Pathogenesis and Natural History of HIV/AIDS

I. Introduction

II. Viral Pathogenesis

A. Origin of Human Retroviruses:

1. Primate lentiviruses that do not cause disease in their natural hosts.

a. HIV-1: Central Common Chimpanzee (*Pan troglodytes troglodytes*) in Gabon and Cameroon and Eastern Common Chimpanzee (*P.t.schwienfurthii*). Entered humans around 1930's presumbably through hunting and butchering of chimps for meat.

(1) Groups M, N and O cause human infection and disease

(a) Clade B of group M most commun in US

b. HIV-2: Sooty mangabey (Colebus) in West Africa (between Senegal and Ivory Coast). Less readily transmitted, and less pathogenic, than HIV-1. Most HIV-2 infected persons live in West Africa.

c. After decades of low-level stable infection rates of humans in isolated communities, road building, increased trade, and migration to cities for work brought HIV-1 out of the countryside. In the 1970's it dispersed throughout Africa and the world.

B. HIV life cycle in cell populations and tissues

1. activated CD4+ lymphoocytes rapidly replicating virus and die in the process

a. 1 - 10 billion virions produced daily in steady state

(1) high mutation rate due to errors made by reverse transcriptase, combined with rapid viral replication, leads to a swarm of genetically variant viruses, rather than a clone of genetically identical viruses, in an infected person.

b. Up to 1 billion CD4+ lymphocytes destroyed and replaced daily.

c. Higher levels of HIV detectable in the plasma indicate that larger numbers of CD4 cells are infected and correlate with rates of CD4 decline and disease progression.

(1) Mechanism of CD4 cell destruction may be direct or indirect. Proposed mechanisms include immune mediated destruction of infected CD4 cells, induction of apoptosis, or activation and killing through superantigens.

2 monocytes: host cells slowly replicating virus and surviving

3. latently infected cells: resting CD4+ memory cells containing non-replicating HIV DNA. These cells, obtained from treated patients whose virus can no longer be detected in plasma, harbor replication competent pro-viral DNA and act as a library of all the viral mutations which occurred during the host person's infection.

4. Most HIV replication occurs in lymphoid tissue

a. Measurements of viral load made in the peripheral blood reflect spill-over from the lymph nodes and other lymphoid aggregates

b. Other tissues may harbor virus replicating independently

(1) Central nervous system

(2) Reproductive tract

5. A cure will require the end of viral replication, plus the eradication of virus from latently infected cells and perhaps from protected sites in various tissue compartments.

B. Immunologic consequences of destruction of CD4+ lymphocytes by HIV

1. Loss of cell mediated immunity through the destruction of large numbers of CD4 lymphocytes, which coordinate the cell-mediated immune response.
   a) Cell mediated immunity defends against intracellular pathogens, including most viruses (such as the Herpes family of viruses and human papillomavirus), some bacteria (including Salmonella and Mycobacteria), some yeast and fungi (such as Cryptococcus and Candida), and some parasites (such as Toxoplasma and Cryptosporidia).
2. Disordered antibody production. Loss of CD4 lymphocyte activity causes a reduced ability to make antibodies against new antigens, especially (but not only) protein antigens.
   a) Antibodies defend against extracellular organisms, especially encapsulated bacteria like Streptococcus pneumoniae and Hemophilus influenza.
   b) Disregulation of antibody production allows for overproduction of non-specific antibodies. This can be detected as a polyclonal gammopathy. It complicates the diagnosis of illnesses for which antibody tests or changes in antibody titers are the main diagnostic method. Antibody overproduction may cause disease as well, such as in immune thrombocytopenia of HIV or hypercoaguable states.
3. As a result of bone marrow failure in late HIV disease, or because of toxicities of anti-infective or anti-cancer therapies, severe neutropenia (neutrophil counts less than 500 cells/mm) may also occur and contribute to immunosuppression. This would increase susceptibility to bacterial infections including Staphlococcus and Pseudomonas, and to fungi such as Aspergillus.

III. Immune Response and Host Factors

A. Antibody response
   1. Early antibodies have no effect on virions but are convenient for testing
   2. Neutralizing antibodies develop later during infection
      a) protective in some primate models
         1) demonstrated by antibody infusion in primates challenged with SIV or SHIV.
         2) protection of two chimps with gp120 vaccine.
      b) no evidence of clinically relevant activity in humans. gp120 mutates rapidly, escaping the effect of neutralizing antibodies produced by the host.

B. Cellular immune response
   1. Cytotoxic CD8+ lymphocyte activity
      a) evidence of anti-HIV cytotoxic T-lymphocyte (CTL) activity early in infection
      b) Early recognition of HIV antigens by CD4 and CD8 lymphocytes correlates with slower disease progression.
      c) Frequency of CD8+ lymphocytes with cytotoxic activity against HIV envelope antigens in early infection inversely correlates with plasma HIV RNA levels and with rates of CD4 lymphocyte decline.

C. Host cell susceptibility

1. Mutations in chemokine receptors, co-receptors for HIV on monocytes
   a) CCR5 32 base pair deletion mutation
      1) Homozygotes resistant to infection
      2) Heterozygotes have slowly progressing disease
2. Mutations in chemokines
   b) SDF-1, natural ligand of CXCR4, the HIV co-receptor of lymphocytes
      1) persons with mutations may have slowly progressing disease

D. Certain HLA (MHC class I) markers are associated with slower disease progression
   1. Presumably some HLA types are associated with a more vigorous and effective cellular immune response to HIV-1.

III. HIV Testing

A. Testing for HIV infection by testing for HIV antibodies
   1. Screening test: a test that will pick up almost everyone who has antibody, and will have some false positive errors.
      a) ELISA technology used for HIV screening
         (1) A single negative test is considered negative
         (2) A positive ELISA must be repeated on the same blood specimen, and only repeatedly reactive specimens (positive two times) are reported as positive screening test.
         (3) Current tests screen for both HIV-1 and HIV-2
         (4) Current tests usually positive within 2-3 weeks of infection (interval between infection and positive antibody test is called the window period).
      b) Confirmatory antibody tests must be performed on the same blood specimen before telling a patient that the test is positive.
         (1) Western Blot is the most often used technology for confirmatory antibody tests.
            (a) Other methods , such as immunoflourscense assays, can also be used as confirmatory antibody tests.
         (2) Western Blot assay looks for at least two of the dozen specific antibodies humans produce against HIV.
            (a) A Western Blot is positive (or reactive) when antibodies against 2 of the following HIV proteins or glycoproteins are detected: gp 120/160; gp 41; p24.
            (b) A Western Blot is negative when no anti-HIV antibodies are detected.
               (i) A negative Western Blot, even following a repeatedly reactive ELISA, indicates that the patient has no HIV antibodies, and was not infected as of 3-6 months ago (ie, prior to the window period).
            (c) A Western Blot which detects some HIV antibodies, but not in the correct combination to be considered positive, is called Indeterminate.

(i) An indeterminate Western Blot can occur for several reasons:
- (a) the coincidental presence of cross-reacting antibodies in a person who is not HIV infected
- (b) the early appearance of antibody in a person with HIV infection who is going through seroconversion, ie, coming to the end of the window period.
- (c) infection with a related virus. Many labs test only for HIV-1, and the rare person with the West African HIV-2 may have an indeterminate HIV-1 Western Blot.
- (d) Recipient of an HIV vaccine. A participant in the study of the recombinant gp120 vaccine will have a positive Elisa and an indeterminate Western Blot with antibody to gp120.

(ii) Because of (I) the importance of treating someone who is going through seroconversion and (2) the possibility of infection with another retrovirus, an individual with an indeterminate result should be referred to a specialist for more sophisticated testing.

3. Additional methods of HIV antibody testing
   - a) Oral secretions collected using special swabs (OraSure) can now be tested by ELISA and Western Blot methods
   - b) Home collection kits allow individuals to collect their own blood and send it to a laboratory anonymously for standard ELISA and confirmatory antibody testing.
   - c) Rapid screening test
     - (1) Test on serum in laboratory
     - (2) Test on whole blood or oral secretions outside of laboratory (Oraquick)
       - (a) Should be followed up by standard confirmatory antibody testing.
       - (b) Used for testing donors of needlesticks in healthcare setting, women in labor who have not been tested during pregnancy, in community outreach in the US, and singly or in tandem for HIV testing in resource poor nations.

B. Direct tests for the virus in current clinical use

1. Several methods are used currently to measure the DNA or RNA of HIV. These tests are quite sensitive but are very expensive and should not be used to screen for HIV infection in the general population.
2. Testing for HIV DNA with a PCR test is used currently to diagnose HIV infection in newborns. Infants born to HIV-infected mothers carry their mothers' antibodies, and test positive by ELISA/Western Blot methods, for up to 15 months after birth whether or not they are infected. Newborns are therefore tested directly for the virus with an HIV DNA test, usually once in the first month of life and again after 2-3 months. A negative HIV DNA test after 3 months means the infant is not HIV infected, even if the infant still has maternal antibodies and tests positive by Elisa/Western Blot.
   a) The HIV DNA test can also be used to diagnose HIV infection in children and adults in the window period. The test costs $200, however, and results may take several weeks, so the DNA assay should only be done when it is clearly indicated.
3. Viral Load testing is the popular term for quantitative plasma HIV RNA testing. Two assays use nucleic acid amplification (RT-PCR or direct RNA amplification) and one uses signal amplification (branched chain DNA). Used before antiretroviral treatment, they provide important prognostic information. During antiretroviral treatment, they measure the effect of the drug regimen on the individual's HIV infection, and to predict the clinical benefit of a given antiretroviral regimen in an individual. These assays cost $75-150 each. These tests are also sometimes used to diagnose HIV infection in newborns and the acute retroviral syndrome.

IV. Natural History

A. Clinical course of HIV-1 infection in adolescents and adults. Without antiretroviral treatment or opportunistic infection prophylaxis, median time to and AIDS defining illness in developed countries was 10 years, and median overall survival with HIV infection was 11 years. Survival may be shorter in less developed nations, where many persons with HIV die of tuberculosis.

1. Acquisition of HIV infection (mucosal [usually sexual] or parenteral)
   a. virus carried on dendritic cells from mucosal surface to regional lymph nodes
   b. replication in regional lymph nodes
   c. next tier of replication in gut-associated lymphoid tissue produces large amount of virus and rapidly destroys large numbers of CD4 cells including memory cells (in primate models)
2. Acute Retroviral Syndrome (seroconversion syndrome) corresponds to the intense virema
   a) fever, adenopathy, rash, oral ulcers, neurologic symptoms and signs, sometimes immunosuppression, occurs in an uncertain proportion of individuals (perhaps as many as 80%) following HIV infection

c) Patients have negative or indeterminate HIV antibody tests, but high levels of HIV RNA in the plasma (or high levels of HIV DNA in cells)

d) Initial high level of viremia coincident with seroconversion. CD4+ lymphocyte count in the peripheral blood transiently falls from normal. The height of the viremia (plasma HIV RNA levels) during seroconversion predicts the long term outcome of the infection!

3. Window period (2 weeks to 6 months) between acquisition of infection and a positive screening and confirmatory antibody test.
4. Asymptomatic HIV. After the acute retroviral syndrome, the level of virus in the plasma decreases and stays fairly level at a 'set point'. Most HIV is replicating in lymphoid tissue, and virus is spilling out into the blood plasma where it is detected. During this period of clinical latency, viral replication and CD4+ lymphocyte destruction is rapid but a steady state is maintained. The set point (level of plasma HIV RNA) is also strongly predictive of the long term outcome of the infection. For practical purposes, a person with a CD4 count above 500-600 may be immunologically normal.
   a) no symptoms or persistent generalized lymphadenopathy (PGL).
   b) May last many 5-10 or more years
5. Symptomatic HIV includes a large range of HIV-associated conditions.
   a) Disease with usual pathogens may be more frequent or more severe among persons with CD4 counts below 500-200.
      1) CD4 500-350: mild immunosuppression.
      2) CD4 350-200 moderate immunosuppression.
   b) Some conditions are neither severe nor life threatening. They are often caused by usual pathogens but disease may be more fequent of more severe because of the mild-moderate immunosuppression. Examples include:
      (1) seborrheic dermatitis, folliculitis, pneumococcal pneumonis, varicella zoster, sinusitis, cervical intraepithelial neoplasia.
   c) Other conditions may be severe or suggestive of moderately impaired cell-mediated immunity. Examples include:
      (1) oral candidiasis and oral hairy leukoplakia (due to Epstein-Barr virus),
6. AIDS-defining conditions: After many years, for reasons that are not known, the amount of virus in the plasma increases more and more rapidly, the number of CD4+ lymphocytes falls more and more rapidly, and clinical disease occurs. CD4 count below 200 is advanced immunosuppression. Patients are susceptible to serious and life threatening diseases due to opportunistic pathogens.
      1) The CDC case surveillance definition, used to track the epidemic rather than for clinical purposes, considers an HIV infected person with a CD4+ lymphocyte count or 200/cu mm or less to have AIDS, regardless of the presence of symptoms or an AIDS defining condition.
      2) A CD4 count below 50 represents advanced immunosuppression, when the most serious of

opportunistic infections are most likely and when untreated survival is likely to be short.

a) 23 serious or life threatening illnesses, most of which are by themselves strong indicators of severely depressed cell mediated immunity. Without antiretroviral treatment, AIDS defining conditions occur in about 50% of adults within 10 years of infection. Some examples include (*this list is not on the exam*):
1) Malignancies (often viral-associated): Kaposi's sarcoma (HHV-8), primary brain lymphoma (EBV), systemic B-cell lymphomas (50% EBV), invasive cervical cancer (HPV)
2) Viral diseases: prolonged mucosal HSV, CMV retinitis or GI tract ulcers, JC papovavirus brain disease (progressive multifocal leukoencephalopathy)
3) Bacterial diseases: tuberculosis, disseminated Mycobacterium avium or other atypical mycobacteria, recurrent Salmonella bacteremia, recurrent bacterial pneumonia
4) Fungal diseases: Pneumocystis jirovecii pneumonia, candida esophagitis, cryptococcal meningitits, disseminated histoplasmosis
5) Parasitic diseases: Toxoplasmic encephalitis, Cryptosporidia or Isospora or Enterocytozoan enterocolitis
6) Caused by HIV itself: HIV dementia or encephalopathy, and HIV wasting syndrome

8. Rapid progressors. Some persons have severe acute retroviral syndrome with very high plasma HIV RNA levels which never decline. They experience rapid falls in their CD4+ lymphocyte count. They develop AIDS-defining illnesses within 1-2 years and die within 2-3 years.
9. Long term non-progressors are persons with HIV infection, who are clinically and immunologically normal, who have normal and stable CD4+ lymphocyte counts despite HIV infection for a minimum of 7-10 years (contrast with long term survivors, above). Most have very low amounts of virus, and may test negative with the viral load (plasma HIV RNA) tests. About five percent of adults with HIV infection may be long term non-progressors. Over additional years, some of these persons develop immune deficiency and become ill.
    1. Some of these patients are infected with a defective HIV, such as transfusion recipients in Australia infected with a nef-deletion mutant.
    2. Some of these patients are heterozygotes for the CCR5 deletion mutation
    3. Others have very high levels of anti-HIV CTL activity
10. There are no well documented cases of spontaneous cure of HIV infection in adults. A small number of perinatally exposed infants have been transiently positive by HIV DNA tests on several occasions, and then have gone on to have negative HIV DNA tests, negative antibody tests, and be clinically and immunologically normal for up to 5 years. Some authorities consider this evidence of spontaneous cure, others believe it is represents laboratory error.

B. Impact of antiretroviral therapy.

1. Potent combinations of 3 antiretroviral drugs can suppress plasma viral loads several logs, to levels below the limit of quantification of current assays (<50 RNA copies/mL) and keep them there for years.
    a. Suppression of viral replication usually allows the host to replenish most CD4 cells and to partly replenish CD4 memory
    b. Near-complete suppression of viral replication prevents drug resistance. Partial suppression allows for selection of drug resistant mutants by the drug regimen. Partial suppression occurs when an inadequate regimen is prescribed, or when the patient does not take enough of their prescribed medication. For some combinations, patients must take more than 95% of doses to avoid emergence of drug resistance.
2. The effectiveness of modern combination antiretroviral therapy is evident in the decrease in new diagnoses of AIDS (ie progression of HIV to severe immunosuppression) and HIV/AIDS-related deaths in the US since late 1995.
3. Our current challenges in regard to HIV treatment: balancing the virologic benefits with the need for excellent adherence and the risk of toxicity and drug resistance.
4. Use of antiretroviral drugs to reduce HIV transmission.
    a. Perinatal transmission: transmission occurs mostly during labor and delivery, less so in utero, and during "mixed" breast feeding.
        i. Antiretroviral therapy during labor greatly reduces HIV transmission
        ii. Elective Ceasarian section (surgical delivery) before onset of labor reduces HIV transmission
        iii. Current US standard:
            1. Combination antiretroviral therapy during 2nd and 3rd trimesters of pregnancy
            2. IV zidovudine (single drug) during during labor
            3. Oral zidovudine (single drug) to newborn for first 6 weeks of life
            4. Elective Ceasarian section if viral load not suppressed on therapy by 36 weeks of pregnancy
    b. Health care worker exposure:
        i. Use of combination antiretroviral therapy for one month following needlestick exposure or severe mucosal exposure to HIV containing blood or body fluids.