Immunology
435

HIV & AIDS

Objectives:

Understand:

1. **The modes of transmission of HIV**
2. **HIV interactions with CD4 positive helper lymphocytes**
3. **Mechanisms involved in immunodeficiency associated with HIV**
4. **the course of immunological events from the time of infection with HIV until the development of AIDS**

Kindly check our editing file before studying the document

References: Girls&boys doctors slides&notes , Team 434,433

Red= important pink= female doctor notes blue= male doctor notes
Gray= extra explanation from **original slides**

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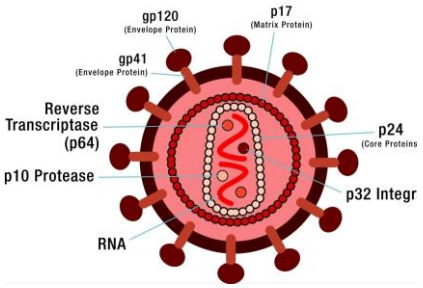
Introduction to HIV (10 min)

Modes of infection

- Sexual transmission at genital or colonic mucosa
- Blood transfusion
- Mother to infant (highest during delivery)
- Accidental occupational exposure

(Oral sex), (mostly rectum because the mucosa is thin, very vascularized & easily hurt)



Viral-host Dynamics

- About 10^{10} (10 billion) virions are produced daily
- Average life-span of an HIV virion in plasma is ~6 hours
- Average life-span of an HIV-infected CD4 lymphocytes is ~1.6 days
- HIV can lie dormant within a cell for many years, especially in resting (memory) CD4 cells, unlike other retroviruses

The extremely high rates of viral replication results in every possible point mutation in the viral genome arising daily. In any given patient, the virus usually varies by 1-6% in the env gene, for example.

How HIV enters cells?

5:13 min

gp120 envelope protein binds to CD4 molecule

(CD4 found on T-cells macrophages, and microglial cells)

Binding to CD4 is not sufficient for entry

(HIV target all cells expressing CD4)

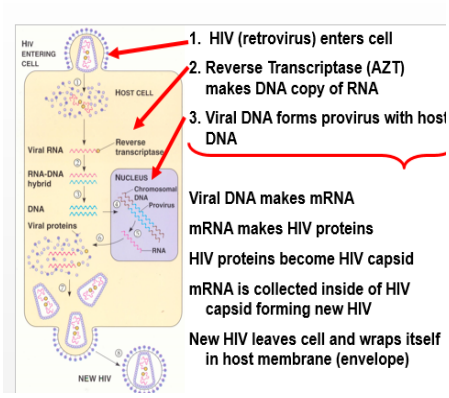
gp120 envelope protein binds to co-receptor

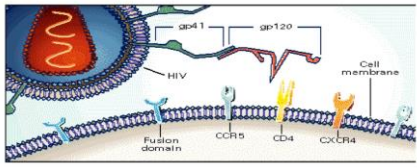
Chemokine receptors: (CCR5 and CXCR4 receptors)

"exposed uninfected" individuals revealed the presence of a mutated CCR5 receptor in some people.
-Patients homozygous for this mutation are relatively resistant to the virus.
-Heterozygous people are not protected from infection but the disease may take longer to develop.

Binding of virus to cell surface results in fusion of viral envelope with cell membrane

Viral core is released into cell cytoplasm.





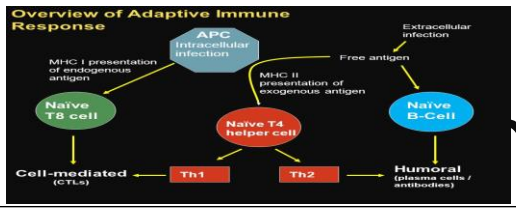
This picture shows HIV's attachment and entry into a host cell.
- gp-120 protein attaches to a CD4 receptor.
- gp-41 is exposed for attachment to the host cell, and fusion of the cell membrane with the viral envelope starts.

General Principles of Viral-host Interactions

- Host: mounts HIV-specific immune responses
  - Cellular (cell-mediated) - most important
  - Humoral (antibody-mediated)
- Virus: subverts the immune system

The virus employ mechanisms to evade the host's response.

  - Infects CD4 cells that control normal immune responses
  - Integrates into host DNA (use cells machinery for its own replication)
  - High rate of mutation (obstacle to treatment)
  - Hides in tissue not readily accessible to immune system (intestinal mucosa)



Both (T&B) cells have antigen specific receptors

The adaptive immune response (as opposed to the innate immune response). In general, the location of the infection (intracellular or extracellular) determines the type of adaptive immune response. Intracellular infections stimulate a cell-mediated response that will ultimately kill the infected cell. This is mediated by T8 cells, and utilizes the MHC I system. Extracellular infections stimulate a humoral response that will help contain these free antigens. Some extracellular antigens will be picked up by APC and be presented by way of MHCII to the Thc, which will further differentiate into either TH1 or TH2.TH1 in turn will augment the cell-mediated response and Th2 augments the humoral. Central to the adaptive immune response is the th4 cell. Because HIV depletes and distrupts the function of this cell, adaptive immunity is impaired.

Cellular Immune Responses to HIV

- CD8 Cytotoxic T lymphocyte (CTL) (protective during HIV)
  - Derived from naïve T8 cells, which recognize viral antigens in context of MHC class I presentation
  - Directly destroy infected cell
  - Activity augmented by Th1 response
- CD4 Helper T Lymphocyte (Th) T-helper
  - Plays an important role in cell-mediated response
  - Recognizes viral antigens by an antigen presenting cell (APC)
    - Utilizes major histocompatibility complex (MHC) class II (MNM: class II 2+2=4 CD4)
  - Differentiated according to the type of "help"
    - Th1 - activate Tc (T cytotoxic) (CD8) lymphocytes, promoting cell-mediated immunity
    - Th2 - activate B lymphocytes, promoting antibody mediated immunity

The Th1 response is mediated by IL-2, (IFN-gamma), and (TNF-beta)

Humoral Immune Response to HIV

- Neutralization
  - Antibodies bind to surface of virus to prevent attachment to target cell
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Fc (fragment crystallization)portion of antibody binds to NK cell
  - Stimulates NK (natural killer) cell to destroy infected cell

Less effective in controlling HIV infection compared to cellular immunity.

Consequence of Cell-mediated Immune Dysfunction (boys slides)

- Inability to respond to intracellular infections and malignancy
- Mycobacteria, Salmonella, Legionella
- Leishmania, Toxoplama, Cryptosporidium, Microsporidium
- Pneumocystis carinii pneumonia, Histoplamosis
- Herpes simplex virus, pox viruses
- Ebstein bar virus-related lymphomas

Decline in immune status parallels the decline in CD4 number and function. Loss of these cells results in failure of normal Th1 response and cell-mediated immunity that is necessary for controlling intracellular infections.

Cells Infected by HIV

Numerous organ systems are infected by HIV:

- **Brain:** macrophages and glial cells
- **Lymph nodes and thymus:** lymphocytes and dendritic cells
- **Blood, semen, vaginal fluids:** macrophages
- **Bone marrow:** lymphocytes
- **Skin:** Langerhans cells
- **Colon, duodenum, rectum:** chromaffin cells
- **Lung:** alveolar macrophages

General Principles of Immune Dysfunction in HIV

- All elements of immune system are affected
- Advanced stages of HIV are associated with substantial disruption of lymphoid tissue
  - Impaired ability to mount immune response to new antigen (1ry response)
  - Impaired ability to maintain memory responses (2ry response)
  - Susceptibility to opportunistic infections (in immunocompromised patients)

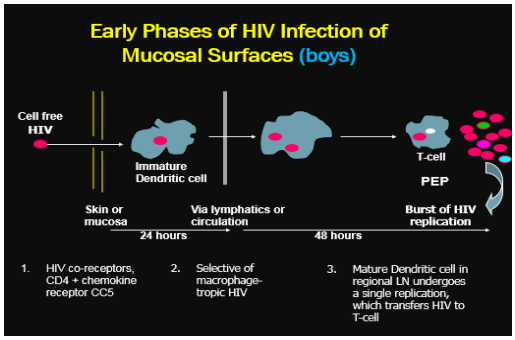
Mechanisms of CD4 Depletion and Dysfunction:

Direct	Indirect		
	Syncytium formation	**Apoptosis**	**Autoimmunity**
• Elimination of HIV-infected cells by virus-specific immune responses • Loss of plasma membrane integrity because of viral budding	• Observed in HIV infection, most commonly in the brain • Uninfected cells may then bind to infected cells due to viral gp120 (bind to CD4 of uninfected cells) • This results in fusion of the cell membranes and subsequent syncytium formation. • These syncytia are highly unstable and die quickly	–	–

Viral gp 120 can be found on the surface of infected host cells after fusion of viral envelope and cell membrane, with retention of viral proteins at the cell surface.

Primary Infection

- 70-80% symptomatic, 3-12 weeks after exposure
- Fever, rash, cervical lymphadenopathy, aseptic meningitis, encephalitis, myelitis, polyneuritis
- Surge in viral RNA copies to >1 million
- Fall in CD4 count to 300-400
- Recovery in 7-14 days



HIV establishes infection across the skin or mucosal surfaces like the cervix or urethra within in 72 hours of its introduction. This information suggests that PEP (post-exposure prophylaxis with antiretroviral drugs after high-risk blood or sexual contacts) should be immediate.

Seroconversion (time in which a person first develops antibodies for HIV)

- Median 8 weeks after infection (max 3 months)
- Level of viral load post sero-conversion correlates with risk of progression of disease

Asymptomatic Phase

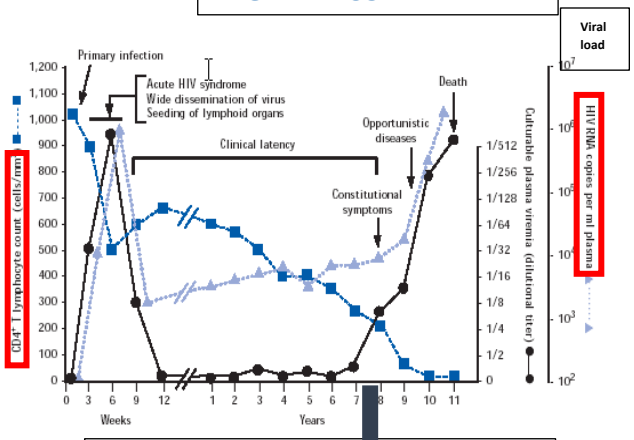
- Remain well with no evidence of HIV disease except for generalized lymphadenopathy
- Fall of CD4 count by about 50-150 cells per year

Acquired Immunodeficiency Syndrome (AIDS)

- **CD4 <200** (MNM: <200 military candidate got pneumonia)
  - Pneumocystis pneumonia
  - Esophageal Candidiasis
  - Miliary/extrapulmonary TB
- **CD <100**
  - Cerebral toxoplasmosis
  - Lymphomas
- **CD4<50**
  - CMV retinitis, gastroenteritis
  - Disseminated Mycobacterium avium complex

YouTube

Diagnosing HIV (10 min)
HIGHLY RECOMMENDED

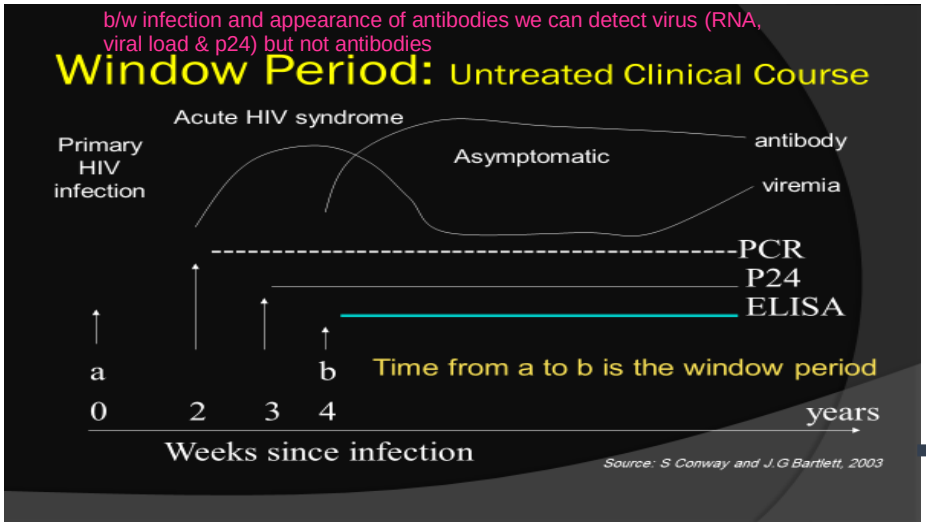


-Acute (primary) retroviral syndrome is the initial event after infection, which is characterized by a rapid decline in CD4 cell count and high plasma viremia.
-Development of cytotoxic T-cell (CTL) response results in clinical recovery of acute infection and a reduction in plasma viremia. The virus reaches "set point" as a result of this immune response. The viral load at this "set point" correlates with the rate of CD4 decline and disease progression. Overtime, HIV RNA levels gradually increase.
In parallel, the CD4 cell count gradually declines over several years, but rapidly drops 1.5 to 2 years before an AIDS-defining diagnosis.
-When the CD4 count falls below 200, patients develop opportunistic infections, tumors, and neurological complications. The median survival after the CD4 count has fallen to <200 is 3.7 years, if untreated.

Important

(You have to recognize this schedule)

PCR is the most sensitive test for b/w infection and appearance of antibodies we can detect virus (RNA, viral load & p24) but not antibodies



-The window period begins at the time of infection and can last 4 to 8 weeks.
-During this period, a person is infected, infectious and viremic, with a high viral load and a negative HIV antibody test.
-The point when the HIV antibody test becomes positive is called the point of seroconversion.

Role of Cytokine Dysregulation in Pathogenesis of HIV:

- **HIV is associated with increased expression of pro-inflammatory cytokines**
  - TNF-alpha, IL-1,IL-6, IL-10, IFN-gamma
  - Associated with up-regulation of HIV replication
- **HIV results in disruption and loss of immuno-regulatory cytokines**
  - IL-2, IL-12
  - Necessary for modulating effective cell-mediated immune responses (CTLs and NK cells).

Not only does the virus destroy and disrupt the immune system, it can manipulate the immune system to its own replicative advantage. This is achieved by immune activation. Clinically, this is demonstrated by the observation that viral load transiently increases in the presence of intercurrent illnesses, such as TB.

Role of Cellular Activation in Pathogenesis of HIV:

HIV induces immune activation: HIV induce (infection) -> increase HIV replication and worsen it

Which may seem paradoxical because HIV ultimately results in severe immunosuppression

Activated T-cells support HIV replication:

- Inter-current infections are associated with transient increases in vremia.
- Accounts for why TB worsens underlying HIV disease

CD4 T-cell Count and Progression to AIDS:

- Gradual reduction in number of circulating CD4 cells is inversely correlated with the viral load
- Any depletion in numbers of CD4 cells renders the body susceptible to opportunistic infections

Laboratory Markers of HIV Infection

- **Viral load** (Marker of HIV replication rate), (Number of HIV RNA copies/mm3 plasma)
- **CD4 count** (Marker of immunologic damage) (depend on immune stages)

Diagnosis

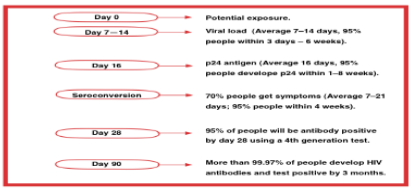
- **Antibody test, ELISA** Screening test
- **Western blot (protein immunoblot)** (Confirmatory test).
  Confirm the presence of Ab and help to diagnose the condition
  Used to detect specific protein using gel electrophoresis
- **HIV RNA viral load (PCR)** Nucleic Acid Amplification Testing (NAAT)

Management

- Treatment recommended when symptomatic or CD4 count below 200.
- Earlier if high viral load, rapidly falling CD4 count, hepatitis C co-infection.
- Antiviral therapy
  - Reverse transcriptase inhibitors
  - Protease inhibitors
  - Fusion inhibitors

Mentioned in objectives not in girls/boys slides just **read it** we already studied it in microbiology

HIV infection stages



	Acute HIV Infection (earliest stage)	**Chronic HIV Infection (asymptomatic/ Clinical Latency)**	**AIDS** (final stage)
duration	Incubation period (2 to 4 weeks)	8-10 years w/o antiretroviral treatment	10 to 12 years w/o treatment
symptoms	Flu-like symptoms (fever, headache, rash, cervical lymphadenopathy, aseptic meningitis, encephalitis, myelitis, polyneuritis)	Asymptomatic	Opportunistic (in immunocompromised patients) infections (e.g.: TB and candida) and cancer.
pathogenesis	HIV multiplies rapidly and spreads throughout the body. destroys the infection-fighting CD4 cells this stage has Greatest risk of transmition	HIV continues to multiply in the body but at **very low levels**.	HIV gradually disrupts the immune system the body can't fight off, kills the CD4 lymphocytes, also destroys the immune system's memory. CD4 cells, which have been programmed to recognize infections, become depleted.
CD4 count	(1 to 3 months): - Peak in HIV RNA copies - Steep decline in CD4 (300-400) in blood during the early days, HIV can replicate without being controlled by the immune system (viral RNA copies to >1 million)	- after acute CD4 cell in the peripheral blood **increases** again. although not as high as before infection.	- Rapid **increase** in HIV RNA - CD4 count **of less than 200** cells/mm^3 in the peripheral blood
	70-80% symptomatic (3-12) weeks after exposure When the body's anti-HIV immune response begins (antibody responses begin to develop 4 to 8 weeks after infection), symptoms of sero-conversion may develop and viral load falls.	People with chronic HIV may not have any HIV-related symptoms, but they can still spread HIV to others.	On average 2-3 years, without antiretroviral treatment-
Viral load	**1- Window period begins at the time of infection During this period, a person is infectious and Viremic,** with a high viral load and a negative HIV antibody test. (4-8 weeks) 2**- Sero-cversion** (is the time in which a person first develops antibodies for HIV)HIV antibody test becomes positive. Level of viral load post sero-conversion correlates with risk of progression of disease (after 8 week) **3- Asymptomatic Phase:** generalized lymphadenopathy **fall** of CD4 count by about 50-150 cells per. 5- Recovery in 7-14 days	**Viral set-point** HIV RNA copy number in the plasma declines again, and the stabilized plasma concentration after the peak of the primary infection.	diagnosed when CD4 count of less than 200 cells/mm^3 and/or one or more opportunistic infections.

	Majority of All mucosal CD4 T lymphocytes are lost, especially in (GIT)-> Increased permeability of GIT->increased circulating lipopolysaccharide (LPS) levels (cell wall component of Gram-negative bacteria in the GIT. -> chronic immune activation (a non-specific way) -> higher susceptibility to HIV. because HIV needs activated CD4 T cells for replication.	Without treatment Usually advances to AIDS in 10 to 12 years.	

Summary

- Infection with HIV usually occurs by sexual transmission, blood transfusion, mother to infant or accidental exposure
- HIV targets the immune system and primarily infects CD4 positive lymphocytes.
- Immunodeficiency associated with HIV infections is mainly due to reduction in CD4 positive helper lymphocyte numbers.
- Increased viral load, significant reduction in CD4 lymphocytes and opportunistic infections are the hallmarks of progression to AIDS.

MCQs

1. HIV target major cells in human body known as:

A. C-lymphocytes

B. B-lymphocytes

C. T-lymphocytes

2. Increased circulating lipopolysaccharide (LPS) levels, increases susceptibility to (from stages table) :

A. HIV

B. HSV

C. Syphilis

3. In acute stage of HIV infection negative HIV antibody test result means:

A. High viral load

B. Fall of CD4 count by about 50-150 cells per

C. None

4. Syncytium formation is related to:

A. Direct mechanisms of CD4 depletion and dysfunction

B. Indirect mechanisms of CD4 depletion and dysfunction

C. Both

5. HIV is associated with increased expression of which of the following pro-inflammatory cytokines:

A. IL-1

B. IL-6

C. Both

6. Mechanisms of HIV entering the cells starts with:

A. gp120 env protein binds to CD4

B. gp1 env protein binds to CD4

C. Only chemokine receptors:

7. Flu-like symptoms are present in which stage of HIV infection:

A. Acute

B. Chronic

C. AIDS

8. CD4 count of less than 200 cells/mm3 means:

A. AIDS

B. HIV infection in chronic phase

C. Asymptomatic

9. Sero-conversion in acute phase on HIV infection indicates which one of the following:

A.HIV antibody test becomes positive.

B. HIV antibody test becomes negative.

C. High viral load

10. Role of cellular activation in pathogenesis of HIV:

A. HIV induces immune activation

B. HIV reduces immune activation

C. None

Answers: 1.C, 2.A, 3.A, 4.B, 5.C, 6.A, 7.A, 8.A, 9.A, 10.A