An HIV-infected T helper cell:
Molecular composition of HIV:

- **Capsid**: bullet-shaped inner shell of protein, encasing RNA/nucleocapsid protein complex
- **Matrix**: (gag) protein derived from host plasma membrane
- **Envelope**: (lipid bilayer) under viral envelope
- **Gag**: core proteins and matrix proteins
- **Pol**: Reverse transcriptase, protease, and integrase enzymes
- **Env**: Transmembrane glycoproteins, gp120 binds CD4 and CCR5; gag is required for virus internalization
- **Tat**: Positive regulator of transcription
- **Rev**: Allows export of unspliced transcripts from nucleus
- **Vif**: Aids particle infectivity
- **Vpr**: Transport of DNA to nucleus. Augments vision production. Cell cycle arrest
- **Vpu**: Unique to HIV-1. Downregulates CD4
- **Nef**: Augments viral replication in vivo and in vitro. Downregulates CD4

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene product/function</th>
</tr>
</thead>
<tbody>
<tr>
<td>gag</td>
<td>Group-specific antigen Core proteins and matrix proteins</td>
</tr>
<tr>
<td>pol</td>
<td>Polymerase RNA-dependent DNA polymerase Reverse transcriptase, protease, and integrase enzymes</td>
</tr>
<tr>
<td>env</td>
<td>Envelope Transmembrane glycoproteins, gp120 binds CD4 and CCR5; gag is required for virus internalization</td>
</tr>
<tr>
<td>tat</td>
<td>Transactivator Positive regulator of transcription</td>
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<tr>
<td>rev</td>
<td>Regulator of viral expression Allows export of unspliced transcripts from nucleus</td>
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<td>vif</td>
<td>Viral infectivity Aids particle infectivity</td>
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<td>vpu</td>
<td>Viral protein U Unique to HIV-1. Downregulates CD4</td>
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<tr>
<td>nef</td>
<td>Negative-regulation factor Augments viral replication in vivo and in vitro. Downregulates CD4</td>
</tr>
</tbody>
</table>

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A HIV-1 GENOME ORGANIZATION

B HIV-1 VIRION

transmembrane envelope protein (gp41, TM)

surface envelope protein (gp120, SU)

matrix (p17, MA)

nucleocapsid (p7, NC)

viral RNA genome

capsid (p24, CA)

protease (p11, PR)

reverse transcriptase (p66/p51, RT)

integrase (p31, IN)

membrane

FIG. 1. Schematic representation of the HIV-1 genome and virion organization. (A) The location of the HIV-1 open reading frames is indicated. The RNA encapsidation signal, ψ, is shown near the 5' end of the genome. The gag open reading frame is enlarged. (B) The HIV-1 virion, indicating the approximate location of Gag proteins, the Env glycoproteins, and the pol-encoded enzymes IN, RT, and PR. The location of p65gag in the virions has not been definitively determined. Colors in the virion correspond to the location of the proteins in the Gag precursor. Details are provided in the text.

process begins when the surface (SU) envelope (Env) glycoprotein gp120 binds CD4 and interacts with coreceptor; (2) A membrane fusion reaction, induced by the transmembrane (TM) Env glycoprotein gp41, occurs between the lipid bilayer of the virion and the host cell plasma membrane, releasing the viral core into the cytoplasm. (3) A series of
Life-cycle of HIV:

1. Virus particle binds to CD4 and co-receptor on T cell.
   - gp120
   - viral genome
   - gp41
   - reverse transcriptase
   - co-receptor (CCR5)

2. Viral envelope fuses with cell membrane allowing viral genome to enter the cell.
   - CD4
   - Cytoplasm

3. Reverse transcriptase copies viral RNA genome into double-stranded cDNA.
   - Chromosomal DNA
   - Provirus

4. Viral cDNA enters nucleus and is integrated into host DNA. It remains quiescent until T cell is activated.

T-cell activation induces low-level transcription of provirus.

RNA transcripts are multiply spliced, allowing translation of early genes tat and rev.

Tat amplifies transcription of viral RNA. Rev increases transport of singly spliced or unspliced viral RNA to cytoplasm.

The late proteins Gag, Pol, and Env are translated and assembled into virus particles which bud from the cell.

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HIV infects macrophages (MΦ) and helper T cells (T_H)

(a)

Envelope Protein binds to CD4 Surface Proteins on T_H Lymphocytes and Macrophages

6 Extra genes (tat, rev, etc.)

Regulatory Proteins

(b)

T_c Memory T_H (latent HIV)

Release of progeny HIV

Lysis and Cell Death

HIV

Macrophages

Continued virus Production

Latency (Reactivation)

No Lysis

Only activated (growing) T_H cells can be productively infected

a non-growing cell (No other retrovirus is able to infect non-growing cells.)

Figure 4-7
Unusual features of HIV.
Course of the disease:

Body makes antibodies against HIV

Depletion of CD4 T cells

CD4 T cells \( (T_H) \)

Virus is killing Th cells partially rebounds as immune system

CD4+ PBL (Th cells) fights virus

Eventually virus wins, \( T_H \rightarrow 0 \)

no Th cells, immune system function

<table>
<thead>
<tr>
<th>&quot;Flu-like disease (chills/fatigue)&quot;</th>
<th>Asymptomatic phase</th>
<th>Symptomatic phase</th>
<th>AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6 weeks</td>
<td>mean of ~10 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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In USA, half of infected men developed AIDS within about 10 years after infection:

Percentage of persons without AIDS

HIV+ hemophiliacs and HIV+ homosexuals (control population)

HIV+ homosexual men and HIV+ hemophiliacs over 20 years old

Expected

present time

HIV infection

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"PBL" = Peripheral blood lymphocytes
"CD4" = surface protein characteristic of helper T cells

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FIGURE 6-1 General Progression of Opportunistic Infections after HIV Infection. Normal T4 cell count in adolescent/adults is, on average, about 1,000/μL of blood. There is a relationship between the drop in T4 lymphocytes and the onset of opportunistic infections (OIs). The first sign of an OI begins under 500 T4 cells/μL. As the T4 cell count continues to drop, the chance of OI infection increases. Note the variety of OIs found in AIDS patients with 200 or less T4 cells/μL.
Initial Infection

 ↓

 Transient early (acute) symptoms

 Asymptomatic

 ↓

 (2–10 yrs)

 Initial Symptoms

 ↓

 1. Lymphadenopathy
 2. Wasting syndrome / Fever / Night sweats
 3. Neurological disease

 Early immune failure

 ↓

 1. Shingles (VZV)
 2. Thrush (Candida)
 3. Hairy Leukoplakia (EBV)

 Frank AIDS ( Opportunistic Infections and Cancers)

 1. Pneumonia (Pneumocystis)
 2. Kaposi's sarcoma
 3. Other protozoan infections
 4. Systemic Fungal Infection
 5. Bacterial infection (TB like)
 6. Viral infection (CMV)
 7. Other cancer (lymphoma)

 Figure 5–1
 The progression of symptoms in AIDS. (The above symptoms may be additive.)
Shortly after infection, virus levels in blood ("viral load") drop to low levels. (Immune system is partially successful in controlling infection.)

Flu symptoms | No symptoms | AIDS

CD-4 lymphocytes (T<sub>H</sub>)

Virus, p25 antigen

Anti-p25 antibodies

Collapse of immune system

Amount of HIV in blood

1 2 3 4 5 6

Months after infection

The level to which virus production drops predicts time to onset of AIDS (after first few months following infection)

Years after infection

Anti-HIV CTL's (Killer T cells)

Immune response (B cells making anti-HIV antibodies)

High viral load ⇒ short time to onset of AIDS

Low viral load ⇒ long time to onset of AIDS

Massive virus production, unhindered by immune system

Explanation of the chief features on the “Course of Infection” diagram from the preceding page:

When the virus first enters the body, it infects many CD-4 (T\text{helper}) lymphocytes (and, not shown, macrophages) and there is a burst of virus production, indicated by the rise in viral p25 antigen (capsid protein). Since infection of CD-4 lymphocytes results in their death, there is a drop in the number of CD-4 cells over the course of the first month or so.

After the first month, the immune system responds to the infection, as indicated by the rise of anti-p25 antibodies in the above diagram. So by the end of the 2\text{nd} month, plasma virus levels have fallen (decline in the p25 antigen level), and CD-4 lymphocyte levels have returned to more normal levels. Since CD-4 cells can be maintained at a sufficiently high level, the body is able to function to fight off infections and the patient has no symptoms of immune deficiency. Throughout the next several years, the virus continues to kill CD-4 cells, but the immune system is able to replace the lost CD-4 cells, thereby maintaining a slowly dwindling supply of CD-4 cells over time. This is the asymptomatic period, lasting 3-10 years. The steady-state level of virus in the patient’s blood during this period predicts the length of the asymptomatic period: high levels of virus, short duration of asymptomatic period.

Eventually, the virus either exhausts the capacity of the immune system to replace lost CD-4 cells, and/or the virus mutates to forms which cannot be effectively recognized by the immune system. When this happens, the immune system fails, and the virus is able to rapidly infect and kill the remaining CD-4 cells; CD-4 cell levels consequently fall while virus levels rise. In the absence of CD-4 cells, the infected person eventually succumbs to any of the multiple opportunistic infections that subsequently occur (AIDS).