PATHOGENESIS OF AIDS

how does HIV cause AIDS?

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PATHOGENESIS OF AIDS

how does HIV cause AIDS?

- Definitions
- Structure of HIV
- HIV entry and cell tropism
- HIV-cell interactions
- Course of HIV infection and AIDS
- HIV variants during infection
- HIV persistence
- How does HIV cause immunodeficiency?
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DEFINITIONS

- **HIV: human immunodeficiency virus**
  HIV is a member of the lentivirus family, a subgroup of retroviruses, RNA viruses that replicate via a DNA intermediate

- **AIDS: acquired immunodeficiency syndrome**
  AIDS is defined by a loss of CD4 T lymphocytes or the occurrence of opportunistic infections or cancers
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STRUCTURE OF HIV
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A diagram of the virus particle to show the internal structure (after Brooks et al, 1998)

VIRUS SPIKE
CONSISTING OF
TWO ENVELOPE PROTEINS
gp120 and gp 41

VIRUS ENVELOPE
(LIPID BILAYER)

VIRUS CAPSID
CONTAINING THE
RNA GENOME
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The genes of HIV in the virion (RNA) and integrated into host cell genome (DNA)
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HIV ENTRY INTO CELLS
AND CELL TROPISM
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HIV attaches to cells in two steps

STEP 1  HIV attaches to its primary receptor, CD4
STEP 2  HIV attaches to a co-receptor, either CCR5 or CXCR4
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HIV infects cells that carry the receptor and co-receptor

**CD4**
Expressed on the surface of CD4 T lymphocytes (helper T lymphocytes) and macrophages (including dendritic cells)

**CCR5**
Expressed on CD4+ T lymphocytes and on macrophages

**CXCR4**
Expressed on CD4+ T lymphocytes and T cell lines

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**R5 VIRUSES**
Macrophage-tropic HIV-1

**X4 VIRUSES**
T cell tropic HIV-1
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HIV-CELL INTERACTIONS
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HIV infection of cultured cells shows (Collman, 1989)

both R5 and X4 viruses infect and kill CD4 T lymphocytes

Only R5 viruses infect macrophages and they are not killed
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COURSE OF HIV INFECTION AND AIDS
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HOW HIV INITIATES HETEROSEXUAL INFECTION (Shattock, 2003)
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THE COURSE OF HIV INFECTION AND AIDS (After Fauci, 1993)

![Graph showing the course of HIV infection and AIDS](image)
HIV VIREMIA BY STAGE OF HIV INFECTION (Bagasra, 1993; Pan, 1993)

<table>
<thead>
<tr>
<th>STAGE OF INFECTION</th>
<th>CD4 CELL COUNT</th>
<th>PLASMA HIV (TCID PER ML)</th>
<th>% CD4+ CELLS INFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASYMPTOMATIC</td>
<td>&gt;500</td>
<td>100</td>
<td>3%</td>
</tr>
<tr>
<td>GENERAL LYMPHADENOPATHY</td>
<td>300-499</td>
<td>200</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>200-299</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>CLINICAL AIDS</td>
<td>&lt;200</td>
<td>1,500</td>
<td>30%</td>
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HIV VARIANTS
DURING INFECTION
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VIRUS VARIATION IS OFTEN SEEN DURING THE COURSE OF HIV INFECTION

<table>
<thead>
<tr>
<th>BIOLOGICAL PHENOTYPE</th>
<th>VIRUS ISOLATED FROM PATIENTS WITH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASYMPTOMATIC EARLY INFECTION</td>
</tr>
<tr>
<td></td>
<td>AIDS</td>
</tr>
<tr>
<td>REPLICATION KINETICS</td>
<td>SLOW/LOW</td>
</tr>
<tr>
<td>SYNCYTIIUM INDUCTION</td>
<td>NON SI</td>
</tr>
<tr>
<td>CELLULAR HOST RANGE</td>
<td>DUO-TROPIC</td>
</tr>
<tr>
<td>CO-RECEPTOR USAGE</td>
<td>R5</td>
</tr>
<tr>
<td></td>
<td>SI</td>
</tr>
<tr>
<td></td>
<td>T CELL-TROPIC</td>
</tr>
<tr>
<td></td>
<td>X4</td>
</tr>
</tbody>
</table>
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DIFFERENTIAL INFECTION OF MONKEYS BY CO-RECEPTOR USAGE (Harouse, 1999)

MACROPHAGE-TROPIC (R5) SHIV INFECTS GUT-ASSOCIATED LYMPHOID TISSUE PREFERENTIALLY WITH MODEST REDUCTION OF CD4 CELLS IN CIRCULATION

T CELL-TROPIC (X5) SHIV INFECTS LYMPH NODES PREFERENTIALLY WITH SEVERE REDUCTION OF CIRCULATING CD4 CELLS
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HIV PERSISTENCE
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HIV INFECTION IN VIVO INCLUDES (Ho, 1999)

- Replication in activated T lymphocytes (1)
- Replication in macrophages (2)
- Latency in resting lymphocytes (3)
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ANTI-RETROVIRAL TREATMENT REFLECTS THE THREE HIV IN VIVO INFECTION CYCLES
(Mittler, 1999; and others)

![Graph showing decrease in viremia.](chart)

- **INFECTED T LYMPHOCYTES (1)**: $t_{1/2} \approx 1$ days
- **INFECTED MACROPHAGES (2)**: $t_{1/2} \approx 14$ days
- **LATENTLY INFECTED T CELLS (3)**: decreased sensitivity
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HOW DOES HIV CAUSE IMMUNODEFICIENCY?
CD4 AND CD8 T LYMPHOCYTES: A CENTRAL PARADOX IN THE PATHOGENESIS OF AIDS

- Opportunistic infections are mainly due to the activation of existing latent infections
- Control of latent infections is mediated by parasite-specific CD8 effector T lymphocytes, which are NOT the direct target of HIV
- Indirect mechanisms must be responsible for the depletion of effector CD8 cells, including
  - Hyperactivation of T cells leading to apoptosis and premature cell death
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Still an enigma?

PICTURE OF HEALTH? This 15-year-old mangabey at the Yerkes National Primate Research Center in Atlanta has been SIV-infected for at least 10 years.

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