

HIV PATHOGENESIS

Immunopathology
of
HIV / AIDS

Dr. Atin Singhai
Department of Pathology
KGMU, Lucknow

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.

www.rerf.or.jp/eigo/glossary/pathogen.htm

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.

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)
 - Subtype 1: **Regulator cells** also known as **helper** or **CD4 cells** ("generals" in army of immune system which recognize "invaders" and summon armies of cells to mount a direct attack)
 - Subtype 2: **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.

Bartlett, J. The Johns Hopkins Hospital 2002 Guide to Medical Care of Patients with HIV Infection

Basic Components of the Immune System

- **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

Grimes D. and Grimes R.: AIDS & HIV Infection
St. Louis, Mosby, 1994.

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.

HIV Viral Dynamics

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

Stages of HIV Disease

Acute/Early Infection (con't)

- Small % of newly infected individuals will develop liver and/or spleen enlargement
- Onset of illness is generally 1-6 weeks following exposure and can last 1-3 weeks
- "Acute Retroviral Syndrome" is often mistaken for the flu
- An inmate presenting with some or all of the previously mentioned conditions should be questioned about recent potential HIV exposures so that testing can be done:

- Needle sharing? Tattooing? Unprotected sex/new partner?

Stages of HIV Disease

Acute/Early Infection (con't)

- 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**.

Stages of HIV Disease

Acute/Early Infection (con't)

HIV Antibody Testing Timeline:

- Baseline
- 6 weeks post-exposure
- 12 weeks post-exposure
- 26 weeks post-exposure

Serocconversion virtually always detected by 6 months

Stages of HIV Disease

Acute/Early Infection (con't)

- Extremely high levels of HIV in the blood during acute infection (hallmark of this disease stage)
- Within days, HIV disseminates into **sanctuary sites** (lymph nodes, central nervous system) where it "hides out" and remains dormant.
- Safer sex practices should be stressed as there is a high risk of spreading infection to others.
- HIV viral levels decrease over the first 4 months post-transmission until plateauing to a **set point** (varies person to person)
- Lower HIV viral setpoint = longer time it will take for an individual's disease to progress over time

Stages of HIV Disease

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 **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.

www.thebody.com (HIV testing)

Stages of HIV Disease

Advanced Stage

- Untreated, the rapid replication of HIV will eventually deplete the immune system in most people to such an extent that the patient will lose critical body defenses and can 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
 - Rashes
 - Recurrent vaginal candidiasis
 - Herpes zoster
 - Thrush
 - Neuropathy
 - Diarrhea
 - Recurrent infections
 - Cancers
 - Anemia

Stages of HIV Disease

Advanced Stage (con't)

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

Stages of HIV Disease

AIDS-Defining Conditions

Candidiasis of esophagus, trachea, bronchi or lungs	Herpes simplex with mucocutaneous ulcer for > 1 month or bronchitis, pneumonitis, esophagitis
Cervical cancer, invasive	Histoplasmosis, extrapulmonary
Coccidioidomycosis, extrapulmonary	HIV-associated dementia: disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living
Cryptococcosis, extrapulmonary	HIV-associated wasting: involuntary weight loss of >10% of baseline plus chronic diarrhea (>2 loose stools/day for >30 days) or chronic weakness and documented enigmatic fever for > 30 days
Cryptosporidiosis with diarrhea for > 1 month	Isoptorosis with diarrhea for >1 month
Cytomegalovirus of any organ other than liver, spleen, or lymph nodes	Kaposi's sarcoma in patient younger than 60 (or older than 60 with positive HIV serology)

Stages of HIV Disease

AIDS-Defining Conditions (con't)

Lymphoma of brain in patient younger than 60 (or older than 60 with positive HIV serology)	Pneumocystis carinii pneumonia
Lymphoma, non-Hodgkin's	Pneumonia, recurrent bacterial with positive HIV serology
Mycobacterium avium or M. kansasii, disseminated	Progressive multifocal leukoencephalopathy
Mycobacterium tuberculosis, disseminated	Salmonella septicemia (non-typhoid), recurrent with positive HIV serology
Mycobacterium tuberculosis, pulmonary	Toxoplasmosis of internal organ

Stages of HIV Disease

- The Centers for Disease Control (CDC) has a disease classification system based on immune function and clinical status.
- Each patient is classified with a number which is reflective of CD₄ count, and a letter reflective of clinical status.
- This provides prognostic information for providers where a patient fits along the continuum of illness and as to what conditions, if any, he or she may be at risk.

Stages of HIV Disease

CDC Classification of HIV Disease

CD4 Cell Categories (cells/cmm)	A Asymptomatic or Acute HIV Infection	B Symptomatic (Not A or C)	C AIDS Indicator Condition
> 500 (>29%)	A1	B1	C1
200-499 (14-28%)	A2	B2	C2
< 200 (<14%)	A3	B3	C3

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/cm (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) 1500 mg at (10 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/cmm for a period of at least 3-6 months.

Opportunistic Infections

- When the CD₄ count falls below 50 cells/cmm, 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/cmm 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

200-500 cells/cmm CD4 count	type
pneumococcal pneumonia	bacterial
pulmonary tuberculosis	bacterial
Kaposi's sarcoma	viral
Herpes zoster	viral
Thrush	fungal
Cryptosporidium	parasitic
Oral hairy leukoplakia	viral
Oro-pharyngeal candida	fungal

Opportunistic Infections

<200 cells/cmm CD4 count	type
pneumocystis carinii pneumonia	fungal (previously thought to be parasitic)
candida esophagitis	fungal
recurrent/disseminated viral herpes simplex	viral
toxoplasmosis	parasitic
histoplasmosis	fungal
Coccidioidomycosis	fungal
progressive multifocal leukoencephalopathy	viral
microsporidiosis	parasitic
extrapulmonary tuberculosis	bacterial

Opportunistic Infections

<50 cells/cmm CD4 count	type
cytomegalovirus	viral
mycobacterium avium complex	bacterial

Resources

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