HIV CURE

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European AIDS Treatment Group

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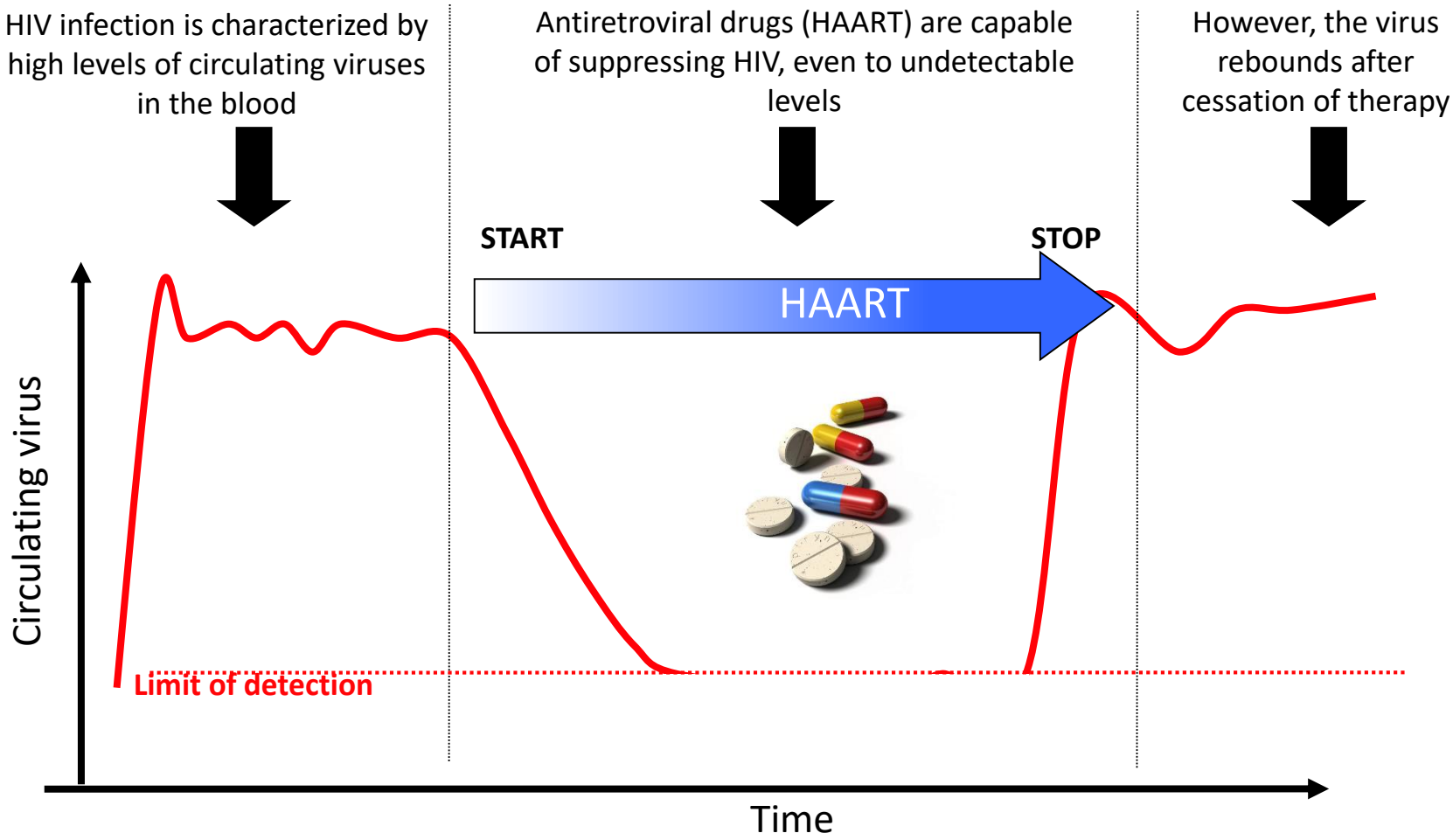
Despite the recent press reports, as of October 2016 there is NO cure for HIV that can be successfully replicated in patients.

Current HIV drugs do not eradicate HIV



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What is a CURE?

Functional	Sterilization
No disease progression without ART's	Eliminate all infected cells
HIV RNA ‹ 50 copies/ml	HIV RNA ‹ 1 copy /ml
	No further medication
?? ART = undetectable = F/C???	

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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.
- HIV RNA ‹ 50 copies/ml
- 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.
- HIV RNA ‹ 1 copy /ml
- Likely involve activation and killing of all infected CD4+ T-cells (and perhaps macrophages and other cells).
- Such individuals might or might not be resistant to reinfection with HIV.
- Proving that all HIV has been eliminated from a person's body is very challenging and not possible with current technologies

What and who we know

Canadian babies

Visconti cohort

18 year old teenager

Timothy Brown

Boston patients

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Visconti cohort (Paris)

14 patients

- All treated in very early stage of infection (triple therapy)
- Remained on treatment for 3 years
- Stopped treatment
- Had very low levels of latent virus
- Showing signs of viral rebound after approx. 7 years

- NO CURE

Canadian Baby's

- Reported that these 2 children had received ART commencing very soon after birth and now cleared of the HIV virus

- WRONG.

- Both children are HIV positive and proceeded to develop big V/L very quickly after stopping ART's

- NO CURE

Mississippi Baby

- Commenced ART @ 30hrs old
- 3 drugs used – AZT, Lamivudine and Nevirapine
- Unusual Nevirapine given twice/day
- This is what is already done!
- We now know NO CURE

BUT….

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All is not bad news!

- This child went a number of years without ART's
- Showed no signs of any virus during that time
- During a routine blood test something happened almost 4 weeks to the day of a viral rebound.
- Was Nevirapine (NNRTI) which we now know is not the best at targeting latent cells.
- Had an Integrase Inhibitor been given we may have seen a different outcome
- Remember this is all VERY new

Timothy Brown

- HIV+ Acute Myeloid Leukemia
- Chemo x 3
- Anti fungal, Anti bacterial agents
- CCR5 stem cell transplant
- Transplant rejection (GVHD)
- Total body irradiation
- ART
- Near death x 2
- CURE

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French Teenager

- HIV+ at birth
- 6 weeks neonatal therapy
- 2 months post treatment high viral load
- Commenced 3 drug therapy for 6 years
- Stopped lost to care
- No virus found
- 12 years on no virus found

Question: is she an elite controller?

or

Did early ART prevent latent reservoirs from establishing?

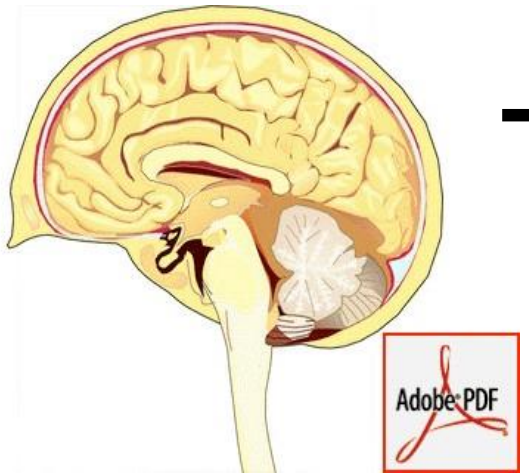
The language is changing!

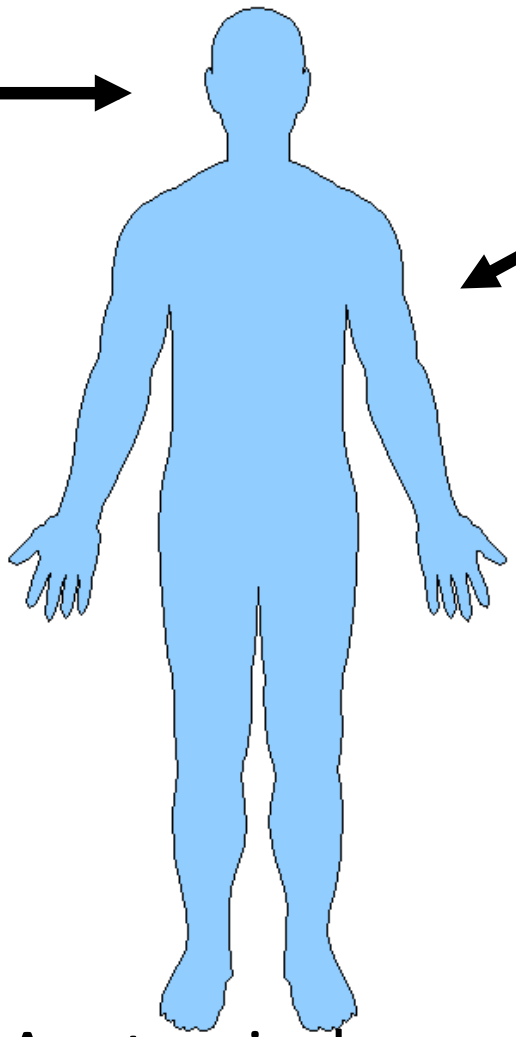
HIV Remission

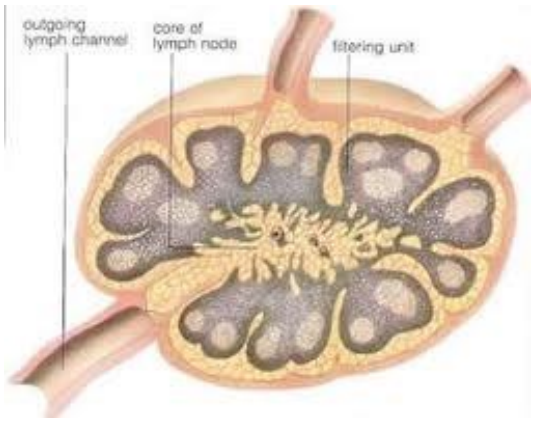
- Curing HIV may be like curing cancer. In both cases, it is impossible to definitively prove the disease (i.e., virus or cancer cells) has been completely eliminated.
- The HIV field should use “remission” rather than “cure”
- Define remission as “the absence of disease (viral replication) for an extended period off therapy”
- This term is a more cautious definition of “functional cure.”

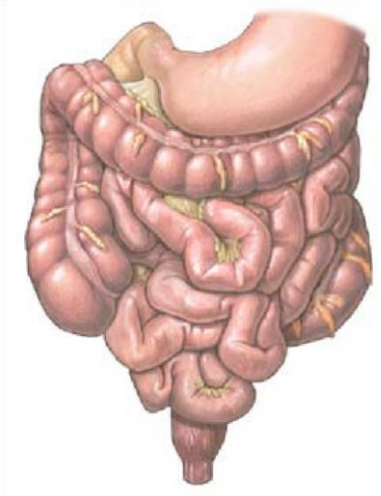
HIV Reservoir

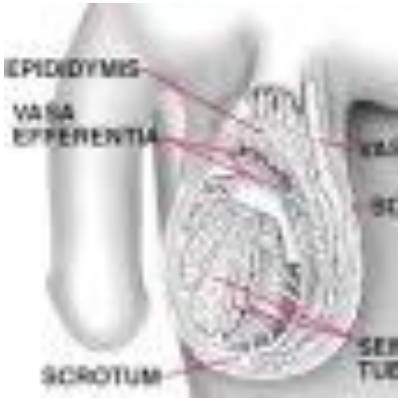
- The cells and tissues that harbor HIV during effective antiretroviral therapy is referred to as the “reservoir.”
- There are several types of reservoirs:
- Latent reservoir (defined as those cells containing silent and hidden HIV)
- “Active” reservoir (defined as those cells which are producing viral proteins)
- Is a focus of intensive investigation.











Anatomical reservoirs

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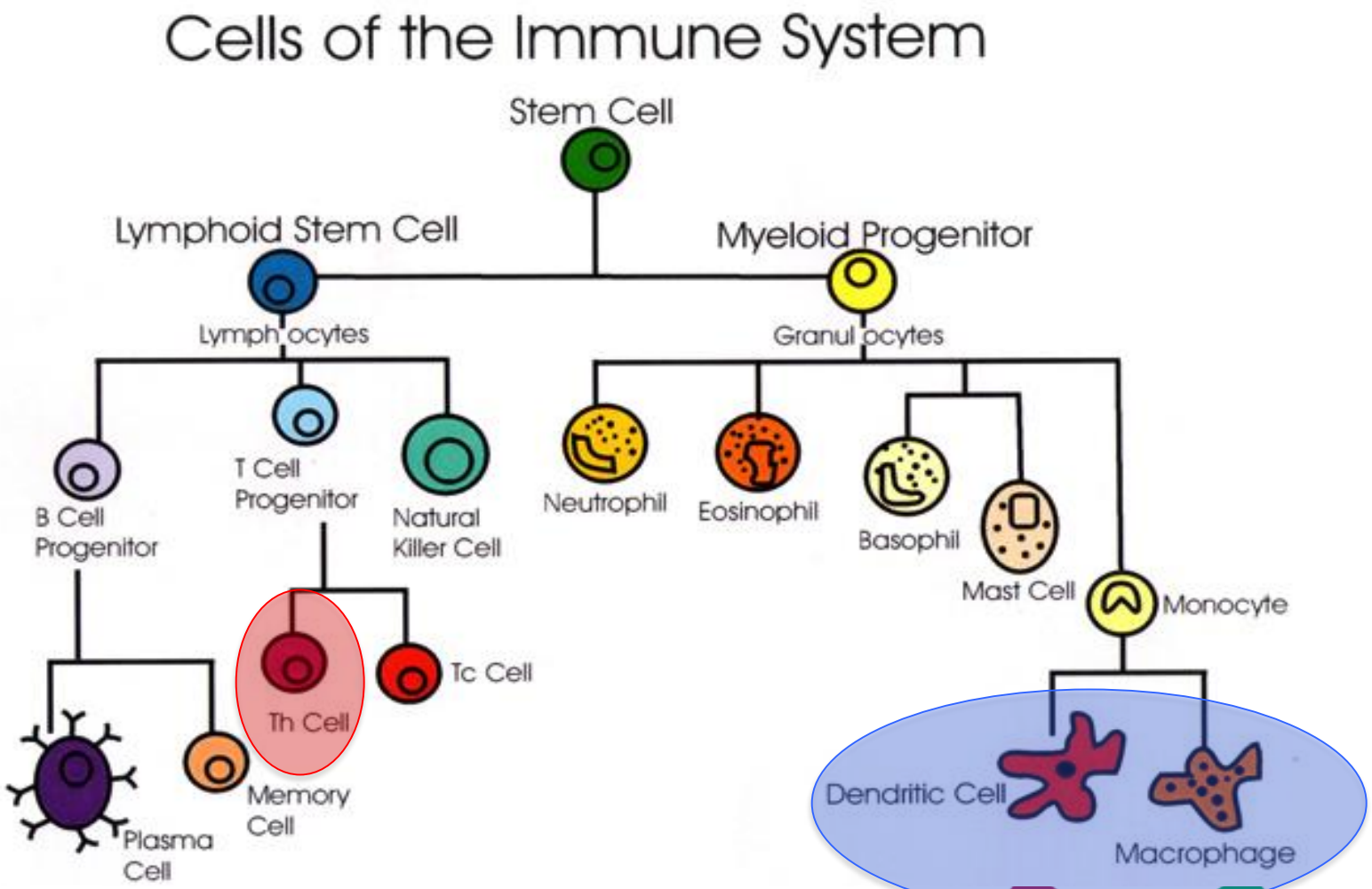
Where is the HIV reservoir?



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From http://textbookofbacteriology.net

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.

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.

C-C chemokine receptor type 5 (CCR5 or CD195)

- Is a protein on the surface of white blood cells that is involved in the immune system as it acts as a receptor for chemokines (signalling protein)

.

- CCR5 is a co-receptor on the surface of CD4+ T-cells.

- During early HIV infection, is essential to entry of HIV into these cells.

- HIV binds to both CD4 and CCR5 receptors to achieve entry.

- A few individuals carry a mutation known as CCR5-Δ32 in the CCR5 gene, protecting them against these strains of HIV (between 4 – 16% of the population)

CD4+ 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
- 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 (big eaters)
- 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 assume these cells are the most important long-lived reservoir for the virus.

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 versions 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.
- 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.

- 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%).

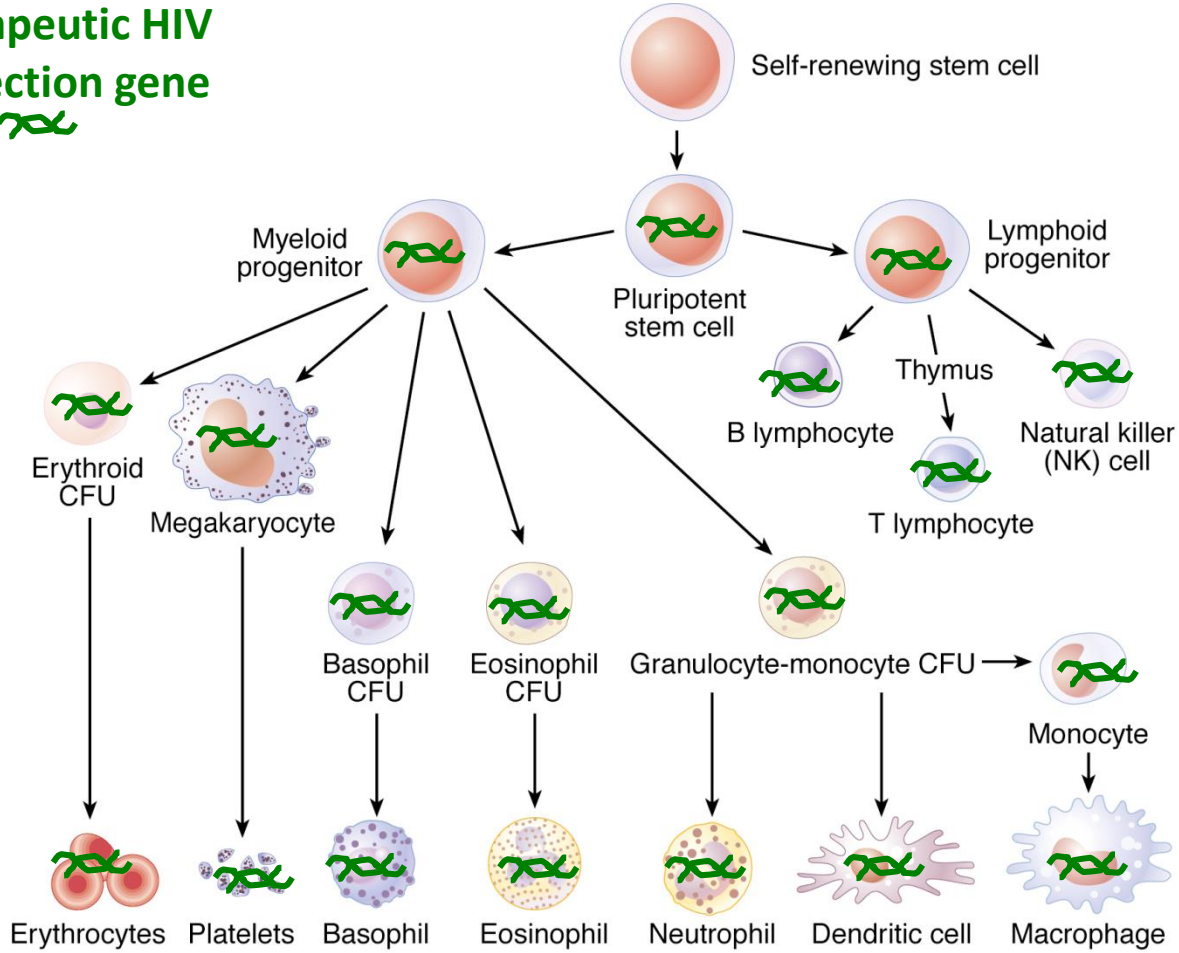
- Are now being studied as a model for a “functional” cure

Gene therapy

- Technique that uses genes to treat or prevent disease
- Inserting a gene into a patient's cells instead of using drugs or surgery
- Researchers are testing several approaches to gene therapy
- Replacing a mutated gene that causes disease with a healthy copy of the gene.
- Inactivating, or "knocking out," a mutated gene that is functioning improperly.
- Introducing a new gene into the body to help fight a disease

Gene therapy in blood cells

Therapeutic HIV protection gene



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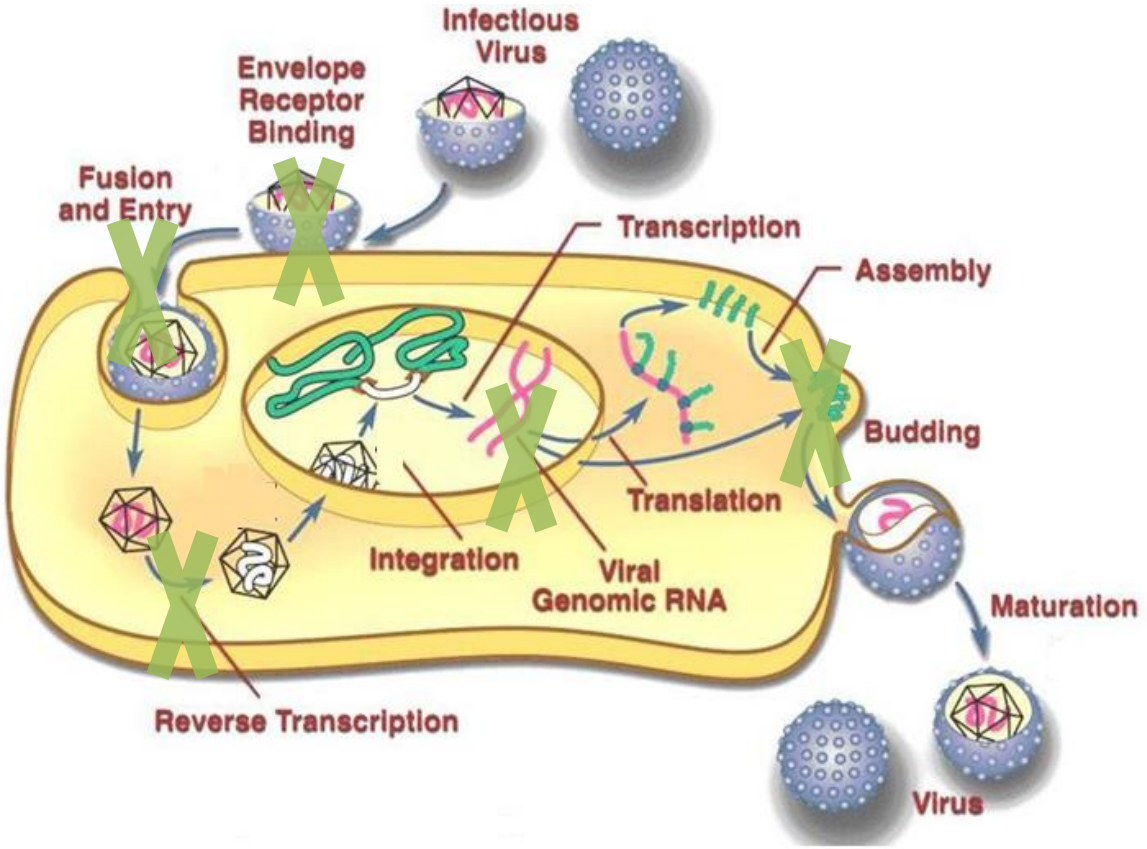
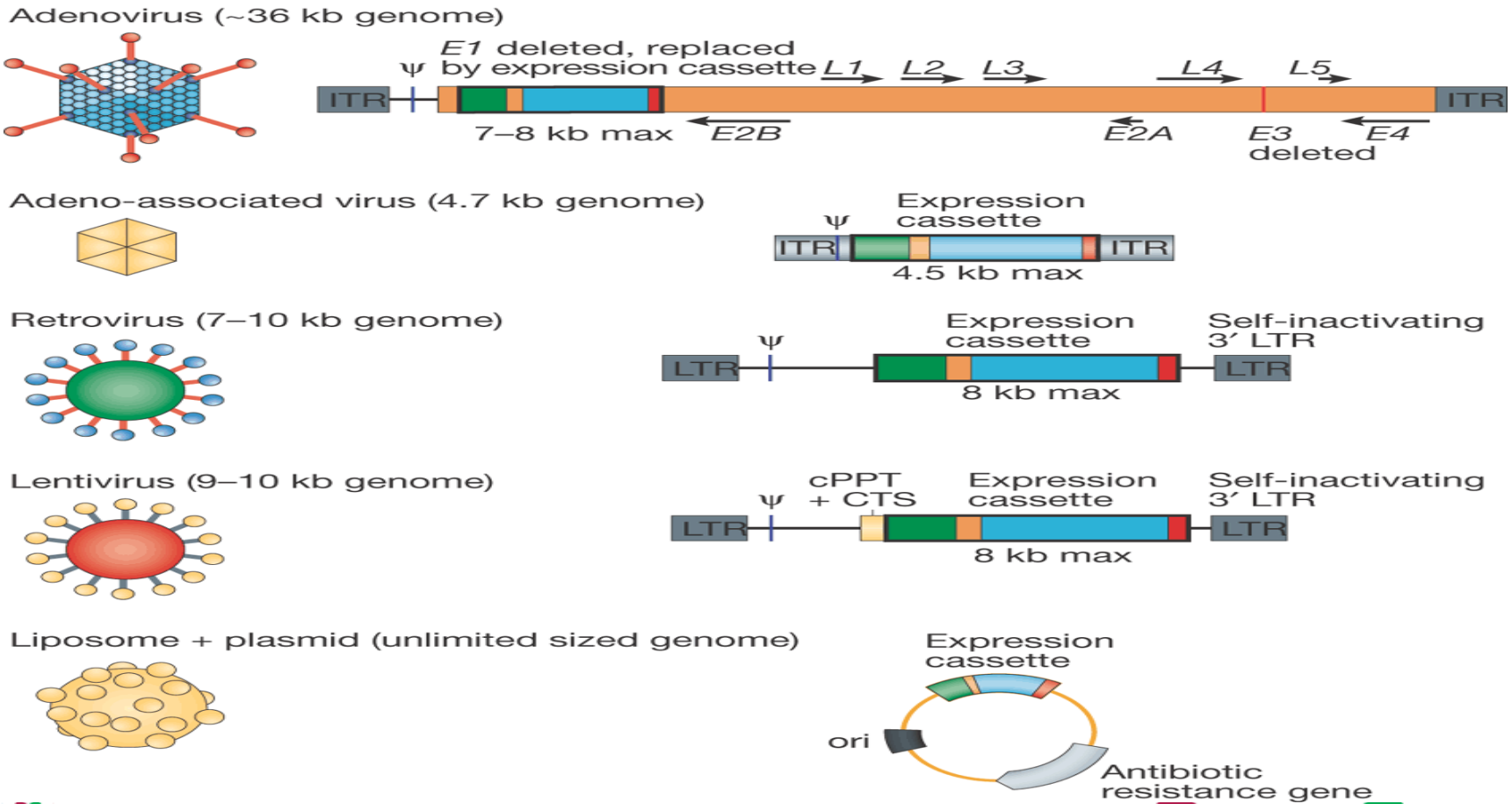
Some targets for gene therapy



Gene therapy vectors to deliver anti - HIV genes



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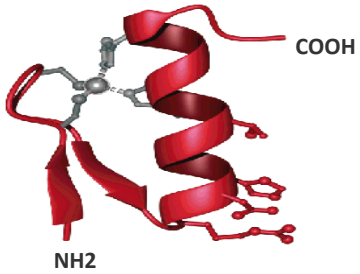
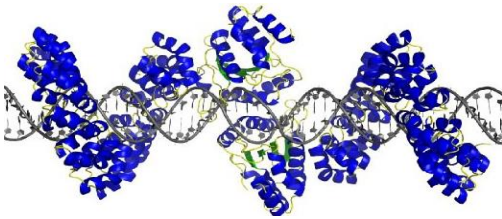
Next generation technologies

Genome editing

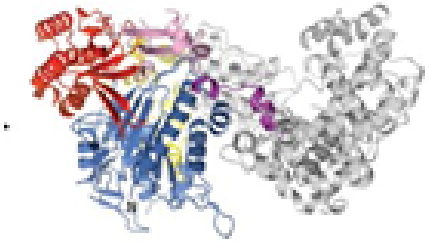
- Zinc finger



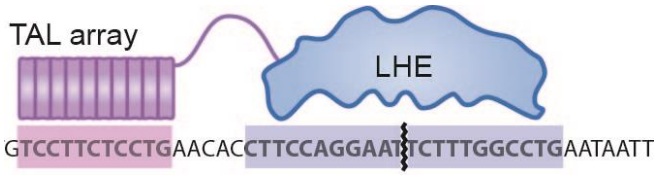
- TAL Effector Nuclease



- CRISPR/Cas9



- MegaTals



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Gut-Associated Lymphoid Tissue (GALT)

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

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.

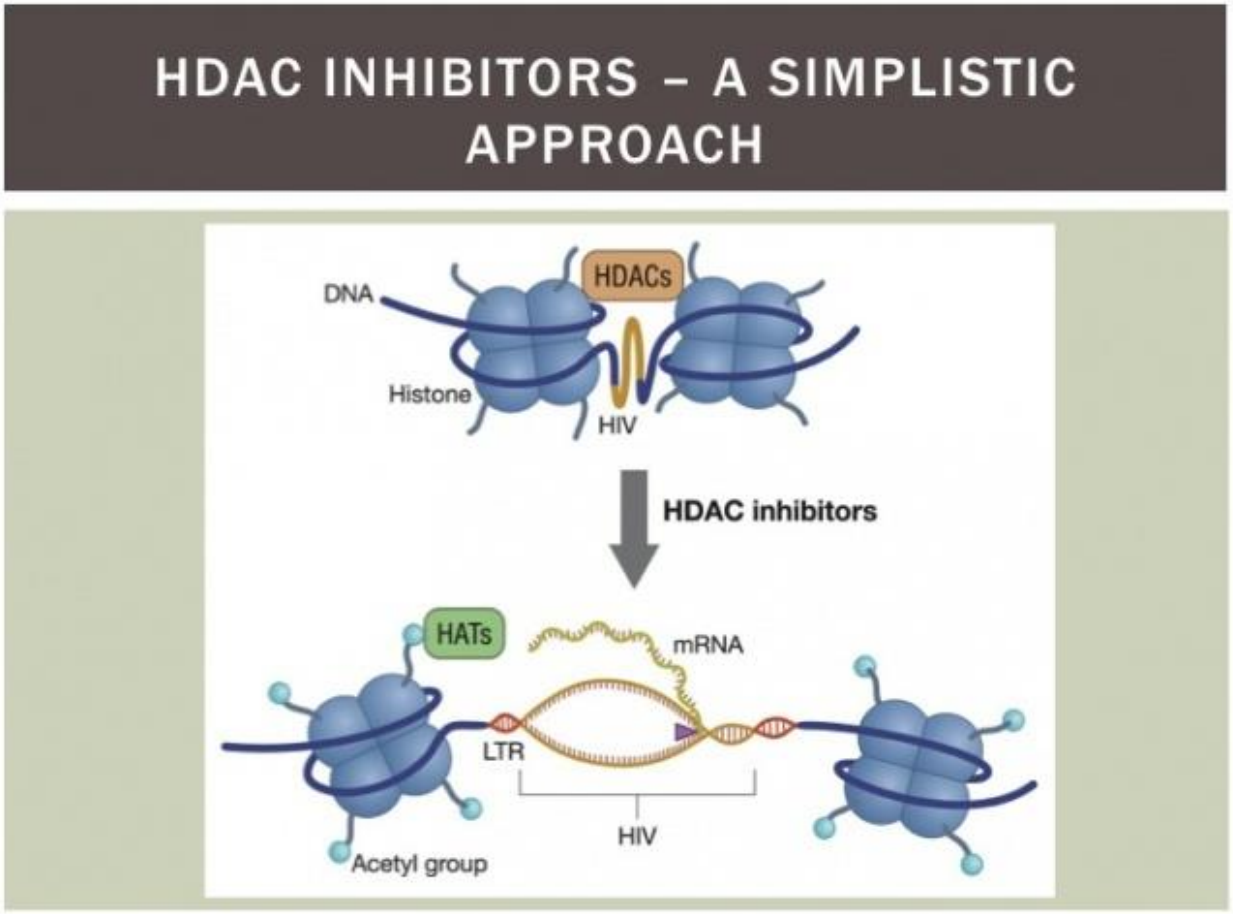
HDAC Inhibitor

- An HDAC inhibitor causes chromatin to become unbound and release HIV provirus DNA to reproduce and become exposed to the immune system and potentially to HIV therapy.

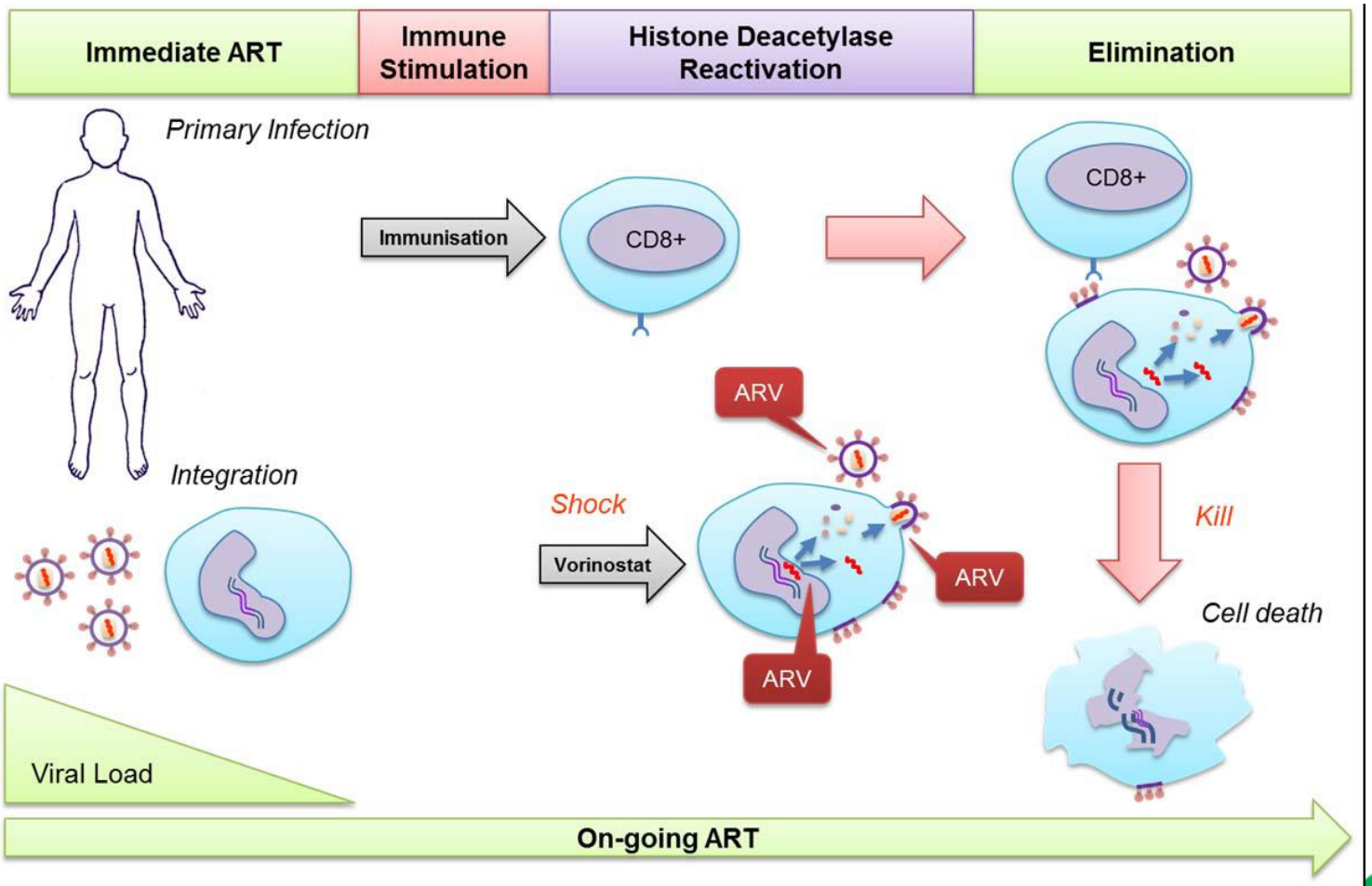
- Examples that have been used in experiments are Vorinostat, Romidepsin and Panobinostat.

These are drugs used to treat Cancer, Psychiatry and neurology

Histone deacetylase inhibitors
HDAC Inhibitors



Kick and Kill approach



HIV (Human Immunodeficiency Virus)

- HIV is he virus that causes Acquired Immunodeficiency Syndrome (AIDS).

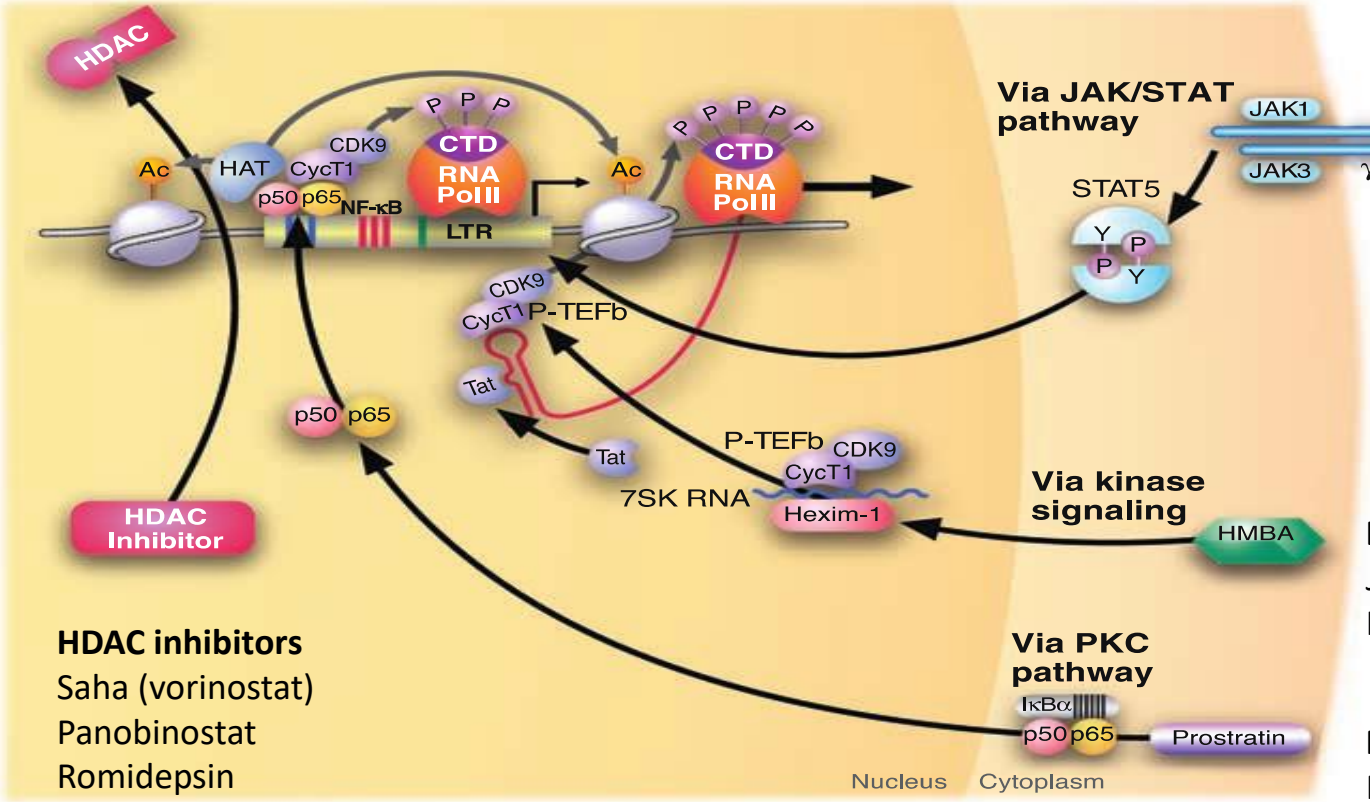
- Without proper therapy, HIV infection results in opportunistic infections and cancers that cause the death of almost every infected person.

HIV Latency

- The DNA (Deoxyribonucleic acid) 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.
- There is universal acceptance that HIV latency persists in memory CD4+ T cells.
- 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.

Latent reservoirs

Targeting molecular mechanisms of HIV latency



HDAC inhibitors
Saha (vorinostat)
Panobinostat
Romidepsin

Gamma-c Cytokines:
IL-7
IL-15

Bromodomain inhibitors
JQ1
I-BET

PKC agonists:
Prostratin
Bryostatin

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HIV Therapeutic Vaccine

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

- They work by “training” the immune system

- Consist of usually two or more injections known as a primer and a booster

Human Leukocyte Antigen HLA-B27 and HLA-B57

- 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.

- Are specific parts of the human leukocyte antigen that are advantageously mutated and significantly expressed in some elite controllers

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.

- For most practical purposes one could say: Immune activation = inflammation.

- Chronic HIV infection, even in those whose virus is either suppressed naturally or by antiretroviral therapy, is known to cause inflammation.

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.

- Evidence suggests these individuals are distinct from elite controllers.

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 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.
- 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.

Microbial Translocation

- Cells and structures 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.

Natural Killer (NK) cells

- These are white blood cells that are responsible for killing infected cells and cancer cells.

- 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.
  - PD-1 is extended family of CD28 T Cell regulators.

- 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, who started antiretroviral therapy within weeks of infection, stayed on therapy for an average of about four years, and then, for various reasons, stopped therapy.

- 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.
- 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

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.

Current Clinical Trials (September 2016)

- ADOPTIVE IMMUNOTHERAPY
- ANTIBODIES
- ANTI-FIBROTIC
- ANTIRETROVIRAL THERAPY
- ANTIRETROVIRAL THERAPY IN HIV CONTROLLERS
- COMBINATIONS
- GENE THERAPIES
- GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCER
- JANUS KINASE INHIBITORS
- LATENCY-REVERSING AGENTS
- mTOR INHIBITORS
- STEM CELL TRANSPLANTATION
- THERAPEUTIC VACCINES
- Traditional Chinese Medicine
- Treatment Intensification

» **http://www.treatmentactiongroup.org/cure/trials**

The Communities Questions

- Safety
- Tolerability
- Ethics
- Involvement in research
- Education
- The law
- Why a cure when tolerable and safe ARV's?
- The cost
- Who is the cure for?
- Others?

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