



Lecture – 3

Human Immunodeficiency Virus (HIV)



Microbiology Team 430

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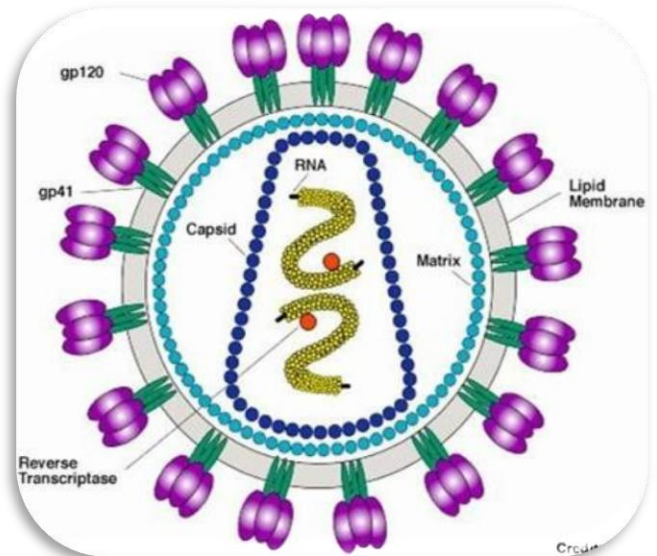
Human Immunodeficiency Virus

- HIV is known to infect mainly **T-helper cells(CD4)** or any cells that have CD4 on their surface such as APCs(**Macrophages**, Dendritic cells, B-Cells)
- Destroying **T-helper cells(CD4)** leads to :
 - severe immunologic impairment
 - Multiple opportunistic infections (the pathogens of these infections , don't affect a healthy host , but a compromised immune system , presents an "opportunity" for these pathogens to infect)
 - Unusual cancers and death.
 - There is two major types of the HIV virus:

HIV-1 (common one)	HIV-2
<ul style="list-style-type: none"> ✓ Causes HIV infection <u>worldwide</u>. ✓ Highly virulent. ✓ Highly susceptible to mutations. 	<ul style="list-style-type: none"> ✓ Causes the infection in specific regions e.g. West Africa ✓ Relatively less virulent. ✓ Relatively less susceptible to mutations.

Structure of HIV:

- Family of **Retroviridae**.
- Virion consist of:
 - **Glycoprotein envelope (gp120, gp41)**→help to attach the HIV virus with T- helper cell
 - Matrix layer (P17).
 - **Capsid (core) - (P24)**.
 - Two copies of ssRNA.
 - **Enzymes (reverse transcriptase, integrase& protease).**



Transmission of HIV

1. Sexually:

- The **most common** mode of HIV infection. At the **genital mucosa through direct contact with infected blood, semen and vaginal secretion.**

2. Parenterally:

- **Direct exposure to infected blood** and blood products.
- Use contaminated needles and syringes as in (**drug abuser**) and Tattooing.
- Through contaminated surgical and **dental instruments.**
- Sharing contaminated razors, tooth brushes, and nail cutters.

3. From mother to child:

Transplacentally (vertical 25%)

- **Treatment of the mother** with antiretroviral Anti-reverse transcriptase (**Zidovudine**) during pregnancy can reduce transmission in most cases.

Perinatally mainly (50%) during delivery

- Given Anti-reverse transcriptase (**Nevirapine**) as single dose **during delivery** can reduce the transmission to the baby.

Breast feeding (25%)

- Antiretroviral treatment **of the mother and infant** after births can also significantly decrease the risk of HIV infection in the newborn.

Virus Inactivation:

HIV is **easily inactivated outside the body** by treatment for 10 min at 37°C with any of the following:

- | | |
|--------|--|
| ▪ 10% | House hold bleach, Sodium Hypochlorite |
| ▪ 50% | Ethanol |
| ▪ 35% | Isopropanol |
| ▪ 0.5% | Paraformaldehyde |
| ▪ 0.3% | Hydrogen peroxide |

The Course of HIV-infection

- Based on CD4+ T cell count and presence of opportunistic infections HIV infection goes into several stages:
- Incubation period(2-4) weeks (no symptoms)→The acute phase (12) weeks =3 months→The chronic phasefor about 1-10 years in adults, 1-5 years in children.→AIDS (end stage of the disease)

1-Acute phase

- **Rapid viral replication (high viral load) with presence of Viral RNA in the serum.**
 - **Gradual decrease in CD4 cell count**
 - 50-70% of patients develop symptoms resemble infectious mononucleosis or Flu (fever, headache, anorexia, fatigue, lymphadenopathy, & skin rash).
 - 20% of patients may develop aseptic meningitis.
- ✓ **Best diagnostic method in this phase → serology**

Serology profile of HIV infection:

1. RNA
2. CD4
3. Core Ag (p24)
4. Anti – core (Anti- p24)
5. Anti-envelop (Anti-gp120,gp41)→**Present in the beginning of acute phase until the patient died**

Serological picture of Acute stage:

- Characterized by appearance of **viral RNA**.
- Normal to slightly **decrease in no of CD4**.
- **Then** the detection **of core antigen (p24 antigen)followed by** appearance of **Anti-envelop (Anti-gp120,gp41)**
- **Anti- core (Anti-P24)**

2-The chronic phase (asymptomatic phase)

- This phase almost **totally asymptomatic**, which lasts for about 1-10 years (**if not treated**) in adults, 1-5 years in children.
- **Patient still contagious (infectious)**

❖ Serological picture of chronic stage:

- Characterized **by low viral load (RNA)**in the circulation
- Continuous **detection of both (Anti-gp120,gp41) and (Anti-p24)**.
- **CD4 counts are generally within normal limits usually above (350 cells/mm³)**

At the end of this stage two syndromes appear:

1. **Persistent generalized lymphadenopathy (PGL)**
2. **AIDS-related complex (ARC).**

A. <u>Persistent Generalized Lymphadenopathy (PGL)</u>	B. <u>AIDS-related complex (ARC)</u>
<ul style="list-style-type: none"> ▪ Enlarged lymph nodes (at least 1 cm in diameter), in two or more extra-inguinal sites, persisting for at least 3-months in the absence of any current illness or medication known to cause enlarge lymph node. 	<ul style="list-style-type: none"> ▪ Is a group of clinical symptoms that <u>come before AIDS</u> and may include the following: <ul style="list-style-type: none"> • Fever of unknown origin that persists > 1 month. • Chronic diarrhea, persisting > 1 month. • Weight loss (Slim disease) > 10% of the original weight. Fatigue. • Neurological disease as myelopathies and peripheral neuropathy.
<u>Serology :</u> <ul style="list-style-type: none"> ▪ Viral RNA ▪ core antigen (p24) indicate active viral replication ▪ Anti-envelop (Anti-gp120,gp41) ▪ CD4 count decrease but still more than 200×10^6 cells/L 	<u>Serology :</u> <ul style="list-style-type: none"> ▪ High load of Viral RNA and ▪ core antigen p24 (indicate active viral replication) ▪ Anti-envelop +ve (Anti-gp120) ▪ CD4 count <u>decreased</u> but still more than (200 cells/mm^3)

3- AIDS

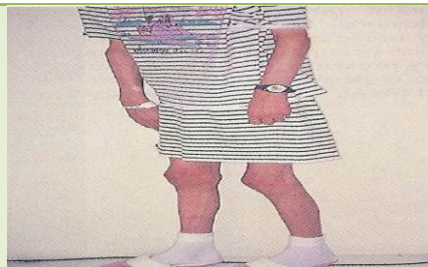
➤ The end stage of the disease characterized by:

- **Marked decrease CD4 T-helper cells $< 200 \times 10^6$ cells/L** lead to :
 - ✓ Opportunistic infections (cell mediated immunity) e.g. **pneumocystis carinii pneumonia**, toxoplasmosis of brain, **disseminated or extra pulmonary myco-bacteriosis**.
 - ✓ **Unusual cancers** (**Kaposi's sarcoma**)

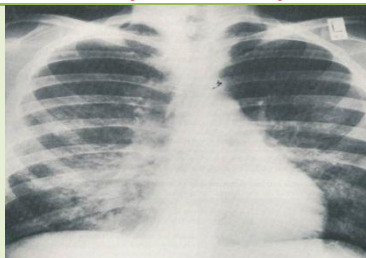
❖ Serological picture of AIDS:

- **Marked increase of Viral RNA**
- **Increase core antigen Ag p24**
- **Anti envelop +ve (Anti-gp120) ,**
- **Marked decrease CD4 count less than 200 cells/mm^3**

Slim disease



Pneumocystis carinii pneumonia



Kaposi's sarcoma



Diagnosis & Management

❖ How to diagnose an HIV patient?

1. **Patient's history** with or without clinical symptoms may give hints for a physician whether the patient has ever exposed to HIV or not.
2. **Screening patient's serum by ELISA** for both (HIV Ag & HIV Ab) if the result is → **+ve** we repeated the **specimen twice** if still giving +ve result will do **confirmatory tests (Western Blot, RIBA, PCR)**.
3. **(Western Blot)** → To confirm the presence of Anti-HIV to the structural proteins of the virus by ELECTROPHORESIS → if +ve will do **PCR**
4. **PCR** For detection of HIV RNA in the blood (viral load) this test is important for
 - ✓ **HIV diagnosis in infant of infected mother**
 - ✓ **and also to monitor the antiviral treatment**

Goals of HIV treatment

- **To inhibit viral replication.**
- To control **chronic immune activation** and keep the immune system close to the normal state.
- To prevent the development of **opportunistic infection.**
- To minimize **the chance of viral transmission** especially from mother to neonate.

Prevention & Control

- **There is no vaccine available yet for HIV**
- Practice safer sex by having one sexual partner
- Do not share razors, tooth brushes, etc
- Do not share needles and syringes
- Avoid direct exposure to body fluids
- Educate the public about HIV-infection

Treatment

- Is a **combined therapy** known as **high active antiretroviral therapy (HAART)**.
- NOTE: HAART does not clear (**eradicate**) the virus from the body, and should be taken all life..
- NOTE: HAART treated **patients are still contagious** even if their blood viral load below detection (< 50 copies/μL).
- HAART is usually composed of two reverse transcriptase inhibitors and one protease inhibitor.
 - ❖ **There are two types of reverse transcriptase inhibitors:**
 1. **Nucleoside analogue RT inhibitors for HIV-1 & HIV-2:**
 - **Zidovudine (AZT)** - Zalcitabine (ddC)
 - Stavudine (d4T) - Lamivudine (3TC)
 2. **Non-nucleoside analogue RT inhibitors for HIV-1 only:**
 - **Nevirapine**- Delavirdine - Efavirenz
 - ❖ **Proteases inhibitors include:**
 - Saquinavir - Indinavir
 - Nelfinavir - Ritonavir

Summary

- HIV infects mainly cells that have CD4 on their surface especially T-helper cells or others such as Macrophages.
- HIV virion is consist of: Glycoprotein envelope “gp120, gp41” (which help HIV to attach to T- helper cells), Matrix layer, Capsid (core) - (P24), 2 copies of ssRNA and most importantly Enzymes (reverse transcriptase, integrase& protease).
- HIV can transmit: 1- sexually (present in blood, semen and vaginal secretions) 2- Parenterally (Direct exposure to infected blood , contaminated needles and syringes or contaminated surgical and dental instruments or even tooth brushes. 3- From mother to child (Transplacentally , during delivery (50%) , Breast feeding)
- Treatment of the infected mother to reduce transmission: 1- Antiretroviral Anti-reverse transcriptase (Zidovudine) during pregnancy 2- Anti-reverse transcriptase (Nevirapine) as single dose during delivery
- Based on CD4+ T cell count HIV goes into 3 stages:
 - Acute Stage:
 - Rapid viral replication (high viral load) and patient will develop flu-like symptoms.
 - Serological picture will shows: 1. appearance of viral RNA (Characteristic) with slightly decrease in no. of CD4 2. Then the detection of core antigen (p24 antigen) 3. followed by appearance of Anti-envelop (Anti-gp120,gp41) and Anti- core (Anti-P24)
 - Chronic Stage:
 - Patient almost totally asymptomatic but still contagious (infectious)
 - Serological picture of chronic stage:
 - 1- Characterized by low viral load (RNA) in the circulation
 - 2- Continuous detection of both (Anti-gp120, gp41) and (Anti-p24).
 - 3- CD4 counts are generally within normal limits usually above (350 cells/mm3)
 - At the end of this stage two syndromes appear:

C. <u>(PGL)</u>	D. <u>(ARC)</u>
<ul style="list-style-type: none"> ▪ <u>Enlarged lymph nodes in two or more extra-inguinal sites</u> 	<ul style="list-style-type: none"> ▪ Group of clinical symptoms <u>come before AIDS</u> : <ul style="list-style-type: none"> • <u>Fever</u> of unknown origin & Chronic diarrhea that <u>persists > 1 month.</u> • <u>Weight loss (Slim disease) & Fatigue.</u> • <u>Neurological</u> disease as myelopathies and peripheral neuropathy.

- AIDS Stage:
 - Marked decrease CD4 T-helper cells < 200 x 10⁶ cells/L lead to : Opportunistic infections (cell mediated immunity) e.g. pneumocystis carinii pneumonia, pulmonary mycobacteriosis. And Unusual cancers (Kaposi's sarcoma)
 - Serological picture of AIDS: 1. Marked increase of Viral RNA
 2. Increase core antigen Ag p24 3. Anti envelop +ve (Anti-gp120)
 4. Marked decrease CD4 count less than 200 cells/mm3

- To diagnose an HIV patient: screen the patient serum by ELISA for both (HIV Ag & HIV Ab) if the result is +ve. Do some confirmatory tests (Western Blot, RIBA, and PCR).
- PCR is used for : HIV diagnosis in infant of infected mother and also to monitor the antiviral treatment
- There is no cure for HIV but there is a treatment to control and inhibit viral replication.
- The treatment is a combined therapy (HAART) which is composed of 2 reverse transcriptase inhibitors (Zidovudine (AZT) & Nevirapine) and 1 protease inhibitor (Saquinavir & Nelfinavir)
- **There is no vaccine available yet for HIV**