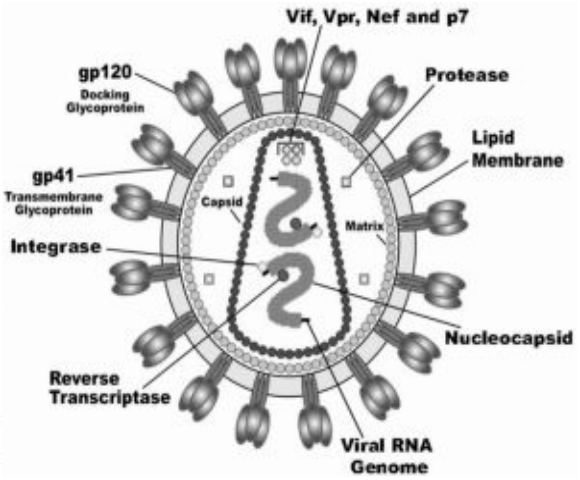
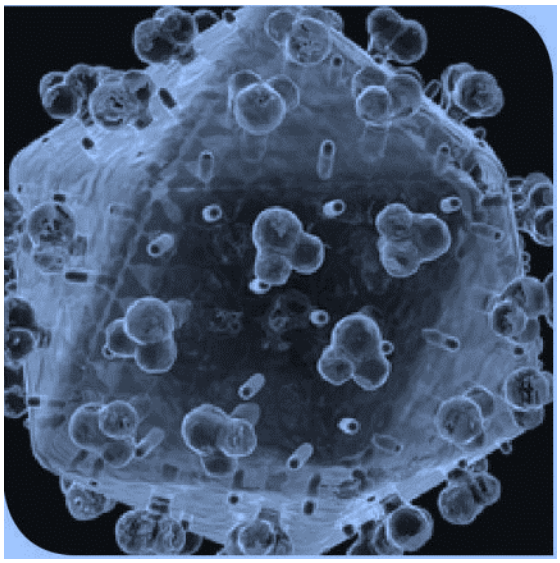
HIV/AIDS Cure Research Introduction & Resource Guide 2017





Cover Design

Upper left: Young woman looking through microscope
Upper right: Cutaway design of an HIV virion (single virus particle)
Lower left: Pipette dropping liquid into test tube
Lower right: Virion surface photomicrograph

HIV/AIDS Cure Research Introduction & Resource Guide 2017

This document is designed to introduce the issues involved in research related to curing HIV infection and provide access to online resources for further information. 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. **COLOR OF HEADERS:** Entries in the Introduction have headers that are color coded to indicate what scientific areas they belong to, as follows:

    - Basic science and biology entries have headers that are **green**.
    - HIV background, that is, entries that aren't specifically related to cure research, and those that span categories have headers that are **blue**.
    - Gene-editing- and transplant-related entries have headers that are **violet**.
    - Entries related to HIV reservoirs, latency reversal, shock and kill, and latency silencing have headers that are **red**.
    - Entries related to individuals and groups of individuals have headers that are **brownish orange**.
    - Entries related to social issues and practical considerations have headers that are **brown**.

2. **LINKS:** Terms that are hyperlinked are defined elsewhere in this document. To use a hyperlink in both the PDF version and the web-page version, simply click on the link. To reduce clutter, for cross-referenced terms that occur more than once in an entry, only the first occurrence is hyperlinked.
3. **HIV, HIV-1 & HIV-2:** References to HIV are to what is more specifically named HIV-1, which is responsible for the pandemic. There is also a variety named HIV-2 that is confined to parts of West Africa and a few small pockets in Europe of immigrants from West Africa. It is likely that any cure strategy for HIV-1 will also work for HIV-2.
4. **RESPONSIBILITY:** This document is a project of the Delaney AIDS Research Enterprise (DARE) to Find a Cure Community Advisory Board (CAB)—which is responsible for its content—with some input from several DARE researchers.
5. **FORMS AND AVAILABILITY OF THIS INTRODUCTION & RESOURCE GUIDE:** This Introduction & Resource Guide is available online on the DARE website as a PDF, that is accessible from the web page at http://daretofindacure.org/cab/cureglossary.html .
6. **SPANISH EDITION:** The Introduction (without the Resource Guide) has been translated into Spanish and is available as a PDF from the DARE website at http://daretofindacure.org/cab/introduccion.html .
7. **CONTACTING THE AUTHOR:** You are welcome to send suggestions for edits and additions to this document's author at hivcureglossary@gmail.com. You may also send questions to the author about items in this document. However, please note that, while an attempt will be made to answer all relevant questions, not all of them will be answered quickly because of time limitations.

Overview

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

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

a sexual partner.

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

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

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

- **Hematopoietic stem cell transplant:** Transplantation of hematopoietic (that is, blood-cell-producing) stem cells that lack a factor essential to most HIV infections is the approach used to cure the one person who has been cured so far, namely, the Berlin patient (Timothy Ray Brown). However, this approach is very impractical. It requires conditioning of the body—wiping out its immune system—so the transplant is not rejected, which makes one open to a wide range of infections until the transplant repopulates the immune system. In fact, Timothy nearly died in the process of his cure. The conditioning and the series of other medical interventions make this approach very time consuming, expensive, and risky. As a result, despite its being effective, this approach is simply not anywhere near generalizable to everyone living with HIV either now or in the near future, though there are researchers working on "transplant in a box."

- **Gene editing:** One reason HIV is so difficult to cure is that, unlike almost all other viruses, it integrates many copies of its genetic material into the DNA of the human cells it infects. Gene editing is a strategy for modifying the HIV DNA in the host's cells, such as removing it entirely or altering one or more of the factors that make those cells susceptible to HIV infection. There are numerous experimental gene editing techniques being investigated. However, the most precise and effective one is named CRISPR or CRISPR/Cas9. A recent mathematical modeling study of gene-editing strategies for HIV cure has shown that achieving positive results requires major improvement of some key components of the strategy.

- **Shock and kill:** Shock and kill is focused on a type of immune-system cells called helper T cells or CD4+ T cells, which are the cells that are the primary focus of HIV infection. In fact, one would not be far wrong to say that HIV *is* a disease of helper T cells because it preferentially infects them and in the process of reproducing HIV virions (single virus particles) it destroys them. After becoming infected, CD4+ T cells go into a state called latency in some bodily organs, particularly lymph nodes. In that state they are not producing new virions, are out of the blood, and are inaccessible to anti-HIV drugs.

  Shock and kill's goal is to reactivate latent infected helper T cells and kill them. It is—obviously—a two-step process. The shock step uses drugs called latency-reversal agents (mostly ones developed for treating cancers) to reawaken the latent infected T cells. The second step uses other drugs to kill them. There are currently two very significant problems with shock and kill: (1) there is no solid way to measure the number of latent infected cells in the body; there are several methods, but they provide vastly different numbers; and (2) despite the variation in measurements, it is clear that all the approaches to reactivation come nowhere near reactivating all the latently infected helper T cells, and there are several cases of people who were thought to be cured turned out to have HIV reappear either quickly or eventually.

  Shock and kill is also known as kick and kill.

- **Latency Silencing:** Latency silencing is

the opposite of shock and kill. Instead of reactivating latent cells to kill them, its goal is to keep latent infected helper T cells and other infected cells from ever being activated. It is particularly important in the central nervous system (the brain and spinal cord) where reactivation could cause a storm of disastrous effects. Several approaches are being explored including using gene editing to make the HIV neither dangerous nor infective, using drugs to inhibit important HIV proteins, and using a protein to block integration of HIV into cellular DNA.

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

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Alleles and Mutations

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

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

Allogeneic Transplant

An allogeneic transplant, in the context of curing HIV infection, involves transplanting hematopoietic stem cells from a donor other than the transplant recipient. As described above, this is being studied as a possible way to perform a sterilizing cure of HIV infection. See autologous transplant below for an alternative.

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

Analytical Treatment Interruption (ATI)

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

Animal Models

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

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

clinical trials.

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

Antigens and Antibodies

An antigen is a pathogen that induces an immune response in the body, particularly the production of an antibody.

An antibody is a mechanism the body has for fighting infections and other foreign substances (antigens). It is a specific protein produced by a B cell in the blood in response to and to counteract an antigen. It forms a chemical combination with the antigen that makes it inert.

Antiretroviral Therapy (ART)

Antiretroviral therapy (ART) involves the use of several (usually three) anti-HIV drugs to halt or greatly decrease production of new virions. ART drugs may target any of several viral enzymes, such as reverse transcriptase, protease, or integrase. Some drugs may instead target essential parts of the infected cell, as the CCR5-blocking drugs do. Some researchers believe that ART will be needed in shock and kill cure strategies to halt HIV reproduction as part of killing them in cells that have been reactivated by latency reversal.

Autologous Transplant

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

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

1. The cells to be transplanted (presumably hematopoietic stem cells) must be modified by some method to make them resistant to HIV infection (rather than being selected to be resistant, for example, by having the CCR5Δ32/Δ32 mutation);
2. There is not yet a safe and effective method for selecting the gene-modified cells, though several have been tried;
3. There must be sufficient numbers of transplanted cells to swamp the already infected blood stem cells.

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

B Cell

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

Berlin Patient (Timothy Ray Brown)

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

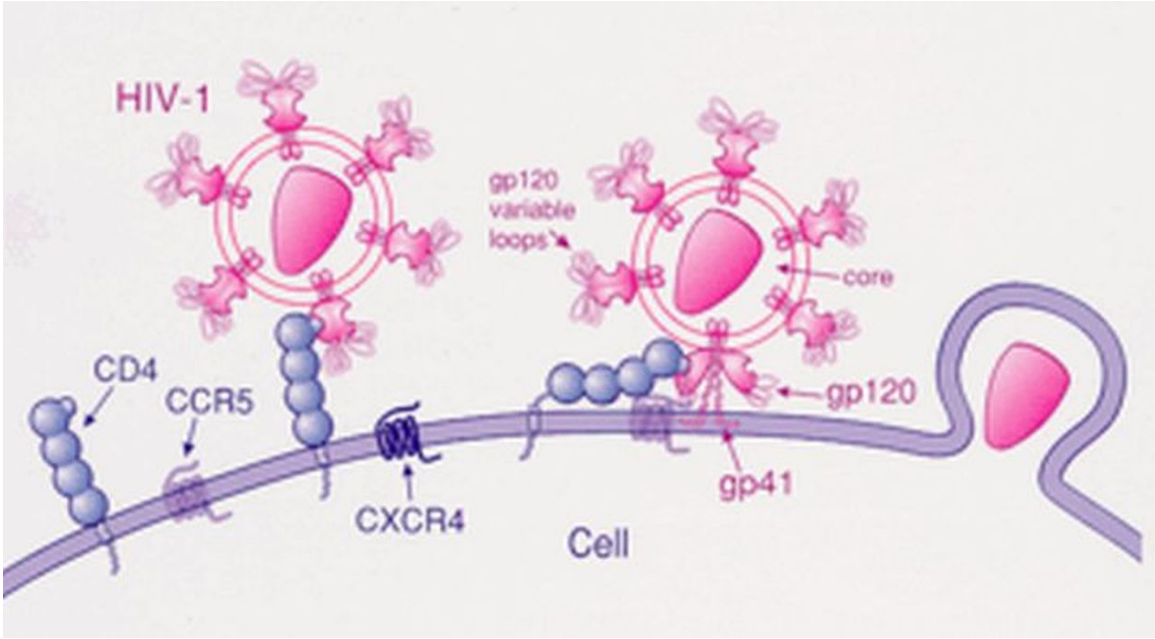

Figure 1. This sequence shows HIV binding to the CD4 receptor, then to the CCR5 co-receptor, and finally having released its genetic material into a CD4+ T cell in four steps: (1) the CD4 receptor and CCR5 co-receptor on the cell surface; (2) the HIV protein named gp120 binds to CD4; (3) gp120 binds to CCR5 and releases the HIV gp41, which pierces the cell surface causing opening of a pore in the cell's coat; (4) the capsid, which contains the most important parts of the virus for its replication enters the CD4+ T cell through the pore.

CCR5

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

CCR5Δ32/Δ32

CCR5Δ32/Δ32 indicates a mutation that deletes 32 base pairs from both parents' copies of the gene that encodes the cellular co-receptor CCR5. The absence of these base pairs eliminates the ability of CCR5 to function on CD4+ T cells; the CCR5 co-receptor is needed by almost all strains of HIV to enter and infect these cells. Notably, the allogeneic immune-system transplants that resulted in a sterilizing cure of HIV infection in the Berlin Patient (Timothy Ray Brown) had this mutation in both strands of the DNA included in the transplant. Unfortunately, only about 10 – 15% of Caucasians have this mutation and almost no one else does, which makes this approach nearly useless for curing HIV infection in all infected persons, unless gene editing can make more instances of the mutation, which is one of the focuses of HIV cure research. Note that "Δ" is the upper-case Greek letter "delta" and stands for the deletion.

CD4

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

CD4+ T Cells

CD4+ T cells are primary white blood cells of the

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

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

CD8

CD8 is a receptor that is necessary to the attachment of virions chemicals, and other cells to CD8+ T cells. CD8 is one of hundreds of receptors known as **c**lusters of **d**ifferentiation that are found on the surfaces of various cell types. CD4 is another example. Note that, in addition to responding to HIV-specific CD4+ T cells, CD8+ T cells also respond to other CD4+ T cells and CD8 is found on other types of immune system cells.

CD8+ T Cells

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

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

Central Nervous System (CNS)

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

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

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

Clinical Trials

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

- Phase I: A Phase I clinical trial involves a small number (usually not more than about 20) of healthy volunteers to test the safety of the medication and any side effects it may have. If the drug is determined to be safe and to have only acceptable side effects, it may proceed to Phase II.
- Phase II: A Phase II clinical trial will usually involve several hundred volunteers. It continues to test for safety and side effects and also adds on determination of effectiveness.
- Phase III: A Phase III clinical trial involves several thousand volunteers and is intended to confirm the effectiveness of the medication, monitor its side effects, compare it to commonly used drugs for the same condition if there are any already, and continue to collect information to determine whether the drug is safe. Only after a successful Phase III study does a medication go before a panel of the U.S. Food and Drug Administration (FDA) or similar agency elsewhere in the world for approval for distribution.

There is also what is sometimes called "Phase IV": a post-marketing phase, in which the medication

or procedure is used in diverse populations and continues to be monitored for side effects.

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

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

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

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

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

Co-Receptor

A co-receptor is a chemical such as CCR5 or CXCR4 that works with a receptor to achieve attachment of a virion or other substance to a cell.

CXCR4

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

Defective Virion

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

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

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

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

Dendritic Cell

A dendritic cell is one variety of cell whose main

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

Diversity and Inclusiveness in Cure Research

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

- It is clear from numerous studies that the immune system's effectiveness decreases with increasing age. This has effects on how well the body can deal with HIV infection among many other types of assaults and it also probably impacts the effectiveness of approaches to HIV cure, though this is currently unknown.
- Similarly, the hormonal and other developmental changes that occur during adolescence and the legal issues involved in obtaining informed consent for research very often exclude adolescents from HIV research studies. A notable positive development in this area is in South Africa, the country with the highest proportion of HIV+ youths and young adults.
- There are barriers to including women in cure research, at the least because current approaches to cure have unknown interactions with pregnancy, both on the mother and the fetus.
- Transgender health is a developing field, but, so far, virtually nothing is known about the impact of hormonal treatment on cure strategies and vice versa.

See also the Women's Involvement in Cure Research Studies entry.

Elite Controllers

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

Enzyme

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

Gene Editing

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

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

Science, the most prominent U.S. scientific journal, declared CRISPR to be the "Breakthrough of the Year" for 2015 because of its very wide applicability and ease of use, and *Nature*, the most prominent British scientific journal, chose it as No. 1 among its ten most important breakthroughs of 2015. Further, in early 2016, it was reported by

two research teams that CRISPR technology, one using Cas9 and another using a different protein, had been used to remove entire HIV proviral DNA from latently infected CD4+ T cells in test tubes and this has more recently been reported in living organisms. Problems remain, however, for generally translating this technology to use in people—in fact another recent study about it reported that CRISPR/Cas9 resulted in the immune system responding to the Cas9 protein as a substance foreign to the body (a pathogen).

Genome

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

Graft-versus-Host Disease (GVHD)

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

Gut-Associated Lymphoid Tissue (GALT)

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

Hematopoietic Stem Cells

Hematopoietic stem cells are blood cells that can differentiate to produce all the types of blood cells.

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

HIV Cure (Sterilizing)

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

HIV Genome

The nucleus of HIV contains the two separate single strands of RNA that make up HIV's genetic material or genome. It comprises nine genes and a stretch of additional RNA at each end. The overlapping of segments in the diagram corresponds to what are known as open reading frames. (Note that the open reading frames in the HIV genome are *never* directly transcribed and translated to proteins: The HIV genome must first be integrated into a host cell's DNA as proviral DNA that is, in turn, transcribed and translated to proteins.) In all, each strand has roughly 9,750 bases, though this varies somewhat with the faulty replication of HIV RNA.

HIV's Uniqueness

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

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

- It also attacks the central nervous system (CNS) very early in infection.

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

Immune System

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

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

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

Inflammation

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

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

Latency Reversal

Latency reversal is fundamental to activating the bound HIV proviral DNA in resting CD4+ T cells in latent reservoirs in the body to make it susceptible to destruction in the approach to cure known as shock and kill. This is considered by many HIV cure researchers to be fundamental to curing HIV. There are at least 16 types of substances and individual substances being tested as latency-reversal drugs.

Latency Silencing

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

Latent Reservoir

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

(1) *A* latent HIV reservoir is a tissue in a person's body that is reachable by HIV. In the context of HIV infection, it is a part of the body that, it is generally believed, is not affected by antiretroviral therapy (ART) as effectively, if at all, as in the blood. Latent reservoirs provide long-lived homes for HIV to reemerge from if therapy is stopped. Examples of confirmed and likely latent reservoirs include a subset of CD4+ T cells named resting memory CD4+ T cells, white blood cells named macrophages and monocytes, and parts of the intestines.

(2) *The* latent HIV reservoir is the totality of the individual latent reservoirs of type (1). The size of the latent reservoir is estimated to be from 1 million to over 50 million HIV-infected resting memory CD4+ T cells.

A 2011 freely available survey article (Richman D **"**Introduction: challenges to finding a cure

for HIV infection" Current Opinion in HIV and AIDS **6**, January 2011, p. 1; it can be downloaded from the webpage http://journals.lww.com/co-hivandaids/toc/2011/01000) noted what we know about the latent reservoir as follows (lightly edited):

a) Latently infected resting memory CD4+ T cells are the best characterized latent reservoir for HIV.
b) Less than 1 cell per million of resting CD4+ T cells from persons on potent antiretroviral therapy harbors proviral DNA that can be used by infected CD4+ T cells to create new virions.
c) Other drug-insensitive reservoirs, including the central nervous system (CNS), may also exist.
d) The genetic information in latent proviruses does not evolve—because it is produced by the body's creating a clone of a single infected cell—which suggests there is no ongoing viral replication within the cells containing them. Discontinuation of antiretroviral therapy permits the rebound of viral replication originating from the latent reservoir.
e) Patients successfully treated with antiretroviral therapy for a decade or more exhibit no appreciable decrease in the size of the latent reservoir.
f) The persistence of the latent reservoir precludes its elimination by antiretroviral therapy for the lifetime of the patient.
g) Latency is likely established by numerous steps of HIV-1 replication, which potentially complicates eradication strategies.

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

Lymph Node

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

Lymph Node Collagen Deposition (Fibrosis)

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

Lymphatic System & Lymphoid Tissues

A lymphoid tissue is an individual component of the lymphatic system. The lymphatic system is made up of lymph nodes; local immune cells in many other lymphoid tissues, such as gut-associated lymphoid tissue (GALT), the spleen, and a series of other tissues; and the lymphatic vessels that lead from lymphatic tissues toward the heart. The lymphatic system is essential to fighting infections.

Measuring the Latent Reservoir

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

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

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

Natural Killer (NK) Cells

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

Pathogen

A pathogen is a foreign substance, bacteria, or virus that may invade a living organism.

Post-Therapy Controllers

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

Proviral DNA

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

Receptor

A receptor, in the context of HIV cure research, is a chemical (such as CD4 and CD8).

Remission

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

Resting Memory CD4+ T Cells

There are at least five types of resting memory CD4+ T cells found in latent reservoirs in the body. 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 stem-cell-like memory CD4+ T cells (T_{SCM}) are the smallest component, but they are thought to be very important because they serve as a source for the other types (except naïve CD4+ T cells) and are very long lived. Thus, targeting HIV-infected T_{SCM} cells for activation and elimination is believed to be essential to latency reversal of HIV latent reservoirs.

Retrovirus

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

RNA

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

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. Shock and kill is called kick and kill by some researchers.

Stakeholder Engagement

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

Thymus Gland

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

adolescence.

Viral Load

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

Virion

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

Women's Involvement in Cure Research Studies

A recent open-access viewpoint article concerning women's involvement in cure research suggests six ways to increase women's involvement. Current barriers and suggested ways to increase involvement are as follows:

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

Resource Guide

The Berlin Patient (Timothy Ray Brown) Story *Timeline*

The Berlin Patient (Timothy Ray Brown) Story *Timeline* is Timothy Ray Brown's outline of his HIV cure in his own words organized by years. It can be found on the Cure Report's website at http://www.cureaidsreport.org/berlin-patient-story/ .

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

"Can Gene Therapy Cure HIV? with David Baltimore & Paula Cannon" is a YouTube video of a community event with Nobel laureate David Baltimore, PhD, and Paula Cannon, PhD, sponsored by the Delaney Cell and Genome Engineering Initiative (defeatHIV) that was recorded on 12 August 2015 as a community addition to the August 2015 Cell & Gene Therapy for HIV Cure conference that took place at the Fred Hutchinson Cancer Research Center (the "Fred Hutch") in Seattle, WA. The video can be found at https://www.youtube.com/watch?v=LVR_-rUQHa0&feature=youtu.be .

CAN GENE THERAPY CURE HIV/AIDS?

"Can Gene Therapy Cure HIV/AIDS?" is a YouTube video of a community event with Paula Cannon, PhD, sponsored by the Delaney Cell and Genome Engineering Initiative (defeatHIV) that was recorded in August 2014 as a community addition to the August 2014 Cell & Gene Therapy for HIV Cure conference that took place at the Fred Hutchinson Cancer Research Center (the "Fred Hutch") in Seattle, WA. The video can be found at https://www.youtube.com/watch?v=plvv07vd5iI .

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.

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

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

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

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

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

1. Slides from STEPS, a community initiative to design the pathway to a long-term remission of HIV infection,
2. This Glossary and Resource Guide,
3. A **POZ** article about Bristol-Myers Squibb's HIV and Hepatitis B cure research grants,
4. A news release titled "University of Pittsburgh Vaccine Scientists Win $6.3M Grants Toward HIV Cure,"
5. The European AIDC Clinical Society's (EACS) 2015 Barcelona conference,
6. EACS's HIV treatment guidelines,
7. 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,
8. The Treatment Action Group's list of clinical trials, and
9. The European Patients' Academy on Therapeutic Initiatives (EUPATI) Glossary for patients.

The Cure for HIV website 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 N Holt Dutton 2014 is a book about the Berlin patient (Timothy Ray Brown) and a German man named Christian Hahn (see the "Essen/Berlin Patient" Glossary entry). Christian Hahn (a pseudonym—he remains anonymous), a German, in fact, was another man who was treated by Heiko Jessen, MD, for HIV infection in Berlin. It's not clear in his case that he was actually cured, which is why Timothy Ray Brown is known as *the* Berlin Patient. It may be that, in Mr. Hahn's case, we have an instance of postexposure prophylaxis: a combination of factors that resulted in HIV infection never truly 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 .

CURED/NOTCURED on Seattle Channel's Town Square
CURED/NOTCURED on Seattle Channel's Town Square is a YouTube video of one of the two Boston Patients, Gary Steinkohl, and his doctor

Timothy Henrich, MD, discussing his case. The Boston patients were three men with lymphoma who were subjected to a cure regimen similar to but much less intense than that undergone by the Berlin Patient (Timothy Ray Brown). They were kept on antiretroviral therapy (ART) afterward; one died from a recurrence of his lymphoma, and the other two were eventually taken off ART and had viral rebound despite viral load reductions of at least a thousand fold. The video can be found at https://www.youtube.com/watch?v=--Jg_bqCGDo .

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

1. HIV/AIDS and Cure Basics
2. Stakeholder Engagement in HIV Cure Research
3. Gene Therapy/Stem Cell Transplant
4. Shock and Kill and Latency-Reversing Agents
5. Measuring the Latent HIV Reservoir
6. Regulatory Issues in HIV Cure Research
7. Early Antiretroviral Treatment
8. Pediatric HIV "Cure"
9. Concepts in Basic Science and Translational Research
10. Therapeutic Vaccines and Immune-Based Therapies
11. Informed Consent in HIV Cure Research
12. Ethics of HIV Cure Research
13. Participation in HIV Cure Research
14. Animal Models in HIV Cure Research
15. History of Cures: Putting HIV Cure Research in Context
16. Combination Approaches and Conclusion - The Science Looking Forward

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/.

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

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

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

Global Cure AIDS Clinical Trials
Global Cure AIDS Clinical Trials is a list of recruiting, not yet recruiting, and ongoing but not recruiting HIV cure clinical trials organized by U.S. state and non-U.S. country. The non-U.S. countries follow the states. The list can be found on the Cure Report website (see above) at http://www.cureaidsreport.org/global-cure-aids-clinical-trials/#PrettyPhoto[416]/1/ .

Global Investment in HIV Cure Research and Development
AVAC, which describes its mission as "Global Advocacy for HIV Prevention" also has issued, so

far, three documents titled “Global Investment in HIV Cure Research and Development” for 2012, 13, and 14. The most recent one can be downloaded from the AVAC website at http://www.avac.org 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 to the GPP guidelines on the Web at http://www.avac.org/good-participatory-practice .

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

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

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

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

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

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

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

Research Toward a Cure Trials
Research Toward a Cure Trials is an annually updated collection of three lists, namely, “Current Clinical Trials,” “Observational Studies,” and “Completed Trials,” including for each one a short

title, trial registry identifier(s), manufacturer/sponsor(s)," "phase," and either "estimated completion date" or "published/presented data" location. The most recent list is dated 28 February 2017, lists about 125 trials, and can be downloaded as a PDF at http://www.treatmentactiongroup.org/cure/trials.

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

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

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

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

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

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

The Legacy Project's mission is to build trust and collaboration between historically underrepresented communities most impacted by the domestic HIV epidemic, researchers, and research institutions; enhance cultural competence; and initiate scientific investigation to increase clinical research participation.