Acquired immune deficiency syndrome (AIDS) was first described in early 1980s. The disease is characterized by massive reduction in the number of CD4 T cells, accompanied by severe infections of pathogens that rarely trouble healthy people or by aggressive forms of Kaposi’s sarcoma or B cell lymphoma. Human immunodeficiency virus (HIV) is the cause of AIDS. Two types of HIV are now recognized: HIV-1 and HIV-2. In most countries, HIV-1 is the principle cause of AIDS. HIV-2 is less virulent causing a slower progression and is endemic in West Africa and is spreading through Asia.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene product/function</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>gag</em></td>
<td>Group-specific antigen</td>
</tr>
<tr>
<td><em>pol</em></td>
<td>Polymerase</td>
</tr>
<tr>
<td><em>env</em></td>
<td>Envelope</td>
</tr>
<tr>
<td><em>tat</em></td>
<td>Transactivator</td>
</tr>
<tr>
<td><em>rev</em></td>
<td>Regulator of viral expression</td>
</tr>
<tr>
<td><em>vif</em></td>
<td>Viral infectivity</td>
</tr>
<tr>
<td><em>vpr</em></td>
<td>Viral protein R</td>
</tr>
<tr>
<td><em>vpu</em></td>
<td>Viral protein U</td>
</tr>
<tr>
<td><em>nef</em></td>
<td>Negative-regulation factor</td>
</tr>
</tbody>
</table>

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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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Virus-cell interactions

- Entry of HIV into host cells is a multistep process involving a primary receptor and co-receptor.
- In all cases, the primary receptor is CD4.
- The co-receptor is one of several members of the chemokine receptor family – CCR5 and CXCR4.
- CCR5 is found on CD4+ T cells and macrophages.
- CXCR4 is expressed on CD4+ T cells but at very low levels on macrophages.
Virus-cell interactions:
HIV strains vary in ability to bind to co-receptors

• Viruses isolated from patients may be roughly classified into 3 groups:

1. those that utilize mainly CCR5 (often called R5 viruses)
2. those that utilize mainly CXCR4 (X4 viruses)
3. those that utilize both CCR5 and CXCR4 (R5X4, or ‘dual-tropic’viruses).
HIV entry is a multi-step process

**FIGURE 14.2** Entry of HIV showing a hypothetical reconstruction of stepwise conformational changes in the SU (gp120) and TM (gp41) proteins. The gp120 protein binds to the CD4 receptor. Binding to CD4 triggers a conformational change (A) that leads to major conformational change (B), this one in the TM (gp41) protein, which unfolds to expose and insert the fusion sequence at its N terminus into the plasma membrane of the cell, producing the pre-hairpin intermediate. In a third conformational change (C), helices in the N and C domains of gp41 associate, producing the hairpin configuration that brings the viral envelope and the plasma membrane into close approximation. Finally, the two membranes fuse, leaving gp41 on the external surface. After Chan DC, Kim PS. HIV entry and its inhibition. *Cell* 1998, 93: 681–684, with permission.
HIV replication & host cell response

• Differentiated cell types – circulating monocytes, tissue macrophages, brain microglia and DCs – are derived from monocyte precursors in bone-marrow.
• Each of these cells plays a role in pathogenesis of HIV infection and some are permissive for HIV.
• Mature DCs are able to bind, sequester & conserve infectious virions at extracellular surface or within endosomes.
• Immature DCs express CCR5 and support low levels of HIV replication.
Transmission, portal of entry and sequential spread of virus

HIV is transmitted by 3 major routes:
1) Sexual contact (accounting for >90% of infections worldwide)
2) Mother to child
3) Blood/blood products

SIV studies have provided important insight into how HIV may be transmitted via sexual contact.

Experimental vaginal infection of SIV reveals first detection of the virus in submucosal/lymphoid tissue primarily in resting CD4+ T cells.

Within a few days, local lymphoid tissue is heavily infected and virus begins to spread to other lymph nodes.
Viremia, cell counts and incubation period

• In absences of antiretroviral therapy, there is an acute phase of infection with high titer viremia followed by a subclinical phase of modest levels of viremia – can last 1 -> 20 years before death, followed by a phase of clinical AIDS that lasts 1-4 years before death.

• During acute infection, a mononucleosis-like syndrome occurs accompanied by a peak in viremia and an acute drop in CD4+ T cells in blood.

• This is followed by induction of an immune response which dampens the infection and is associated with a dramatic drop in blood virus.

• However, infection is never completely cleared and viremia usually stabilizes 4-6 months after infection at a level often called the virus “setpoint”.
Greatest loss of CD4+ T cells is in GALT (gastrointestinal-associated lymphoid tissue), particularly following infection with R5 virus. Naïve T cells in GALT are CCR5- whereas memory T cells are CCR5+ rendering them susceptible to viral infection.
HIV produces a viremia that persists throughout lifetime and can be used to monitor the course of infection. Within the blood, HIV is present both with infected cells and as free infectious virus in plasma. Another useful surrogate for disease course is the concentration of CD4+ T cells in blood which is inversely related to virus titer and a harbinger for functional loss of immune responses during clinical AIDS.
Viremia, cell counts and incubation period

Outcome of infection is related to virus setpoint. In cohort of infected patients, 90% of quartile with highest setpoints progress to AIDS in 5 years while <10% of quartile with lowest setpoint has developed AIDS in that time. Patients with slowest progression are often dubbed long-term non-progressors, generally defined as subjects who are AIDS-free 10 years after infection.
CD8+ T cell responses are critical in protection against SIV infection.

**Figure 14.9** The cellular immune response plays an important role in the control of SIV infection. Monkeys infected with dual-tropic virulent SIVmac for >9 months had established stable virus setpoints. They were then treated with a potent antibody against CD8, which reduced the level of CD8 T lymphocytes in the blood by >99%. Data on two animals demonstrate the rise in viremia level during the period of immunosuppression and the reconstitution of immune control when immunosuppressive treatment was terminated. The effect of treatment is more pronounced in monkey A with initially lower viremia. After Schmitz JE, Kuroda MJ, Santra S et al. Control of viremia in simian immunodeficiency virus infection by CD8+ lymphocytes. Science 1999, 283: 857–860, with permission.
Following commencing HAART, there is a dramatic drop in plasma viremia that can be divided into 3 phases: rapid drop of ~100 fold over first 10 days due to interruption of most cell-to-cell spread of virus and die off of infected activated T cells; slower decrease of ~10-fold over 2 months reflecting death of cells with a longer life (probably macrophages); and a plateau that may be below the level of detection but reflects indefinite persistence of residual latent virus.
DRUGS
Target RT and viral protease – affects replication, cleavage and assembly

RT inhibitor – blocks pro-viral synthesis
Protease inhibitor – blocks assembly

~ 10e9 to 10e10 virions generated every day – combine this with mutation frequency results in many different viral variants

Why such high # of errors?
- RT has low fidelity i.e. lacks the ability to proof-read during replication
- Copy of integrated proviral DNA -> RNA generated by RNA polymerase -> also low-fidelity

*These factors all combine to result in the accumulation of resistant mutants rapidly

VIRAL RESERVOIRS

Viral load is often measured in blood (look at RNA copies)

However -> virus can persist within tissues and these act as reservoirs i.e. resistant to treatment
Immune Response and HIV

*can control BUT NOT eliminate
signs of adaptive immune response:
1) seroconversion
2) CTL activity -> clear but can cause tissue pathology (think brain)

CTL’s are very important in control of virus. Studies with SIV-infected monkeys have emphasized this. Elimination of CD8 T cells -> monkeys die with large viral load.

Both Ab and CTL escape mutants arise during course of immune response to virus
Opportunistic infections and neoplasms

- Drop in CD4+ T cells counts below a critical threshold (200-300 cells/µl blood) is often accompanied by rise in virus setpoint signaling the advent of AIDS-defining illnesses.
- Constitutional symptoms include fever, fatigue, malaise, lymphadenopathy, GI symptoms, and oral candidiasis.
- Infections are caused by wide spectrum of parasites including protozoa, fungi, bacteria, and viruses.
- In addition, increased risk of neoplasms also occur including Burkitt’s lymphoma, cervical carcinoma, and Kaposi’s sarcoma.
CD4 LOSS IS KEY EVENT IN HIV PATHOGENESIS

How are CD4 T cell eliminated?
1) direct viral killing
2) increased susceptibility to apoptosis
3) CTL-mediated killing

When CD4 levels drop below ~200 cells/ul results in increased susceptibility to opportunistic infections

<table>
<thead>
<tr>
<th>Infections</th>
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<tbody>
<tr>
<td>Parasites</td>
<td>Toxoplasma spp.</td>
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<tr>
<td></td>
<td>Cryptosporidium spp.</td>
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<tr>
<td></td>
<td>Leishmania spp.</td>
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<td></td>
<td>Microsporidium spp.</td>
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<tr>
<td>Intracellular bacteria</td>
<td><em>Mycobacterium tuberculosis</em></td>
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<tr>
<td></td>
<td><em>Mycobacterium avium intracellulare</em></td>
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<tr>
<td></td>
<td><em>Salmonella</em> spp.</td>
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<tr>
<td>Fungi</td>
<td><em>Pneumocystis carinii</em></td>
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<td><em>Cryptococcus neoformans</em></td>
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<td><em>Candida</em> spp.</td>
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<td><em>Histoplasma capsulatum</em></td>
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<td><em>Coccidioides immitis</em></td>
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<td>Viruses</td>
<td><em>Herpes simplex</em></td>
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<td></td>
<td><em>Cytomegalovirus</em></td>
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<td><em>Varicella zoster</em></td>
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<tr>
<td>Malignancies</td>
<td><em>Kaposi's sarcoma</em></td>
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<td></td>
<td><em>Non-Hodgkin's lymphoma, including EBV-positive Burkitt's lymphoma</em></td>
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<td></td>
<td><em>Primary lymphoma of the brain</em></td>
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</tbody>
</table>

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