HIV and AIDS

DR. BADRI PAUDEL

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
  – isolated in West African patients
  – significant differences in the envelope glycoproteins
  – most infected are currently asymptomatic
  – less pathogenic or have a longer latency period

AIDS

AIDS generally occurs when the CD4 count is below 200/ul or a CD4 lymphocyte percentage below 14% 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 data, 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 0.38 million
• Adult AIDS deaths in 2006 2.9 million
• Child AIDS deaths in 2006 2.6 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>
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</thead>
<tbody>
<tr>
<td>Nepal</td>
<td>74,000</td>
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<td>16,000</td>
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<tr>
<td>India</td>
<td>5,600,000</td>
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<td>1.4%</td>
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<td>USA</td>
<td>1,200,000</td>
<td>0.6%</td>
<td>300,000</td>
<td>16,000</td>
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</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:
  A. Immunodeficiency
  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:
    – low incidence of certain infections such as listeriosis 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 infiltration of organs (eg, lymphocytic interstitial pneumonitis)
  - autoantibody production (eg, 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

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

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.
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
Methenamine silver stain of a bronchoalveolar lavage specimen: a cluster of P. carinii cysts.

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 mycobacterium 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

**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**

2. Sinopulmonary disease contd
- d. Sinusitis
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)

Toxoplasmosis is the most common space-occupying lesion in HIV-infected patients.
- Sym: headache, focal neurologic deficits, seizures, or altered mental status.
- The diagnosis: typical cerebral imaging with in seropositive for toxoplasma.
- CT scan: multiple contrast-enhancing lesions

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/simplex 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, correlates 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, zalcitabine, 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

Prophylaxis

Pneumocystis pneumonia:

- if CD4 counts below 200 cells/μL, a CD4 lymphocyte percentage below 14%, or unexplained fever for >2 weeks or oral candidiasis is present:
  - Trimethoprim-sulfamethoxazole (TMP/SMX )
  - 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/μL
- 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 allitretinoin 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