

A study material for M.Sc. Biochemistry (Semester: IV) Students
on the topic (EC-1; Unit IV)

AIDS

(Acquired Immunodeficiency Syndrome)

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- **Some Terminologies:**

- **Plaques:**

- Group of killed cells in tissue culture have been used in the enumeration of viruses. Number of plaques is proportional to the number of infectious virus particles.

- **Polykaryotes:** Formation of giant cells.

- Creation of genetic changes such as chromosomal breakage, induction of interferon production by infected cells that prevent infection of healthy cells.

- **Inclusion bodies:**

- Aggregates of unassembled virus subunit and intact virions in infected cells.
- It is extremely difficult to remove inclusion bodies from the cells and used them as inoculum to infect other cells.

Acquired Immunodeficiency Syndrome (AIDS)

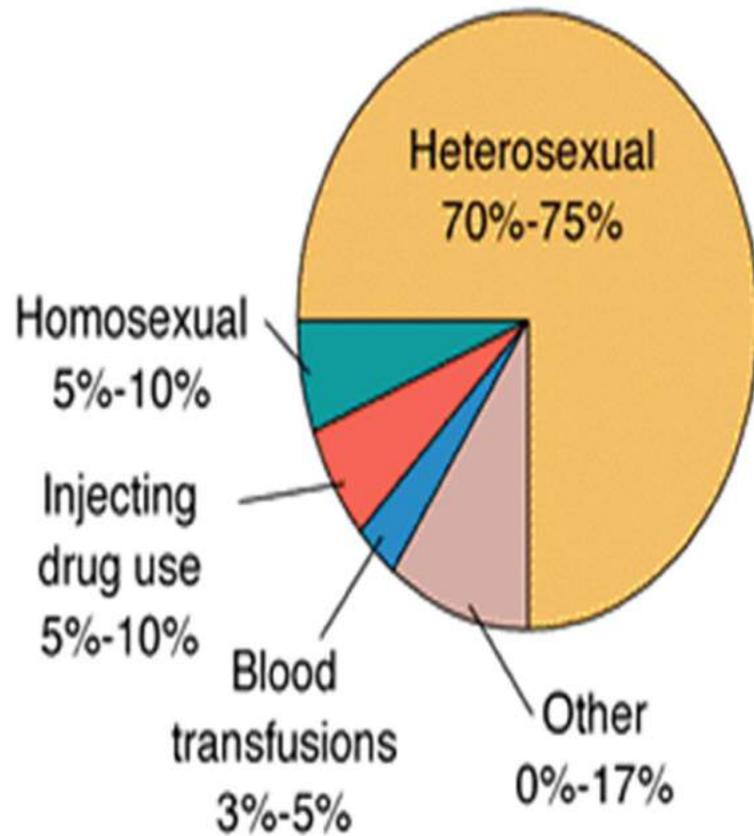
History

- ❑ 1950s: Blood samples from Africa have HIV antibodies.
- ❑ 1976: First *known* AIDS patient died.
- ❑ 1980: First human retrovirus isolated (HTLV-1).
- ❑ 1981: First reports of “Acquired Immuno-deficiency Syndrome” in Los Angeles.
- ❑ 1983: Virus first isolated in France (LAV).
- ❑ 1984: Virus isolated in the U.S. (called HTLV-III and AIDS-Related Virus, ARV).
- ❑ 1985: Development and implementation of antibody test to screen blood donors.
- ❑ 1986: Consensus name Human Immunodeficiency Virus (HIV-1).
- ❑ Related virus (HIV-2) identified.
- ❑ 1992: AIDS becomes the leading cause of death among adults ages 25-44 in the U.S.
- ❑ 1997: Mortality rates of AIDS starts to decline due to the introduction of new drug cocktails.
- ❑ 2001: World Health Organization predicts up to 40 million infected individuals. More than 22 million have already died.

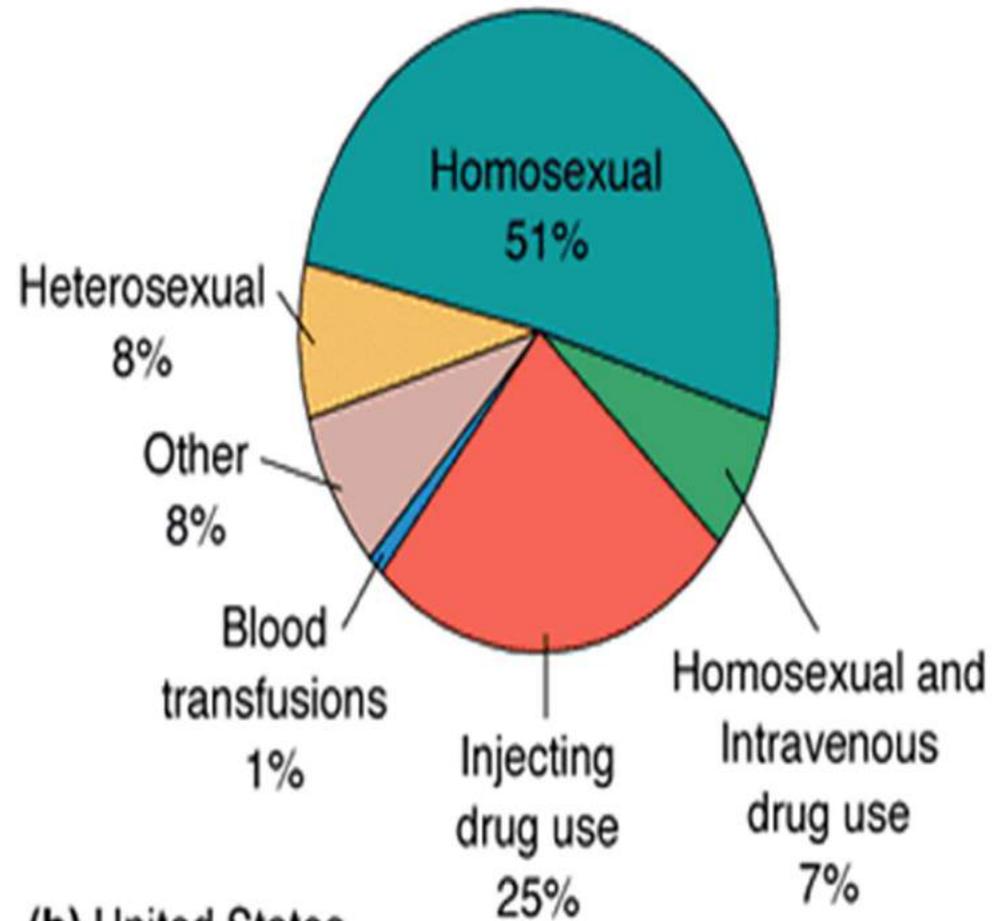
Transmission of AIDS (Worldwide)

- 1. Sexual contact with infected individual: All forms of sexual intercourse (homosexual and heterosexual). 75% of transmission.**
- 2. Sharing of unsterilized needles by intravenous drug users and unsafe medical practices: 5-10% of transmission.**
- 3. Transfusions and Blood Products: Hemophiliac population was decimated in 1980s. Risk is low today. 3-5% of transmission.**
- 4. Mother to Infant (Perinatal): 25% of children become infected in utero, during delivery, or by breast-feeding (with AZT only 3%). 5-10% of transmission.**

HIV Transmission in United States and Rest of the World



(a) World



(b) United States

Global summary of the AIDS epidemic | 2011

Number of people living with HIV

Total	34.2 million [31.8 million–35.9 million]
Adults	30.7 million [28.6 million–32.2 million]
Children (<15 years)	3.4 million [3.1 million–3.9 million]

People newly infected with HIV in 2011

Total	2.5 million [2.2 million–2.8 million]
Adults	2.2 million [2.0 million–2.4 million]
Children (<15 years)	330 000 [280 000–380 000]

AIDS deaths in 2011

Total	1.7 million [1.6 million–2.0 million]
Adults	1.5 million [1.3 million–1.7 million]
Children (<15 years)	230 000 [200 000–270 000]

HIV/AIDS

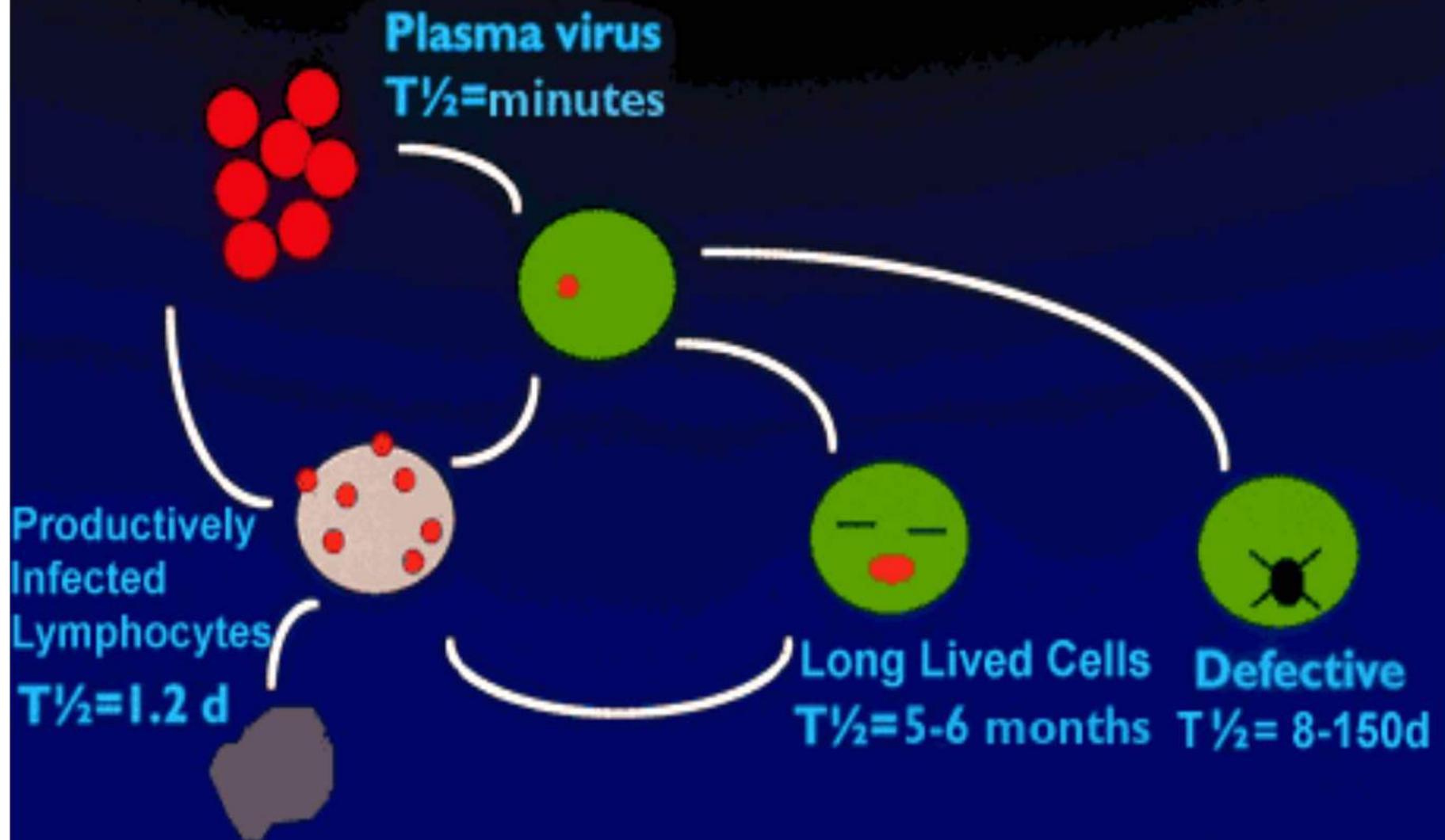
Infection:

- 4 main types of cells infected, esp. T helper cells
 - Have CD4 glycoprotein on surface
- After RNA is copied into cDNA, cDNA inserts
 - Infection is for life
- Chronic infection
 - T cells continually made, continually destroyed
 - Eventually, host loses
- AIDS diagnosis:
 - CD4 count below 200/ μ l; opportunistic infections

HIV half-lives

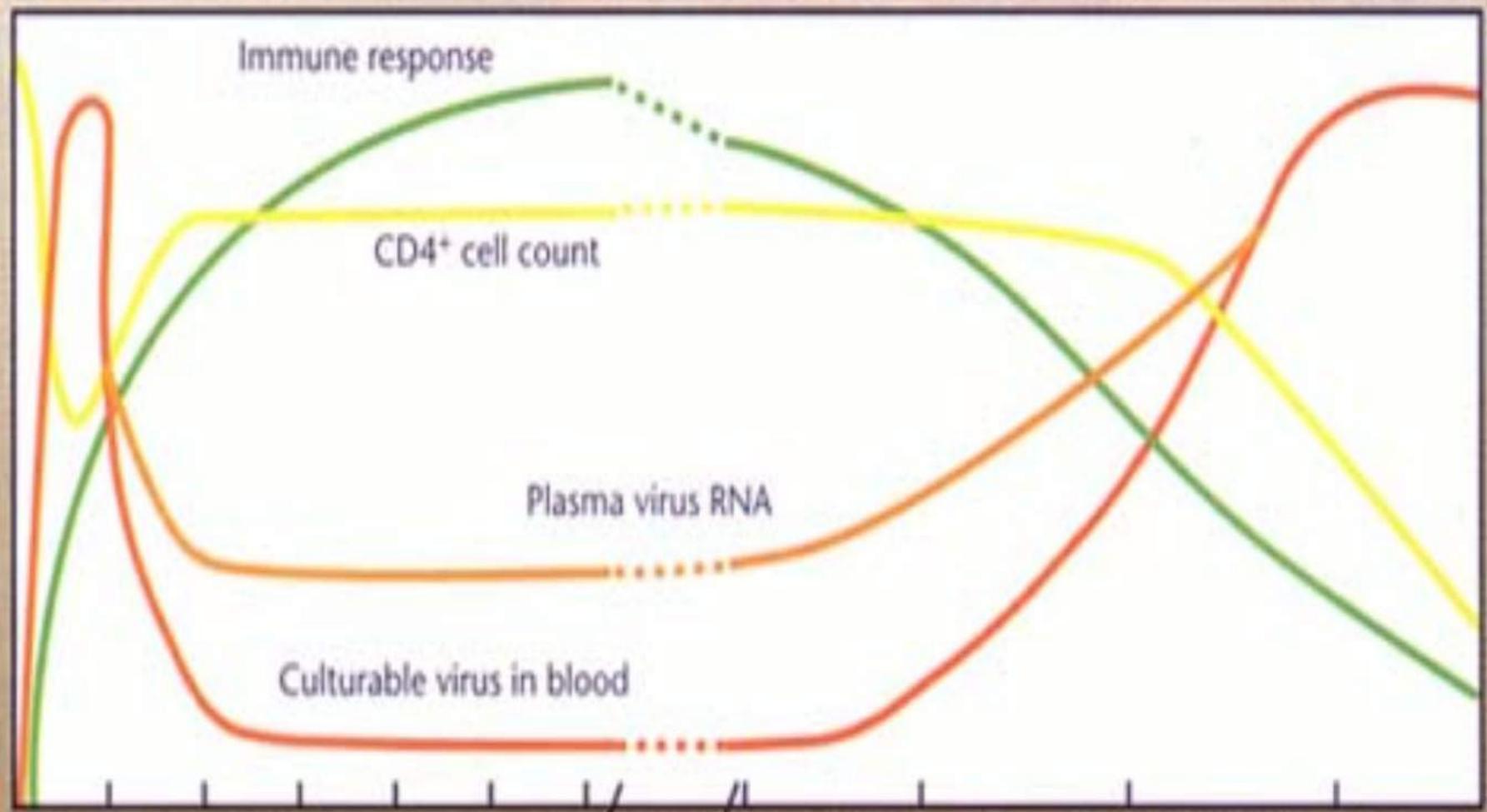
- Activated cells that become infected with HIV produce virus immediately and die within one to two days.
- Production of virus by short-lived, activated cells accounts for the vast majority of virus present in the plasma.
- The time required to complete a single HIV life-cycle is approximately 1.5 days.
- Resting cells that become infected produce virus only after immune stimulation; these cells have a half-life of at least 5-6 months.
- Some cells are infected with defective virus that cannot complete the virus life-cycle. Such cells are very long lived, and have an estimated half-life of approximately three to six months.
- Such long-lived cell populations present a major challenge for anti-retroviral therapy.

HIV-1 half-lives



HIV Pathogenesis

- The profound immunosuppression seen in AIDS is due to the depletion of T4 helper lymphocytes.
- In the immediate period following exposure, HIV is present at a high level in the blood (as detected by HIV Antigen and HIV-RNA assays).
- It then settles down to a certain low level (set-point) during the incubation period. During the incubation period, there is a massive turnover of CD4 cells, whereby CD4 cells killed by HIV are replaced efficiently.
- Eventually, the immune system succumbs and AIDS develops when killed CD4 cells can no longer be replaced (witnessed by high HIV-RNA, HIV-antigen, and low CD4 counts).



Months →

Years →

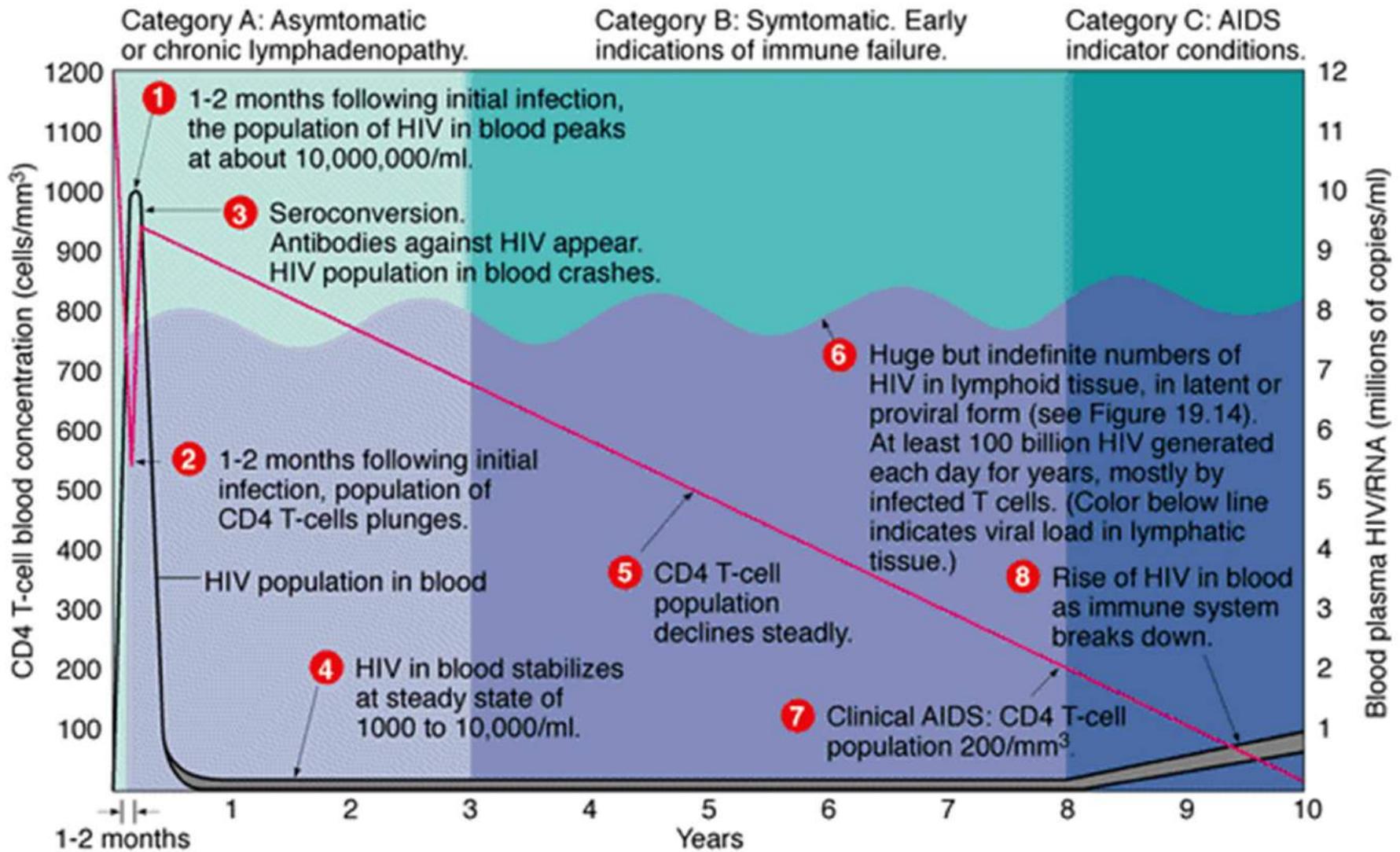


Symptoms

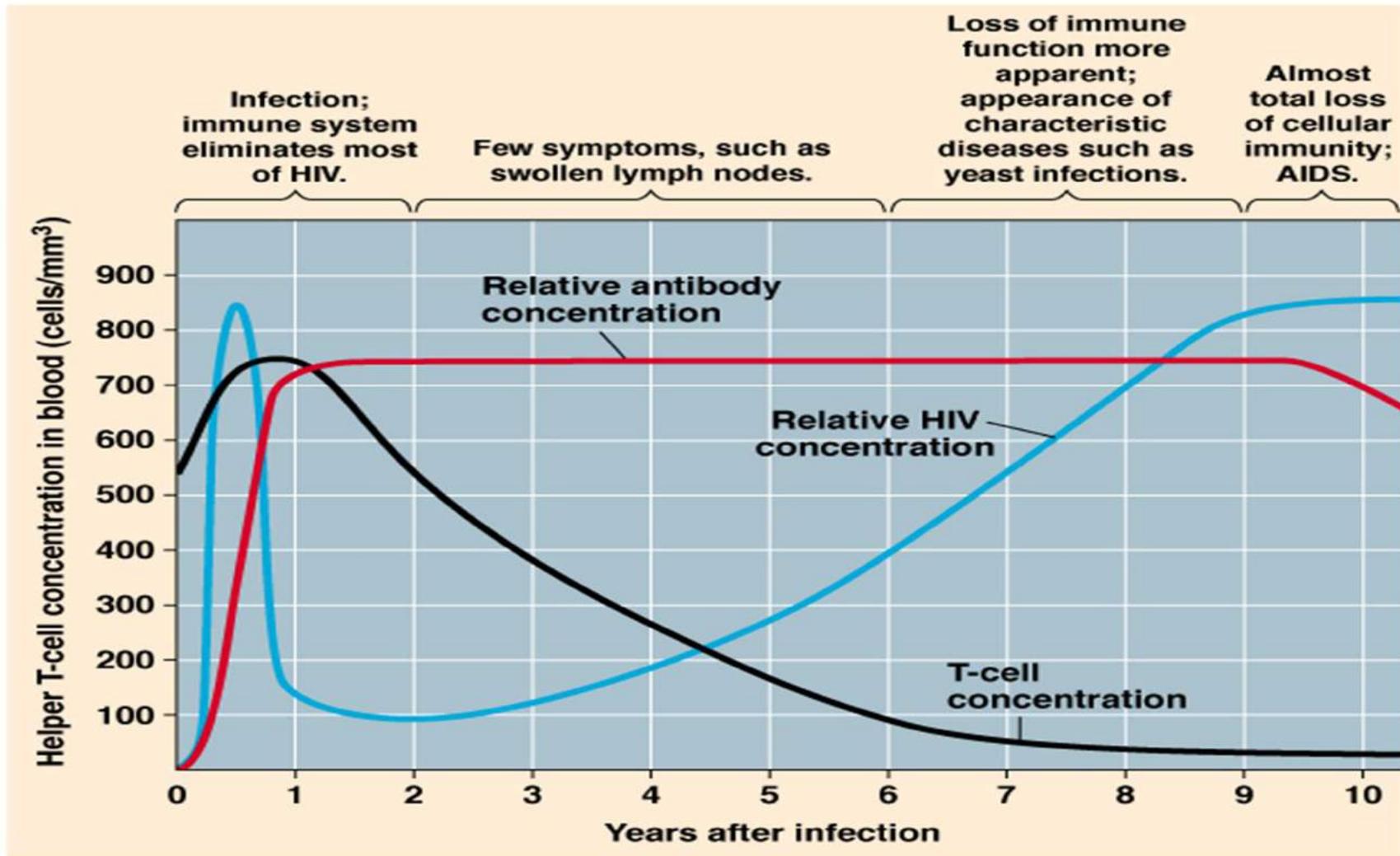


Symptoms

Stages of HIV Infection

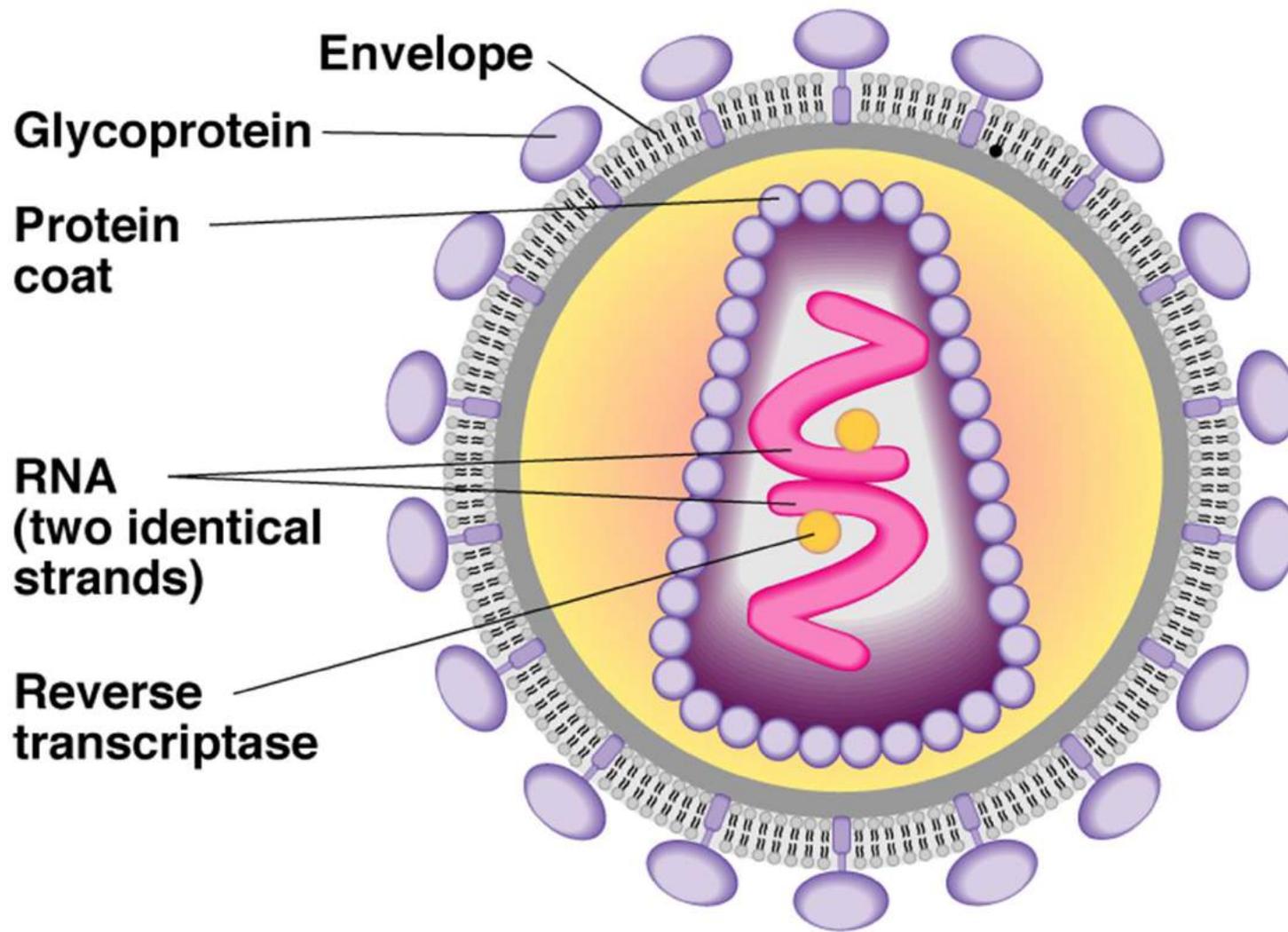


Antibody Levels, T Cell Counts, and HIV Concentration After Infection



Structure of the Human Immunodeficiency Virus

HIV is a Retrovirus



Life Cycle of HIV

1. **Attachment:** Virus binds to surface molecule (CD4) of T helper cells and macrophages.
 - **Coreceptors:** Required for HIV infection.
 - CXCR4 and CCR5 mutants are resistant to infection.

2. **Fusion:** Viral envelope fuses with cell membrane, releasing contents into the cell.

Reverse Transcription: Viral RNA is converted into DNA by unique enzyme *reverse transcriptase*.

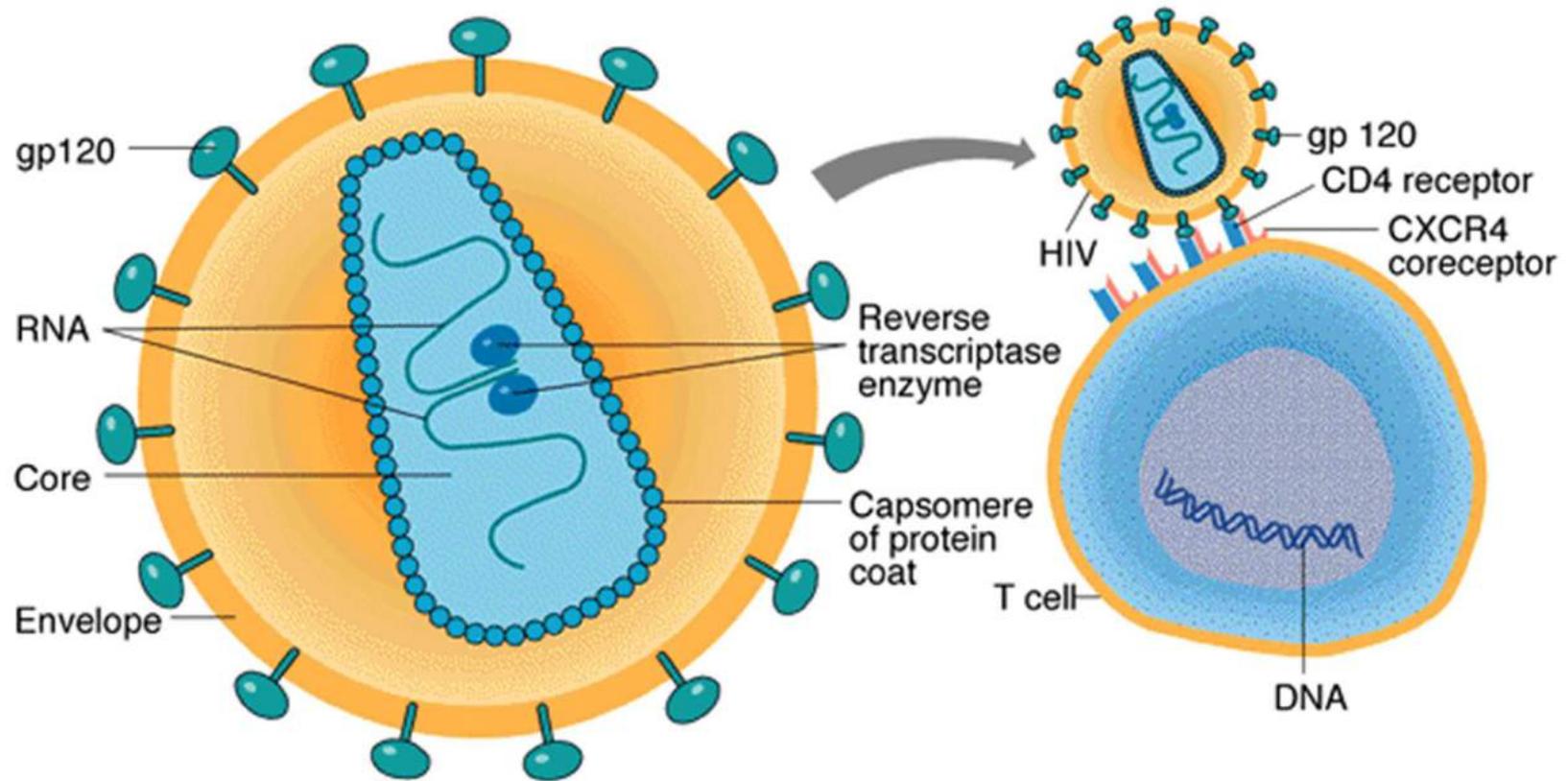


Reverse transcriptase is the target of several HIV drugs: AZT, ddI (Didanosine (2',3'-dideoxyinosine)), and ddC (Zalcitabine (2'-3'-dideoxycytidine)).

4. **Integration:** Viral DNA is inserted into host cell chromosome by unique enzyme *integrase*. Integrated viral DNA may remain latent for years and is called a *provirus*.
5. **Replication:** Viral DNA is transcribed and RNA is translated, making viral proteins.

Viral genome is replicated.
6. **Assembly:** New viruses are made.
7. **Release:** New viruses bud through the cell membrane.

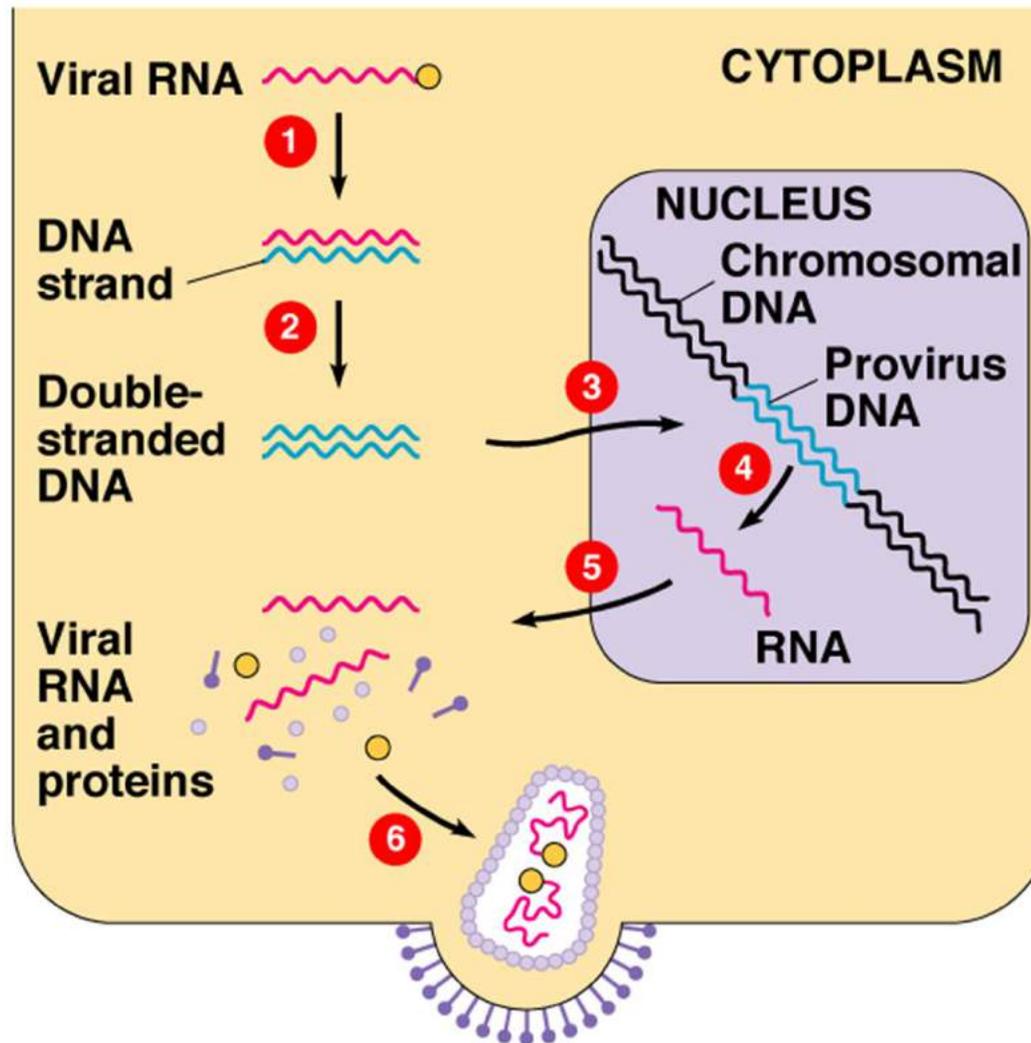
HIV Life Cycle: Attachment Requires CD4 Receptor plus a Coreceptor



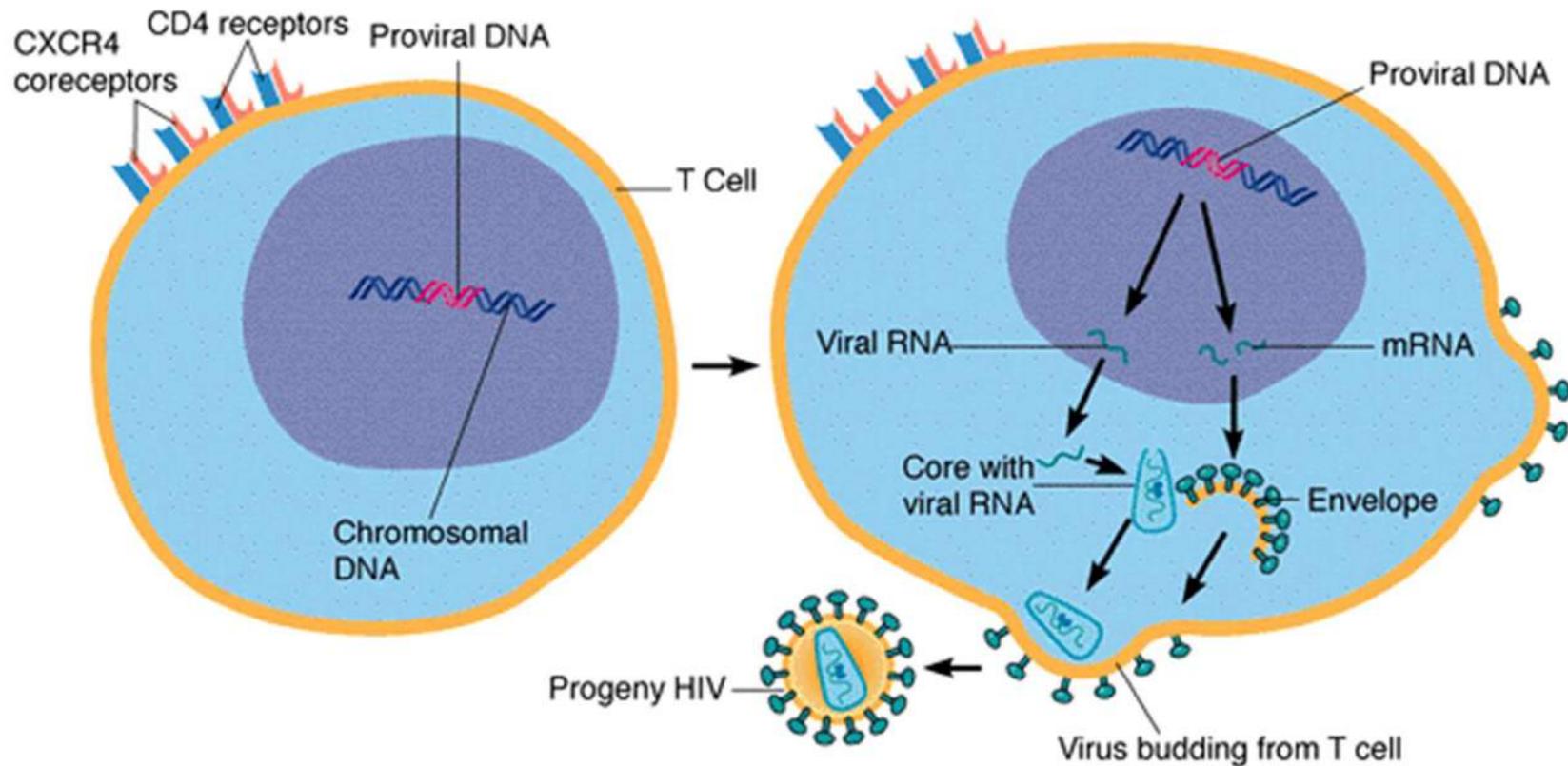
(a) Structure of HIV

(b) HIV infecting a T cell with CD4 receptors, and CXCR4 coreceptors which are distributed over the surface of the cell

HIV Life Cycle: Reverse Transcriptase Converts RNA into DNA



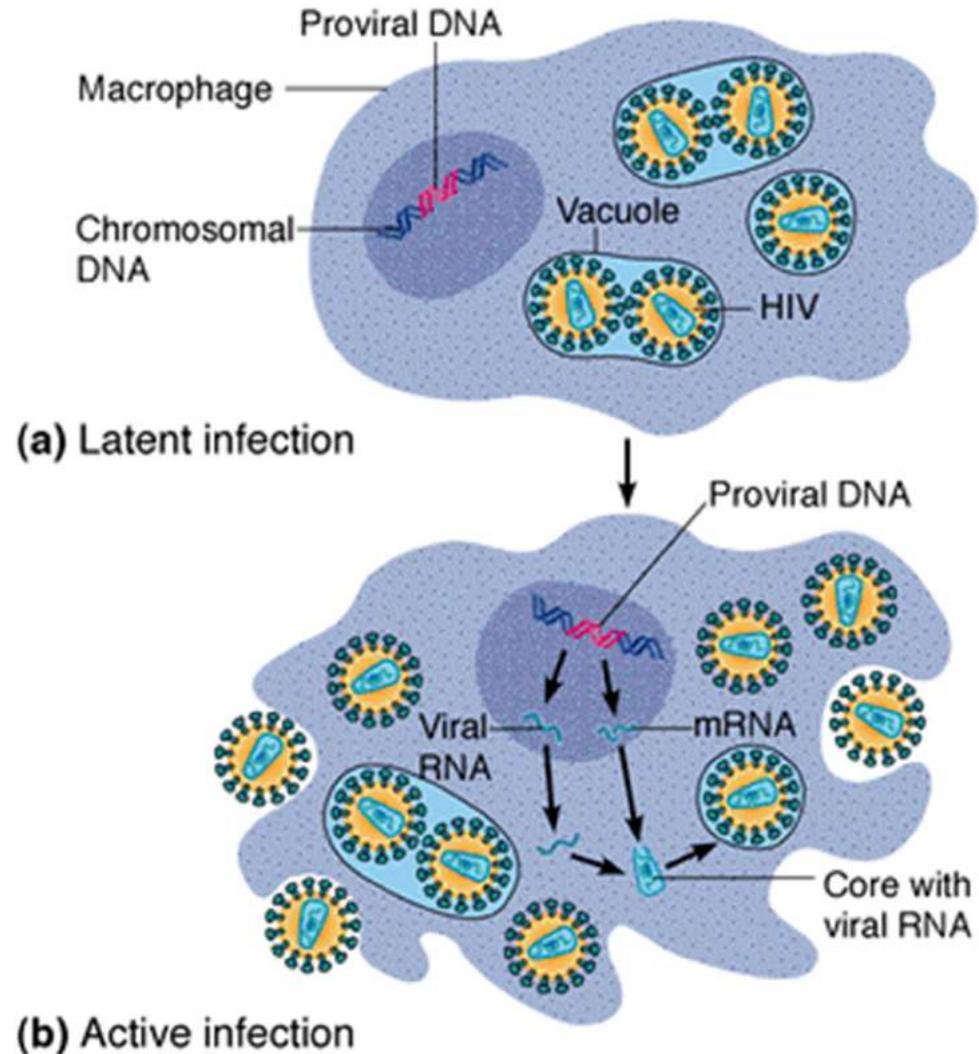
HIV Life Cycle: Latent versus Active Infection



(a) Latent infection

(b) Active infection

HIV Life Cycle: Latent versus Active Infection in Macrophages



AIDS Associated Disease Categories

1. Gastrointestinal: Cause most of illness and death of late AIDS.

- **Symptoms:**
- **Diarrhea**
- **Wasting (extreme weight loss)**
- **Abdominal pain**
- **Infections of the mouth and esophagus.**

Pathogens: *Candida albicans*, cytomegalovirus, Microsporidia, and Cryptosporidia.

2. Respiratory: 70% of AIDS patients develop serious respiratory problems.

Partial list of respiratory problems associated with AIDS:

- **Bronchitis**
- **Pneumonia**
- **Tuberculosis**
- **Lung cancer**
- **Sinusitis**
- **Pneumonitis**

3. Neurological: Opportunistic diseases and tumors of central nervous system.

Symptoms many include: Headaches, peripheral nerve problems, and *AIDS dementia complex* (Memory loss, motor problems, difficulty concentration, and paralysis).

4. Skin Disorders: 90% of AIDS patients develop skin or mucous membrane disorders.

- Kaposi's sarcoma
 - 1/3 male AIDS patients develop KS
 - Most common type of cancer in AIDS patients
- Herpes zoster (shingles)
- Herpes simplex
- Thrush
- Invasive cervical carcinoma

5. Eye Infections: 50-75% patients develop eye conditions.

- CMV retinitis
- Conjunctivitis
- Dry eye syndrome

Treatment and prevention

- Prevention is easy
 - Practice monogamous sex, avoid shared needles
 - HIV cannot be spread by casual contact,
 - Fastest growing victim demographic
 - Not just a “gay disease”
- Treatment is expensive, but usually works
 - Nucleoside analogs, protease inhibitors
 - Processing viral proteins requires protease
 - About \$1500 a month for drugs
 - Reverse Transcriptase Inhibitors: Competitive enzyme inhibitors. Example: AZT, ddI, ddC.
 - Protease Inhibitors: Inhibit the viral proteases. Prevent viral maturation.
 - Problem with individual drug treatments: Resistance.
 - Drug Cocktails: A combination of:
 - One or two reverse transcriptase inhibitors
 - One or two protease inhibitors.
 - Drug cocktails have been very effective in suppressing HIV replication and prolonging the life of HIV infected individuals, but long term effectiveness is not clear.

Acknowledgement and Suggested Readings:

1. Medical Microbiology, A guide to Microbial Infections: Pathogenesis, Immunity, Laboratory Investigation and Control; Barber, Irving, Swann and Perera; Elsevier Publication
2. Microbiology, An Introduction; Tortora, Funke and Case; Pearson Publication
3. Microbiology; Prescott, Harley and Klein; The MacGraw-Hill Companies
4. Microbiology: Principles and Explorations; Jacquelyn G Black; John Wiley and Sons Inc.
5. Brock Biology of Microorganisms; Madigan, Martinko, Stahl and Clark; Benjamin Cummings (Pearson Publication)

Thanks