**HIV and AIDS**

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**HIV**
- HIV is retrovirus, uses reverse transcriptase (RNA-directed DNA polymerase) to replicate within host cells
- great variability in the viral envelope → problems for vaccine development
- the classic AIDS virus → HIV-1
- HIV-2
- HIV-2
- HIV-2

**AIDS**
AIDS generally occurs when the CD4 count is below 200/ul or and is characterized by the appearance of opportunistic infections, eg.:
- Pneumocystis carinii pneumonia
- Toxoplasmosis
- Tuberculosis
- Extreme weight loss and wasting; exacerbated by diarrhea
- Meningitis and other brain infections
- Fungal infections
- Syphilis
- Malignancies: lymphoma, cervical Ca., Kaposi's sarcoma

**STATISTICS**
UNAIDS/WHO estimated datas, November 2006
- People living with HIV/AIDS in 2006 39.5 million
- Adults living with HIV/AIDS in 2006 37.2 million
- Women living with HIV/AIDS in 2006 17.7 million
- Children living with HIV/AIDS in 2006 2.3 million
- People newly infected with HIV in 2006 4.3 million
- Adults newly infected with HIV in 2006 3.8 million
- Children newly infected with HIV in 2006 0.53 million
- AIDS deaths in 2006 2.9 million
- Adult AIDS deaths in 2006 2.6 million
- Child AIDS deaths in 2006 0.38 million

**COUNTRY STATISTICS**
in 2005

<table>
<thead>
<tr>
<th>Country</th>
<th>Adults age 15-49</th>
<th>Adult HIV prevalence</th>
<th>Women age 15-49</th>
<th>AIDS deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal</td>
<td>74,000</td>
<td>0.5%</td>
<td>16,000</td>
<td>5,100</td>
</tr>
<tr>
<td>India</td>
<td>5,600,000</td>
<td>0.9%</td>
<td>1,600,000</td>
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<tr>
<td>Sri Lanka</td>
<td>5,000</td>
<td>&lt;0.1%</td>
<td>&lt;1000</td>
<td>&lt;500</td>
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<td>China</td>
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<td>180,000</td>
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<tr>
<td>Thailand</td>
<td>560,000</td>
<td>1.4%</td>
<td>220,000</td>
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<tr>
<td>UK</td>
<td>67,000</td>
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<td>&lt;1000</td>
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<tr>
<td>USA</td>
<td>12,000,000</td>
<td>0.6%</td>
<td>300,000</td>
<td>16,000</td>
</tr>
</tbody>
</table>

The number of people living with HIV has risen from around 8 million in 1990 to nearly 40 million today, and is still growing. Around 63% of people living with HIV are in sub-Saharan Africa.
over 80% of persons with counts below 200/ul will develop AIDS within 3 years in the absence of effective antiretroviral therapy.

Mode of Transmission: sexual, parenteral, and vertical transmission.

Risk of HIV transmission (if source is HIV infected)
- receptive anal intercourse 1:100 to 1:30
- insertive anal intercourse 1:1000
- receptive vaginal intercourse 1:1000
- insertive vaginal intercourse 1:10,000
- needlestick with infected blood 1:300
- iv. drug use with sharing needles 1:150
- blood transfusion from infected donor 95%
- maternal transmission in the absence of perinatal HIV prophylaxis 13% to 40%

Etiology
- Depends upon a unique enzyme, reverse transcriptase (RNA-directed DNA polymerase), to replicate within host cells.
- HIV genomes contains genes for three basic structural proteins and >5 regulatory proteins
1. Gag: group antigen proteins
2. Pol: polymerase
3. Env: external envelop protein: quite variable

Pathogenesis
- the cell principally infected is the CD4 (helper-inducer) lymphocyte, which directs many other cells in the immune network
- B lymphocytes and macrophages can also be infected → mixed humoral and cellular immunodeficiency
- HIV uses T4 (CD4) antigen to attach to the cell, and once it enters a cell, HIV can replicate and cause cell fusion or death
- latent state is also established, with integration of the HIV genome into the cell's genome

Pathophysiology
- Clinically, the syndromes caused by HIV infection are usually explicable by one of three known mechanisms:
  B. Autoimmunity
  C. Neurologic, Renal, and Gastrointestinal Dysfunction

A. Immunodeficiency
- direct result of the effects of HIV upon immune cells
- a spectrum of infections and neoplasms is seen, as in other congenital or acquired immunodeficiency states
- two remarkable features of HIV immunodeficiency:
  - and aspergillosis
  - frequent occurrence of certain neoplasms such as lymphoma or Kaposi's sarcoma
B. Autoimmunity
- result of disordered cellular immune function or B lymphocyte dysfunction
- it may be the only clinically apparent disease or may coexist with obvious immunodeficiency
  - lymphocytic interstitial pneumonitis
  - autoantibody production (e.g., immunologic thrombocytopenia).

C. Neurologic, Renal, and Gastrointestinal Dysfunction
- neurologic dysfunction due to release of cytokines and other neurotoxins by infected macrophages, perturbations of excitatory neurotransmitters and calcium flux
- direct HIV infection of renal tubular cells and gastrointestinal epithelium may contribute to these organ system manifestations of infection

Clinical Findings
A. Symptoms and Signs
- Many remain asymptomatic for years even without antiretroviral therapy
- mean time of approx. 10 years between exposure and development of AIDS.
- A combination of complaints is more suggestive of HIV infection than any one symptom.
- Findings that are predictive of HIV infection include:
  - hairy leukoplakia of the tongue
  - disseminated Kaposi's sarcoma
  - cutaneous bacillary angiomatosis

1. Systemic complaints
- Fever, night sweats, and weight loss are common symptoms
- Evaluation of patients with persistent fever and no localizing symptoms:
  - careful examination
  - chest radiograph (pneumocystis pneumonia can present without respiratory symptoms)
  - blood cultures if the fever is greater than 38.5°C
  - serum cryptococcal antigen, and mycobacterial cultures of the blood
  - sinus CT scans or sinus radiographs to evaluate occult sinusitis

2. Sinopulmonary disease
A. Pneumocystis pneumonia
1. the most common opportunistic infection
2. difficult to diagnose: fever, cough, and SOB
3. Hypoxemia may be severe
4. The cornerstone of diagnosis is the chest radiograph.
5. Diffuse or perihilar infiltrates are most characteristic, but only two-thirds of patients with pneumocystis pneumonia have this finding.
6. Normal chest radiographs are seen in 5-10% of patients with pneumocystis pneumonia, while the remainder have atypical infiltrates.

Weight loss
- distressing complication of long-standing HIV infection
- disproportionate loss of muscle mass, with less loss of fat stores
- mechanism is multifactorial:
  - anorexia, nausea, and vomiting - primary effect of HIV or due to sec. infections like viral hepatitis
  - malabsorption
  - diarrhea from infections with bacterial, viral, or parasitic agents
  - increased metabolic rate - it accelerates with disease progression and secondary infection
B/L diffuse opacity in the lower lungs

Ventilator-associated right-sided pneumothorax in the same patient.

Interstitial infiltration as in PCP

a. Gomori methenamine
b. Wright–Giemsa staining
c. Calcofluor white fungal cyst-wall stain
d. Immunofluorescence staining
2. Sinopulmonary disease contd

b. Other infectious pulmonary diseases — bacterial, mycobacterial, and viral pneumonias
   - Community-acquired pneumonia: is the most common cause of pulmonary disease in HIV infected patients.
   - Pneumococcal pneumonia with septicemia and H. influenzae pneumonia, Pseudomonas infection are increased.

- Mycobacterium tuberculosis infection has markedly increased: HIV infection; homelessness.
- Apical infiltrates and disseminated disease occur more commonly
- PPD test should be performed on all HIV-infected persons but it may be nonreactive if the CD4 cell count lower.

- Atypical mycobacteria can cause pulmonary disease in AIDS patients with or without preexisting lung disease and responds variably to treatment.
- M tuberculosis and atypical mycobacteria requires culture of sputum for distinguishing.

Mycobacterium avium disease.
- X-ray and CT scan of elderly man with cavitary avium disease

2. Sinopulmonary disease contd

c. Noninfectious pulmonary diseases — Kaposi’s sarcoma, non-Hodgkin’s lymphoma, and interstitial pneumonitis
• pulmonary involvement is rare presenting manifestation Kaposi’s sarcoma
• Non-Hodgkin’s lymphoma may involve the lung as the sole site of disease
• CXR: nodular or diffuse parenchymal involvement, pleural effusions, and mediastinal adenopathy

2. Sinopulmonary disease contd
• d. Sinusitis

Kaposi’s sarcoma
• Associated with human herpes virus 8 infection
• May appear anywhere, careful examination of the eyelids, conjunctiva, pinnae, palate, and toe webs
• Is red or purple, flat or raised papules and macules and nodules. They are generally first seen on the skin, that generally do not blanch.
• May mimic bacillary angiomatosis, biopsy confirms
• In the mouth, lesions are most often palatal papules, though exophytic lesions of the tongue and gingivae may also be seen.
• May develop visceral disease (eg, gastrointestinal, pulmonary).

intraoral Kaposi’s sarcoma

intraoral Kaposi’s sarcoma lesion with an overlying candidiasis infection
3. **Central nervous system disease**

- **intracerebral space-occupying lesions:**
  - Toxoplasmosis
  - Central nervous system lymphoma
- AIDS dementia complex (HIV-associated cognitive-motor complex)
- Cryptococcal meningitis
- HIV myelopathy
- Progressive multifocal leukoencephalopathy (PML)

4. **Peripheral nervous system:**

- Inflammatory polyneuropathies, sensory neuropathies, and mononeuropathies

5. **Rheumatologic manifestations:**

- Arthritis, involving single or multiple joints, with or without effusion

6. **Myopathies:**

- Proximal muscle weakness

7. **Retinitis**

8. **Oral lesions:**

- Oral candidiasis and hairy leukoplakia

Hairy leukoplakia

1. Leathery white callus on the side of the tongue.
2. It is not easily scraped off.
3. By the Epstein-Barr virus
4. Occurs only when the body's own immune system is at a low level.
5. The most frequently associated mononucleosis.
9. Gastrointestinal manifestations —
   a. Candidal esophagitis
   b. Hepatic disease: infections or neoplasms
   c. Biliary disease: acalculous cholecystitis, sclerosing cholangitis and papillary stenosis
   d. Enterocolitis
   e. Gastropathy
   f. Malabsorption

10. Endocrinologic manifestations:
    adrenal gland - infection, infiltration, or injury from hemorrhage or autoimmunity

11. HIV-related malignancies:
    - Kaposi's sarcoma
    - non-Hodgkin's lymphoma
    - primary lymphoma of the brain
    - invasive cervical carcinoma

12. Skin manifestations: viral, bacterial, fungal, neoplastic, and nonspecific dermatitides
    Herpes zoster/simpex is a common manifestation of HIV infection.

**Bacillary angiomatosis:**
- is a well-described entity in HIV-infected patients.
- It is caused by Bartonella.
- raised, reddish, highly vascular skin lesions that can mimic the lesions of Kaposi's sarcoma. Biopsy confirms
- Fever
- involvement of bone, lymph nodes, and liver
Laboratory Findings

- screening serology is done by ELISA
- positive specimens are then confirmed by a different method (e.g., Western blot for presence of at least p24, gp41, gp120/160) or repeated ELISA
- isolated positive ELISA should not be reported until it is confirmed by western blot.
- absolute CD4 lymphocyte count – normal range is 600-1500 cells/ul, risk for opp.inf. or malignancy high if <200 cells/ul
- CD4 lymph. percentage – risk for opp.inf. or malign. high if <20%.
- HIV viral load test – measures the amount of actively replicating HIV virus, correlate well with disease progression and response to ART drugs.

Essentials of Diagnosis

- Risk factors: sexual contact with an infected person, parenteral exposure to infected blood by transfusion or needle sharing, perinatal exposure.
- Prominent systemic complaints such as sweats, diarrhea, weight loss, and wasting.
- Opportunistic infections due to diminished cellular immunity — often life-threatening.
- Aggressive cancers, particularly Kaposi's sarcoma and extranodal lymphoma.
- Neurologic manifestations, including dementia, aseptic meningitis, and neuropathy.

Antiretroviral Therapy (ART)

1. Therapy should be initiated in patients with a CD4 count <200 cells/ul or in the symptomatic patient (with AIDS, thrush, or unexplained fever).
2. In the asymptomatic patient, if CD4 count is between 200 and 350 cells/ul, initiation of ART is recommended, although some controversy still exists.
3. In the asymptomatic patient, if CD4 count >350 cells/ul, there is no strong evidence of clinical benefit of early initiation of ART.

Monitoring of therapy

- Plasma HIV RNA load is monitored.
- Goal is to reduce the viral load levels below the detection limit.
- CD4 counts should be checked periodically to assess the immune status and to define the start of the prophylactic therapy.
- After starting or changing therapy, viral load should be checked after 4 weeks.
- When HIV RNA becomes undetectable, and the patient is on stable regimen, monitoring can be done 3 monthly.

Highly Active Anti-Retroviral Therapy (HAART)

- HAART resulted in a profound decline in the number of deaths due to AIDS in the Western World. In USA in recent years the number of AIDS deaths has decreased by 70%.
- The benefits of HAART have been linked with decreased rates of AIDS opportunistic infections, improved quality of life and increased survival.
- There are three main classes of drugs:
  - Protease Inhibitors (PI)
  - Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
  - Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Protease inhibitors (PI):

- indinavir, nelfinavir, ritonavir, amprenavir, saquinavir, and lopinavir
- very potent group of drugs that block the action of the viral protease required for protein processing late in the viral cycle
- used in combination regimens
- can produce increased bleeding in hemophiliacs, GI intolerance, and LFT ↑
- associated with metabolic abnormalities, such as glucose intolerance, increases in cholesterol and TG, and body fat redistribution
- they have important interactions, and concomitant medications should be reviewed carefully
- combinations of two PIs, especially with ritonavir, can decrease the dosage requirement of the other PIs.
Nonnucleoside reverse transcriptase inhibitors (NNRTI)
- nevirapine, efavirenz, delavirdine
- inhibit HIV by binding noncompetitively to the reverse transcriptase
- a single dosage of Nevirapine at the time of labor has been shown to decrease perinatal transmission of the virus
- Side effects: rash, increased AST and ALT, Stevens-Johnson syndrome

Nucleoside reverse transcriptase inhibitors (NRTI)
- zidovudine, didanosine, stavudine, lamivudine, emtricitabine, abacavir, zalciatbine, tenofovir
- constrain HIV replication by incorporation into the elongating strand of DNA, causing chain termination
- associated with lactic acidosis, presumably related to mitochondrial toxicity

New therapy
- HIV entry inhibitors
  - New class of antiretroviral agents
  - Target different stages of the HIV entry process
  - T-20 (enfuvirtide) – fusion inhibitor, only available for use as sc. injection
  - Side effect: local reaction at the injection site

Initial therapy
- ART is usually started in the outpatient setting by a physician with expertise in the management of patients with HIV infection
- adherence is the key factor for success of ART
- treatment should be individualized and adapted to the patient’s lifestyle
- any treatment decision influences future therapeutic options because of the possibility of drug cross-resistance
- potent ART consists of either a combination of two NRTIs plus one or two PIs or an NNRTI
- DUOVIR-N 1 tab. BD (lamivudine 150mg + zidovudine 300mg + nevirapine 200mg in one tab.)
- alternatively, three NRTIs can be used such as zidovudine + lamivudine + abacavir

Treatment failure
- (1) less than a log (10-fold) reduction of the viral load 4-6 weeks after starting a new antiretroviral regimen
- (2) failure to reach undetectable viral load after 4-6 months of treatment
- (3) detection of the virus after initial complete suppression of viral load, which suggests development of resistance
- (4) persistent decline of CD4 cells or clinical deterioration
- confirmed treatment failure should prompt changes in ART
- at least two of the drugs should be substituted with other drugs that have no expected cross-resistance
- HIV resistance testing may help determine a salvage regimen in the patients with prior antiretroviral experience
- the importance of adherence should be stressed
- referral to an HIV specialist is highly recommended

Prophylaxis Pneumocystis pneumonia:
- if CD4 counts below 200 cells/ul, a CD4 lymphocyte percentage below 14%, or unexplained fever for >2 weeks or oral candidiasis is present:
  - Trimethoprim-sulfamethoxazole (TMP/SMX)
    - 160/800 mg is dosed as one double-strength tablet three times a week to once daily
  - Atovaquone 1.5 g/day
  - Inhaled pentamidine 300 mg once a month
Prophylaxis for M. tuberculosis
• if positive PPD reactions (defined for HIV-infected patients as > 5 mm of induration)
• recent contact with active TB
Rx : isoniazid 300 mg daily plus pyridoxine 50 mg orally daily for 9 months to a year
Rifampin 10mg/kg/d plus Pyrazinamide 20mg/kg/d for 2 months

Prophylaxis for M. avium
• if CD4 counts fall below 75-100 cells/µL.
  – Clarithromycin (500 mg orally twice daily)
  – azithromycin (1200 mg orally weekly)

Prophylaxis of fungal infection
Candidiasis: Local application/ fluconazole 100-200 mg/d
Cryptococcus neoformans: Amphotericin B 0.7 mg/kg/d IV with 5-flucytosine 25 mg/kg/d q6h for 2 wk then fluconazole 400mg/d 8-10 wk then 200mg/d to continue

Prophylaxis for Toxoplasmosis
• if CD4 count is below 100 cells/ul
• TMP/SMX DS 1 Tab OD
Prophylaxis for Cytomegalovirus
• if CD4 counts below 50 cells/µL
• oral ganciclovir 5mg/kg IV q12h BD X 14d as induction; maintenance 5mg/kg/d IV

Prophylaxis of Kaposi’s sarcoma
• Potent ART can regress the lesions
• Local therapy with liquid nitrogen or intralesional injection of alitretinoin or vinblastine
• Radiation Rx may useful
• Chemotherapy with doxorubicin/ interferon - alpha

Withdrawal Prophylaxis
• If immune reconstitution has occurred
• CD4 cell counts consistently above 150-200 cell/µL