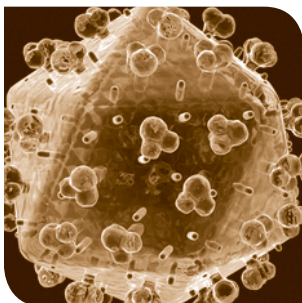




HIV & AIDS
cure research



■ **Antiretroviral Therapy (ART)**

ART involves the use of several (usually a “cocktail” of three or more) antiretroviral drugs to halt HIV replication. ART drugs may target any of several viral enzymes, such as reverse transcriptase, integrase, and protease, or entry of HIV into cells. Some drugs may also target cellular structures, i.e. the CCR5 blockers. Most experts believe that ART will be needed in many cure strategies to halt HIV reproduction in cells that have been perturbed by latency-reversing medication, such as HDAC inhibitors (described below).

■ **ART Intensification**

ART intensification involves adding drugs to a traditional three-drug regimen to reduce inflammation caused by HIV and residual HIV replication and hence the size of HIV reservoirs. There is mixed data indicating whether intensifying ART will be necessary in cure strategies.

■ **CCR5**

CCR5 is a co-receptor on the surface of CD4+ T-cells that, during early HIV infection, is essential to entry of HIV into these cells. HIV binds to both CD4 and CCR5 receptors to achieve entry.

■ **CD4+ T-cells (“Helper” T-cells)**

These are primary white blood cells of the immune system. These cells act, in part, as the “generals” of the immune system that signal to other immune system cells how and when to fight infections. HIV, which reverse transcribes and integrates its own genes into the cell’s DNA, preferentially infects CD4+ T-cells. HIV-infected T-cells, when “activated,” produce copies

of HIV instead of reproducing or conducting other immune functions. CD4+ T-cells that specifically target parts of an infectious agent or pathogen can develop, and such cells become activated in response to infection by that pathogen. After the infection is cleared or controlled, they can then become “resting” memory cells that lie in wait for future occurrences of the pathogen to which they respond. These memory CD4+ T-cells are thought to constitute most of the latent reservoir of HIV.

■ **CD8+ T-cells (“Killer” T-cells)**

These are primary white blood cells that are responsible for recognizing infected CD4 T-cells and macrophages, among other duties. The most important of these is killing infected or disabled cells as directed by CD4+ T-cells. CD8+ T-cells can be created that are specific to HIV. CD8+ T-cells are also known as cytotoxic T lymphocytes or CTLs.

■ **Memory CD4+ T-cell**

Once a CD4+ T-cell responds to a pathogen, it can go into a resting state, which allows it to lie in wait for further instances of infection by that pathogen, to replicate, and to mount a quick immune response. Such memory cells can live for years. In HIV infection, a small proportion (approximately 1 in 100) of memory cells are infected with the virus. These cells can remain invisible to the immune system and persist for years to decades. The virus likely emerges from these cells when antiretroviral therapy is stopped. It is widely assumed these cells are the most important long-lived reservoir for the virus.

■ **Chromatin**

Chromatin is the material of which the chromosomes of organisms other than bacteria are composed. It consists of proteins and DNA. Chromatin can be thought of as a packaging mechanism that keeps DNA contained within a cell. Once HIV integrates into a cell's DNA, chromatin influences whether the HIV genes are able to make more virions or are kept packaged in a latent form.

■ **Compartment**

A compartment is an anatomical part of a person's body that may be cells or a tissue reachable by HIV. In the context of HIV infection, the term is used to describe some regions of the body where the virus is known to reside in a concentrated manner. Designing drugs that penetrate all compartments is a focus of both standard antiretroviral drug and curative drug development. Examples of compartments include the brain and the genital tract.

■ **Elite Controllers**

These are rare HIV-infected individuals who maintain undetectable viral loads in the absence of any antiretroviral therapy. Evidence suggests that of known cases, multiple factors contribute to spontaneous control of HIV, including particularly strong and effective immune system responses, such as robust CD4+ and CD8+ T cells. A significant percentage of these individuals, but not all, possess certain protective immune-system genes, such as HLA-B*57 (44%) and HLA-B*27 (10%), that appear to enhance immune recognition of HIV. Many if not most elite controllers do well for years to decades without therapy, and are now being studied as a model for a “functional” cure (defined elsewhere).

■ **Gut-Associated Lymphoid Tissue (GALT)**

Gut-associated lymphoid tissue consists of immune cells lining the gut, which is a critical component of immune response to pathogens. It is usually damaged and depleted very early in the course of HIV infection.

■ **HDAC Inhibitor**

An HDAC inhibitor causes chromatin to become unbound and release HIV proviral DNA to reproduce and become exposed to the immune system and potentially to HIV therapy. Two examples that have been used in experiments are vorinostat and panobinostat.

■ **Histone Deacetylase (HDAC)**

This enzyme causes chromatin in CD4+ T-cells to bind its DNA and stop reproducing and become inactive in resting memory cells. Because of this process, HIV-infected cells can have bound DNA that keeps the virus in latent form, does not lead to production of any (virus) proteins and therefore leaves the cell unexposed to either CD8+ T-cells or antiretroviral therapy.

■ **HIV (Human Immunodeficiency Virus)**

HIV is the virus that causes Acquired Immuno-deficiency Syndrome (AIDS). Without proper therapy, HIV infection results in opportunistic infections and cancers that cause the death of almost every infected person.

■ **HIV Cure (functional)**

This type of cure allows some infected cells to persist in an HIV-infected person's body but means that antiretroviral therapy is no longer necessary, at least for a long time. With this approach, the immune system should be able to

handle the virus that is still in the body. Because such individuals would typically have very low levels of HIV, they would be less likely to transmit HIV to others than most infected people but might be vulnerable to reinfection with other strains of HIV than the one with which they are already infected.

■ **HIV Cure (Sterilizing)**

This type of cure requires complete elimination of replication-competent HIV from an HIV-infected person's body, which would likely involve activation and killing of all infected CD4+ T-cells (and perhaps macrophages and other cells). Depending on the strategy used, such individuals might or might not be resistant to reinfection with HIV but would not be able to transmit HIV to others. Proving that all HIV has been eliminated from a person's body is very challenging and not possible with current technologies.

■ **HIV Remission**

Curing HIV may be like curing cancer. In both cases, it is impossible to definitively prove the disease (i.e., virus or cancer cells) has been completely eliminated. Borrowing from the cancer field, many now believe that the HIV field should use "remission" rather than "cure", and define remission as the absence of disease (viral replication) for an extended period off therapy. This term is sometimes used as a more cautious definition of "functional cure."

■ **HIV Reservoir**

The cells and tissues that harbor HIV during effective antiretroviral therapy is often referred to as the "reservoir." There are several types of

reservoirs, including latent reservoir (defined as those cells containing silent and hidden HIV) and “active” reservoir (defined as those cells which are producing viral proteins). How a reservoir is maintained is controversial and is a focus of intensive investigation.

■ **HIV Latency**

The DNA for HIV becomes integrated in the host DNA. This DNA can remain completely silent and, hence, hidden from the immune system and difficult to target with therapy. This fully silent state is generally referred to as “latent” infection. There is universal acceptance that HIV latency persists in memory CD4+ T cells. It is unknown if other cells can durably support latent infection. True latency appears to be maintained primarily in resting cells, which are not actively reproducing or producing chemical messages to cause an immune response against a pathogen. These “resting” memory cells provide a reservoir of viruses that are latent and can be reawakened to begin actively reproducing HIV virions if antiretroviral therapy is stopped.

■ **HIV Therapeutic Vaccine**

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

■ **HLA-B27 and HLA-B57**

HLA stands for “Human Leukocyte Antigen” and is the cellular mechanism that causes the human body to recognize non-self pathogens and grafted tissues and reject them. HLA is the human version of the Major Histocompatibility Complex (MHC) found in almost all vertebrates. HLA-B57 and HLA-B27, in particular,

are specific parts of the human leukocyte antigen that are advantageously mutated and significantly expressed in some elite controllers (see above) and contribute to their ability to control HIV without antiretroviral therapy.

■ **Immune System Stimulation**

Many HIV researchers believe that some form of immune-system stimulation to kill infected immune-system cells is necessary to cure HIV infection.

■ **Inflammation**

When immune system cells are “activated” they are stimulated to reproduce and can produce “inflammatory” chemical messengers that stimulate other cells. Inflamed immune system cells can signal other immune system cells to reproduce or respond to a pathogen. This is usually helpful. Chronic HIV infection, even in those whose virus is either suppressed naturally or by antiretroviral therapy, is known to cause inflammation, which can lead to cardiovascular disease, cancers, and other serious health conditions. Activated cells can also produce scarring (fibrosis) in lymph node tissue, a critical network of the immune system. For most practical purposes one could say: Immune activation = inflammation. (i.e., every inflammation leads to immune activation and vice versa).

■ **Long-Term Non-Progressors (LTNPs)**

These individuals have the ability to maintain normal CD4+ T-cell counts for prolonged periods of time (greater than 10 years), proliferate robust CD8+ T-cells (Killer T-cells or CTLs) that possess high levels of cytotoxic proteins, and typically exhibit undetectable viral loads

without HIV antiretroviral therapy. Evidence suggests these individuals are distinct from elite controllers (see above), however, some overlap does occur between these groups.

■ **Lymphatic System**

The lymphatic system is made up of lymph nodes, gut-associated lymphoid tissue, and the lymphatic vessels that lead from lymphatic tissues toward the heart. It is essential to fighting infections.

■ **Lymph Node**

A lymph node is an organ containing immune system cells: a site where such cells collect in order to come into contact with other immune system cells, such as CD8+ T-cells that have recognized a pathogen.

■ **Lymph Node Collagen Deposition**

When functional cells die in the body, they are sometimes replaced by scar tissue. This process is called “fibrosis.” A sign of fibrosis is the deposition of collagen instead of functional tissue. When lymph nodes are inflamed by HIV replication they can lay down collagen, also known as scar or fibrotic tissue. This can begin within days of infection and may be largely complete within months after HIV infection. Experts currently believe that when lymph nodes are scarred in this way, it may be difficult to regain the ability to respond to HIV and other infections as effectively as before collagen deposition occurred, potentially causing lasting damage to the immune system.

■ **Microbial Translocation**

Cells and structures (lymph nodes and Peyer's patches) in the stomach and colon contain bacteria that may be either helpful in digestion or harmful, but which, preferably, should not leak into the blood. In HIV disease, these cells and structures can become damaged and may release harmful bacteria into the blood. These bacteria lead to further inflammation, which can lead to infection of CD4+ T-cells and macrophages and more generalized infection leading to diseases and other conditions, such as cancers, that are harmful to the body.

■ **Natural Killer (NK) cells**

These are white blood cells that are responsible for killing infected cells and cancer cells. They are "natural" in the sense that they are preprogrammed to respond to particular infected or disabled cells, unlike CD4+ and CD8+ T-cells, which must be trained to respond to their target pathogens.

■ **PD1 and PD-L1 Inhibitors**

PD1 and PD-1 ligand (abbreviated PD-L1) inhibitors are proteins that block the PD-1 or PD-L1 molecule on immune system cells. In cancers, these drugs have shown efficacy by enhancing the ability of the immune system to recognize and eliminate cancerous cells. In HIV, these inhibitors might cause HIV-killing cells (CD8+ T-cells) to function better. PD-1 and PD-L1 inhibitors might also cause resting memory CD4+ T-cells to reproduce HIV and become exposed to the immune system for recognition and killing.

■ Post-Therapy Controllers

This is a small group of HIV-infected individuals, so far mostly in France, who started anti-retroviral therapy within weeks of infection, stayed on therapy for an average of about four years, and then, for various reasons, stopped therapy. Because there has been no large or lasting rebound of HIV, these individuals are able to stay off therapy for long periods, so far for up to 10 years. Unlike a percentage of elite controllers, these post-therapy controllers mostly lack advantageous immune system genes (e.g., HLA-B57 or HLA-B27).

■ Viral Replication

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

■ Zinc-Finger Nucleases (ZFNs)

These enzymes cut strands of cellular DNA into segments that must be repaired by the immune system. When ZFNs against DNA that produces the cellular co-receptor CCR5 are introduced into cells, those cells' ability to produce the co-receptor is inhibited, at least to a degree. This can potentially make those cells resistant to HIV infection by virus that requires CCR5 to infect cells.

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