HIV

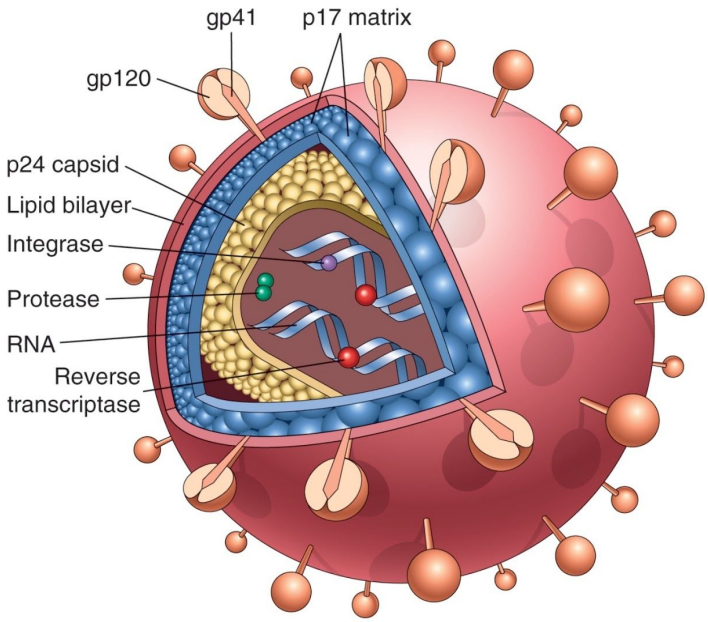
Important note: **Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all or our work: Pathology Edit.**

Grey = Extra
Red = Important

HIV

Introduction

- Human immunodeficiency virus (HIV) is the causative agent for AIDS (Acquired Immune deficiency syndrome).
  - AIDS is the (last stage) of HIV infection.
- **Retrovirus of the lentivirus family that contains only RNA** .
- Discovered in the early 1980's, then spread to infect millions of people.
- The most common type is **HIV-1**. It has led to the worldwide AIDS *epidemic*.
- HIV-2 that is much less common.
- The result of HIV infection is the destruction of the **immune system.**
- All HIV infected persons are at risk for illness and death from development of **opportunistic infections, unusual tumors,** and the inevitable manifestations of **AIDS.**

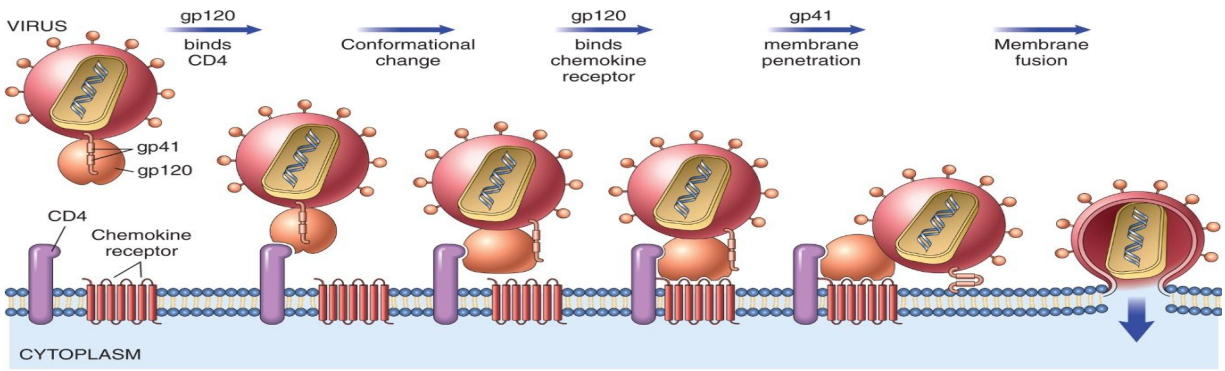


Structure

- The mature virus consists of an electron dense core containing the viral genome consisting of the **2 short strands of RNA** (ribonucleic acid) → covered by **P24 capsid**→ All are encased by bilayer lipid envelope→ which contain glycoprotein receptors (inner **gp41** and outer **gp120**)
- Contains three genes responsible for structural and replication (gag, env, pol)
- It also contains the enzymes **reverse transcriptase**, **protease**, **ribonuclease**, and **integrase**.

Pathogenesis

1. Virus expresses a cell surface protein/antigen called gp120 → is responsible for tropism/attraction to CD4+ receptor → aids in the **binding** & **entry** of the virus to the target cells.
2. In addition, gp120 also binds to two co-receptors **CXCR4** (mostly on T cells) & **CCR5** (mostly on macrophages) on the host cell surface which **assist** in the entry of the virus into the host cell.
    - **The target cells are:** blood monocytes‹tissue macrophages, T & B lymphocytes, natural killer (NK) lymphocytes, dendritic cells (i.e. the Langerhans cells of epithelia and follicular dendritic cells in lymph nodes), hematopoietic stem cells, endothelial cells, microglial cells in brain, and gastrointestinal epithelial cells. (Cells which contains CD4 receptor + CXCR4 &/or CCR5)
    - *Retroviruses are **unable** to replicate outside of host cells because they contain only RNA (and not DNA).*
3. When HIV infects a cell, it uses its **reverse transcriptase enzyme** to transcribe/convert its RNA to *host cell proviral DNA* for replication → then it's inserted into host cell genomic DNA by the **integrase enzyme.**
4. HIV provirus[1] is replicated by the host cell to produce → HIV virions which are released by surface budding or infected cell lysis → then HIV infect additional cells.



NOTE: The probability of infection depends on both the number of infective HIV virions in the body fluid which contacts the host as well as the number of cells with CD4 receptors available at the site of contact.

Establishment Infection

- HIV has the ability to mutate easily resulting in the emergence of HIV variants within the infected person's cells → become more toxic and can resist drug therapy→ Over time, different tissues of the body may harbor different HIV variants.
- **Macrophages** ,**Langerhans cells** **&** dendritic cells (**FDC's**) can be HIV-infected but are not destroyed themselves, That's why they are important as reservoirs and vectors for the spread of HIV carried elsewhere in the body including the CNS.

Example: Once the infection extends to the lymph nodes → the HIV viruses are trapped in the processes of follicular dendritic cells (**FDC's**) → providing a reservoir → HIV then infect CD4+ T lymphocytes that are passing through the lymph node.

[1] A provirus is a virus genome that is integrated into the DNA of a host cell.

Modes of transmission

HIV can be present in body fluids and secretions include: Genital secretions, blood, and breast milk, saliva, urine, tears, and sweat.
NOTE: Saliva, urine, tears, and sweat is not major transmission of HIV → because of the low concentration of HIV in these fluids.

1. HIV is primarily spread as a **sexually transmission** through :
   - From male to male. (Homosexual or bisexual men 75% of cases in the US)
   - Male to female, and female to male. (male to female is more potent)
   - Female to female transmission remains extremely rare.

2. HIV can be transmitted through parenteral route, e.g:
   - **Intravenous drug users sharing infected needles**.
   - Tattoo needles. (less common)
   - Health care workers with **percutaneous exposures** such as needle puncture HIV-containing blood.(rare)
   - Persons receiving multiple **blood transfusions** e.g Hemophiliacs.

Note: Screening of blood products for HIV has significantly reduced HIV transmission by this means.

3. HIV infection can also be acquired as a **congenital infection (**from the infected mother) by:

   - **Perinatally**
     - Transplacentally i.e. in utero.
     - At the time of delivery through the birth canal (intrapartum).
   - **Infancy**
     - Through breast milk.

NOTE: HIV infection is not spread by casual contact in public places, households, or in the workplace. HIV is not spread by insect vectors. There is no vaccine to prevent HIV infection because it keeps mutating (changing its genome) all the time.

Diagnosis

1. Use rapid test (ELISA) technique: detect the HIV antibodies and antigen.
2. If rapid test is positive → then repeate the test. (Twice)
3. If repeated test is positive → Confirm HIV infection with Western blot or immunofluorescence assay (IFA).

NOTE: The average HIV-infected person may take up to several weeks to become seropositive, and then may live up to 8 or 10 years (on average) before development of the clinical signs and symptoms of AIDS.

Primary Infection

- Primary HIV infection may go:
  1. Unnoticed in at least half of cases or,
  2. Produce a mild disease (which quickly subside) or,
  3. Produce acute HIV infection followed by a long clinical "latent" period lasting years.

- Primary acute infection symptoms may include:

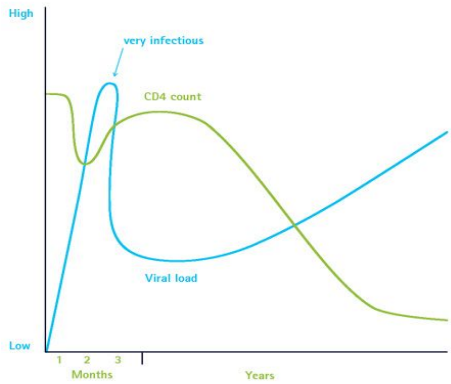
Fever, generalized lymphadenopathy, pharyngitis, rash, arthralgia and diarrhea. These symptoms diminish over 1 to 2 months.

Acquired Immunodeficiency Syndrome (AIDS)

The stage of clinical AIDS is reached years after initial infection of HIV and is marked by the development of *one or more of the typical opportunistic infections* or *neoplasms* common to AIDS.

Pathogenesis & Clinical :

- The primary target of HIV is the **immune system**, which is gradually destroyed.(producing clinical symptoms)
- Clinically, HIV infection may appear "latent" for years. During this period there is ongoing immune system destruction but still enough of the immune system remains intact to provide immunity and prevent most infections. (at this stage patient is mostly asymptomatic)



- Eventually, when a significant number of CD4+ T lymphocytes have been destroyed and when production of new CD4 cells cannot match destruction, then **failure of the immune system leads to the appearance of clinical AIDS.**
- The progression to clinical AIDS is also marked by the appearance of syncytia-forming (SI) variants of HIV in about half of HIV infected patients. These SI variants are associated with more rapid CD4+ cell decline. Once the syncytial-forming variants starts to **appear** in the blood, the patient is going to go into rapid decline.
- The development of signs and symptoms of AIDS typically **parallels** laboratory testing for CD4 lymphocytes. When the CD4 lymphocyte count drops below **200/microliter,** then the stage of **clinical AIDS** has been reached. Patients who are HIV positive are tested every few months to check progression into AIDS. This is the point at which the characteristic **opportunistic infections and neoplasms** of AIDS appear. **The CD4+T /CD8+T cells ratio** in peripheral blood is also greatly **reduced**, often to less than **1.0**.

Common complications seen with AIDS	
Infections	● pneumocystis jiroveci **(most common),** CMV, mycobacteria, fungal etc.
Neoplasms	● **Kaposi's sarcoma** (KS) ● **Malignant lymphomas**
Miscellaneous	● **lymphoid interstitial pneumonitis** is a condition involving the lung that can be seen in AIDS in **children**.

Infections related to AIDS:

Pneumocystis jiroveci:(formerly carinii)

- **Pneumocystis jiroveci or Pneumocystis** carinii *is the most frequent opportunistic infection* seen with AIDS. It commonly produces a **pulmonary infection.**
- **Diagnosis:**
  1. Histologically in cytologic (bronchoalveolar lavage).
  2. Biopsy (transbronchial biopsy) material from lung, (shows soap bubble pattern"cotton candy exudate").
  3. In the lung, there is soap bubble like intra-alveolar exudate and the organism appears as cyst or (coma) like structures that are positive with silver stain.

Cytomegalovirus:

- It causes : 1- **Pneumonia**
  2- Serious disease in the **brain and gastrointestinal** tract.
  3 -**Retinitis and blindness** in persons with AIDS.

Mycobacterial infections:

1- Mycobacterium tuberculosis.
2- **Mycobacterium avium complex** (MAC) infection (other type of TB).
Definitive diagnosis by: 1- Culture 2- PCR.

Fungal Infections: not important

1- **Candidiasis** :of the esophagus, trachea, bronchi, or lungs.
2- **Cryptococcus neoformans** (produces pneumonia and meningitis).
3- Histoplasma capsulatum. 4- Coccidioides immitis.

Other infections: not important

- **Toxoplasmosis** caused by *Toxoplasma gondii* is a protozoan parasite that most often leads to **infection of the brain** with AIDS.
- Herpes simplex infection in the mucosa.
- Aspergillosis especially in the lung.
- **Cryptosporidium and Microsporidium** produce voluminous watery diarrhea in patients with AIDS.
- Viral HIV encephalitis.
- Syphilis (primary, secondary and tertiary).

Malignant Neoplasms related to AIDS:

- **Kaposi's sarcoma** (KS) produces (low grade malignant proliferation of endothelial cells.).
  - **It is a sarcoma of the blood vessels**.
  - Visceral organ can also be involved.
  - It is associated with HHV-8[2].

Clinical presentation: Reddish purple patches or nodules over the skin.

Diagnosed: Skin biopsy.

Histology: It shows malignant spindle cells of vascular origin.

Malignant lymphomas[3].

- Commonly it is **B-cell Non Hodgkin's Lymphoma**.
- They are typically of a high grade and often in the **brain**.
- They are very aggressive and respond poorly to therapy.

[2] Kaposi sarcoma herpesvirus (KSHV), or human herpesvirus-8 (HHV-8)
[3] primary lymphoma of the brain is considered an AIDS-defining condition.

Summary

Mode of transmission	Sexual transmission	Parenteral transmission	Mother-to-Infant Transmission
Pathogenesis of HIV	● The virus expresses a surface antigen, gp120, which attaches to CD4 (along with co-receptors CXCR4 & CCR5) on T-Lymphocytes. This will facilitate virus entry to host cell. ● Once entry to host cell occurs, viral enzyme **reverse transcriptase** converts viral RNA to proviral DNA. Then, **Integrase enzyme** inserts proviral DNA into host genome for replication.		
Pathogenesis of AIDs	HIV first causes a **primary infection**, then the virus appears **latent** for years. During which, ongoing immune system destruction occurs. Up to a point where CD4 T-Lymphocytes drops **below 200/microliter**, clinical stage of **AIDS is reached.**		
Diagnosis	1- **ELISA** to detect viral antibodies. 2- If positive, (**Western blot or IFA**).		
Opportunistic infections	**Pneumocystis jirovecai:** is the most frequent opportunistic infection seen with AIDS. It commonly produces a pulmonary infection. histological finding (shows soap bubble pattern, and silver staining shows the organism which is comma shaped)	**Cytomegalovirus:** It causes : 1- **Pneumonia** 2- Serious disease in the **brain and gastrointestinal** tract. 3 -**Retinitis and blindness** in persons with AIDS	**Mycobacterial infections** 1- Mycobacterium tuberculosis. 2-**Mycobacterium avium complex** (MAC) infection (other type of TB). **Definitive diagnosis** by: 1- Culture 2- PCR
Malignant Neoplasm	**Kaposi's sarcoma** ○ **It is a sarcoma of the blood vessels**. ○ Visceral organ can also be involved. ○ It is associated with HHV-8 [4].	**Malignant lymphomas** ● Commonly it is **B-cell Non Hodgkin's Lymphoma**. ● They are typically of a high grade and often in the **brain**. ● They are very aggressive and respond poorly to therapy.	

[4] Kaposi sarcoma herpesvirus (KSHV), or human herpesvirus-8 (HHV-8)

MCQ

Q1-HIV belongs to the Retroviridae family and is made up of ?

A. Two single stranded RNA
B. Double stranded DNA
C. Single stranded RNA

Q2-In the acute Phase CD4 cells show?

A. ncrease in number
B. Gradual decrease in number
C. Steep drop in number

Q3- What immune cells does HIV infect?

A. CD4 positive cells
B. Macrophages
C. Both a and b

Q4-What is Acute HIV Syndrome?

A. When HIV progresses into AIDS
B. The stage immediately after HIV
C. infection when patient falls ill
D. The final fatal disease for AIDS patient

Answers: 1-A ,2-B, 3-C, 4-B

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com
Twitter: @Pathology434
Ask us: www.ask.fm/Pathology434

Good luck!

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روى العوهلي
رزان صبحي
آسماء الرصيص
مها الربيعة

حسين الكاف
مصعب العقيل
سلمان القزلان
عبدالاله المطيري
عبدالله العماري
سامي القرني
خالد الدريبي

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- Thanks to every member that supported this team, Without you it wouldn't happen.

Finally !! Done with basic science years !