HIV PATHOGENESIS

Immunopathology of HIV/AIDS

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Basic Components of the Immune System

- **Immunology**: cells and tissues involved in recognizing and attacking foreign substances in the body e.g. bacteria, viruses, fungi and parasites.
- **Immunity**: the condition of being immune. Immunity can be innate or the result of a previous exposure.
- **Antigen**: any substance capable of triggering an immune response.

Pathogenesis

**Definition:**

The development of morbid conditions or of disease; more specifically, the cellular events and reactions and other pathologic mechanisms occurring in the development of a disease.

Basic Components of the Immune System

- Of the white blood cell pool, **lymphocytes** primarily drive the immune system.
- **Lymphocytes** (2 major types which protect host):
  1. **B cells**: formed in bone marrow and produce antibodies after exposure to an antigen.
  2. **T cells**: processed in the thymus (two subtypes)
- **Subtypes**. **Regulator cells** also known as helper or CD4 cells (“generals” in army of immune system which recognize “strategists” and summon armies of cells to mount a direct attack).
- **Subtypes**: **Fighter** or **effector cells** also known as cytotoxic or CD8 cells (bind directly to antigen and kill it).
Basic Components of the Immune System

- 2 types of CD4 cells:
  1. Memory cells: those programmed to recognize a specific antigen after it has been previously seen
  2. Naïve cells: non-specific responders
- CD4 cells replicate 100 million times a day.
- CD4 cells are the target cells of HIV.

Lymphatic vessels and nodes:
- designed to trap and destroy antigen and play a critical role in fighting all infections including HIV

Phagocytes:
- "scavengers" of the immune system
  - By digesting/processing antigen, their role is to initiate the immune response by presenting antigen to the lymphocytes.
  - Serve a secretory function critical to mounting the inflammatory response and regulating immune responses

HIV Viral Dynamics

- HIV is classified as a retrovirus
  - Once HIV enters the host (CD4) cell, it converts its RNA (ribonucleic acid) to DNA (deoxyribonucleic acid) via its enzyme reverse transcriptase.
- HIV is completely dependent upon CD4 cells for replication and survival.

Replication and survival of HIV occurs through a number of steps:
- HIV gains entry into the CD4 cell by binding onto receptors on the outside of the CD4 cell and fusing with the lipid outer layer of the cell.
- Once inside the cell, HIV removes its outer coating, exposing its RNA, and releases reverse transcriptase enzyme to convert the HIV RNA to DNA.
- HIV/DNA then enters the nucleus of the CD4 cell and is integrated into the host (CD4) DNA.
HIV Viral Dynamics

Replication and survival of HIV (con't)

Once the cellular DNA has been altered in this way, it is known as proviral DNA (part virus/part cell) and begins the process to produce more virus.

The CD4 cell is now programmed to be an “HIV factory.”

Long viral protein chains are produced which are then cut into the necessary pieces to produce more HIV. This process is activated by the viral protease enzyme.

Each step in this process is a target for antiretroviral therapy (to date, reverse transcriptase, protease inhibitors and fusion inhibitors have been approved).

Stages of HIV Disease

Acute/Early Infection:

Following HIV transmission, approximately 50% of individuals will develop a febrile, flu-like illness with some or all of the following conditions:

- Swollen glands
- Rash
- Oral ulcers
- Sore throat
- Diarrhea
- Headache
- Muscle aches
- Nausea or vomiting

Testing for HIV antibody may be negative at this time.

Diagnosis of acute HIV can be made by obtaining a quantitative HIV RNA PCR (viral load test) or a pro viral cDNA test.

A positive HIV antibody usually develops by 4-6 weeks following transmission, but rarely could be up to 12-24 weeks.

Infection must ultimately be confirmed with an HIV Elisa/Western Blot assay.
**Stages of HIV Disease**

**Acute/Early Infection (con’t)**

- **Window period:** interval between where HIV actually appears, and is ultimately detectable by an antibody test.
- Inmates potentially exposed to HIV must be counseled that a negative antibody test during this period does **not** guarantee HIV transmission has not occurred.
- If an inmate’s HIV test is negative, but suspicion for HIV exposure is high, repeated antibody testing should be performed at 12-26 weeks.

**HIV Antibody Testing Timeline:**
- Baseline
- 6 weeks post-exposure
- 12 weeks post-exposure
- 26 weeks post-exposure

Serocoversion virtually always detected by 6 months

**Intermediate Stage**

- T cell destruction by HIV begins to weaken the immune system over time (in contrast to the acute stage, where the immune system “keeps pace” by producing an equivalent amount of CD4 cells).
- In general, if untreated, there is an 8-10 year period during which an HIV+ individual undergoes a gradual decline in immune function (monitored by laboratory testing of CD4 count) and an increase in HIV viral load (monitored by laboratory testing of viral load).
- Often no symptoms exhibited during the intermediate disease stage
Stages of HIV Disease

Intermediate Stage (con’t)

- Factors which influence how long individuals will remain in this stage before progressing to advanced disease:
  1) How high the viral setpoint is
  2) If and when antiretroviral treatment is initiated
- More than 50% of people do not know they are HIV-infected until they become symptomatic (an indicator of advanced disease).
- As the correctional setting is often an inmate's first interaction with the health care system, a thorough history of risk factors is important and HIV testing should be recommended to all new intakes.

Advanced Stage

- Untreated, the rapid replication of HIV will eventually deplete the immune system, often causing it to succumb to infections, AIDS, and ultimately death.
- Symptomatic HIV can present in a variety of forms.
- Hallmarks of this stage of the disease include:
  - Opportunistic infections or malignancies
  - Neuropathy
  - Anemia

Advanced Stage (con’t)

- Actual diagnosis of AIDS is made when the CD4 count falls below 200 cells/mcm or when an AIDS-defining condition is diagnosed.
- Once a diagnosis of AIDS has been made, it remains with the patient even if higher CD4 count returns to above 200 with antiretroviral therapy.

AIDS-Defining Conditions

<table>
<thead>
<tr>
<th>Condition of Kaposi's sarcoma, invasive breast or lung</th>
<th>Herpes simplex with mucocutaneous ulcer for &gt;1 month of bronchitis, pneumonitis, epistaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer, invasive</td>
<td>HIV-associated dementia due to cerebral edema associated with occupational or daily activities</td>
</tr>
<tr>
<td>Coccidioidomycosis, extrapulmonary</td>
<td>HIV-associated wasting syndrome (weight loss of 10% of baseline body weight over &gt;30 days or chronic weakness and documented weight loss for &gt;30 days)</td>
</tr>
<tr>
<td>Cryptosporidiosis with diarrhea for &gt;1 month</td>
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<tr>
<td>Cytomegalovirus of any organ other than liver, spleen, or lymph node</td>
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<tr>
<td>Encephalopathy of any organ other than liver, spleen, or lymph node</td>
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<td>HIV-Associated wasting (weight loss of 10% of baseline body weight over &gt;30 days)</td>
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</table>
### Stages of HIV Disease

**AIDS-Defining Conditions (con’t)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma of brain in patient younger than 60 (or older than 60 with positive HIV serology)</td>
<td>A1</td>
</tr>
<tr>
<td>Lymphoma, non-Hodgkin’s</td>
<td>B1</td>
</tr>
<tr>
<td>Mycobacterium avium or M. kansasii, disseminated</td>
<td>C1</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>A2</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>B2</td>
</tr>
<tr>
<td>Recurrent bacterial with positive HIV serology</td>
<td>C2</td>
</tr>
<tr>
<td>Toxoplasmosis of internal organ</td>
<td>A3</td>
</tr>
<tr>
<td>Transplantation of internal organ</td>
<td>B3</td>
</tr>
</tbody>
</table>

### Opportunistic Infections

- When CD4 count is in normal range (500-1,600 cells/cmm or 28-50%), the immune system defends itself against most antigens.
- As T-cell count declines with HIV disease progression, the HIV+ patient is at increased risk for infection.
Opportunistic Infections

- When the T-cell count drops below 200 cells/cm² (14%), there is increased risk of an AIDS-defining condition occurring.
- Treatment guidelines recommend prophylactic treatment against pneumocystis carinii pneumonia (PCP) for patients in this category.
- This is given as TMP-SMZ (Bactrim) 1 DS or 1 SS a day, Dapsone 100 mg a day, or Atovaquone (Mepron) 500 mg or 1 ml/day.
- Alternate prophylaxis options are listed in the prophylaxis guidelines (Department of Health & Human Services).

Opportunistic Infections

- If the patient develops oral candidiasis (thrush), PCP prophylaxis is recommended, regardless of CD4 count.
- Thrush is an independent risk factor for development of PCP, presumably because it indicates a decline in immune function.
- Primary prophylaxis (treatment in an individual who has never had PCP) can be discontinued if the CD4 count rises above 200 cells/cm² for a period of at least 3-6 months.

Opportunistic Infections

- When the CD4 count falls below 50 cells/cm², the patient should be started on prophylaxis to protect against mycobacterium avium complex (MAC).
- Lifelong treatment is recommended unless the CD4 count rises above 100 cells/cm² for at least 3-6 months.
- Prophylaxis options include: Azithromycin (Zithromax) 1200 mg/week, Clarithromycin (Biaxin) 500 mg BID, or Mycobutin (Rifabutin) 300 mg/day.

Opportunistic Infections

<table>
<thead>
<tr>
<th>200-500 cells/cm²</th>
<th>type</th>
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<tbody>
<tr>
<td>CD4 count</td>
<td></td>
</tr>
<tr>
<td>pneumococcal pneumonia</td>
<td>bacterial</td>
</tr>
<tr>
<td>pulmonary tuberculosis</td>
<td>bacterial</td>
</tr>
<tr>
<td>Kaposi's sarcoma</td>
<td>viral</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>viral</td>
</tr>
<tr>
<td>Thrush</td>
<td>fungal</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>parasitic</td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td>viral</td>
</tr>
<tr>
<td>Oro-pharyngeal candida</td>
<td>fungal</td>
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Opportunistic Infections

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<th>CD4 count</th>
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<tr>
<td>&lt;200 cells/cmm</td>
<td>pneumocystis carinii pneumonia, fungal (previously thought to be parasitic)</td>
</tr>
<tr>
<td></td>
<td>candida esophagitis, fungal</td>
</tr>
<tr>
<td></td>
<td>recurrent disseminated viral herpes simplex, viral</td>
</tr>
<tr>
<td></td>
<td>toxoplasmosis, parasitic</td>
</tr>
<tr>
<td></td>
<td>histoplasmosis, fungal</td>
</tr>
<tr>
<td></td>
<td>Coccidioidomykosis, fungal</td>
</tr>
<tr>
<td></td>
<td>progressive multifocal leukosinphalopathy, viral</td>
</tr>
<tr>
<td></td>
<td>microsporidiosis, parasitic</td>
</tr>
<tr>
<td></td>
<td>extrapulmonary tuberculosis, bacterial</td>
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Opportunistic Infections

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<tr>
<td>&lt;50 cells/cmm</td>
<td>cytomegalovirus, viral</td>
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<tr>
<td></td>
<td>mycobacterium avium complex, bacterial</td>
</tr>
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Resources

- AIDS Education & Training Centers National Resource Center
  [www.aids-etc.org/](http://www.aids-etc.org/)
- AIDS Education Global Information System
  [www.aegis.com/](http://www.aegis.com/)
- CDC National Prevention Information Network
  [www.cdcnpin.org](http://www.cdcnpin.org)
- HIV Clinical Resource, New York State Department of Health AIDS Institute
  [www.hivguidelines.org](http://www.hivguidelines.org)
- Johns Hopkins AIDS Service
  [www.hopkins-aids.edu](http://www.hopkins-aids.edu)