS) for the journal PLOS ONE at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0216332.

Contact the author at hivcureresearch@gmail.com