Human Immunodeficiency Virus (HIV) to Acquired Immunodeficiency Syndrome (AIDS)
HIV-1 → world wide
HIV-2 → west Africa

HISTORY

AIDS
RETROVIRIDAE FAMILY

• Retro = reverse

• 2 medically important groups:
  1-Oncovirus = sarcoma & leukemia v. (e.g: HTLV)

• 2-Lentivirus
  \[ \text{human (HIV)} \rightarrow \text{animal (visna v.)} \]

• 3-spumaviruses
  \[ \text{non human pathogens.} \]
Virion Structure

- virion is ~120nm in diameter, spherical
- Lipid membrane – host derived and contains viral glycoproteins – gp120 and gp41
- Matrix protein (p17) surrounds the conical---shaped capsid (p24), which encloses two copies of the single---stranded RNA genome(diploid genome).
- Nucleocapsid proteins p6 and p7 interact with the RNA to prevent degradation by nucleases
HIV Genome

- **Universal**
  - *Present in all retroviruses*
  - Gag - structural
  - Pol - replication
  - Env - structural

- **Essential**
  - *Required for HIV replication*
  - Tat - transcription
  - Rev - RNA transport
  - Vif - genome fidelity

- **Accessory**
  - *Enhance HIV production*
  - Nef
  - Vpr
  - Vpu
Pathogenesis

• One of the human T-cell lymphototropic v. (other: HTCL v.)

• HIV === CD4- CMI-opportunistic inf.
  === macrophages
  === monocytes
  === dendritic cells
**Viral Entry**

- HIV entry requires the presence of CD4 + one of two co---receptors: CCR5 or CXCR4
- CD4 is the major determinant of viral tropism –expressed : T cells, macrophages, monocytes and dendritic cells
- CCR5 and CXCR4 are chemokine receptors.
- CCR5 is found on both CD4+ T cells and macrophages. CXCR4 is only found on T cells.
- Entry of HIV is initially mediated by the attachment of the viral envelope glycoprotein, gp120, to CD4.
Fig. 1. Env conformational changes during fusion
Schematic of HIV Replication
Central role of CD4+ T cell in immune response
HIV-mediated disruption of CD4$^+$ T cell mediated immune responses
Clinical Features

1. Early stage- infectious mononucleosis like illness.

2. Latent period - this is the period when the patient is completely asymptomatic and may vary from a few months to a more than 10 years. The median incubation period is 8-10 years.

   AIDS-related complex or persistent generalized lymphadenopathy.

3. Late- Full-blown AIDS.
The cellular and immunological picture - The course of the disease, virus & CD4

![Graph showing the course of HIV infection and immune response](image-url)
The cellular and immunological picture - The course of the disease CD8
cellular and immunological picture
The course of the disease

1. Acute Infection

- **High** virus titer • Mild symptoms

- **Fall** in CD4+ cells but recovers

- **Rise** in CD8+ cells but recovers

- **A high** virus titer (up to 10 million viruses per ml blood)

- **Macrophages**: infected Macrophages bring HIV into the body if sexually transmitted
2. A strong immune response

Virus almost disappears from circulation

- **Good** cytotoxic T cell response

- Soluble antibodies appear later against both surface and internal proteins

- Most virus at this stage comes from recently activated (dividing) and infected CD4+ cells

- **CD4+** cell production compensates for loss due to lysis of cells by virus production and destruction of infected cells by CTLs
3. A latent state

Latency of virus and of symptoms

- **Virus persists** in extra-vascular tissues
- **Lymph node** dendritic cells
- Resting CD4+ memory cells (last a very long time - a very **stable** population of cells) carry provirus
4. The beginning of disease

Massive loss of CD4+ cells

• CD4+ cells are the targets of the virus

• Cells that proliferate to respond to the virus are killed by it

• Dendritic cells present antigen and virus to CD4 cells

• Epitope variation allows more and more HIV to escape from immune response just as response wanes

• Apoptosis of CD4+ cells

• HIV patients with high T4 cell counts do not develop AIDS
CD8+ cells destroy more CD4+ cells
• CD4 cell loss means virus and infected cells no longer controlled
• As CD4+ cells fall below 200 per cu mm virus titer rises rapidly and remaining immune response collapses
• CD8+ cell number collapses
• Opportunistic infections
• Death in ~2 years without intervention
Good correlation between number of HIV particles measured by PCR and progression to disease

Viral load predicts survival time
# Opportunistic Infections

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protozoal</td>
<td>pneumocystis carinii <em>(now thought to be a fungi)</em>, toxoplasmosis, crytosporidiosis</td>
</tr>
<tr>
<td>Fungal</td>
<td>candidiasis, cryptococcosis</td>
</tr>
<tr>
<td></td>
<td>histoplasmosis, coccidiodomycosis</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Mycobacterium avium complex, MTB</td>
</tr>
<tr>
<td></td>
<td>atypical mycobacterial disease</td>
</tr>
<tr>
<td></td>
<td>salmonella septicaemia</td>
</tr>
<tr>
<td></td>
<td>multiple or recurrent pyogenic bacterial infection</td>
</tr>
<tr>
<td>Viral</td>
<td>CMV, HSV, VZV, JCV</td>
</tr>
</tbody>
</table>
Opportunistic Tumours

• The most frequent opportunistic tumour, Kaposi's sarcoma, is observed in 20% of patients with AIDS.

• KS is observed mostly in homosexuals and its relative incidence is declining. It is now associated with a human herpes virus 8 (HHV-8).

• Malignant lymphomas are also frequently seen in AIDS patients.
Other Manifestations

• It is now recognised that HIV-infected patients may develop a number of manifestations that are not explained by opportunistic infections or tumours.

• The most frequent neurological disorder is AIDS encephalopathy which is seen in two thirds of cases.

• Other manifestations include characteristic skin eruptions and persistent diarrhoea.
Kaposi’s Sarcoma
HIV
can destroy CD4 T cells in several different ways

• Accumulation of the nonintegrated DNA copies of the viral genome,
• increased permeability of the plasma membrane,
• syncytia formation,
• induction of apoptosis. Or persistent noncytoidal infection
• CD8 T cells are important in delayed type hypersensitivity (DTH) responses, which eliminate viral, fungal, and mycobacterial infections as well as malignant cells.
• HIV-infected monocytes and microglial cells in the brain die and release neurotoxic substances or chemotactic factors that promote inflammation in the brain.
• ability to produce antibodies in response to an infection is reduced, making bacterial infections more common
• Acts as superantigene=activate CD4====demise
Epidemiology

1. Sexual transmission - male homosexuals = N. America and Western Europe.

   - heterosexual spread = developing countries

2. Blood/blood products - IV drug abusers
   - Haemophiliacs

3. Vertical transmission - from mother to the newborn, may occur:
   transplacentally,
   perinatally,
   or
   postnatally
HIV is **NOT** transmitted by:

casual contact

touching,
hugging,
kissing,
coughing,
sneezing,
insect bites,
water, food,
utesils, toilets,
and swimming pools or public baths.
genetic groups of HIV-1

• **M (main)** highly prevalent
  10 envelope subtypes === A – J
  
  subtype B === Europe and in North and South America
  subtype C === sub-Saharan Africa

• **O (outlier)**

*HIV-positive persons are infectious during both asymptomatic and symptomatic stages of infection.*
In 2003,
4.8 million people (4.2–6.3 million) = newly infected
2.9 million (2.6–3.3 million) = death

And
> 20 million since the first cases of AIDS in 1981.

Recent data,
37.8 million (34.6–42.3 million) are living with HIV
Adults and children estimated to be living with HIV/AIDS as of end 2003

Total: 34 – 46 million
HIV half-lives

- **Activated cells** infected with HIV produce and die within **1-2 days**.
  - i.e. virus present in the plasma.
  - **HIV life-cycle = 1.5 days**.

- **Resting cells** 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 **3-6 months**.

- **Such** long-lived cell present a **major challenge** for **anti-retroviral therapy**.
## Diagnostic Tests Used to Detect HIV Infection

<table>
<thead>
<tr>
<th>tests</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ELISA</strong></td>
<td>Initial screening; two different ELISA results must be positive before a confirmatory test is performed</td>
</tr>
<tr>
<td>Latex agglutination</td>
<td>Initial screening</td>
</tr>
<tr>
<td><strong>Western blot analysis</strong></td>
<td>Confirmatory test</td>
</tr>
<tr>
<td><strong>p24 antigen</strong></td>
<td>Early marker of infection (detection of a recent infection)</td>
</tr>
<tr>
<td><strong>RT-PCR</strong></td>
<td>Detection of virus RNA in blood (detection of a recent infection) and to confirm treatment efficacy</td>
</tr>
<tr>
<td><strong>CD4:CD8 (T-cell ratio)</strong></td>
<td>Staging the disease and to confirm treatment efficacy</td>
</tr>
<tr>
<td>Isolation and culture of virus</td>
<td>Only available in research laboratories</td>
</tr>
</tbody>
</table>
Microplate ELISA for HIV antibody: coloured wells indicate reactivity
Prognostic tests

to monitor the patient for:

- signs of disease *progression* and
- *response* to antiviral chemotherapy.

**HIV viral load** - detect HIV-RNA e.g. RT-PCR (bad >10,000 copies)

**HIV Antigen tests**

**serial CD4 counts.**
# Antiretroviral Drugs Used in HAART

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Mechanism of Action</th>
<th>Name of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)</td>
<td>inhibit HIV reverse transcriptase. This prevents virus replication and spread</td>
<td>zidovudine (AZT), didanosine (DDI), lamivudine (3TC)</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitors (NNRTIs)</td>
<td>=</td>
<td>Efavirenz (EFV), nevirapine,</td>
</tr>
<tr>
<td>Protease inhibitors (PIs)</td>
<td>inhibit the retroviral protease from cleaving the viral proteins. Slow the spread of the virus to other uninfected cells.</td>
<td>ritonavir, indinavir</td>
</tr>
<tr>
<td>Fusion entry inhibitors</td>
<td>interferes with the viral gp41 and prevents fusion of HIV with the host cell.</td>
<td>Enfuvirtide</td>
</tr>
<tr>
<td>CCR5 entry inhibitors</td>
<td>block binding of the HIV virion to the surface of the CD4 cells.</td>
<td>Maraviroc</td>
</tr>
</tbody>
</table>
Highly Active Anti-Retroviral Therapy

* 2NRTI + 1 NNRTI
* * 1 or 2 PIs + 2 NRTIs
* * * Triple NRTI regimens

• Effective in prolonging life
• Improving the quality of life
• Reduced viral load
• Does not cure the chronic HIV(latent)
• Increased CD4 cell count
HIV life cycle

1. Attachment/entry inhibitors
2. Binding-entry inhibitors
3. Envelope
4. Reverse transcription
5. Integrase inhibitors
6. Protease inhibitors
7. Integration
8. RT inhibitors
9. Neutralizing antibodies
10. Release
11. Maturation
12. Source Undetermined
Prevention methods

1. **safe-sex** practices (condom use),
2. blood donor **screening** in many countries
3. **safe use** of needles (no needle sharing), and early screening for HIV infection.
4. **Circumcised** men are less likely to acquire HIV infections
5. Treatment of HIV-1 infected **pregnant women** (AZT)
There is **no vaccine** currently available to prevent HIV-1 infection or the progression from HIV infection to AIDS.

**vaccines types:**

- **Killed vaccine (not used)**
- **Live attenuated vaccine**
- **Synthetic peptide of env**
- **Subunite vaccine**(env)
- **Target cell protection**(covering CD4)
- **Gene therapy:** genetically alter the target cell make them resistant to HIV