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: HIV virion surface photomicrograph
Introduction to HIV/AIDS Cure Research

Overview

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

1. Despite treatment that reduces HIV viral load to an undetectable level in almost everyone who can stand that treatment and stick to taking it daily, everyone—including almost all elite controllers, who achieve undetectability 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.

Notes to the Reader:

1. STRUCTURE OF THIS DOCUMENT: This document is divided into two sections titled “Introduction to HIV/AIDS Cure Research” and “Resource Guide” in that order.

2. COLORS OF HEADERS: Introduction entries have headers that are color coded to indicate what scientific areas they belong to, as follows:

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

All other entries in the entire document have headers that are black.

Items are arranged in each of the four parts alphabetically by the first nontrivial word; thus, for example, the Resource Guide entry THE BODY is under “B”, not “T”.

3. CROSSREFERENCES: Terms that are underlined are defined elsewhere in this document. To reduce clutter, for cross-referenced terms that occur more than once in an entry only the first occurrence is underlined. There are also URLs for external resources.

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 members of some of the other Martin Delaney Collaboratories for HIV Cure Research CABs and several DARE researchers.

5. INTRODUCTION IN SPANISH: The Introduction section has been transformed to a self-contained version that has been translated to Spanish. It is available as a PDF on this website by selecting the “Recursos ...”

6. 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.
2. Despite having undetectable viral load one still has a tiny possibility of passing HIV on to a sexual partner. Note that these reasons make it essential to cure HIV as soon as possible after one becomes infected. There are two types of cures that are the subject of research. The more ambitious is sterilizing, which removes all HIV from the body, or at least all HIV that can replicate. This is the kind of cure that is achieved for most diseases. It is increasingly being realized that sterilizing cure is likely not to be achievable for HIV, or at least not in the foreseeable future. The more realistic is functional cure, also known as remission, whose goal is to make the body able to control the disease without needing antiretroviral therapy (ART) for some period of time, preferably measured in years, and to have remission be repeatable.

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

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

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

- **Shock and kill:** Shock and kill (also called kick and kill) is focused on a type of immune-system cells called helper T cells or CD4+ T cells, which are the cells that are the primary focus of HIV infection. In fact, one would not be far wrong to say that HIV is a disease of helper T cells because it preferentially infects them and in the process of replicating HIV virions (single virus particles) it destroys them. After becoming infected, many CD4+ T cells go into a state called latency in some bodily organs, particularly lymph nodes. In that state they are not producing new virions, are out of the blood, and are inaccessible to anti-HIV drugs. Shock and kill’s goal is to reactivate latent infected helper T cells and kill them. It is—obviously—a two-step process. The shock step uses drugs called latency-reversal agents (mostly ones developed for treating cancers) to reactivate the latent infected T cells. The second step uses other drugs to kill them. There are currently two very significant problems with shock and kill: (1) until very recently there has been no accurate way to measure the number of latent infected cells; and (2) despite the variation in measurements, it is clear that all the approaches to reactivation come nowhere near reactivating all the latently infected helper T cells, and there are several cases of people who were thought to be cured turning out to have viral rebound either quickly or eventually.

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

- **Immune-Based Therapies:** Immune-based therapies use drugs to alter some part of HIV’s replication process or enhance the effects of other approaches. An example is the use of drugs called TLR7 agonists (an agonist is a substance that cause another one 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.
AIDS (Acquired Immune Deficiency Syndrome)

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

Alleles and Mutations

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

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

Allogeneic Transplant

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

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

Analytical Treatment Interruption (ATI)

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

The monitoring is almost always done by the researchers performing the study or by clinicians working with them. The purpose of the interruption is to determine the effect of the intervention used in the study on one or more measures of, for example, latent reservoir reactivation. Analytical treatment interruptions pose important ethical issues, such as the possibility that the participant’s viral load becomes high enough that he or she infects one or more other persons or that her or his virus population becomes resistant to all available antiretrovirals (ARV); for a discussion of the ethical issues see the article that the Ethics of ART interruption after stem-cell transplantation Resource Guide entry concerns.

Animal Models

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

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

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

Antigens and Antibodies

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

Antiretroviral Therapy (ART)

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

**Autologous Transplant**

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

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

1. The cells to be transplanted must be modified to make them resistant to HIV infection;
2. There is not yet a safe and effective method for selecting the gene-modified cells, though several have been tried;
3. The transplanted cells must totally replace the already infected blood stem cells.

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

**B Cell**

A B cell is a variety of immune-system cell that originates in the bone marrow (hence the “B”). It produces antibodies (see the Antigens and Antibodies Introduction entry) 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 CCR5Δ32/Δ32 allogeneic transplant of blood 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. While Timothy is the only person to have been definitively cured so far, there are two people called the London Patient and the Düsseldorf Patient who may also have been cured, though it is too soon to be certain of that.

**Berlin Patient No. 2**

The person I’m calling Berlin Patient No. 2 was a man who used the pseudonym Christian Hahn and had a blood cancer named Non-Hodgkin’s lymphoma, HIV infection that used the CCR5 co-receptor for cell entry, and a pair of protective mutations. Because of the poor prognosis for his lymphoma, he underwent a CCR5Δ32/Δ32 bone-marrow transplant. However, following the transplant, he was found to have HIV that used either the CXCR4 co-receptor or both CCR5 and CXCR4, and he subsequently died from a recurrence of his lymphoma. It is not well understood why the CXCR4 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’ entry mechanism are the clinical factors most likely to predispose a transition from using CCR5 to using CXCR4.

**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 the CD4 receptor 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.

**CCR5Δ32/Δ32**

CCR5Δ32/Δ32 indicates a mutation (see the Alleles and Mutations Introduction entry) that deletes 32 consecutive base pairs from both parents’ copies of the gene that encodes the CCR5 co-receptor. The absence of these base pairs eliminates the ability of the CCR5 co-receptor to attach most varieties of HIV to CD4+ T cells; an intact CCR5 co-receptor is needed by almost all strains of HIV to enter and infect these cells. Almost all genes in human cells are present as two copies. Notably, the allogeneic immune-system transplants that resulted in a sterilizing cure of HIV infection in the Berlin Patient (Timothy Ray Brown) had this mutation in both strands of the DNA included in the transplant.
Unfortunately, only about 10 – 15% of Caucasians have this mutation and almost no one else does, which makes this approach nearly useless for curing HIV infection unless gene editing can make more instances of the mutation, which is one of the major focuses of HIV cure research. Note that “Δ” is the upper-case Greek letter “delta” and stands for the deletion. Further, CCR5Δ32/Δ32 is unfortunately associated with increased susceptibility to West Nile virus infection and a variety of encephalitis.

**CD4**

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

**CD4+ T Cell**

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

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

**CD8**

CD8 is a receptor that is necessary to the attachment of virions, chemicals, and other cells to CD8+ T cells. CD8 is one of hundreds of receptors known as clusters of differentiation that are found on the surfaces of various cell types and facilitate attachment of virions, chemicals, and other cells. CD4 is another example.

**CD8+ T Cell**

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

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

**Central Nervous System (CNS)**

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

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

**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 (almost always fewer than 20) of healthy volunteers to test the safety of the medication and any side effects it may have. If the medication is determined to be safe and to have only acceptable side effects, it may proceed to Phase II.
- **Phase II**: A Phase II clinical trial will usually involve several hundred volunteers. It continues to test for safety and side effects and adds on determination of the medication’s effectiveness in people who need it.
- **Phase III**: A Phase III clinical trial involves several thousand volunteers and is intended to confirm the effectiveness of the medication, monitor its side effects, compare it to commonly used drugs if there are any already, and continue to collect information to determine whether the drug is safe.
Only after a successful Phase III study does a medication go before an advisory panel of the U.S. Food and Drug Administration (FDA) or similar agency elsewhere in the world for approval for distribution. Clinical trials done outside the United States are required to follow the same or a very similar rigorous testing process.

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

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

CXCR4
CXCR4 is a co-receptor on the surface of CD4+ T cells that, during late stages of untreated HIV infection, is essential to entry of HIV into these cells. (Some variants of HIV use a co-receptor named CCR5 rather than CXCR4; these variants almost always occur in all but the last part of the course of HIV infection: HIV transmitted from one person to another almost always uses the CCR5 co-receptor though rare cases with the CXCR4 co-receptor do occur.) 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 viral replication. This results from the single-stranded nature of HIV's RNA. All living organisms have linked double-stranded DNA making up the well-known double helix; the cross links in the helix provide a self-checking mechanism to prevent frequent mutations (see the Alleles and Mutations Introduction entry). 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 a result. In fact, mutations occur in each base position in the HIV genome 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 to render a virion incapable of infectivity, that is, make it defective. Even in persons on suppressive antiretroviral therapy (ART), the accumulation of mutations that make new virions defective is very common. Despite the frequency of mutations this is insufficient to cure HIV/AIDS.

Dendritic Cell
A dendritic cell is one variety of cell that presents antigens to B cells and CD4+ T cells. They are found in the skin and other areas that are effectively on the surface 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 trend 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 uncertain.
- Similarly, the hormonal and other developmental changes that occur during adolescence and the legal issues involved in obtaining informed consent for participation in research very often exclude adolescents from HIV research studies. A notable positive development in this area is in South Africa, the country with the highest frequency of HIV+ youths and young adults.
- There are barriers to including women in cure research, at 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 almost nothing is known about the interaction of hormonal treatment and cure strategies.

Elite Controllers
Elite controllers are rare HIV+ individuals who maintain undetectable viral loads without ever having had—in most cases—any antiretroviral therapy (ART). In about 2/3 of known cases, the people have immune-system mutations that appear to enhance recognition and
removal of HIV virions. In some elite controllers, undetectable viral loads are found in the absence of protective genes, indicating that they 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 chemical, in most cases a protein or peptide, that acts as a catalyst: It facilitates a biochemical process without itself being modified, so it can be used again. Almost all proteins that are enzymes have names ending in “ase”.

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

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

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

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

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

**Gut-Associated Lymphoid Tissue (GALT)**
Gut-associated lymphoid tissue (GALT) consists of immune cells lining the gut that are a critical component of the immune response to pathogens. It is usually severely depleted very early in the course of HIV infection. It is believed that the depletion is not reversible.

**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 be much less likely to transmit HIV to others than most infected people but might themselves be vulnerable to reinfection with other strains of HIV than the one with which they are already infected. This type of cure is also commonly called remission.

**HIV Cure (Sterilizing)**
This type of cure completely eliminates HIV from a person’s body, which would likely require activation and killing of all infected resting memory CD4+ T cells plus eliminating or silencing other cells contained in latent reservoirs. Depending on the strategy used, such individuals might or might not be resistant to reinfection with HIV. This approach results in there being no HIV capable of viral replication left in the body, so the person would not be able to transmit HIV to others. However, proving that all HIV has been eliminated from a person’s body is impossible with current approaches, including in the case of the Berlin Patient (Timothy Ray Brown), though he has been HIV- since 2009.
**HIV Genome**
The nucleus of HIV contains the two separate single strands of RNA that make up HIV's genetic material or genome. Each strand comprises nine genes and two long terminal repeats, one at each end, the right-hand one of which is crucial for beginning the production of proteins from the resulting proviral DNA. The overlapping of segments in the diagram corresponds to what are known as open reading frames. (Note that the open reading frames in the HIV genome are never directly transcribed and translated to proteins: The HIV genome must first be integrated into a host cell's DNA as proviral DNA that is, in turn, transcribed and translated to proteins.) In all, each strand has roughly 9,750 bases (nucleosides), though this varies somewhat with the faulty replication of HIV RNA.

Nucleosides come in four varieties for each of DNA and RNA. Three of them are common to both: adenine, cytosine, and guanine, abbreviated A, C, and G, respectively. The fourth one differs: For DNA it is thymine (T), and for RNA it is uracil (U). In DNA adenine pairs with thymine and cytosine pairs with guanine to make the familiar double helix. In helical RNAs the pairing is the same except that thymine is replaced by uracil. However, there are numerous varieties of RNAs, including ones that are single stranded, such as HIV's RNA genome.

**HIV’s Uniqueness**
HIV is unique among human pathogens in several respects, as follows (adapted in part from a slide created and provided for use by Prof. David Baltimore of California Institute of Technology):

- It preferentially attacks CD4+ T cells, the “directors” of the adaptive immune system.
- It eludes control by antibodies (see the Antigens and Antibodies Introduction entry).
- 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 a viral protein named gp120 has bound to the CD4 site. As a result, very few antiviral antibodies can neutralize HIV, and fewer still are both broad and potent. Broad refers to the range of variants of HIV that the antibody is active against.
- It destroys the gut-associated lymphoid tissue (GALT) very early in infection altering the gut's bacterial community.
- It also attacks the central nervous system (CNS) very early in infection.

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

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

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

The adaptive immune system comprises B cells, T cells, antibodies (see the Antigens and Antibodies Introduction entry) 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 including CD4+ T cells, CD8+ T cells, and at least a half dozen other types.

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

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

**Latency Reversal**
Latency reversal is fundamental to activating resting CD4+ T cells containing HIV proviral DNA 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.

**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:

A latent reservoir is a tissue in which resting CD4+ T cells, effectively, go to sleep. Further, it is a part of the body that, it is generally believed, is not affected by antiretroviral therapy (ART) as effectively, if at all, as in the blood. Latent reservoirs provide long-lived homes for HIV to reemerge from if therapy is stopped. The only definite latent reservoir is resting memory CD4+ T cells in lymph nodes. Other tissues that contain significant amounts of infected CD4+ T cells and might be latent reservoirs are at least the following: the brain; the innermost layer of fat (technically called the stromal vascular layer), whose cells display the CD4 receptor and both the CCR5 and CXCR4 co-receptors; the female and male genital tracts; Peyer's patches and other parts of the intestines; and follicular dendritic cells.

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

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

It is known that:

- Latently infected resting memory CD4+ T cells are the best characterized latent reservoir for HIV-1.
- Less than 1 cell per million of resting CD4+ T cells from persons on potent antiretroviral therapy harbors replication-competent latent provirus.
- Other drug-insensitive reservoirs, including the brain, and blood stem cells, may also exist.
- The genetic information in latent proviruses does not evolve—because it is produced by clonal expansion of a single infected cell—which suggests there is no ongoing viral replication within the cells containing them. Discontinuation of antiretroviral therapy permits the rebound of viral replication originating from the latent reservoir.
- Patients successfully treated with antiretroviral therapy for a decade or more exhibit no appreciable decrease in the size of the latent reservoir.
- The persistence of the latent reservoir precludes its elimination by antiretroviral therapy for the lifetime of the patient.
- Latency is likely established by numerous steps of HIV-1 replication, which potentially complicates eradication strategies.

Lymph
Lymph is a fluid derived from the blood plasma that returns proteins and the unneeded fluid between cells in the blood to lymph nodes and the rest of the lymphatic system (see the Lymphatic Tissues & the Lymphatic System Introduction entry). Most of the lymph is clear, and, in fact, the word is derived from Lympha, the name of the Roman goddess of water, but the lymph from the intestines is milky white because it also contains fats.

**Lymph Node**
A lymph node is a small organ containing immune-system cells named lymphocytes that filter lymph. Prominent clusters of lymph nodes are found in the underarms, the groin, and the neck.

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

**Lymphoid Tissues & the Lymphatic System**
A lymphoid tissue is a component of the lymphatic...
system. The tissues are found in lymph nodes, the thymus gland, gut-associated lymphoid tissue (GALT), the spleen, and several other organs.

The lymphatic system is made up of the lymphoid tissues listed above and lymphatic vessels, which parallel the veins and carry lymph toward the heart. The system is essential to fighting infections.

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

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

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

2. The Intact Proviral DNA Assay (IPDA) is the most accurate assay as of 2019. It uses two DNA sequences to probe the HIV genome. One sequence detects deletions in the genome large enough to make the virion defective; the other detects RNA that is so seriously mutated as to be unquestionably defective. It uses a biological tool named droplet digital polymerase chain reaction (ddPCR) to perform the measurement, which is almost sufficient to detect defective provirus and separate it from replication-competent latent provirus. Early measurements using IPDA eliminate ~95% of defective proviruses. IPDA is predicted to overestimate the replication-competent latent reservoir by about 1.9 fold and so is much more accurate than any other method. In addition, it requires very much less blood than QVOA and is much faster.

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

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.

Post-Therapy Controller
A post-therapy controller is HIV+ individual, so far mostly members of the VISCONTI (Viro-immunologic Sustained Control after Treatment Interruption) cohort in France, who started antiretroviral therapy (ART) within weeks of infection, stayed on therapy for an average of about four years, and then stopped therapy. Because there has been no large or lasting rebound of HIV in these individuals they 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 transforming HIV RNA that is integrated into cellular DNA. It results from HIV infection and is the sine qua non of making new virions—put simply, without it there would be no transmission of HIV infection from one person to another.

Receptor
A receptor is a cell-surface protein that provides two things: (1) a signal to other cells, viruses, or substances, and (2) in most cases, a way for the virus or substance to attach to the cell and often to enter it. Some cells and receptors such as CD4+ T cells and CD4 require a co-receptor, e.g., CCR5 or CXCR4 to enter the cell.

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

Replication-Competent Latent Provirus
Replication-competent latent provirus is DNA resulting from transforming HIV RNA to DNA integrated into cellular DNA (probably always or almost always CD4+ T cells) that may produce new HIV virions.
**Resting Memory CD4+ T Cell**  
A resting memory CD4+ T cell is a CD4+ T cell that has been exposed to a pathogen, i.e., a foreign substance, cell, or virus, and “remembers” it for future exposure to the pathogen. Further, it has gone into a resting state in a lymphoid tissue in wait for future instances of the pathogen to cause it to be activated and signal CD8+ T cells to destroy the pathogen.

**Retrovirus**  
A retrovirus is a virus, such as HIV, whose genetic material is RNA rather than DNA, and that can integrate its RNA into the host DNA as proviral DNA, which enables the creation of new virions.

**RNA**  
RNA stands for ribonucleic acid. Unlike DNA, which exists only in the well-known double helix structure found in all living things or as single strands in some viruses, there are at least 40 types of RNA with distinct functions. One form serves as the two unconnected strands of genetic material in HIV.

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

**Sterilizing Cure**  
A sterilizing cure of HIV infection is what is more formally described as an HIV cure (sterilizing).

**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 usually with an external envelope. It is the extracellular infective form of a virus.

**Women’s Involvement in Cure Research Studies**  
A recent open-access viewpoint article concerning women’s involvement in cure research suggests six ways to increase women’s involvement. Current barriers and suggested ways to increase involvement are as follows:

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

There are also several related items in the Resource Guide.

**The Resource Guide**

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

The AIDS Clinical Trials Group (ACTG) HIV Reservoirs and Viral Eradication Translational Science Group (Cure TSG) organizes and directs clinical trials of drugs that may be useful in curing HIV infection. The ACTG is funded by the U.S. National Institutes of Health. Its active trials are listed on the https://ClinicalTrials.gov website.
amfAR Institute for HIV Cure Research
The amfAR Institute for Cure Research, announced on 30 November 2015 and funded initially with a five-year $20M grant, is headquartered at the University of California, San Francisco's AIDS Research Institute (website: https://ari.ucsf.edu/) and is a “virtual institute” composed of researchers from UCSF's Medical School, the co-located Gladstone Institute of Virology and Immunology, the University of California, Berkeley, Blood Systems Research Institute (BSRI) (San Francisco, CA), Oregon Health and Science University (Portland, OR), Gilead Sciences (Foster City, CA), GeoVax (Atlanta, GA), the Infectious Disease Research Institute (IDRI) (Seattle, WA), Monogram Biosciences (South San Francisco, CA), and RainDance Technologies (Lexington, MA). The institute's “dream team” of researchers initially included UCSF's Steven Deeks, MD, and Joseph M. “Mike” McCune, MD, the Gladstone Institute's Warner Greene, MD, PhD, and the Blood Systems Research Institute's Satish Pillai, PhD. Dr. McCune has since left to take a position in industry.

The institute’s mission is to

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

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

Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication (BELIEVE)
Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication (BELIEVE) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. Its principal investigators are Douglas Nixon, MD, PhD, of George Washington University in Washington, DC, and R. Brad Jones, Weill Cornell Medicine, New York, NY. Its primary purposes are

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

BELIEVE is partnering with two companies: ALTOR Bioscience Corp. (website: http://www.altorbioscience.com/ ), whose cancer drug candidate ALT-803, a proprietary interleukin-15 superagonist, has been found to not only reverse HIV latency, but also to enhance the immune system's ability to kill the resulting cells; and Torque (website: http://www.torquebtx.com/ ), a biomedical engineering company with the technology to deliver drugs to CD8+ T-cells that they plan to use to clear the reservoir. It also has a Community Advisory Board (CAB). BELIEVE does not have a website at the time of this writing. Studies will be conducted in concert with communities at local clinics and a wide variety of agencies associated with institutions in Canada, Brazil, and Mexico plus the U.S.

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

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. The video can be found at https://www.youtube.com/watch?v=LVR_-rUQHla0&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 a conference that took place in Seattle, WA. The video can be found at https://www.youtube.com/watch?v=plv07vd5iI.

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

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

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

Combined Immunologic Approaches to Cure HIV-1 (I4C)
Combined Immunologic Approaches to Cure HIV-1 (I4C) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. Its headquarters is at Beth Israel Deaconess Medical Center, Boston (website: http://www.bidmc.org/). Its principal investigators are Dan Barouch of Harvard University, John Mellors of Pittsburgh University, and Nelson Michael of the U.S. Military HIV Research Program. Its two main focuses are to determine the "efficacy of combination immunologic approaches to target the viral reservoir" and "mechanisms and next generation strategies to target the viral reservoir."

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

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

A Crack in Creation
A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution Doudna J A Sternberg SH Houghton Mifflin Harcourt 2017 is a lay introduction to CRISPR and more specifically CRISPR/Cas9, whose broad and profound power was discovered in the first author’s lab among others. It traces the discovery of CRISPR, explains its mechanism of action, describes its applicability, explicates the scientific and public policy implications of its power, and calls for a moratorium on its use in humans until these issues have been, at the least, very carefully thought out. The book has copious endnotes, most of which are references to journal articles related to its subject. Even the title on the dust jacket refers to CRISPR’s use: occurrences of the letters A, C, G, and T, which abbreviate the names of the four nucleic acids making up DNA, are a different color from the others.

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

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

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

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

CURED/NOT CURED on Seattle Channel’s Town Square
CURED/NOT CURED on Seattle Channel’s Town Square is a YouTube video of one of the two living Boston Patients, Gary Steinkohl, and his doctor Timothy Henrich, MD, discussing his case. The video was published in August 2016 and can be found at https://www.youtube.com/watch?v=--Jg_bqCGDo.

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

1. HIV/AIDS and Cure Basics
2. Stakeholder Engagement in HIV Cure Research
3. Gene Therapy/Stem Cell Transplant
4. Shock and Kill and Latency-Reversing Agents
5. Measuring the Latent HIV Reservoir
6. Regulatory Issues in HIV Cure Trials
7. Early ART
8. Pediatric HIV Cure 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

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

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

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

DARE is initially

• defining the role of reservoirs that enable SIV or HIV to persist during antiretroviral therapy (ART) and using the monkey model to develop therapies to breach them;
• characterizing the distribution of replication-competent latent provirus in lymphoid tissues in ART-suppressed adults and developing positron emission tomography (PET) imaging techniques to quantify the reservoir; defining the role of immune checkpoints, such as PD-1, and their blockade on T cell function in monkeys and people; positron
emission tomography (PET) is a nuclear medicine imaging technique used to observe metabolic processes in the body. It detects pairs of gamma rays emitted indirectly by a positron-emitting tracer compound. Three-dimensional images of tracer concentration within the body are then constructed by computer analysis in a PET scanning machine;• defining the role of immune checkpoints, such as PD-1, and their blockade on T cell function in monkeys and people; and• defining the safety, immunogenicity, and anti-HIV effectiveness of a human cytomegalovirus (HCMV)-vecteded HIV vaccine in HIV-infected adults on ART.

Delaney Cell and Gene Therapy Initiative (defeatHIV)
The Delaney Cell and Gene Therapy Initiative (defeatHIV) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. It is a consortium of academic and industrial investigators working together to eradicate HIV by gene editing. Its principal investigators are Keith Jerome, MD, PhD, and Hans-Peter Kiem, MD, both from the Fred Hutchinson Cancer Research Center (known as the Fred Hutch) in Seattle, WA. Its projects are

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

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

Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy (BEAT-HIV)
The Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy (BEAT-HIV) is one of the six collaboratories making up the Martin Delaney Collaboratories for HIV Cure Research. It is a consortium of academic and industrial investigators with principal investigators Luis J. Montaner, DVM, D Phil, and James L. Riley, PhD, of the Wistar Institute (website: https://www.wistar.org/). BEAT-HIV has three objectives, namely,

• to identify the locations of latent reservoirs;
• to stimulate the innate immune system with a combination of highly potent antibodies (see the Antigens and Antibodies Introduction entry) and pegylated interferon α2b. Pegylation is an organic chemical process that attaches PolyEthylene Glycol (hence the “peg” in the term) polymers to a drug to mask the drug from the host’s immune system and increase its time in the body. Pegylated preceding a drug name refers to the result of pegylation of the drug. and
• a gene therapy strategy using CCR5Δ32/Δ32 CD8+ T cells.

EU Clinical Trials Register
The EU (European Union) Clinical Trials Register is a searchable database of all clinical trials that include EU sites or that are run by companies or research institutions located in EU countries. It also includes a “Glossary of Terms used in the EU Clinical Trials Register.” Its website is https://www.clinicaltrialsregister.eu. It currently provides access to over 35,000 trials of which over 1,100 are HIV related.

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

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

The HIV Life Cycle
The HIV Life Cycle is a work in progress that was presented at a conference by its developer Janet Iwasa of the University of Utah in 2018. It’s a truly stunning animation of the process of HIV infection of a CD4+ T cell and its replication. An early version can be seen at http://scienceofhiv.org/wp/?page_id=20. The narrated version can be downloaded from http://scienceofhiv.org/downloads/HIV_narrated.mov.

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

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

**IrsiCaixa (Institut de Recerca de la Sida)**
IrsiCaixa (Institut de Recerca de la Sida) is a research center located in Barcelona, Spain, that focuses on many of the issues involved in HIV/AIDS research. Its specific cure-related foci include achieving remission or eradication of HIV by combinations of therapeutic vaccines, antibodies (see the Antigens and Antibodies Introduction entry), and latency reversal. Its website is http://www.irsicaixa.es/en.

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

**Journal of Medical Ethics, vol. 43, no. 2, February 2017**
The Journal of Medical Ethics is the official journal of the (British) Institute of Medical Ethics and one of the BMJ journals published by the BMJ Group, a wholly owned subsidiary of the British Medical Association. The particular issue cited here is devoted entirely to issues in curing HIV infection, and most of the articles are freely available to download from the table of contents webpage at http://jme.bmj.com/content/43/2 and are quite accessible to lay readers. They provide an introduction to the subject, background information, articles concerning risks, benefits to clinical trial participants and nonparticipants, and an afterword.

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

1. Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy (BEAT-HIV),
2. Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication (BELIEVE),
3. the Collaboratory of AIDS Researchers for Eradication (CARE),
4. the Delaney AIDS Research Enterprise to Cure HIV (DARE),
5. the Delaney Cell and Gene Therapy for HIV Cure (defeatHIV), and
6. Combined Immunologic Approaches to Cure HIV-1 (i4C).

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

Martin Delaney (1945 – 2009) was the founding director of Project Inform, one of the nation’s oldest and best-known non-profit foundations working to combat HIV and AIDS by providing information and advocating for treatment. Project Inform, unfortunately, closed its doors in spring 2019.

In 2009, Martin and five coauthors wrote “We conceive an initiative, termed here a collaboratory, in which the government contributes funding, regulatory oversight, and coordination; industry contributes funding, drug discovery, technology, and expertise; and academia contributes ideas and investigative capacity.” in Richman D Margolis D Delaney M et al. The Challenge of Finding a Cure for HIV Infection Science 323 (5919), 1304 – 1307.

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

**NATAP/ National AIDS Treatment Advocacy Project**
Despite its name, NATAP does include information about curing HIV. The easiest way to find that information on its website is to go to http://natap.org/ and search for “cure”.

**National Association of People with HIV Australia’s HIV CURE**
The National Association of People with HIV Australia’s HIV CURE website includes information about cure
Perceptions of HIV cure research among people living with HIV in Australia

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

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

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

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

The articles do an excellent job of covering the field of HIV cure research for the general reader. In addition to being published as a magazine, the articles are all available in the Positively Aware archive, whose website is https://www.positivelyaware.com/archive.

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

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

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

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

Research Toward a Cure Trials
Research Toward a Cure Trials is a collection prepared by Richard Jefferys of the Treatment Action Group that is updated roughly every three months. It consists of three lists, namely, “Current Clinical Trials,” “Observational Studies,” and “Completed Studies,” including for each one a short title, trial registry identifier(s), manufacturer/sponsor(s), phase, and either estimated completion date or published/presented data. The most recent list is dated 18 April 2019, lists about 125 studies, and can be downloaded as a PDF at http://www.treatmentactiongroup.org/cure/trials.

Role of Residual Viral Replication
Role of Residual Viral Replication is a YouTube video by Javier Martinez-Picado, PhD, that presents the issue of persistent low-level HIV replication in persons with very low viral loads and its implications for curing HIV. Although it was constructed to be a presentation to the American Society for Microbiology, much of it should be accessible to most readers of this document. It can be found at https://www.youtube.com/watch?v=qIAOSWC1TGQ

Scared — and brave
Scared — and brave is an article about defeatHIV Community Advisory Board member Laurie Sylla presenting at Seattle’s Gay City LGBTQ (lesbian, gay, bisexual, transgender, queer) Center about the results of survey research done by a group of community members. The research was designed to ascertain what issues community members have about HIV cure research clinical trial participation. The article has been archived at http://www.fredhutch.org/en/news.html in the Story Archive under June 2017.

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

Stakeholder Engagement

Strategies for an HIV Cure
The Strategies for an HIV Cure meetings (so far for 2012, 2014, 2016, and 2018) were convened by the NIH various locations in and near Washington, DC. The purpose of the first two meetings was to bring together researchers associated with each of the three original NIH-funded Martin Delaney Collaboratories, other researchers engaged in HIV cure research, investigators in complementary disciplines, and community members to share scientific results and engage in active discussion about the merits of various approaches under investigation. It was hoped that these discussions would stimulate new ideas for research projects and lead to new scientific collaborations. The 2012 agenda can be downloaded by searching for “Strategies for an HIV Cure, November 28 - 30, 2012” on Google, and downloading it from the resulting page. The 2014 agenda can be downloaded from https://www.blsmeetings.net/hivcuremeeting2014/ and a videocast of Day 2 can be downloaded from https://videocast.nih.gov/summary.asp?Live=20242&bhc=1.

In 2016 the three original collaboratories were joined by three more. The 2016 agenda can be downloaded as a PDF from the webpage https://respond.niaid.nih.gov/conferences/hivcuremeeting2016/Pages/Agenda.aspx. The event page for the 2018 meeting is http://www.cvent.com/events/strategies-for-an-hiv-cure-2018/event-summary-67d64ae8621247079e009b4757f45c9e.aspx and videocasts of the three days’ sessions can be downloaded from that page.
**TAG HIV Basic Science, Vaccines, and Cure Project Blog**

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

**Treatment Action Group (TAG)**

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

**“We Need to Deploy Them Very Thoughtfully and Carefully”: Perceptions of Analytical Treatment Interruptions in HIV Cure Research in the United States—A Qualitative Inquiry**

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

**What risk of death would people take to be cured of HIV and why? A survey of people living with HIV**

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

**Why cure, why now?**

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

**Why HIV cure research needs to involve more women**

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

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

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

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

Women and HIV Cure: A Three-Part Webinar Series

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

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

Women’s views about contraceptive requirements for biomedical research participation

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

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