

HIV

human immunodeficiency virus



By Susi Smith

Prevalence

- Between 39 and 44 million people around the world live with AIDS.
- 60% of people with AIDS live in sub-Saharan Africa.
- Between 2.8 and 3.5 million people died with AIDS in 2004.
- AIDS is a pandemic comparable to the bubonic plague.

Infection Risks

- When pricked by a needle used by an infected person: less than 1/200. Post exposure within 24 hours a person should start a 28 day regimen of HIV drugs, which prevents HIV infection almost 99%. After 72 hours the effectiveness of the regimen decreases to 52%.
- .3% chance of getting infected per sexual interaction with use of a condom.
- The presence of cervical ectopia, use of oral contraceptive, or pregnancy raises the infection risk.

History of HIV/AIDS

- CDC in 1981 noticed unusual clusters of Kaposi's sarcoma in gay men in NY and San Francisco, which led to the disease to be called GRID (Gay Related Immune Deficiency).
- By 1982 the disease was apparent in heterosexuals and was renamed AIDS (Acquired Immune Deficiency).
- AIDS was not recognized as a new clinical syndrome until 1981.
- However, researchers examining the earlier medical literature identified cases appearing to fit the AIDS surveillance definition as early as the 1950s and 1960s.
- The virus is thought to native to monkeys in Africa, specifically of Western Africa.

Transmission

- Vaginal Intercourse
- Anal Intercourse (10x higher infection rate than vaginal intercourse because of tissue tear)
- Oral Intercourse
- Blood Transfusion (risk greater than 90% if sample is already infected)
- Needles (tattoos, injections)
- Infected mother to the infant through:
Pregnancy (placenta), Birth, and breastfeeding.

Symptoms

- AIDS as when a person with HIV has either a CD4 cell count below 200.
- A person contracts an opportunistic infection:
 - Kaposi's Sarcomas
 - Wasting caused by HIV infection
 - Toxoplasmosis of the brain
 - Salmonella : septicemia, recurrent
 - Pneumonia, recurrent
 - Lymphoma: Burkitt's, immunoblastic primary, of
brain (primary central nervous system lymphoma)
 - Disease caused by Mycobacterium tuberculosis, Herpes simplex
 - Candidiasis of bronchi, trachea, lungs, or esophageal
 - Cervical cancer, Invasive (medical)

Diagnosis

- The HIV test used by Americans quantitatively tests for a CD4 cell count lower than 200 per microliter of blood.
- However, countries that cannot afford the HIV test use symptomatic diagnosis set out by the CDC and the World Health Organization in 2004. An individual must have:
“...prolonged fevers for a month or more, weight loss of over 10% and prolonged diarrhea...”

This leads to over diagnosis of HIV in these countries.

<http://en.wikipedia.org/wiki/AIDS>

CDC Classification of HIV

- Category 1: > 500 cells/mm³ (or CD4% $> 28\%$)
- Category 2: 200-499 cells/mm³ (or CD4% 14% - 28%)
- Category 3: < 200 cells/mm³ (or CD4% $< 14\%$)
(CD4+ T-lymphocyte counts per microliter of blood)

The percentages were derived from correlating counts and percentages from 7 different data sources

AIDS and Children

Methods that prevent transmission from a mother to a child:

1. Strict adherence to antiretroviral drugs
2. Cesarean Section
3. Formula

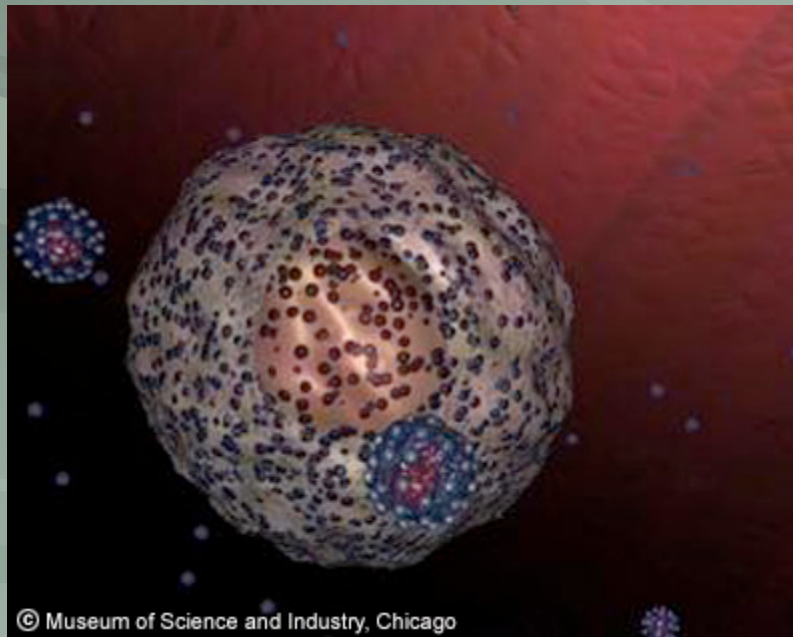
The earlier stage of HIV infection during pregnancy the better chance the baby will be unaffected.

1 in 4 babies born from HIV infected mothers are infected



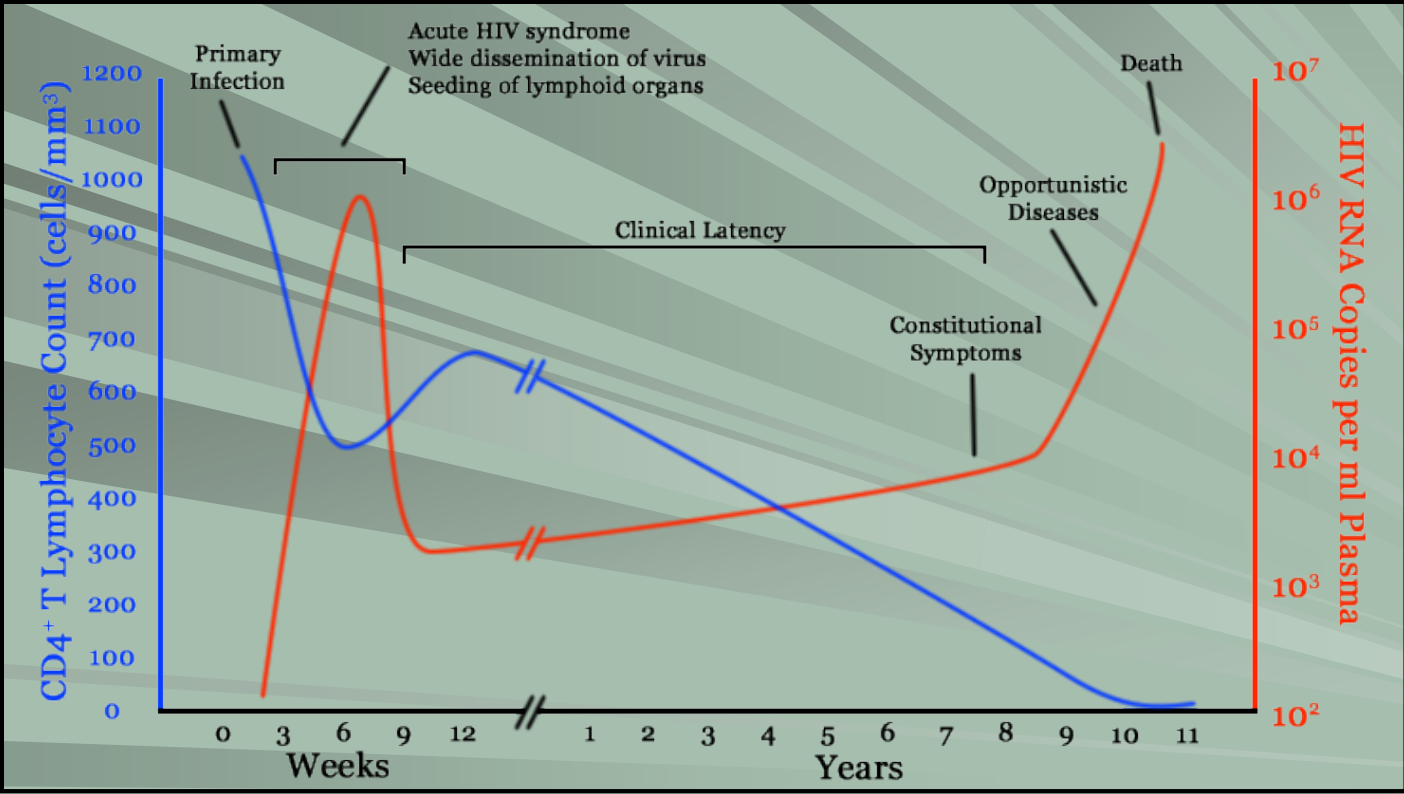
Infection

- <http://www.avert.org/pictures/aidshiv2.htm>
- HIV infects the T Helper cell because it has the protein CD4 on its surface. HIV needs to use CD4 to enter cells it infects. This is why the T helper cell is referred to as a CD4 lymphocyte.



Correlation between CD4 and HIV

<http://upload.wikimedia.org/wikipedia/en/thumb/3/34/500px-Hiv-timecourse.png>



Infections throughout the Body

Within the inflammatory cells of the infection (T cells)

Site of replication shifts to lymphoid tissues:

Lymph nodes

Spleen

Liver

Bone marrow

Macrophages and Langerhans cells become reservoirs and sites of replication but do not die themselves.

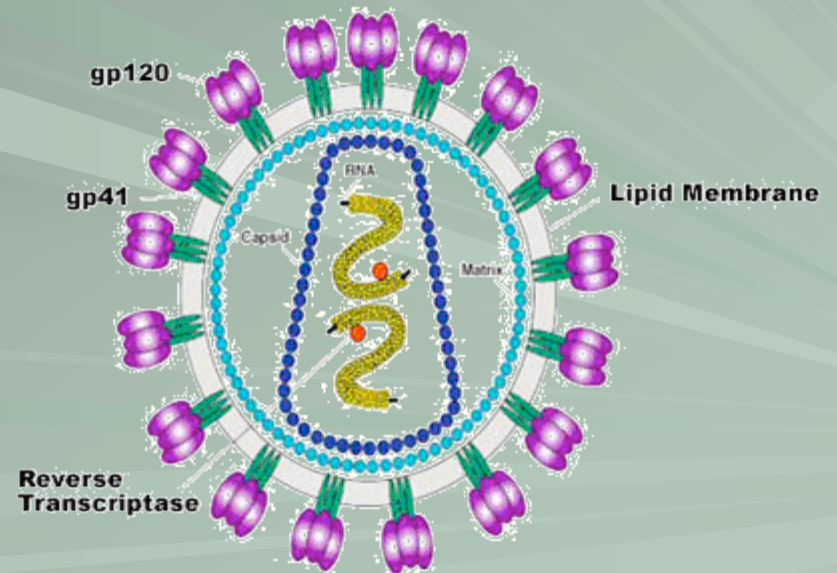
Infected lymph nodes infect the follicular dendritic cells (FDC), which infect the CD4 cells percolating through the node. The FDC do not die.

The virus replicates quickly because infected T cells have a half life of two days. Therefore, there is a rapid host cell turnover.

Structure of HIV

- Spherical
- 120 nm in diameter
- env proteins make the spikes on the membrane.
- Conical capsid.
- Electron dense core.

Organization of the HIV-1 Virion



HIV Life Cycle

HIV enters the CD4 helper T cell by bonding with CXCR4.

Fusin, a cofactor helps HIV bind to the membrane.

GP41, the viral protein, penetrates the cell and the reverse transcriptase, integrase, protease and various other enzymes are injected into the cell.

Using reverse transcriptase and the T-cell's machinery the HIV replicates its RNA into DNA.

Integrase then inserts the viral DNA into the T cell's genome. The host is fully infected, but not producing proteins so it not infectious (latent stage).

The T cell's transcription factor, NF Kappa B, causes the viral genes to be transcribed once the T Cell becomes activated by fighting an infection.

Splicing then occurs producing regulatory proteins, tat and rev. Rev then inhibits the splicing.

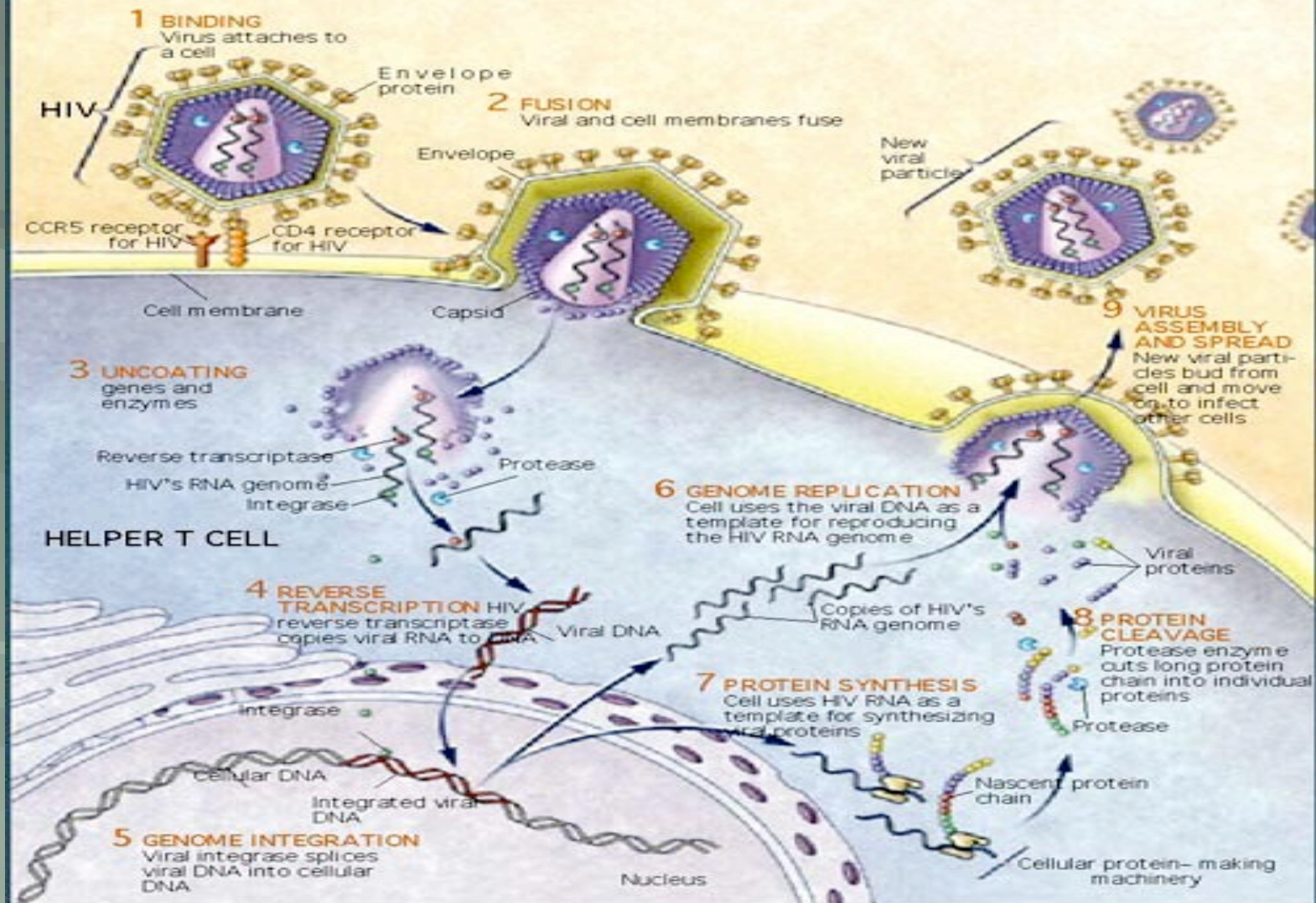
From the full length mRNA, gag and env are made. The full length RNA (HIV's genome) attaches to gag.

The virus reforms in a cholesterol rich region under the membrane and then buds outside the cell.

Once outside, the virus matures, cleaving gag into smaller proteins and becomes infectious.

HIV LIFE CYCLE, deciphered with the help of genomic analyses, is unusually complex in its details, but all viruses undergo the same basic steps to infect cells and repro-

duce. They enter a cell (bind to it and inject their genes into the interior), copy their genes and proteins (by co-opting the cell's machinery and raw materials), and pack

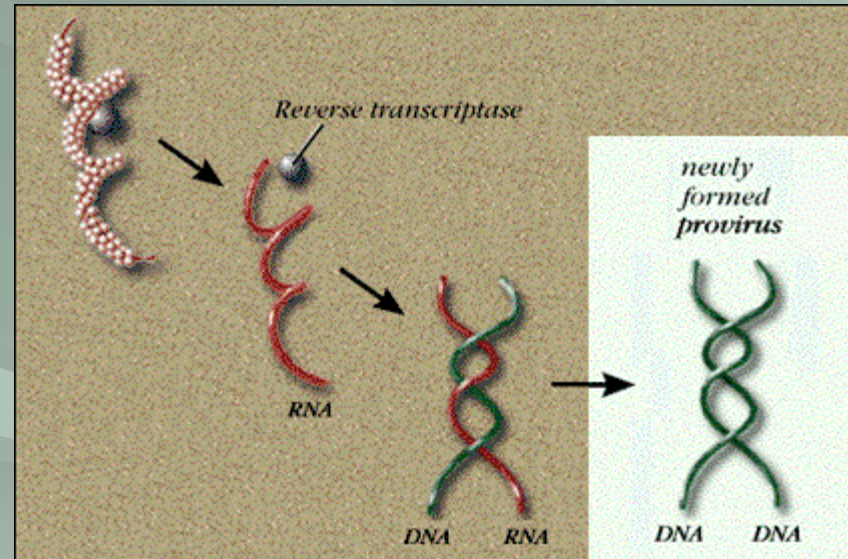


Reverse Transcriptase



Reverse Transcriptase

- RNA>DNA>RNA.
- Occurs in the cytosol.
- Has a lipid coating surrounding the capsid (wash your hands).
- Reverse transcription does not undergo “proofreading,” leading to a mutation every 2000 integrated nucleotides. These mutations create variants of the HIV virus, making the creation of a vaccine very hard.



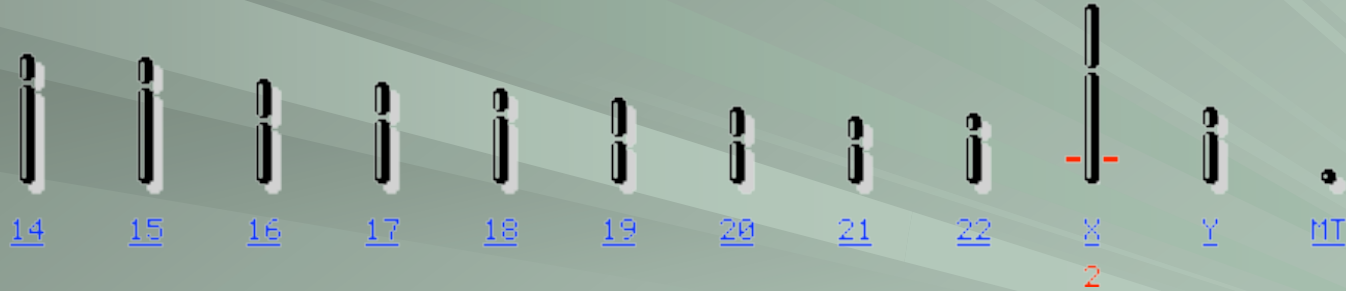
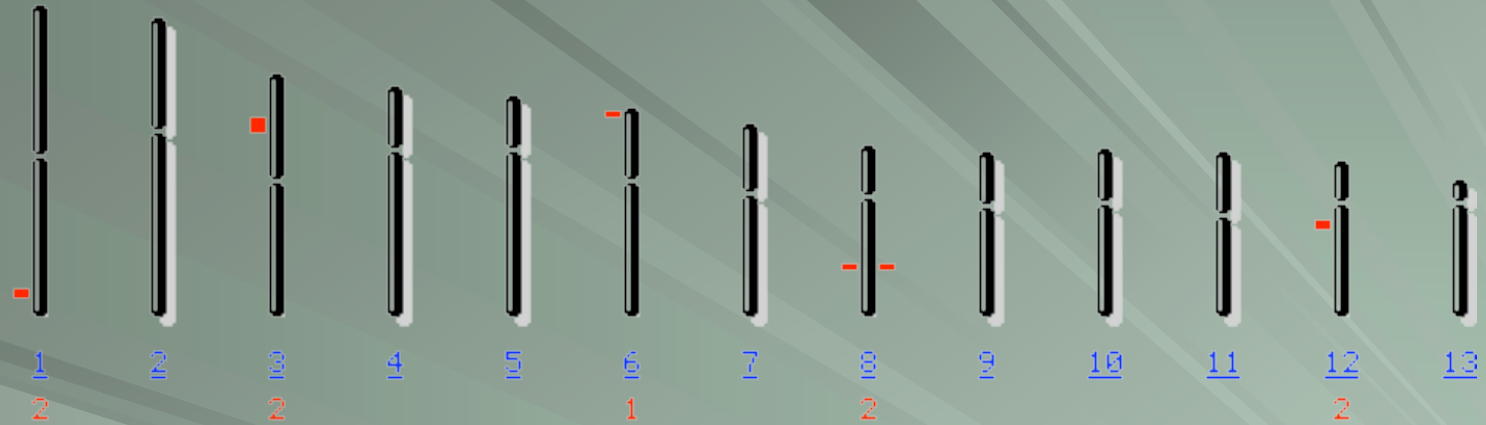
Retroviral Genes

- gag (group-specific antigen): makes the cone-shaped viral capsid.
- pol (polymerase): codes for viral enzymes, reverse transcriptase, integrase, and viral protease.
- env (envelope): makes surface protein gp120 and transmembrane gp41, enabling HIV to fuse to CD4 cells.

HIV Genes

- **tat**: eliminates the hairpin structure in RNA by phosphorylating CdK9/CycT. This increases transcription and creates a positive feedback loop.
- **vpr**: is involved in getting the viral RNA into the nucleus of the T cell. It causes the cell to stop growing, stimulating an immune dysfunction.
- **rev**: creates a rev Response Unit that exports the HIV RNA into the cytoplasm before it is spliced. It is also a positive feedback loop.
- **nef**: down regulates CD4 on the T cell, inhibiting response to infectious agents.
- **vif**: helps HIV infect other cells, though it is still unclear how. It is thought that it interferes with the T cell's proteins that modify RNA.
- **vpu**: enhances HIV release from the cell.

Human Genome and HIV

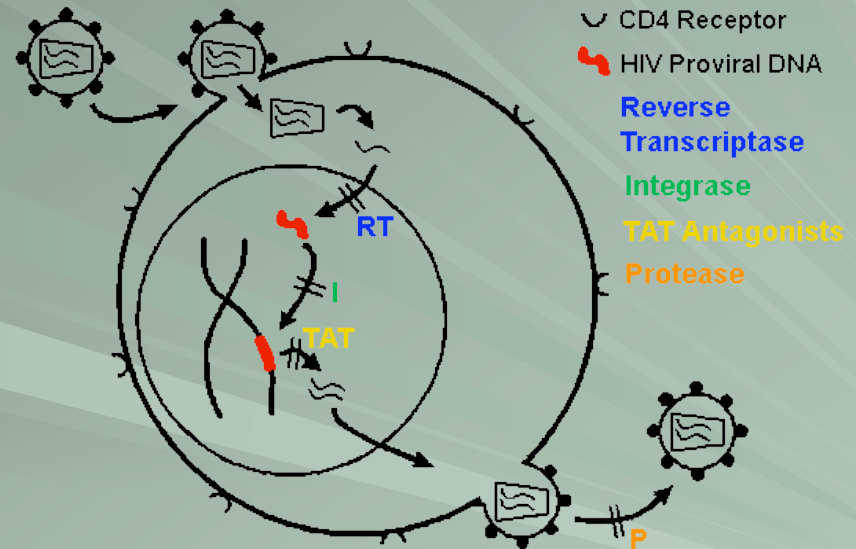


http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi?taxid=9606&query=HIV&qchr=&strain=All&advsrch=off&neighb=

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Where Drugs Can Interfere

- The life cycle of HIV shown with the points at which pharmacologic agents may block viral maturation, including points for inhibition of reverse transcriptase, integrase, TAT transcription, and protease, in this diagram.



Treatment

- Physicians consider 200 to 350 CD4 cells/mm³ as the range to consider starting HAART (Highly Active Antiretroviral Therapy). HAART combines two types of antiretroviral drugs.
- Average rate of adherence to HAART is approximately 70%. Long-term viral suppression requires near-perfect adherence.
- **Protease inhibitors (PIs):** Protease inhibitors inhibit the activity of protease, an enzyme used by HIV to cleave nascent proteins for final assembly of new HIV virions, and so prevent viral replication.
- **Fusion Inhibitors:** Fusion inhibitors inhibit fusion (entry) of HIV with the cell membrane, preventing infection of uninfected cells
- **Synergistic enhancers:** While most of these substances do not possess any antiretroviral properties, when they are taken concurrently with antiretroviral drugs they enhance the effect of that drug (ex. grapefruit juice).



Future Treatment Possibilities

- Vaccine research using gene therapy: VRX496 is inserted into a modified lentivirus to suppress HIV. In 2003 it entered clinical trial phase I.
- Chemokines: naturally occurring compound that can block HIV from binding to CD4 receptor and halt progression of AIDS.

Prevention by Common Sense

- ABC rule: Abstinence, Be faithful (one partner), Condom.
- Antiretroviral drugs
- Cesarean delivery
- Formula