Molecular Biology and Pathogenesis of HIV

Acquired Immune Deficiency Syndrome (AIDS)

- 1981 – first reported cases (pneumocystic pneumonia in gay men)
- indications are that the disease had been spreading silently for several years prior to ID
- 1983 – isolated and identified as HIV (Luc Montagnier)
- Over 600,000 cases reported in the US since 1981
- World pandemic
- Characterized by susceptibility to infection w/ opportunistic pathogens

HIV Genome

Lentivirus – ‘slow virus’
Enveloped
Retrovirus
+-strand RNA genome
Encodes 9 gene products
  Gag, Pol, Env, Tat, Rev, Nef, Vif, Vpr, Vpu

Life Cycle

**Binding to permissive cell**

CD4 receptor
  CD4 present on monocytes, macrophages, dendritic cells
Coreceptor CCR5 and/or CXCR4
  G-protein coupled 7 transmembrane receptor family
Fusion
  Viral membrane actually fuses with host cell membrane
  Not fully described mechanistically
  Release of viral contents into the cellular interior

**Reverse Transcription**

RNA genome converted to DNA genome via viral RT

**Nuclear Transport and Integration into Host Genome**

dsDNA copies migrate to nucleus as part of a pre-integration complex (PIC)
  Integrase protein cleaves the host genome and then inserts and ligates the viral and host DNA
  PROVIRUS
  From this point on, HIV becomes a genetic disease
  The viral genome is integrated and becomes a permanent component of the host genome

**Transcription of viral transcripts**

Stimulated by Tat and cellular transcription factors
Tat (Trans-acting activator of transcription)
  Enhances viral mRNA transcription by binding to the RNA
Nuclear export of viral mRNA

Rev (Regulator of virion protein expression) cont’d.
Stabilizes the mRNA by direct interaction during transport
Without Rev – no Gag, Env, Pol proteins are translated

Assembly of virion particles
Complete process not mechanistically derived
Gag protein precursor (Pr55gag) produced in the cytoplasm and then moves to the inner plasma membrane for assembly
Other viral proteins, two ssRNA copies, and some cellular proteins

Viral Budding
Individual virions bud from the cell surface and diffuse outward
Virions mature and become infectious
Gag polyprotein cleaved into individual proteins
Structural changes within the virion: core formation

Pathogenesis
HIV breaks down the body’s immune system, its natural defense system against foreign substances and invading organisms, such as bacteria that cause disease

Hallmark: Destruction of CD4+ T cells

Time course
Acute infection
infectious mononucleosis-like illness
headache, rash, lymphadenopathy
Many people do not develop any symptoms when they first become infected with HIV.
These symptoms usually disappear within a week to a month and are often mistaken for those of another viral infection. People are very infectious during this period, and HIV is present in large quantities in genital secretions

Seroconversion
Window period
ab production & activation of T cells that attempt to eradicate HIV
As soon as 1 month after infection
As late as 6 months after infection

Asymptomatic infection
Clinical latency but not virologic latency
Some people may begin to have symptoms in as soon as a few months, whereas others may be symptom-free for more than 10 years

Early manifestations of disease
Clinical immunodeficiency: AIDS
The term AIDS applies to the most advanced stages of HIV infection. Official criteria for the definition of AIDS are developed by the CDC in Atlanta, Ga., which is responsible for tracking the spread of AIDS in the United States.

In 1993, CDC revised its definition of AIDS to include all HIV-infected people who have fewer than 200 CD4+ T cells. (Healthy adults usually have CD4+ T-cell counts of 1,000 or more.) In addition, the definition
includes 26 clinical conditions that affect people with advanced HIV disease.

- Infections rare in immunocompetent individuals – ‘opportunistic’
  - pneumocystis carinii pneumonia; recurrent bacterial infections;
  - Tuberculosis; invasive fungal infections such as esophageal candidiasis; neoplasma including Kaposi’s sarcoma, polyclonal B-cell lymphoma, and cervical carcinoma; diarrhea; CMV; Hepatitis A/B; HSV; idiioiopathic thrombocytopenic purpura; Nocardia infections of lung

- Neurologic illnesses and wasting
  - Toxoplasma gondii in the brain
  - Toxoplastic encephalitis

**Testing**

**ELISA + Western Blot**

**Serologic diagnosis**
- Takes 6 months for body to produce measurable quantities of ab
- ELISA – ‘enzyme linked immunosorbent assay’
  - Detection of immune response to invading pathogene
  - Very sensitive and detects almost all persons infected except for first few weeks of infection
- Western Blot – detects HIV proteins
  - Hardly ever gives a false positive result

**Nucleic acid detection**

**Viral load testing**
- Measurement of the HIV levels in your blood
  - 10,000 viruses/mL blood are considered high

**CD4 lymphocyte cell count**
- CD4 cells are a type of white blood cell
  - Typically around 1000 cells/mm$^3$
  - 200 cells/mm$^3$ denotes immunodeficiency

**Therapeutics**

**HAART**
- ‘Highly Active Antiretroviral Therapy’
- Drugs used to slow down the growth of the virus
- Drugs work by affecting different steps of the life cycle

**Therapy During Pregnancy**
- Multiple Studies
  - 20% transmission to fetus reduced to ~7%
  - Prenatal treatment throughout pregnancy
  - Treatment during labor less effective and must be followed by a multi-week treatment of the infant

**Nucleoside reverse transcriptase inhibitors**
- **AZT** (ZDV, zidovudine, Retrovir®)
- ddI (didanosine, Videx®)
- ddc (zalcitabine, Hivid®)
- 3TC (lamivudine, Epivir®)
- Combivir® (AZT/3TC combo)
Trizivir? (AZT/3TC/Abacavir combo)

Non-nucleoside reverse transcriptase inhibitors
  Nevirapine (Viramune?)
  Delavirdine (Rescriptor?)
  Efavirenz (Sustiva?)

Protease inhibitors
  Saquinavir (Invirase? and Fortovase?)
  Indinavir (Crixivan?)
  Ritonavir (Norvir?)
  Nelfinavir (Viracept?)
  Amprenavir (Agenerase?)
  Lopinavir (Kaletra?)

Complications
  LT effectiveness
  Side effects of drugs making up cocktail
  Resistance
  Do not work for all patients

Compliance
  Skipping doses
  ‘Drug holidays’ for days/weeks
  Reservoir populations

CDC National AIDS Hotline
  1-800-342-AIDS

CDC National Prevention Information Network
  800-458-5231

http://www.cdc.gov/nchstp/od/nchstp.html
http://www.cdc.gov/nchstp/hiv_aids/dhap.htm
http://www.cdcnpin.org