Introduction

This Glossary and Resource Guide is 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. The Glossary and Resource Guide is divided into two sections, the “Glossary” and “Resource Guide.” The Resource Guide section follows the Glossary. Entries in the Glossary have headers that are color coded to indicate what areas they belong to, as follows:
   - Basic science and biology entries have headers that are green.
   - HIV background, i.e., 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, latency silencing, and shock and kill 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 are black.

We must conclude this description with an apology to readers who are color blind to one degree or another: While you may not gain much from the color coding, you should at least not lose anything from it.

2. Terms that are hyperlinked are defined elsewhere in this Glossary & Resource Guide. To use a hyperlink in the PDF version, hold down CTRL and click on the hyperlink. In the HTML version, simply click on the link.

3. To reduce clutter, for cross-referenced terms that occur more than once in an entry, only the first occurrence is underlined.

4. References to HIV in this Glossary and Resource Guide are to what is more specifically named HIV-1. There is also a variety named HIV-2; see that Glossary entry for an explanation of why there is so little attention to it in this document.

5. This HIV/AIDS Cure Research Glossary and Resource Guide is a project of the Delaney AIDS Research Enterprise (DARE) to Defeat HIV Cure Community Advisory Board with input from members of the Community Advisory Boards of the other two Martin Delaney Collaboratories (MDC): Towards an HIV and several of DARE’s researchers.

6. The Glossary and Resource Guide is available online on the Project Inform Web site as a printable PDF at http://www.projectinform.org/pdf/HIVCureglossary.pdf and at ??? In HTML. It is also available for download from other cure-related web sites that are listed as having it in this document.

7. You are welcome to send suggestions for edits and additions to the Glossary and Resource Guide's author at hivcureglossary@gmail.com. You may also send questions to the editor about items in the Glossary and Resource Guide, but 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.

Glossary

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). The quantities of 1-LTR and 2-LTR circles are measured because they are one of the indications of the quantity of defective virions being made by reactivation in the shock and kill approach to purging latent reservoirs of HIV.

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

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

Adoptive Immunotherapy
Adoptive immunotherapy is transfer of immunity from a donor to a recipient 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.

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

Allele
An allele is a variant of a gene at a particular position on a chromosome. Humans and all other living organisms have two alleles for each gene, one 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.

Amino Acid
An amino acid is one of twenty types of organic compounds that make up proteins. Biologists and other researchers use both three-letter and single-letter codes to denote them. For example, the amino acid proline is denoted both by “Pro” and by “P”, and tyrosine is denoted by “Tyr” and “Y”.

Animal Models
Animal models, such as bone-marrow-liver-thymus (BLT) mice and nonhuman primates (NHP), are particularly useful in HIV cure research and biological research in general, because

- They are obviously more compliant than humans may be;
- 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 almost always not possible in human clinical trials.

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 makes it inert.

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 many cure strategies to halt HIV reproduction in cells that have been perturbed by latency reversal.

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

Apoptosis
Apoptosis is a form of cell death in which a programmed sequence of events leads to the elimination of the cell. It plays a crucial role in developing and maintaining the health of the body by eliminating old, unneeded, and unhealthy cells. Pronunciation hint: the second “p” is silent.
Auranofin
Auranofin (brand name Ridaura) is a gold-containing drug used to treat rheumatoid arthritis. It has a partially selective killing effect against central memory T cells (TCM) and transitional memory T cells (TTM). It has also been shown in the macaque nonhuman primate, when combined with antiretroviral therapy (ART), to produce a long-term reduction in simian immunovirus (SIV) viral set point after stopping ART.

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. This is being studied as a possible way of performing a sterilizing cure of HIV infection. It has been argued that autologous transplantation is likely significantly more likely to be more easily scalable to larger patient populations than allogeneic transplant for at least two reasons, namely, (1) it avoids the issue of having to find a very well-matched donor, since the recipient is the donor; and (2) it greatly reduces the risk of graft-versus-host disease, 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, e.g., by having the CCR5 Δ32/Δ32 mutation (see the Zinc-Finger Nuclease (ZFN) Glossary entry under the Gene Editing heading 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 selected;
3. There must be sufficient numbers of transplanted cells to “swamp” the already infected stem cells in the recipient.

Finally, autologous transplants, so far (and this is shared with allogeneic transplants), are very expensive making this simply technologically infeasible. What is needed has been referred to as “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 likely still far in the future.

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

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

Berlin Patient (Timothy Ray Brown)
The Berlin Patient (Timothy Ray Brown) is the only person to have achieved a sterilizing cure of his HIV infection so far. His cure occurred after he had been diagnosed with 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 CCR5 Δ32/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. Timothy wrote an article titled “I Am the Berlin Patient: A Personal Reflection” about his cure that can be freely downloaded as HTML or as a PDF from http://online.liebertpub.com/doi/full/10.1089/aid.2014.0224. See also the Essen/Berlin Patient Glossary entry for another less successful German cure attempt and the Resource Guide entry for the book CURED: How the Berlin Patients Defeated HIV and Forever Changed Medical Science.

Biomarker 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 biological marker (called 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 below, since it measures defective as well as replication-competent latent virus.

Blood-Liver-Thymus (BLT) Mouse
A blood-liver-thymus (BLT) mouse, developed in the 1990s by Joseph M. McCune, MD (one of the principal investigators of the Delaney AIDS Research Enterprise (DARE) to Cure HIV) is a NOD/SCID/γ (NSG) mouse that has been “humanized” by having human hematopoietic
stem cells, liver tissue, and thymus-gland tissue grafted into it. It develops robust human blood 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 primates (NHPs), such as rhesus and pigtail macaques. However, they are quite susceptible to lymphoma (a type of cancer) of the thymus gland and tend not to live longer than about 8½ months after grafting, so they are not suitable for long-term research studies. One researcher has suggested they be called NPHs for “non-primate humans.”

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

**Boston Patients**

The Boston patients were three men with lymphoma (a cancer of the lymphatic system) and HIV infection who underwent CCR5 Δ32/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 underwent 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 rebounds. 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”

**CD4+ T Cells**

CD4+ T cells are primary white blood cells of the immune system; 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 such cells become activated in response to infection by that pathogen. After the infection is cleared or controlled, they can then become resting memory CD4+ T cells that lie in wait for future occurrences of the pathogen to which they then respond. These resting memory CD4+ T cells are thought to constitute most of the latent reservoir of HIV. CD4+ T cells all have the CD4 receptor on their surfaces.

**CD8**

CD8 is a receptor that is necessary to the attachment

**Broadly Neutralizing Antibodies (bNAb)**

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 some cases, used in clinical trials, to defend humans against HIV infection, treat HIV infection, and kill HIV-infected CD4+ T cells in latent reservoirs.

**CCR5**

CCR5, which abbreviates C-C chemokine receptor type 5, is a co-receptor on the surface of CD4+ T cells that, during early HIV infection, is essential to entry of HIV into these cells. HIV attaches to both CD4 and CCR5 to achieve entry. (Some variants of HIV use a co-receptor called CXCR4 rather than CCR5; these 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 1 (adapted from [https://en.wikipedia.org/wiki/CCR5](https://en.wikipedia.org/wiki/CCR5)) shows the sequence HIV binding to CD4, then to CCR5, and finally having released its genetic material into a CD4+ T cell.

**CD34**

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

**CD4**

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

Figure 1. 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; (4) the capsid (see HIV Structure) enters the CD4+ T cell.

**CD8+ T Cells**

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

**Cell-Associated RNA (caRNA)**

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

**Cell-to-Cell HIV Infection**

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

**Central Memory CD4+ T Cell (T<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 replicate, producing many copies of itself, and mount a quick immune response. Such memory cells can live for many years. In HIV infection, central memory CD4+ T cells may be infected with the virus, but are invisible to
the immune system, which allows HIV to reemerge in individuals whose immune systems can't control the virus over long periods of time or who have been on successful antiretroviral therapy and then stop that therapy.

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

(1) it is a latent reservoir for HIV that is affected by chronic inflammation established very early in HIV infection;
(2) it can only be reached by a small minority of HIV antiretroviral medications;
(3) HIV gp120 glycoprotein impacts the function of neurons; and
(4) since the brain is so very essential, there is concern among cure researchers that approaches other than shock and kill, such as latency silencing of reactivation entirely, will be necessary to achieve a cure in the CNS because of the seriously toxic effect the release of HIV virions by 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 physical support of the cells that constitute the blood-brain barrier (a filter composed of capillaries that carry blood to the CNS that blocks certain substances, such as nerve poisons, while allowing the passage of water, some gasses, glucose, and amino acids), providing nutrients to nerve cells, repairing the CNS after trauma, and maintaining electrolyte balance in the fluid surrounding neurons.

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

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

Chemokine
A chemokine is a small cytokine that is a signaling protein secreted by a cell to produce a reaction in a nearby cell; the reaction is frequently chemotaxis, which is defined as movement of the target cell in response to the chemokine.

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

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

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

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

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

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 25) of healthy volunteers to test the safety of the medical procedure and any unwanted side effects it may have. If the procedure is determined to be safe and to have only acceptable side effects, it may proceed to phase II.
- Phase II: A phase II clinical trial will usually involve several hundred volunteers. Its goal depends on what is being tested. For a medical procedure, it continues to test for safety and side effects and also adds on determination of whether it is effective.
- Phase III: A phase III clinical trial may involve several thousand volunteers and is intended to confirm the effectiveness of the medical procedure, monitor its side effects, compare it to commonly used procedures if there are any yet, and continue to collect information to determine whether the procedure is safe.

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

Clonal Expansion

Clonal expansion is the production of numerous daughter cells 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 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 C-X-C chemokine receptor type 4, is a co-receptor on the surface of CD4+ T cells that, during late HIV infection, is essential to entry of HIV into these cells. Some HIV variants attach to CD4 and CXCR4 to achieve entry. (Some variants of HIV use a co-receptor called CCR5 rather than CXCR4; these
variants almost always occur early in the course of untreated HIV infection; HIV transmitted from one person to another almost always uses the CCR5 co-receptor, though 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.

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.

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 mutations are one of the mechanisms that cause cancers. However, the separated 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!

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 (i.e., 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 about 16,000 times each day!

Compared to a living organism's mutation rate, this is absolutely staggering! It’s especially so with no mechanism to detect defective virions. In addition to the lack of a built-in checking mechanism for defects in viral replication, new research reported in late 2015 shows that there is a family of cellular enzymes called A3 that contributes very heavily to the creation of defective virions; in particular, the A3 enzymes are believed to be at least partially responsible for about 98% of the mutations that occur.

It doesn't require very many mutations in genes encoding critical proteins, such as reverse transcriptase or integrase (see the HIV Structure Glossary entry), to render a virion incapable of infectivity, i.e., make it defective. Nevertheless, even in persons on suppressive antiretroviral therapy (ART), the accumulation of mutations that render new virions defective is staggeringly 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, i.e., creation of a new virion is simply not even completed.

Dendritic Cell
A dendritic cell is an “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 and so in contact with the environment, such as the mouth, nose, lungs, stomach, and intestines.

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. 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, where, e.g., 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 web site is http://www.caprisa.org/Default.

- Initial research on the effects of female hormones on HIV cure research are described in the Estradiol, Estrogen, Progesterone, and Estrogen Receptors Glossary entry 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 (web site https://web.emmes.com/study/amc/public/) 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.
- 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 provides access to other more relevant resources.

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 superinfected CD4+ T cells.
3. The third study used what it calls bispecific antibodies that bind to the Env epitope recognized by the broadly neutralizing antibody VRC07 and the CD3 receptor to reduce HIV DNA in most of the laboratory isolates of infected cells tested. A broadly neutralizing antibody is one that is effective against a large class of antigens. “VRC” abbreviates the Vaccine Research Center at NIH that was responsible for discovering and characterizing the antibody.

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

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

Early Initiation of Antiretroviral Therapy (ART) and Remission
At least one recent study has shown that initiation of antiretroviral therapy 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 CD4+ T<sub>EM</sub> cells to levels typically found in T<sub>N</sub> cells, resting memory T<sub>TM</sub> cells being the major reservoir of HIV, and significant restriction of HIV mutation. Further, continuing ART for a total of six years can drive reservoir size and distribution down to levels close to those seen in post-therapy controllers, such as the VISCONTI cohort.

Effector Memory CD4+ T Cell (T<sub>EM</sub>)
An effector memory CD4+ T cell (T<sub>EM</sub>) is a CD4+ T cell that is replicating in response to a pathogen and mounting a quick immune response to the pathogen.

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

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

The 2014 study mentioned above examined how these definitions applied to a to a cohort of over 25,000 HIV-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 ribozyme described in the Gene Editing Glossary entry below), that acts as a catalyst: It facilitates a biochemical process without itself being modified so it can be used again. Almost all proteins that are enzymes have names ending in “ase”.

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

Escape Mutation
An escape mutation, in the context of HIV, is a genetic change (mutation, also called antigenic drift) in a daughter HIV virion that makes the resulting virion unable to be treated by antiretroviral therapy (ART) and impervious to clearance of latent cells infected with daughters of the resulting HIV virion that has the escape mutation.

Essen/Berlin Patient
The Essen/Berlin patient is a man who goes by the pseudonym Christian Hahn (see the Resource Guide entry for the book CURED: How the Berlin Patients Defeated HIV and Forever Changed Medical Science) with Non-Hodgkin’s lymphoma, 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 CCR5 Δ32/Δ32 bone-marrow transplant. However, following the transplant, he was found to have either CXCR4-tropic or dual CCR5- plus CXCR4-tropic HIV infection and subsequently died from a recurrence of his lymphoma. It is not well understood why the CXCR4- or dual-tropic HIV infection was not detected: it may have been simply because there were very, very few such virions. Alternately, the detection failure may have been because the patient’s particular lymphoma is an AIDS-defining condition, and progress to AIDS and some biological changes that occur in parts of CD4+ T cells’ gp120 spikes are the clinical factors most likely to predispose a transition from CCR5 tropism to CXCR4 tropism.

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

- Estradiol, at peak menstrual levels, is a powerful inhibitor of HIV viral replication, which may explain part of the observation that women seem to have generally 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 S Gianella A Tsibiris L Barr C Godfrey “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);

| Effects of Estrogen on Immune-System Cells |
|------------------|------------------|
| **Cell Type**    | **Effects**       |
| T cells          | • Increases expression of CCR5 and CCR1;  
                  | • Lower doses enhance T$_{i}1$ cell response;  
                  | • Higher doses enhance T$_{i}2$ cell response;  
                  | • Expands Treg cells |
| B cells          | • Increases survival;  
                  | • Decreases apoptosis; and  
                  | • Increases certain immunoglobulins |
| NK cells         | • Lower doses increase CD8+$^+$ T cell activity; and  
                  | • Higher doses decrease CD8+$^+$ T cell activity |
| Dendritic cells  | • Increases production of several cytokines; and  
                  | • Promotes cell differentiation |
| Neutrophils      | Enhances anti-inflammatory activity |
| Macrophages & Monocytes | • Lower doses promote cell differentiation and stimulate cytokine production; and  
                          | • Higher doses reduce expression of CD16 and decrease cytokine production |

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

- Progesterone is a component of the injectable birth-control drug medroxyprogesterone (brand name Depo-Provera) that, when administered as a drug, enhances HIV infection.
- Agonists of the estrogen receptor ESR-1 on resting memory CD4+$^+$ T cells, such as the breast cancer drug Tamoxifen, weakly enhance latency reversal of HIV-infected cells. In contrast, ESR-1 inhibitors, such as diethylstilbestrol, 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).

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

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

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

<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 (721)</td>
</tr>
<tr>
<td>I</td>
<td>Viral RNA+</td>
<td>7 (510)</td>
</tr>
<tr>
<td>II</td>
<td>p24 antigen+</td>
<td>5 (48)</td>
</tr>
<tr>
<td>III</td>
<td>Antibody ELISA+</td>
<td>3 (25)</td>
</tr>
<tr>
<td>IV</td>
<td>Western blot+ or -</td>
<td>6 (48)</td>
</tr>
<tr>
<td>V</td>
<td>Western blot+ &amp; integrase-</td>
<td>70 (40122)</td>
</tr>
<tr>
<td>VI</td>
<td>Western blot &amp;, integrase+</td>
<td>Open ended</td>
</tr>
</tbody>
</table>

Table 2. Fiebig stages, characterizations, and durations.

Note: Western blot is typically used as a confirmatory test for HIV infection; it uses electrophoresis to separate a purified antigen mixture into bands that correspond to the gp160, gp120, p66, p55, p51, gp41, p31, p24, p17, and p15 proteins (see the HIV Genome Glossary entry for descriptions of the proteins).

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 strategy for modifying genetic information in cells, such as removing HIV proviral DNA from the DNA in them or altering the CD4 receptor, CCR5 co-receptor, or anti-HIV restriction factors to make CD4+ T cells resistant to HIV infection. There are numerous experimental gene editing techniques being investigated (many targeting the gene that encodes CCR5—the ones listed are designed to do so unless specified as having other or more general targets) as described. Though we list 11 approaches, CRISPR is by far the most important, and zinc-finger nucleases and TALENs are the only ones that have so far been used in significant clinical trials of gene editing intended as a step toward a functional cure of HIV infection. A recent mathematical modeling study of gene editing strategies for HIV cure has shown that achieving positive results is possible only under narrow range of conditions and that further improvement of engraftment is likely to be necessary to improve outcomes.

1. CRISPR: CRISPR is a combination of two drugs, CRISPR (clustered regularly interspaced short palindromic repeats) and either a Cas protein (CRISPR associated protein—most often Cas9) or Cpf1 (CRISPR from Prevotella and Francisella), that is currently the most effective and easy to use method for gene editing. 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. Prevotella and Francisella are two varieties of bacteria that are relevant because CRISPR turns out to be a primitive immune-like system found in bacteria.

2. Homing Endonuclease: A homing endonuclease is an enzyme (either a protein or a small RNA) that homes in on a specific segment of DNA or RNA and either cuts out or replaces that part of it. If a DNA segment is cut, it is then reconnected by the enzyme DNA ligase, a DNA repair mechanism found in all human cells. It is a goal of cure research to design homing endonucleases such that the repair will make the cells unable to make new HIV virions. Meganucleases, megaTALs, transcription-activator-like effector nucleases (TALENs) and zinc finger nucleases (ZFNs) discussed below are four types of homing endonucleases.

3. Intrabody: An intrabody is a variety of antibody that can bind to a protein and make it dysfunctional. CCR5 intrabodies have been found to be more effective than the intrakines described immediately below.

4. Intrakine: An intrakine is a chemokine found inside a cell that can target newly formed CCR5...
blocking its transport to the cell surface. Unfortunately this approach resulted in incomplete inhibition of CCR5, i.e., only some CCR5 co-receptors were blocked from reaching the cell surface.

5. **Meganuclease**: A meganuclease is a relatively long engineered peptide that has been used to edit DNA in genes to remove HIV proviral DNA.

6. **Mega-Transcription-Activator-Like (MegaTAL)**: A mega-transcription-activator-like (megaTAL) is a long peptide useful for removing HIV proviral DNA from CD4+ T cells. It consists of a meganuclease bound to part of a transcription-activator-like endonuclease (TALEN). A megaTAL has greater specificity and is more effective than either of its component parts. MegaTALs also have more general application than just CCR5 gene editing.

7. **Ribozyme**: A ribozyme is a small strand of RNA that acts as if it were an enzyme, which is a protein that catalyzes an organic reaction, i.e., facilitates its occurrence but is itself unchanged in the process. Ribozymes have been used in several clinical trials to target HIV genes with some success. In combination with other approaches, one type of ribozyme targeted to the CCR5 co-receptor has been effective for as long as 24 months to curtail the effectiveness of CCR5.

8. **Short Hairpin RNA (shRNA)**: A short hairpin RNA (shRNA) is an artificially produced RNA molecule that has a quite small hairpin-shaped segment and that can be used to silence expression of a gene via a mechanism called RNA interference; it requires delivery by a viral vector.

9. **Short Interfering RNA (siRNA)**: A short interfering RNA (siRNA) is a very short synthetic strand of RNA that can be used to edit out the gene for CCR5; however they are somewhat problematic because they tend to have off-target effects also.

10. **Transcription-Activator-Like Effector Nuclease (TALEN)**: A transcription-activator-like effector nuclease (TALEN) is a peptide useful for gene editing to remove HIV proviral DNA from CD4+ T cells.

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

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

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

**Glycoprotein**
A glycoprotein is a complex of a sugar (the “glyco” part of the word) and a protein. In particular, HIV’s gp120 and gp41 are glycoproteins, though there are many others found in viruses and cells.

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

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

**Graft-versus-Host Disease (GVHD)**
Graft-versus-host disease (GVHD), also called rejection, is a natural reaction by the body’s immune system to a graft or transplant that typically results in elimination of the graft or transplant unless immunosuppressing drugs, such as cyclosporine, are administered. The reaction is predominantly carried out by CD8+ T cells. Nevertheless, in the case of the Berlin Patient (Timothy Ray Brown), graft-versus-host disease may have played a significant 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 almost always severely depleted very early in the course of HIV infection. It is believed that the depletion is mostly irreversible.

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

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

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

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

Histone Deacetylase (HDAC)
A histone deacetylase (HDAC) is an enzyme that causes chromatin in CD4+ T cells to bind its DNA, stop reproducing, and become inactive in resting memory 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, and therefore leaves the cell unexposed to both CD8+ T cells and antiretroviral therapy (ART).

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

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

~9,750 bases (nucleic acids)

**HIV Genome**
The nucleus of HIV (see the HIV Structure Glossary entry) contains the two separate single strands of RNA that comprise HIV's genetic material or genome. The structure of each strand of RNA is shown in Figure 2 (produced by Janie Vinson Productions, San Francisco, 14
It comprises nine genes and the two long terminal repeats (LTR), 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 to proteins: The HIV genome must first be integrated into a host cell’s DNA as proviral DNA that is, in turn, transcribed and translated to proteins.) In all each strand has roughly 9,750 bases (nucleic acids), though this varies somewhat with the faulty replication of HIV RNA (see the Defective Virion Glossary entry).

The components of the HIV RNA genome and their functions are described below; the gag, pol, and env genes shown in gray in Figure 2 are found in all retroviruses.

- **env** encodes the protein Env, which creates the glycoproteins gp120 and gp41 that make up the spikes shown in the HIV Structure 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, is cleaved to produce six regulatory proteins and one probably nonfunctional spacer, as follows:
  - matrix polypeptide (MA), also called p17, which becomes part of the virion’s plasma membrane,
  - capsid protein (CA), also called p24, which forms the virion’s capsid,
  - spacer peptide 1 (SP1), also called p2, whose function is to cause the capsid protein CA to become part of the virion’s capsid,
  - nucleocapsid protein (NC), which forms the virion’s nucleocapsids, which are the membranes containing the RNA genome,
  - spacer peptide 2 (SP2), also called p1, which serves as a separator between NC and p6 (described next) and may have an as-yet unknown additional function, and
  - p6, a peptide that recruits cellular proteins essential to the budding of mature virions from the cell in which they are assembled;
- **pol** (polymerase) encodes a gene that 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),
  - 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 to produce proteins; 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 the HIV envelope Env;
- **vif, vpr, and nef** encode the proteins Vif, Vpr, and Nef, respectively, which are discussed in the HIV Structure Glossary entry; and
- finally, LTR is a long terminal repeat; it is a sequence of ~640 bases that are identical across the two LTRs; HIV’s right-end long terminal repeat is reverse transcribed to produce five double-stranded DNA sequences, as follows:
  - TAR, the transactivation response element, interacts with Tat and other HIV proteins in an unknown manner,
  - Poly A, which is involved in creating mature virions,
  - PBS, the primer binding site, is an 18-base sequence that encodes a peptide involved in initiation of retrotranscription of HIV RNA,
  - Ψ, the Psi packaging element, is involved in packing the viral genome into the capsid; it varies from ~80 to ~150 bases, depending on the strain of HIV, and
  - DIS, the dimer initiation site, takes part in preparing the viral RNA for packaging by Ψ.

Note that the genome in Figure 2 is a simplification: It shows only the genes in the RNA that is the actual genome. RNA is composed of a chain of units of the form shown in Figure 3 (from https://en.wikipedia.org/wiki/RNA ), which actually shows a pair of consecutive units. Each pair of units has the structure shown in the figure. The backbone consists of molecules of a sugar named ribose (hence the “ribo” part of the name), with a ring structure consisting of four carbon atoms (by convention the carbons are only shown as unlabeled corners) and an
oxygen, and consecutive riboses are connected with phosphate groups. The atoms in the ribose ring are labeled 1’ through 5’, and the 3’ position of one ribose is connected to the phosphate, which is in turn connected to the 4’ position of the next ribose. Each of the nucleic acid bases 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 adenine, cytosine, guanine, or uracil, the four bases that occur in RNA.

Figure 3. Pair of units comprising RNA (see note below).
HIV Latency
Although antiretroviral therapy can keep activated and 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 or latent state and not actively reproducing or producing chemical messages to cause an immune response against a pathogen. The resting memory CD4+ T cells provide a latent reservoir of virus that can be reawakened to begin actively reproducing HIV virions if antiretroviral therapy (ART) is stopped.

HIV Remission
HIV remission is another term for HIV cure (functional) 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 a new virion “buds” from; 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). 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 pierces the 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, i.e., 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, along with the cell’s CD4 receptor and either of the two co-receptors CCR5 or CXCR4, accomplishes entry into the cell;
- Inside the virion’s membrane is a protein layer called the matrix (light blue) made up of matrix protein or p17, which contains essential proteins and the nucleus;
- Protease (black squares with light blue inside) is an enzyme that cleaves newly formed HIV polyproteins during viral replication into their constituent protein components;
- The capsid (dark blue) is the outer membrane of the virion’s nucleus and is composed of molecules of a protein known as p24; the capsid’s contents are as follows:
  - The genome (black lines sticking out of the nucleocapsids) consists of two single strands of RNA, as described in the HIV Genome Glossary entry; partially encased in the nucleocapsids (grayish green);
  - The capsid also contains several proteins, namely, reverse transcriptase (RT), integrase (IN), Vif, Vpr, Nef, and p7, which are described below.
    - Reverse transcriptase (RT) (black circles with red insides) is the enzyme responsible for reverse transcribing HIV RNA to HIV proviral DNA;
    - Integrase (IN) (light blue open circles) is the enzyme responsible for integrating the reverse-transcribed DNA into the host cell’s DNA;
    - Nef (negative regulatory factor) (one of the circles in the black bracket) is a small protein that causes numerous changes in an infected cell to adapt it to reproducing HIV;
    - Vpr (viral protein R) (another of the circles in the black bracket) is a small protein that is essential to HIV viral replication in non-dividing cells, such as macrophages;
    - Vif (viral infectivity factor) (another of the circles in the black bracket) is a small protein that is essential to HIV viral replication; and
    - p7 (another of the circles in the black bracket) is a peptide that facilitates reverse transcription.

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

HIV Therapeutic Vaccine
An HIV therapeutic vaccine is an immune-system-stimulating vaccine that prompts or boosts immune responses to HIV in infected individuals.

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

- It preferentially attacks CD4+ T cells, the “directors” of the adaptive immune system.
• It eludes control by antibodies.
  • Sugars cover almost its entire accessible surface.
    The only notable exception is the CD4 binding site, but that site is deep inside the protein coat, where it can't be reached by most antibodies.
• It employs a remarkable two-part entry mechanism, using CCR5 or CXCR4 in addition to CD4, that only takes place after 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 broad and potent.
• It destroys the gut-associated lymphatic tract (GALT) very early in infection altering the gut's microbiome.
• It also attacks the central nervous system (CNS) very early,
  o can have anywhere from minor to profound consequences there,
  o can be very hard to reach by therapies there, and,
  o 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 as simply HIV throughout this Glossary and Resource Guide. 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 with large numbers of immigrants from West Africa.
• HIV-2's zoonotic (i.e., 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.
• Finally, but most important, approaches to curing HIV-1 disease are almost certain to be applicable to HIV-2 disease.

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

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. HLA is the human version of the Major Histocompatibility Complex (MHC) found in all vertebrates. HLA-B*5701 and HLA-B*2701, in particular, are specific parts of the human leukocyte antigen that are advantageously mutated in a majority of elite controllers of HIV infection, and they are one of the mechanisms that contribute to their control of HIV infection without antiretroviral therapy (ART).

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

Immune Correlate of Persistence
An immune correlate of persistence of HIV infection is a measurable sign that statistically correlates well with the degree to which one's HIV infection remains latent in the body.

Immune System
The immune system is the bodily system that protects against disease processes. 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 not part of the body. Pathogens that make it through the biological barriers may be recognized by KIR components that they are primed for. If a KIR component recognizes a pathogen, it activates natural killer cells (NK cells)—see the Natural Killer (NK) Cells 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 cell-surface proteins that regulate the adaptive immune system in humans; it is the human instance of a system named the Major Histocompatibility Complex (MHC) system 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 naïve (T_{N}), central (T_{CM}), effector (T_{E}), transitional (T_{TM}), and stem-cell-like (T_{SCM}) memory T cells), CD8+ T cells, T follicular helper (T_{fh}) cells, T helper 17 (T_{H17}) cells, and at least a half dozen other types; see the entries for the underlined cell types for descriptions of their roles in immunity.

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

Infant CD4+ T Cells
Recent research has shown that the CD4+ T cell populations in infants have a distinctly different distribution of the types of cells described in the Resting Memory CD4+ T Cells Glossary entry for adults. In particular, naïve, i.e., undifferentiated, CD4+ T cells (T_{N} cells) constitute a significantly larger fraction than in adults. Understanding the implications of this distinction may provide insight into how best to cure HIV infection in infants differently from how it might be done in adults.

Inflammation
Inflamed immune-system cells can signal other immune-system cells to reproduce or respond to a pathogen. The key white blood cell in inflammation is the macrophage. Macrophages can assemble within themselves specialized platforms that produce the substances that promote inflammation. These platforms are named inflammasomes, and they are assembled when needed and destroyed when they are no longer needed. This is usually helpful. However, chronic HIV infection, even in those whose virus is either suppressed naturally or by antiretroviral therapy (ART), is known to cause chronic inflammation, which can lead to cardiovascular disease, cancers, and other serious health conditions. Activated cells can also produce scarring (also called fibrosis) in lymph nodes, a critical part of the immune system. For most purposes one could say that immune activation equals inflammation (i.e., every inflammation leads to immune activation and vice versa). In most cases, short-term inflammation is a good thing because it controls many types of infections, though not HIV infection. The first few paragraphs of the New Yorker article “INFLAMED” in the November 30, 2015 issue available at http://www.newyorker.com/magazine/2015/11/30/inflamed provide an excellent layperson’s introduction to inflammation.

Kick and Kill
Kick and kill is a synonym used by some researchers for shock and kill.

Latency Reversal
Latency reversal is fundamental to activating the bound HIV proviral DNA in CD4+ T cells in latent reservoirs in the body to make it susceptible to destruction via the approach known as kick and kill or shock and kill. This is considered by many HIV cure researchers to be fundamental to curing HIV. The following are 16 of the many substances and classes of substances being tested as latency-reversal agents; most (though not all) are either experimental cancer drugs or ones already on the market as such:

1. Bromodomain Inhibitors: A bromodomain inhibitor attaches to proteins called histones in chromatin, causing the chromatin to release its bound DNA. The name has no connection with the element bromine; instead it is derived from its discovery in fruit flies in association with a gene named brahma. JQ1 is a potent bromodomain inhibitor.

2. Bryostatin or Prostratin Analogue: A bryostatin or prostratin analogue is a drug that has been shown to potently induce activation of latent HIV in CD4+ T cells in laboratory experiments. An analogue, in this context, is an organic compound created in a laboratory that is similar to the naturally occurring chemical it is analogous to. Bryostatin is named from its discovery in undersea animals named bryozoa. Prostratin is found in the bark of a tree from Samoa. Given the difficulty of obtaining both drugs, it has become essential to develop methods to synthesize analogous chemicals with the same properties. Because bryostatin analogues can be quite toxic, some cure researchers have investigated delivering them inside lipid (fatty) nanoparticles.

3. Checkpoint Inhibitors: Immune checkpoints, such as Programmed Cell Death 1 (PD-1) (described in this entry), Lymphocyte-Activation Gene 3 (LAG-3), and T cell Immunoreceptor with Immunoglobulin type g and ITIM domains (TIGIT), are cell-surface markers for specific types of CD4+ T cells. In particular, PD-1 and LAG-3 mark T_{CM} and T_{EM} cells and TIGIT marks T_{EM} cells. Checkpoint inhibitors, in turn, block the activity of checkpoints. This makes checkpoint inhibitors useful for latency reversal.

4. Disulfiram (DSM): Disulfiram (DSM) is a drug that was used for several decades to treat alcohol dependence because drinking alcohol while taking it causes a severe generalized physical reaction. It is rarely used for that purpose now because, in a
few cases, the reaction caused the person taking it to die.

5. **DNA Methyltransferase Inhibitors**: A DNA methyltransferase is an enzyme that attaches methyl groups to locations in DNA. A DNA methyltransferase inhibitor blocks the activity of DNA methyltransferase. One DNA methyltransferase inhibitor that has been tested for latency reversal is decitabine (brand name Dacogen).

6. **Farnesyl Transferase Inhibitor (FTI)**: A farnesyl transferase inhibitor (FTI) inhibits the action of an enzyme named farnesyl transferase.

7. **Histone Deacetylase Inhibitor (HDACi)**: A histone deacetylase inhibitor (HDACi) causes chromatin to release HIV proviral DNA to reproduce and become exposed to the immune system and potentially to HIV antiretroviral therapy (ART). Numerous examples that have been used in experiments are belinostat, druzoxostat, givinostat, oxamflatin A (brand name Metacept 3), panobinostat, romidepsin (brand name Istodax), Scriptaid, trichostatin A, and vorinostat (formerly and still occasionally called SAHA and brand named Zolinza). As of late 2015, romidepsin appeared to be the most effective drug for reversing latency.

8. **Histone Methyltransferase Inhibitor (HMTi)**: Histone methyl transferases (HMTs) are enzymes that facilitate the transfer of methyl groups to two types of amino acids in histones. A histone methyltransferase inhibitor (HMTi) keeps this transfer from happening. Two HMTis are currently in testing as latency reversal agents, namely, one as yet unnamed one called BIX-01294 and the other named chaetocin, which was isolated from a fungus. Both are supplied by several drug companies.

9. **Interleukin-7 and -15 (IL7 and IL15)**: Interleukin-7 and -15 (IL7 and IL15) are essential to the maturation of all types of T cells.

10. **Ingenols**: Ingenols are drugs used primarily for the treatment of certain skin cancers but that have also been used experimentally in latency reversal of DNA in resting memory CD4+ T cells.

11. **Programmed Cell Death 1 (PD-1) and Programmed Cell Death Ligand 1 (PD-L1) Inhibitors**: Programmed cell death 1 (PD-1), also known as CD279, is a receptor found on the surface of some T cells. It both promotes and inhibits apoptosis, depending on the type and location of the T cells it is found on. Recently developed drugs inhibit its effect, thereby activating the immune system to fight certain types of tumors. Programmed cell death ligand 1 (PD-L1), also known as CD274, is a receptor found on the surface of some T cells. It suppresses the immune system during pregnancy, 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.

12. **Proteasome Inhibitors**: A proteasome is an organelle (a tiny organ-like body within a cell) that destroys proteins by breaking them up into their constituent amino acids. A proteasome inhibitor acts against a proteasome by blocking this action and can, as a result, inhibit latency, thus reactivating latent HIV-infected CD4+ T cells.

13. **Protein Kinase C (PKC) Agonists**: Protein kinase C (PKC) is a family of proteins that add phosphate groups to amino acids in other proteins. Protein kinase C agonists have been used experimentally to induce latency reversal.

14. **Rottlerin**: Rottlerin is an inhibitor of a protein named kinase C, which is essential to HIV viral replication. Laboratory experiments are ongoing to determine its effectiveness as a latency-reversal agent. “ii” is the lower-case Greek letter theta.

15. **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.

16. **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’ 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 SIV-infected rhesus macaques resulted two of the nine macaques maintaining undetectable viral loads for three to four months. A further, recently reported study showed that repeated administration of GS-9620 can lead to longer remission in SIV-infected rhesus macaques. Gilead Sciences has developed another TLR7 agonist named GS-986 that is being studied in nonhuman primates (NHPs).

**Latency Reversal by Combinations of Drugs**
Several articles published in 2015 discuss combinations
of latency reversal agents tested in cell lines (i.e., human cells grown in a laboratory) outside the body and found them to be more effective than single agents. The determination of effectiveness was made by the observation of biological signaling pathways associated with latency reversal. The combinations are as follows:

- Ingenol-3-angelate (brand name Picato) and JQ1,
- Vorinostat and chaetocin,
- Vorinostat and prostratin,
- Histone deacetylase inhibitor (HDACi) and anti-PD-1,
- Anti-PD-1 and the antiretroviral therapy (ART) drug raltegravir,
- Bryostatin-1 and JQ1,
- Ingenol-B and JQ1, and
- A selective estrogen receptor modulator (SERM) (see the Estradiol, Estrogen, Progesterone, and Estrogen Receptors Glossary entry) and a histone deacetylase inhibitor (HDACi).

Note that all the underlined items in this entry are discussed in the Latency Reversal Glossary entry. It is not known whether any of these 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. Several approaches are being explored, as follows:

- Using gene therapy to modify the HIV tat gene 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 mTOR (mammalian target of rapamycin) pathway inhibitors to suppress HIV transcription; 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 very closely related senses:

1. A latent HIV reservoir is an anatomical part of a person’s body that may be cells or a tissue that is reachable by HIV. In the context of HIV infection, it is a part of the body that, it is generally believed, is not affected by antiretroviral therapy as effectively, if at all, as in the blood. Latent reservoirs provide long-lived homes for HIV to reemerge from if therapy is stopped. Examples of latent reservoirs include
   - resting memory CD4+ T cells,
   - macrophages and monocytes,
   - lymph nodes,
   - 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 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).

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

It is generally accepted that the latent reservoir of at least HIV-infected resting memory CD4+ T cells containing proviral DNA and almost certainly other types of HIV-infected cells is established within days after infection, and the existence of the latent reservoir has been known since 1995. The establishment of the latent reservoir and its reactivation are shown in Figure 5 (used with permission from DS Ruelas WC Greene WC “An Integrated Overview of HIV-1 Latency” Cell 155, October 24, 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.

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

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

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

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

**Lentivirus**

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

**Leukapheresis**

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

**Los Angeles Baby**

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

**Lymph Node**

A lymph node is a small organ containing immune-system cells, i.e., a site where such cells are collected in order to come into contact with antigens and other immune-system cells, such as CD8+ T cells that have recognized a pathogen presented by a CD4+ T cell. Prominent clusters of them are found in the underarms, the groin, and the neck. See the Lymphatic System & Lymphoid Tissues Glossary entry for more information about them.

**Lymph Node Collagen Deposition (Fibrosis)**

When functional cells die in the body, they are
sometimes replaced by scar tissue, which is composed of collagen. This process 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 in this way, it may be difficult to regain their ability to respond to HIV and other infections as effectively as before collagen deposition had occurred, potentially causing lasting damage to the immune system that a cure may not be able to reverse.

**Lymphatic System & Lymphoid Tissues**
The lymphatic system is made up of lymphoid tissues and lymphatic vessels. Lymphoid tissues comprise lymph nodes, spleen, tonsils, adenoids, gut-associated lymphoid tissue (GALT), Peyer’s patches, and local immune cells in many other tissues. The lymphatic vessels lead from lymphatic tissues toward the heart. The lymphatic system is essential to fighting infections. Figure 6 shows the human lymphatic system in green (from http://lymphatictherapy.co.za/manual-lymph-drainage/the-lymphatic-system/, used courtesy of Carolyn Hoffman, B.Sc., T.M.T., Vincent Pallotti Hospital, Pinelands, South Africa).

**Macrophage**
A macrophage is a type of white blood cell that may be infected with HIV and, hence, serves as a latent reservoir component. 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, also from Greek, “cell-eating process”—which describes exactly what they do, namely engulf cellular debris, bacteria, viruses, cancer cells, and other foreign substances—essentially anything that doesn’t have the proteins found on the surfaces of healthy native cells. In particular, macrophages devour HIV-infected CD4+ T cells. A subset of HIV virions use any of at least nine co-receptors other than CCR5 and CXCR4; some of these attack macrophages directly. Thus, it is very likely that macrophages provide additional latent reservoirs beyond those containing resting memory CD4+ T cells.

**Measuring the Latent Reservoir**
Measuring the latent HIV reservoir(s) is a vital step in determining the effectiveness of approaches to both latency reversal and latency silencing. It is estimated that the latent reservoir typically contains anywhere from about 1 million to over 50 million HIV-infected resting memory CD4+ T cells. The ultimate goal of measuring the latent reservoir is to count all and only replication-competent provirus, which no measurement tool (see Figure 7 from KM Barton SE Palmer “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/ ) is yet capable of doing. There are several imperfect approaches to measuring the number of HIV-infected CD4+ T cells in the latent reservoir, as follows:

1. The quantitative viral outgrowth assay (QVOA) attempts to count replication-competent latent provirus. It begins by collecting very pure latent resting memory CD4+ T cells by leukapheresis. It then dilutes the cells in several steps and reactivates them. Then activated CD4+ T cells also collected by leukapheresis from an uninfected person or persons are added to the diluted cells and mixed with the infected CD4+ T cells to infect them and thus propagate the virus. The quantitative viral outgrowth assay is complex and expensive and has the added disadvantage of being very likely to underestimate the actual size of the latent reservoir. However, some recent studies show a significant correlation between the results of QVOA and total HIV DNA, suggesting that it may be a reasonable measure of the latent reservoir. Approaches to improving the effectiveness of QVOA are a subject of research—see, for example, item 4.

2. The quantitative polymerase chain reaction assay (qPCR) measures total HIV DNA or cell-associated HIV RNA (caRNA) in cells in a latent reservoir. This assay is most frequently used to measure persistent HIV infection, but it can be used to measure the latent reservoir. This assay has the disadvantage of massively overestimating the magnitude of the latent reservoir (as much as 300 times) because it does not discriminate among functional (i.e., replication competent) and defective (i.e., not capable of replicating HIV—see the Defective Virion Glossary entry for an explanation of this) HIV RNA. It is relatively inexpensive compared to QVOA.

3. The single-copy assay of latent HIV RNA is an extremely sensitive method that measures as few as one HIV+ CD4+ T cell at a time. It is most often used to detect low-level viremia in people on antiretroviral therapy (ART), but it may be useful for measuring the latent reservoir. A variant named droplet digital polymerase chain reaction (ddPCR) can be used to precisely measure very low levels of HIV RNA or cell-associated RNA (caRNA). This approach (obviously) detects single copies of latent HIV RNA, but efficient counting techniques are under development to enable it to measure the magnitude of the latent reservoir. This may turn
out to be the most effective way to perform such measurements if it can be refined to distinguish replication-competent HIV-infected resting memory cells from defective ones.

Figure 6. The lymphatic system in green and major blood vessels in blue.
4. The inducible Cell-associated RNA Expression in Dilution (iCARED) assay is an improved version of the quantitative viral outgrowth assay described in item 1. It is simpler, more accurate, faster to perform, and less expensive. So far it has only been described at a conference.

5. The Tat/Rev Inducible Limiting Dilution Assay (TILDA) is a polymerase-chain-reaction-based (PCR-based) assay that measures multiply spliced HIV-1 RNA (see the Splicing of HIV RNA & Measurement of Unspliced and Multiply Spliced RNA in Cure Research Glossary entry). Studies suggest that TILDA is a better predictor of actual reservoir size than other PCR-based assays. Several other assays have been proposed and used to measure the latent reservoir, such as measuring through 3 are the most commonly used ones at present.

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

Measuring the contributions of types of resting memory CD4+ T cells (central, transitional, and effector) and is a current topic of research, and the first results of this research are expected to be announced in 2016.

**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 gene that encodes a protein to a complementary RNA that is used by the translation mechanism in a cell to create that protein. Detailed description of the transcription and translation processes are beyond the scope of this document.

**Microbial Translocation**

The gut contains bacteria that may be either helpful in digestion or harmful, but which, preferably, should not leak into the blood, because parts of the bacteria can trigger severe and long-lasting inflammation. The gut-associated lymphatic tissue (GALT) in the lining of the gut contains most of the immune cells that keep these bacteria in check. In HIV disease, these cells and tissues 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 infection leading to opportunistic infections and other conditions, such as cancers, that are harmful to the body.

**Mississippi Baby**

The Mississippi baby is a young girl who was found to be HIV+ very soon after birth, having been infected by her HIV+ mother, and was put on intensive antiretroviral therapy 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 the medical system, 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 her having resurgent HIV infection.

**Monoclonal Antibody**
A monoclonal antibody is a clone or cluster of identical antibodies that are made by identical immune cells that are all clones (identical copies) of a specific parent cell.

**Monocyte**
A monocyte is a type of blood cell that accounts for 210% of the population of white cells. Like natural killer (NK) cells, monocytes are part of the innate immune system. In response to infections, they differentiate into macrophages and dendritic cells to produce inflammation.

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

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

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

**Natural Killer (NK) Cells**
Natural killer (NK) cells are white blood cells that are 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 infected or disabled cells, unlike CD4+ T cells and CD8+ T cells, which must be trained to respond to their target pathogens; however, recent evidence suggests that there are memory-like subsets of natural killer cells in mice; the clearest evidence for such memory-like properties in people is in response to cytomegalovirus (CMV) infection, which is very common in HIV+ persons. They have also been found in nonhuman primates, such as rhesus macaques infected with SHIV. There is ongoing research with regard to whether such memory-like natural killer cells may play a role in curing HIV infection. Some recent and ongoing research is directed to “supercharging” natural killer cells to make them more effective at killing latently HIV-infected 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 Blood-Liver-Thymus (BLT) Mouse for a description of another model mammal used in cure research.

**Nucleic Acid (Base)**
A nucleic acid or base is a component of DNA or RNA. Each of them has four types of nucleic acids, three of which are common to both.

**p, gp, and S Numbers**
p and gp numbers indicate the atomic weight in thousands of the amino acids strung together to make a protein (“pn”) or glycoprotein (“gpn”), where n is a numeral. For example, p24 (see the relevant item in the HIV Structure entry) is a protein with roughly 24 x 1,000 = 24,000 atomic mass units (protons or neutrons). The unit of measure is called a Dalton, abbreviated Da from the name of the 19th century English chemist John Dalton. The “k” abbreviates kilo, a factor of 1,000, as in kg for kilogram. In contrast, S numbers, of the form “nS”, named for the Swedish chemist Theodor Svedberg, are sedimentation rates in a centrifuge. Note that unlike “p” and “gp” numbers they don’t add, even roughly; e.g., “gp41” and “gp120” do roughly add up to “gp160”, but the subunits of the ribosome (see the Protein Synthesis entry) are named “40S” and “60S”, while the whole ribosome has Svedberg number “80S”.

**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.

**Peyer’s Patch**
A Peyer’s patch is a small mass of lymphatic tissue found throughout the ileum region of the small intestine (the last section before the large intestine). Peyer’s patches are latent reservoirs for latently HIV-infected CD4+ T cells.

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

**Post-Therapy Controllers**
Post-therapy controllers are a small group of individuals living with HIV, so far mostly the VISCONTI (Viro-I mmunologic Sustained CONtrol after T reatment Interruption) cohort in France, who started antiretroviral therapy (ART) within weeks of infection, stayed on therapy for an average of about four years, and then, for various reasons, stopped therapy. Because there has been no large or lasting rebound of HIV, these individuals are able to stay off therapy for long periods, so far as long as 10 years. Unlike the majority of elite controllers, these post-therapy controllers mostly lack advantageous immune-system mutations (e.g., HLA-B*5701 and HLA-B*2701). NK cells are believed to be largely responsible for controlling HIV in this cohort. Another cohort 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, 100% 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 consideration 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.
2. There are several gene therapy strategies that might be used, including adoptive immunotherapy of modified messenger RNA (mRNA), RNA interference (RNAi), molecules that compete with HIV RNA, ribozymes, and several others.
3. There are several major barriers to the use of gene therapy including (a) the very large number of infected persons who would need to be treated, (b) the lack of safety of the conditioning necessary before therapy can be applied, as exemplified by the Berlin Patient (Timothy Ray Brown)—though his transplants were allogeneic, (c) risk-benefit analysis for clinical trials, (d) the lack of a completely safe method for identifying the cells to be modified, and (e) the very high cost so far of the therapy.

**Preclinical Model**
A preclinical model is an organism (usually an animal) that has sufficient similarity to humans to be useful in testing a medication or medical procedure. For HIV, Blood-Liver-Thymus (BLT) mice and macaques are commonly used preclinical models.

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

**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 in HIV cure research, specifically to measure the latent reservoir of HIV-infected CD4+ T cells. Droplet digital polymerase chain reaction (ddPCR) is the most widely used version of it.

**Radioimmunotherapy**
Radioimmunotherapy (also called targeted α-particle therapy) is an approach currently in trials for curing certain cancers—notably advanced forms of the skin cancer melanoma and the lymphatic-system cancer lymphoma—that may have the potential for contributing to curing HIV infection. It combines monoclonal antibodies with radioactive elements that emit electrons. In cancer therapy, the antibodies home in on the cancers and seem to have the potential for
making the α particles’ (electrons) deliver their radiation exclusively to the cancerous cells. It is hoped that this will be useful in killing activated CD4+ T cells. “α” is the lower-case Greek letter alpha.

**Receptor**
A receptor, in the context of HIV medicine (including cure research), is a chemical (such as CD3, CD4, CD8, CD34, CD274, and CD279) attached to the surface of a cell that marks its function. 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.

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

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

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

**Replication-Competent Latent Provirus**
A replication-competent latent provirus is a virion in the latent reservoir that may be reactivated to circulate in the blood and infect a cell. Such proviruses contain replication-competent latent proviral DNA.

**Reservoir**
The term reservoir is frequently used for what is more accurately called a latent reservoir in 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 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 latent reservoirs of the HIV-infected cells they contain.

**Restriction Factor**
An HIV restriction factor is a protein that significantly decreases HIV replication. Several examples are the APOBEC3 family, Tetherin, and SAMHD1. HIV has evolved mechanisms to counter all known restriction factors. Also, all restriction factors are strongly related to innate immunity (see the Immune System Glossary entry for a description of innate immunity).

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

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

**Ribozyme**
See the Gene Editing Glossary entry.

**RNA**
RNA stands for ribonucleic acid. Unlike DNA, which exists only as single strands in some viruses or in the double helix structure found in all living things, there are more than 30 forms of RNA with distinct functions. Several of them are described in entries in this Glossary and Resource Guide, namely, cell-associated RNA (caRNA), multiply spliced RNA, ribozyme, short hairpin RNA (shRNA), short interfering RNA (siRNA), transfer RNA (tRNA), and unspliced RNA. Another form is messenger RNA, which is the result of transcription of cellular DNA, in the first step of producing proteins.

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

**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) first tests positive.

**Shock and Kill**
The shock and kill strategy combines “shocking” latent HIV proviral-DNA-containing CD4+ T cells in latent reservoirs out of latency and killing them by apoptosis or another means, such as a monoclonal antibody. Shock and kill is also called kick and kill by some researchers.

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

**Short Hairpin RNA (shRNA)**
See the Gene Editing Glossary entry.

**Short Interfering RNA (siRNA)**
See the Gene Editing Glossary entry.

**Simian Human Immunodeficiency Virus (SHIV)**
Simian/human immunodeficiency virus (SHIV) is a series of chimeras created in laboratories whose genetic material is a combination of simian immunodeficiency virus (SIV) genes and HIV genes. It is capable of infecting almost every type of nonhuman primate that can be infected with SIV.

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

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

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

**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 5, Furtado MS Calloway DS et al. NEJM 340: May 27, 1999; used with permission from the Massachusetts Medical Society). The first step in the creation of new virions is transcription of the proviral HIV DNA to make short completely spliced messenger RNAs called multiply spliced mRNAs that are exported from the nucleus to the cytoplasm (i.e., outside the nucleus) of an infected cell. The multiply spliced mRNAs make proteins that are essential for next making unspliced RNA. These 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). The viral protein Tat is needed to boost synthesis of unspliced RNA. The viral protein Rev is needed to chaperone the unspliced RNA out of the nucleus. The unspliced RNA, in turn, makes the proteins Gag, Pol, Env, Vif, Vpu, and Vpr encoded by the HIV gag, pol, env, vif, vpu, and vpr genes, respectively, that are essential to the creation of new HIV virions. Unspliced (full-length) RNA is essential to make new virions and is also incorporated into them as the viral genome. Unspliced and multiply spliced RNA are also collectively called cell-associated RNA 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 so. The detection of unspliced RNA in latently infected cells
indicates that latency is not fully silent, i.e., 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 heading.

Stem-Cell-Like Memory CD4+ T Cell (TSCM)
A stem-cell-like memory CD4+ T cell (TSCM) is a memory CD4+ T cell that contains large amounts of HIV DNA and, thus, is a very important target for elimination from the latent reservoir it inhabits. Stem-example of a therapeutic vaccine is Vacc-4x, which is discussed in the Shock and Kill Trial Glossary entry.

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

Transcription of DNA
Transcription of DNA is the first step in the process of making proteins or, in the case of HIV, its RNA from proviral DNA. It involves many steps of the creation of messenger RNA (mRNA), each of which codes for a particular amino acid that is one of the components of the resulting protein.

Transfer RNA (tRNA)
A transfer RNA (tRNA) is an adaptor that serves as the

Utrecht/ EPI STEM Patients
The Utrecht/EPISTEM patients are two patients with HIV infection and two different forms of leukemia. Both received allogeneic CCR5 Δ32/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, and that seems to have contributed to his lower viral load post-transplant.

Sterilizing Cure
See HIV Cure (Sterilizing).

T Follicular Helper Cell (Tfh)
T follicular helper cells (Tfh) are found in lymph nodes and other lymphoid components including the spleen and Peyer’s patches and are a minor latent reservoir for latent HIV proviral DNA.

T Helper 17 Cell (Th17)
T helper 17 cells (Th17) are CD4+ T cells that are very easily infected with HIV and, hence, HIV-infected ones are an important target for latency reversal and elimination. Th17 cells have the co-receptor CCR6 in addition to CD4.

Therapeutic Vaccine
A therapeutic vaccine is one that is administered as a therapy for a disease rather than to prevent it. One link between a messenger RNA (mRNA) that carries (hence “transfer”) an amino acid to the end of a protein in the process of being assembled. It moves the amino acid from the mRNA to the organelle called the ribosome that actually builds the amino acid sequences of proteins.

Transitional Memory CD4+ T Cells (TTM)
Transitional memory CD4+ T cells (TTM) are a type of memory CD4+ T cells that are in the process of transitioning from being central memory CD4+ T cells (TCM) to effector memory CD8+ T cells (TEM).

Tropic and Tropism
Tropism (adjective and combining form “tropic”) means “turning toward” in general and, in the specific context of HIV co-receptors, it refers to the choice of CCR5 or CXCR4 that a CD4+ T cell is marked with and hence the types of HIV that attach to its envelope.

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

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

Viral Rebound and Remission
Viral rebound refers to the level of virus found in the blood after an antiretroviral therapy (ART) interruption, possibly because it is believed one has achieved remission. Achieving decreases in viral rebound on the order of a factor of $10^5$ to $10^6$ is thought to be necessary by many researchers to be essential to achieve remission for up to 30 years—effectively life-long for many HIV+ people—and up to a factor of 1,000 to achieve a year-long remission. Unfortunately, there is no therapy that comes close to achieving even this at present. Some researchers, in particular a group of Danes and Australians who published in 2015, believe a very significantly smaller decrease may be sufficient to achieve remission for a year.

Viral Replication
Viral replication is the process by which HIV reproduces, making more HIV virions. To do so, HIV must first reverse transcribe its genetic material from ribonucleic acid (RNA) to deoxyribonucleic acid (DNA). The HIV DNA is then integrated into the infected cell’s DNA. When activated, infected CD4+ T cells produce HIV virions, damaging the

Figure 8. CD4+ T cell with unspliced and multiply spliced messenger RNAs (mRNAs) in the nucleus and cytoplasm.
normal function of the cells and, usually, leading to cell death by apoptosis.

**Viral Set Point**
HIV viral set point is the viral load which stabilizes after the acute infection phase. It also applies to SIV and SHIV infection in the nonhuman primate model.

**Virion**
A virion is a complete virus particle that consists of an RNA or DNA core with a protein coat, often with an external envelope, that is the extracellular infective form of a virus. An HIV virion has two strands of RNA, several proteins (such as reverse transcriptase, protease, and integrase, all three of which are targets for antiretroviral therapy (ART) drugs), and an external envelope.

**Women’s Involvement in Cure Research Studies**
A recent viewpoint article that can be downloaded as a PDF is Grewe ME Ma Y Gilbertson A et al. Women in HIV cure research: multilevel interventions to improve sex equity in recruitment from the open-access article http://viruseradication.com/journal-details/Women_in_HIV_cure_research:_multilevel_interventions_to_improve_sex_equity_in_recruitment 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 above, which makes clear several very important biological reasons for increasing women’s involvement in cure research. The existing barriers to 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. 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 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 (downloadable from http://online.liebertpub.com/doi/pdf/10.1089/apc.2013.0015) is an excellent example that specifically included recruitment of women that can serve as a model for other studies.

**Resource Guide**

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

**American Society for Blood and Marrow Transplantation (ASBMT)**
The American Society for Blood and Marrow Transplantation (ASBMT) does has numerous HIV-related resources (among others on its home page) on its web site at http://www.asbmt.org/search/all.asp?bst=hiv . It also publishes a journal titled Biology of Blood and Marrow Transplantation whose searchable web site is at http://www.bbmt.org/ .

**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 in a building soon to be built at the University of California, San Francisco, CA, 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, the 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 includes 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’, Satish Pillai, PhD. The institute’s mission is to

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


California Institute of Regenerative Medicine (CIRM) HIV Cure Research Grants
The California Institute of Regenerative Medicine (CIRM/"California’s Stem Cell Agency") has given out, as of late 2015, 15 grants for HIV cure research. They can be found listed at https://www.cirm.ca.gov/grants?field_public_web_disease_focus_tid[]=826.

CAN GENE THERAPY CURE HIV? With DAVID BALTIMORE & PAULA CANNON
“Can Gene Therapy Cure HIV? with David Baltimore & Paula Cannon” is a YouTube video of a community event with Nobel laureate David Baltimore, PhD, and Paula Cannon, PhD, sponsored by the Delaney Cell and Genome Engineering Initiative (defeattHIV) 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.

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

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

It lists over 40 publications as of early 2016, and a Web site whose URL is http://www.cancurehiv.org/.

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

City of Hope Clinical Studies
City of Hope in Duarte, CA, is doing clinical studies to alter hematopoietic stem cells to fight HIV/AIDS. As of early 2016, its Alpha Clinic is doing two clinical trials, as follows: (1) with the goal of “resetting” the immune system to produce T cells resistant to HIV infection (COH Protocol #13282) and (2) in cooperation with Sangamo Biosciences and the Keck School of Medicine at the University of Southern California, using a zinc-finger nuclease (see the Gene Editing Glossary entry) to edit a gene in the hematopoietic stem cells that is needed for HIV infection; the resulting T cells will then lack a key protein (CCR5) required to infect cells (COH Protocol #14017). The Web site for the clinical trial is http://www.cityofhope.org/research/research-overview/alpha-clinic-for-cell-therapy-and-innovation/alpha-clinic-clinical-studies, and Sangamo Biosciences’ Web site is http://www.sangamo.com/index.html.
Clinical Trials List
A list of both currently active and completed clinical trials related to curing HIV infection is maintained by the Treatment Action Group and can be found online at http://www.treatmentactiongroup.org/cure/trials. It can be downloaded as a PDF from that page in addition to being viewed there. Also, clicking on the trial number there will take you to the https://clinicaltrials.gov entry for a full description of the trial. See also the EU Clinical Trials Register Resource Guide entry.

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

Collaboratory of AIDS Researchers for Eradication (CARE)
The Collaboratory of AIDS Researchers for Eradication (CARE) is one of the three collaboratories making up the Martin Delaney Collaboratory (MDC): Towards an HIV Cure. Its principal investigator is David Margolis, MD, of the University of North Carolina. Its primary purposes are to characterize HIV latency and develop methods for determining the size of the latent reservoirs. It also has a Community Advisory Board (CAB). Its Web site is http://www.delaneycare.org/.

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

CURE for HIV
Cure for HIV is a United Kingdom Web site that is an information resource for HIV/AIDS cure. It includes at least links to

- Slides from STEPSA community initiative to design the pathway to a long-term remission of HIV infection,
- this Glossary and Resource Guide, both for download and as searchable HTML,
- a POZ article about Bristol-Myers Squibb’s HIV and Hepatitis B cure research grants,
- a news release titled “University of Pittsburgh Vaccine Scientists Win $6.3M Grants Toward HIV Cure,”
- the European AIDS Clinical Society’s (EACS) 2015 Barcelona conference,
- EACS’s HIV treatment guidelines,
- A description of the multinational (23 languages) ECRAN (European Communication on Research Awareness Needs) Project, which is designed to make clinical trials easily understandable for patients,
- the Treatment Action Group’s list of clinical trials, and
- the European Patients’ Academy on Therapeutic Initiatives (EUPATI) Glossary for patients.

The Cure for HIV Web site is http://www.cureforhiv.co.uk/.

CURED: How the Berlin Patients Defeated HIV and Forever Changed Medical Science
CURED: How the Berlin Patients Defeated HIV and Forever Changed Medical Science, Holt N, Dutton, 2014, is a book about the Berlin patient (Timothy Ray Brown) and a German man named Christian Hahn (see the Essen/Berlin Patient Glossary entry). Christian Hahn (a pseudonym—he remains anonymous), a German, in fact, was another man who was treated by Heiko Jessen, MD, for HIV infection in Berlin. It’s not clear in his case that he was actually cured, which is why Timothy Ray Brown is known as the Berlin Patient. It may be that, in Mr. Hahn’s case, we have an instance of postexposure prophylaxis: a combination of factors that resulted in HIV infection never truly being established or post-treatment control.

CURED OF HIV: A COMMUNITY Q&A with TIMOTHY RAY BROWN & GERO HÜTTER, M.D.
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.
**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 Web site is [http://www.avac.org/cureiculum](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 Web site. 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 Research
7. Early Antiretroviral Treatment
8. Pediatric HIV “Cure”
9. Concepts in Basic Science and Translational Research
10. Therapeutic Vaccines and Immune-Based Therapies
11. Informed Consent in HIV Cure Research
12. Ethics of HIV Cure Research
13. Participation in HIV Cure Research
15. History of Cures: Putting HIV Cure Research in Context
16. Combination Approaches and Conclusion - The Science Looking Forward

**CURE REPORT**

The CURE REPORT is an online project about HIV/AIDS cure research efforts founded by Dave Purdy and the Berlin Patient (Timothy Ray Brown). It can be found online at [http://www.cureaidsreport.org/](http://www.cureaidsreport.org/).

**Delaney AIDS Research Enterprise to Defeat HIV (DARE)**

The Delaney AIDS Research Enterprise to Defeat HIV (DARE) is one of the three collaboratories making up the Martin Delaney Collaboratory (MDC): Towards an HIV Cure. Its primary purposes are to characterize the latent reservoirs of HIV-infected cells, identify immune correlates of persistence and compounds to measure them, and to devise techniques to eradicate those cells. Its principal investigators are Steven G. Deeks, MD, Joseph M. “Mike” McCune, MD, PhD, both from the University of California, San Francisco; and Sharon Lewin, FRACP, PhD, from Monash University, Melbourne, Australia. It also has a Community Advisory Board (CAB). Its Web site is [http://delaneydare.org/](http://delaneydare.org/).

**Delaney Cell and Genome Engineering Initiative (defeatHIV)**

The Delaney Cell and Genome Engineering Initiative (defeatHIV) is one of the three collaboratories making up the Martin Delaney Collaboratory (MDC): Towards an HIV Cure. It is a consortium of academic and industrial investigators working together to eradicate HIV by gene editing. Its principal investigators are Keith Jerome, MD, PhD, and Hans-Peter Kiem, MD, both from the Fred Hutchinson Cancer Research Center in Seattle, WA. It also has a Community Advisory Board (CAB). Its Web site is [http://defeathiv.org](http://defeathiv.org).

**Estradiol, Estrogen, Progesterone, and Estrogen Receptors**

Several groups funded by amfAR’s Research Consortium on HIV Eradication (ARCHE) (Web site [http://www.amfar.org/cure/](http://www.amfar.org/cure/)) are studying differences in inflammation and antiretroviral therapy (ART) of HIV infection between women and men that may lead to differences in cure research between the sexes.

**EU Clinical Trials Register**

The EU (European Union) Clinical Trials Register is offline as of early 2016. However, when it becomes available again—which is expected to be before this document is published—it will be a searchable database of all clinical trials that include EU sites or that are run by companies and research institutions located in EU countries. Its Web site is
European AIDS Clinical Society (EACS)
The European AIDS Clinical Society (EACS) sponsors the European AIDS Conferences, among other activities. The 15th such conference includes six webcasts concerning “Prospects for HIV Cure and Post Treatment Remission” that are available on the society's Web site at http://eacs.multilearning.com/eacs/ under its subject heading.

Global Investment in HIV Cure Research and Development - AVAC, which describes its mission as “Global Advocacy for HIV Prevention” also has issued, so far, three documents titled “Global Investment in HIV Cure Research and Development” for 2012, 13, and 14. The most recent one can be downloaded from the AVAC web site at http://www.avac.org and searching for “Global Investment in HIV Cure”. AVAC also hosts this Glossary and Resource Guide.

Good Manufacturing Practices (GMP)
Good manufacturing practices (GMP) refers to the practices required to conform to the guidelines recommended by agencies that control licensing for manufacture and sale of food, drug products, and other medical products and devices. The agencies include the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA). The International Society for Pharmaceutical Engineering (ISPE) provides access to Australian, Canadian, European Union, Japanese, U.S. FDA, and World Health Organization GMP guidelines on the Web at http://www.ispe.org/gmp-resources/gmp-guidelines.

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

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 Web site is http://i-base.info.

Journal of Viral Eradication - The Journal of Viral Eradication is an open-access online and print journal devoted to cure research 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
In June 2015 the U.S. National Institutes of Health issued a funding opportunity announcement (RFA-AI-15-029) intended to restructure the Martin Delaney Collaboratory (MDC): Towards an HIV Cure with a different funding mechanism and several other important changes, as follows:

17. There are intended to be more than three collaboratories, each of which will be smaller;
18. Though basic research is likely to continue to be funded, there will be a much stronger focus on translational research, i.e., research whose results can be applied to real-world issues in curing HIV infection and clinical trials must be included in plans for the new collaboratories;
19. To quote directly from the RFA, “Funded projects will be expected to expand the knowledge base on HIV latency and persistence in HIV-infected persons treated with suppressive antiretroviral drug regimens, design and evaluate innovative cure strategies, and translate findings to the clinical setting.”;
20. Each collaboratory must include a cooperative arrangement between university researchers and an industry partner;
21. A community member must be included as a member of the executive body of each collaboratory; and
22. The three existing collaboratories may or may not continue.

Martin Delaney Collaboratory (MDC): Towards an HIV Cure
The Martin Delaney Collaboratory (MDC): Towards an HIV Cure is a group of three collaboratories that are organizations consisting of researchers devoted to studying cures for HIV infection and promoting them via clinical trials. The three collaboratories are the Collaboratory of AIDS Researchers for Eradication (CARE), the Delaney AIDS Research Enterprise to Cure HIV (DARE), and the Delaney Cell and Genome Engineering Initiative (defeatHIV). Each of the three consists of scientists and a Community Advisory Board (CAB). The overall Collaboratory is funded by the U.S. National Institutes of Health. The Collaboratory also has a National Community Advisory Board (NCAB) made up of two members from each of the CARE, DARE, and defeatHIV CABs. 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.

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

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 web site is to go to http://natap.org/ and search for “cure”.

Project Inform HIV Cure Advocacy
Project Inform’s HIV cure advocacy page provides up-to-date information about a variety of cure topics, including at least the following:

1. Cure topics at the IAS 2015 conference in Vancouver, BC, Canada;
2. Access to this Glossary and Resource Guide;
3. Cure topics at the most recent Conference on Retroviruses and Opportunistic Infections (CROI);
4. A community forum in San Francisco on World AIDS Day (1 December 2015) presented by the Getting to Zero Consortium; and
5. News on a variety of cure-related topics.

The relevant Web page is http://www.projectinform.org/category/cure-advocacy/ .

Qura Therapeutics
Qura Therapeutics is a partnership between the University of North Carolina-Chapel Hill and GlaxoSmithKline announced in May 2015 that “will focus exclusively on finding a cure for HIV/AIDS … including a leading research approach toward an HIV cure, sometimes called “shock and kill.” The announcement is available at http://uncnews.unc.edu/2015/05/10/unc-chapel-hill-and-gsk-announce-novel-partnership-to-accelerate-search-for-hiv-cure/ .

Stakeholder Engagement
This particularly echoes the 1983 Denver Principles for involvement of civil society in every level of HIV-related decision making. See http://www.actupny.org/documents/Denver.html or perform a search for gipa1983denverprinciples_en.pdf .

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

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

**Strategies for an HIV Cure: 2016**
The meeting Strategies for an HIV Cure: 2016 will be convened by the NIH on its campus in Bethesda, MD, to give the Martin Delaney Collaboratories an opportunity to present their progress and to discuss future prospects for and approaches to curing HIV infection. The agenda for the meeting is not yet available at the time of publication of this document.

**THE BODY**

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