AIDS

- Human Immunodeficiency Virus
- Acquired ImmunoDeficiency Syndrome.
- AIDS results from CD4+ T cell depletion causing severe immunosuppression and an increase in opportunistic infections.

Opportunistic Infections

**Kaposi's Sarcoma**

Kaposi's sarcoma is a classic opportunistic infection which is only seen in AIDS patients in the U.S.

Caused by Kaposi's Sarcoma herpesvirus OR
Human Herpes Virus-8.
HIV Classification

◆ Family: Retroviridae
◆ Genus: lentiviruses
◆ Cytopathic retroviruses
  – Human immunodeficiency virus-1 (HIV-1)
  – Human immunodeficiency virus-2 (HIV-2)
  – Simian immunodeficiency virus (SIV)
  – Feline immunodeficiency virus (FIV)
◆ Transforming retroviruses.
  – Human T cell lymphotropic virus (HTLV)-1 can cause T cell leukemia.

HIV-1 and HIV-2 (50% homology) cause similar immunodeficiency disease in humans.
HIV-1 found in 80% of cases in the world.
HIV-1 is broken up into "clades".

Worldwide HIV Infections

42 millions of infected
5 millions contaminated in 2003
3 millions died
14000 infected per day
29 millions in Africa
10 millions between 15-24 years old
1/50 have access to a treatment
1% of pregnant women are treated
5 millions contaminated in 2003
3 millions died
Enveloped RNA virus

HIV Structure

HIV Genome

env gene encodes envelope glycoprotein (gp)160 (precursor protein split into gp120 and gp41).

HIV Genome

HIV Regulatory/accessory genes

- Tat (transcriptional activation domain) and Rev promote viral replication
- The HIV promoter is located in the 5' LTR and contains an enhancer with two NF-kB binding sites and the transactivation response element (where Tat binds).
Glycoprotein (gp) 120 molecule is noncovalently bound to gp41, which is embedded in the envelope membrane.

Gp120 is the viral attachment receptor for host cell entry and target for neutralizing antibodies.

HIV infects:
- CD4+ T cells: activated and naive
- Macrophages
- Dendritic cells.

The two primary co-receptors are CXCR4 and CCR5.

Individuals with a 32 bp deletion in their CCR5 gene appear to be resistant to HIV.

Individuals with increased levels of the chemokines that bind to CCR5 (MIP1-α, MIP1-β, and RANTES) have reduced levels of viral replication and may have greater resistance to infection.
HIV Life Cycle
Replication or Integration

Once viral RNA in cytoplasm----
  – ssRNA uses RT to make cDNA copy and then double-stranded viral DNA.
  
  – dsDNA can make mRNA and viral RNA to initiate replication  ------- lytic infection
  **OR**
  – dsDNA migrates to nucleus and integrates into the genome using a viral integrase ---- latent infection

HIV Life Cycle
Integration establishes Latency

◆ Once integrated, the virus can remain latent for long periods.
◆ Provirus is the integrated DNA copy of the viral RNA.

HIV Life Cycle
Activation of Latently Infected Cell

Transcription factors (such as NF-κB) can act on the HIV enhancer regions to initiate transcription of viral DNA into RNA.
  – mRNA transcripts are used for protein
  – genomic ssRNA transcripts are made for inclusion in viral particles that initiate lytic infection.
HIV Life Cycle
Activation of Latently Infected Cell

Clinical Aspects
Transmission

- HIV is transmitted through contact with blood or body fluids.
- Routes of transmission
  - Contact with rectal or genital mucosa with infected semen or vaginal secretions.
  - By injections of HIV-infected blood.
  - During pregnancy, childbirth, or nursing (vertical transmission).

DC-SIGN Captures HIV-1

Initial HIV-1 exposure migration

Productive HIV-1 infection in lymphoid organs

DC-SIGN binds HIV-1

To-trans-infection of T cells by DC-SIGN

DC-SIGN Captures HIV-1 and Retains Long-Term Infectivity
Immune response to HIV

Humoral immune response

◆ Neutralizing antibodies to gp120.
  – Most important epitopes are found in the third hypervariable region of gp120 termed the V3 loop.
  – These antibodies may play an important role in vivo especially during resolution of primary infection.
  – However the antibody titer does not decrease as immunodeficiency occurs.

Immune response to HIV

CMI response to HIV

During the prolonged period of asymptomatic infection there is a vigorous CMI that is initially effective at eliminating virally infected cells but as CMI begins to decline immunodeficiency begins.

Immune response to HIV

CD4+ Th

◆ CD4+ cells are the primary HIV infected cells.
◆ Uninfected HIV-specific CD4+ T cells found during long asymptomatic phase help eliminate virus.
  – Increased proliferation of HIV-specific CD4+ Th cells from infected individuals correlates with reduced viral loads.
Immune response to HIV

CTLs crucial for anti-HIV CMI

Why?

- The emergence of HIV-specific CTL during primary infection correlates with acute viral load reduction.
- Inverse correlation between CTL activity and plasma viral RNA load.
- HIV specific CTLs have been found with activity against Env, gag, nef, pol.
- CTL escape mutants of HIV have been identified.
- CTLs produce high levels of MIP-1α, MIP-1β, and RANTES.

Immune response to HIV

CTLs crucial for anti-HIV CMI

- HIV-1 specific CTLs decline with increased disease and decreased CD4+ T cell numbers.
- But remember CD8+ T cells need CD4+ T cell cytokine help.

CD4+ T cell Depletion

Why are there low numbers of infected CD4+ T cells in peripheral blood?

- Few infected CD4+ T cells detected in blood during the clinically latent period.
- However HIV found in lymph nodes.
  - Keep in mind that 98% of lymphocytes are in immune organs and tissues not in peripheral blood.

CD4+ T cell Depletion

Pathogenic Process in Lymph Nodes

- HIV remains active in the lymph nodes, and large numbers of viral particles can be detected in lymphoid follicles.
  - Activity of the virus in these sites eventually leads to loss of follicular dendritic cells and disruption of lymphoid architecture.
CD4+ T cell Depletion
Why are there low numbers of infected CD4+ T cells in peripheral blood?

Steady State Model of Infection
◆ CD4 T cell decline is a gradual losing of long immune struggle involving a cycle of
  CD4+ T cell infection
  CD4+ T cell death
  CD4+ T cell replacement.

Steady State Model of Infection
What goes on during long asymptomatic phase?

Steady State Model of Infection
 Constant battles
 HIV vs Immune System

CD4+ T cell Depletion
Steady state model of infection

◆ Constant turnover of CD4+ T cells drives the pathogenic process and constant viral replication contributes to development of HIV genetic variation.

◆ Finally the CD4+ T cell regeneration is exhausted, CD4+ T cell number declines, and AIDS develops.
**Potential Mechanisms of CD4+ T cell depletion**

- Infected CD4+ T cells killed directly by HIV, or by virus-specific CD8+ CTL.
- Uninfected CD4 cells
  - Cross-linking of CD4 by gp120 can cause T cells to undergo apoptosis.
  - Gp120 may bind CD4+ T cells in the thymus and interfere with positive selection.

**Clinical aspects of HIV Infection Diagnostics**

- Detection of exposure to HIV determined by ELISA measuring antibodies to gp120.
  - Confirmed by Western Blot measuring antibody response to all viral proteins.
- HIV Viral RNA detected by PCR.

**Drug Therapy Antivirals**

- Nucleoside analogs. Nucleoside chain terminators
  - AZT (3'-azidothymidine), ddi (dideoxy-inosine), ddC (dideoxy-cytidine), D4T, 3TC.
- Reverse transcriptase inhibitors
  - nevirapine.
- Protease inhibitors which inhibit protein processing of large polyproteins.
  - ritonavir, saquinavir -many more.
- Combination drug therapy is most beneficial.
Mechanism for antivirals

Effect of Antivirals on AIDS Deaths

Clinical aspects of HIV Infection
Monitoring Infection

- Amount or viral particles measured in plasma by PCR test detecting viral RNA. Known as "viral load".
- CD4 T cell counts measured by flow cytometry.

Effect of Antivirals on Viral Load
Effect of Antivirals

After antiviral therapy viral load goes down and CD4 T cells up.

HIV Vaccine Issues

- Animal model not reproducible.
- HIV protein sequence variation.
  - high mutation rate of HIV allows rapid antigenic variation.
- What immune response will provide protection?
- Need to identify good immunogens.
- Stimulate immunity on mucosal surfaces.

Original HIV Vaccines

- Various preparations of gp120 injected with adjuvant.
- Good for antibody responses but poor for CTLs.
Current Vaccine in humans
Canarypox-HIV and synthetic proteins

Canarypox virus with gp160 gene (and other genes) followed by immunization with recombinant gp120 and or gp41 proteins as a booster.

Thus the canarypox vaccine primes eliciting both CTL and some ab responses followed by boost with recombinant protein to elicit increased ab responses.