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HIV Pathology

{ ومن لم يذق مرّ التعلُّمِ **ساعةً**.. تجرع ذلَّ الجهل **طوال** حياتهِ }

Lecture Ten

Objectives:

At the end of this lecture, the student should be able to:

- Understand the pathogenesis of the Aids syndrome.
- Recognize the systemic manifestations of the Aids syndrome with special emphasis on Kaposi sarcoma and principal opportunistic infections that could be encountered in Aids patients.

References: Lecture Slides & Robbins

Revised by

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Red: Important. Grey: Extra Notes Doctors Notes

Introduction:

- **Human immunodeficiency virus (HIV)** is the causative agent for AIDS.
- HIV is a retrovirus of the lentivirus family that contains only RNA.
- It was unknown until the early 1980's, but since then has spread around the world to infect millions of people.
- The most common type of HIV infection is known as **HIV-1** and is the type that has led to the worldwide AIDS epidemic. There is also an 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 and tumors and the inevitable manifestations of AIDS, and neurologic manifestations.

Structure:

- The mature virus is spherical and consists of an electron dense core containing the viral genome consisting of the 2 short strands of RNA (ribonucleic acid).
- cone-shaped core surrounded by a lipid envelope derived from the host cell membrane.
- It also contains the enzymes reverse transcriptase, protease, ribonuclease, and integrase.
- All are encased by an outer lipid envelope. Also The virus core contains:
  - Major capsid protein p24[1].
  - Nucleocapsid protein p7/p9.

The major modes of transmission of HIV (the high-risk population):

It can be present in a variety of body fluids & secretions. They include genital secretions, blood, and breast milk.	NOTE: saliva, urine, tears, and sweat is of no major clinical importance, as transmission through these fluids does not routinely occur because of the low concentration of HIV in these fluids.	Primarily spreads as a sexually transmissible disease. It can occur from male to male, male to female, and female to male. Female to female transmission remains extremely rare.
HIV can be transmitted through parenteral route, e.g. Intravenous drug users sharing infected needles.	Less common practices like use of instruments such as tattoo needles not properly disinfected also carries a potential risk. Health care workers with percutaneous exposures (needle puncture) to HIV-containing blood.	Persons receiving multiple blood transfusions e.g hemophiliacs. Screening of blood products for HIV has significantly reduced HIV transmission by this means.
Can also be acquired as a congenital infection either perinatally or in infancy.	Mothers with HIV infection can pass the virus transplacentally i.e. in utero at the time of delivery through the birth canal through breast milk.	NOTE: Doesn't spread by casual contact in public places, households, or in the workplace or by insect vectors. There is no vaccine to prevent HIV infection

[1] The p24 protein is the most readily detected viral antigen and is therefore the target for the antibodies used to diagnose HIV infection in blood screening.

Pathogenesis of HIV:

Any cell that is CD4 positive will link to gp 120 (HIV), so HIV infect all CD4 positive cells.

The two major targets of HIV infection are the **immune system and the CNS.**

The HIV virion expresses a cell surface protein/antigen called gp120. What does it do?

- Aids in the binding of the virus to the target cells.
- Responsible for tropism/attraction to CD4+ receptors. This function helps in entry of HIV into the host cell.
- Binds to two co-receptors CXCR4 and CCR5 on the host cell surface. They also assist in the entry of the virus into the host cell.

Once the virus enters the human body

- It attaches itself to the target cell via the CD4 receptors on the surface of the target cell and therefore gains entry into the target cell
- This requirement explains the tropism of the virus for CD4+ T cells and its ability to infect other CD4+ cells, particularly macrophages and DCs.

The coreceptors (critical components of the HIV infection process)	
CCR5	**CXCR4**
▪ Used by R5 virus strains (Macrophage-tropic strains). ▪ CCR5 is expressed on both monocytes and T cells, hence, these cells are susceptible to infection by R5 strains. Most infections **initially** are transmitted by R5 strains.	X4 strains bind to CXCR4, which is expressed on T cell lines (and not on monocytes/ macrophages), so that only activated T cells are susceptible. Over the course of infection, X4 viruses gradually accumulate (& R5 strains evolve into X4 strains, because of mutations in genes that encode gp120); these are especially virulent and are responsible for T cell depletion in the **final, rapid phase** of disease progression.

The T-lymphocytes have surface CD4 receptors (CD4+ T lymphocytes) to which HIV can attach to promote entry into the cell.

→ Retroviruses are unable to replicate outside of living host cells because they contain only RNA and do not contain DNA.

→ So once HIV infects a cell, it must use its reverse transcriptase enzyme to convert its RNA to host cell proviral DNA for replication. AKA complementary DNA.

This HIV proviral DNA is then inserted into host cell genomic DNA by the integrase enzyme.

→ Then the HIV provirus is replicated by the host cell to produce additional HIV virions which are released by surface budding.

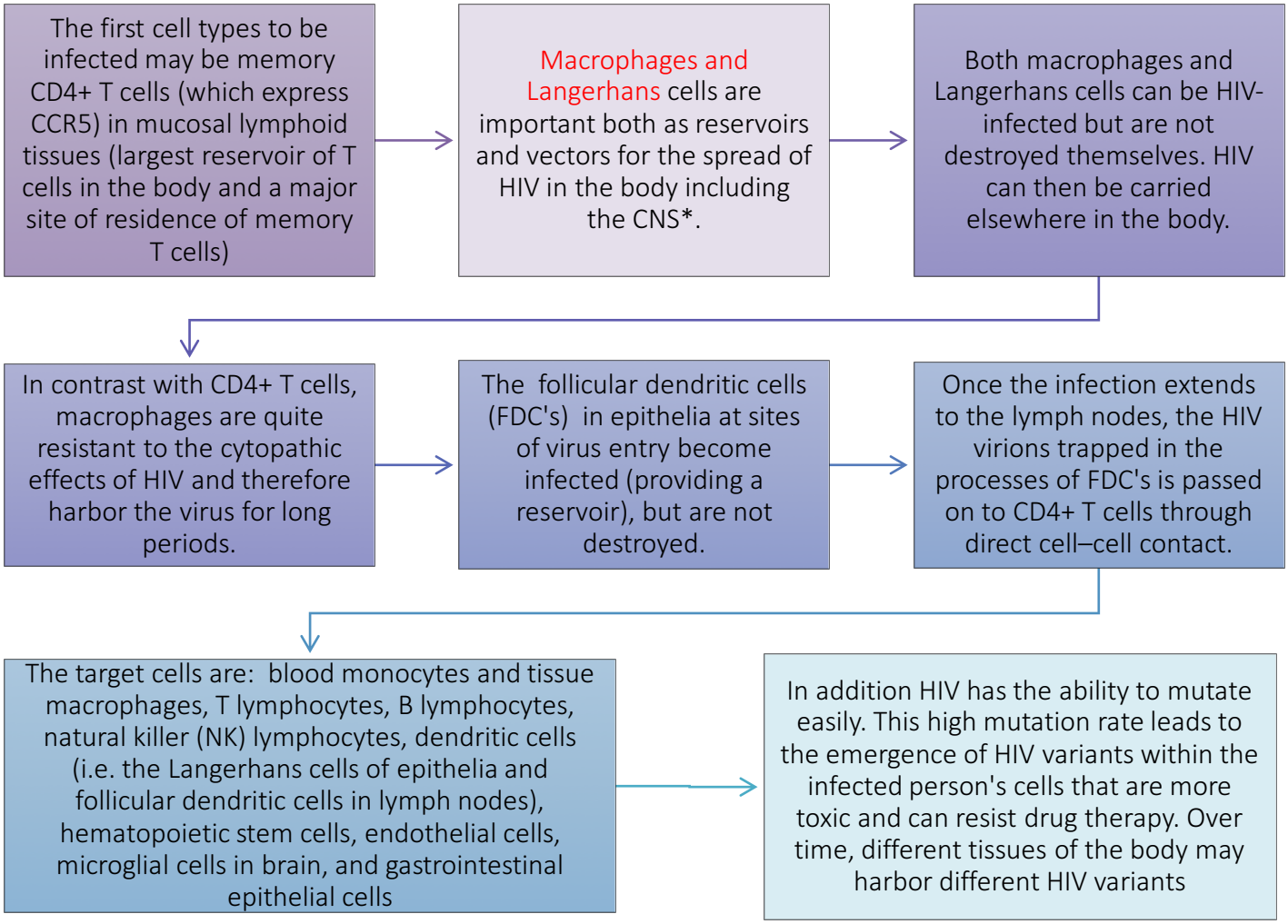
In quiescent T cells, HIV proviral cDNA may remain in the cytoplasm in a linear episomal form.

Although HIV-1 can infect resting T cells, the initiation of proviral DNA transcription (and hence productive infection) occurs only when the infected cell is activated by exposure to antigens or cytokines (as a physiologic response to infections and other stimuli).

Such productive infections, associated with extensive viral budding, lead to cell death.

→ Alternatively the infected cells can undergo lysis with release of new HIV virions which can then infect additional cells.

Establishment of HIV Infection: (after replication takes place, what happens?)



- The main reservoirs and vectors of HIV are the macrophages, langerhans and FDC, these cells really help in collecting the viruses, allowing them to multiply and storing them and then transporting them to different part of the body.
- Remember when you have multiplication of anything such as mitosis the chances of mutations are high, but in our body we have certain mechanisms that stop this mutations from happening such as P53, these mechanisms do not work here so now you have mutations of the HIV and get a lot of mutant viruses, that means 1% who gets the infection first it multiply to another thousand viruses, and out of these thousand 30 become mutant and will have different strains of viruses so it is very hard to treat something that have multiple strains and features.

* The nervous system is a major target of HIV infection, It's most likely carried into the brain by infected monocytes) Because neurons are not infected by HIV most experts believe that the neurologic deficit is caused indirectly by viral products and soluble factors (e.g., cytokines such as TNF) produced by macrophages and microglial cells

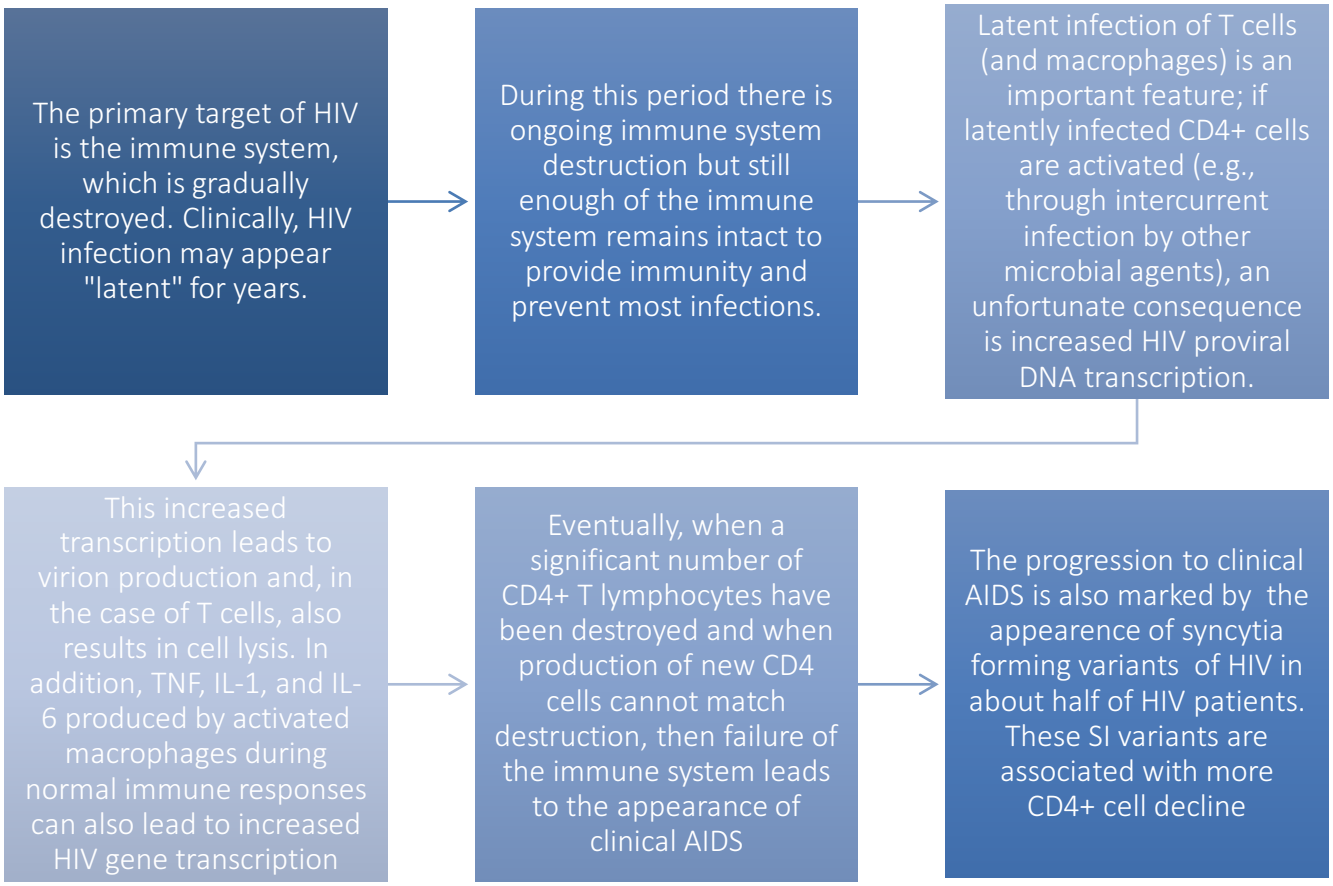
Primary HIV Infection:

- Primary HIV infection may go unnoticed in at least half of cases or produce a mild disease which quickly subsides, or produce acute HIV infection, followed by a long clinical "latent" period lasting years.
- Primary acute HIV infections 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 and is marked by the development of one or more of the typical opportunistic infections or neoplasms common to AIDS.

Pathogenesis of AIDS/clinical AIDS:



- We have nice bone marrows which are producing these cells multiplying every time.

Development of Signs & Symptoms of AIDS:

- The development is 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.
  - This is the point at which the characteristic opportunistic infections and neoplasms of AIDS appear.
  - The CD4+T cells to CD8+T cells ratio is also greatly reduced, often to less than 1.0.
  - How? The loss of CD4+ cells leads to an inversion of the CD4+/ CD8+ ratio in the peripheral blood. Thus, while the normal CD4+/CD8+ ratio is 1 to 2, patients with AIDS have a ratio of 0.5 or less.

Following are some of the more common complications seen with AIDS:

- Infections e.g. pneumocystis jiroveci, CMV, mycobacteria, fungal etc.
- Neoplasms
- Miscellaneous e.g. lymphoid interstitial pneumonitis is a condition involving the lung that can be seen in AIDS in children.

Diagnosis OF HIV:

- Test for HIV antibodies is done with a rapid test using an enzyme-linked immunosorbent assay (ELISA) technique.
- If rapid test is positive, then the next step is to 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. If someone get infected with the HIV it takes along time to become seropositive, so it is not necessarily that every seropositive person will have symptoms of AIDS, without treatment the symptoms of AIDS will develop a couple of years of seropositivity.

Infections associated with AIDS:

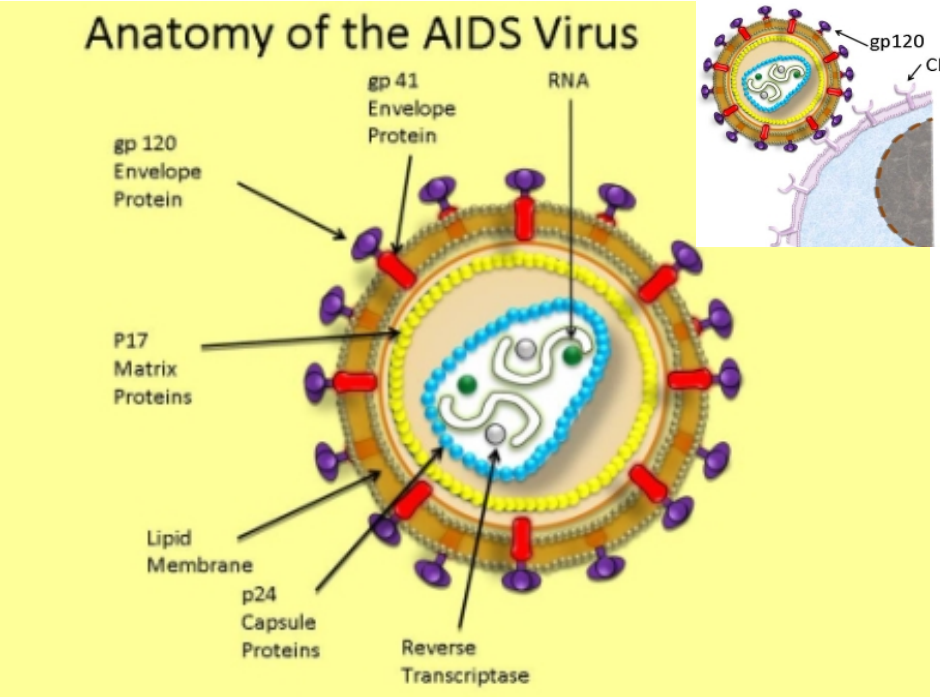
	Info
Pneumocystis jiroveci (formerly carinii)	• The most frequent opportunistic infection seen with AIDS. • It commonly produces a pulmonary infection. • Diagnosis is made histologically by finding the organisms in cytologic (bronchoalveolar lavage) or biopsy (transbronchial biopsy) material from lung. lavage is a procedure where we pass some fluid into the lung and we collect that fluid back. • In the lung, there is soap bubble like intra-alveolar exudate and the organism appears as cyst like structures that are positive with silver stain.
CMV	Cytomegalovirus (CMV) infection causes pneumonia and can also cause serious disease in the brain and gastrointestinal tract. It is also a common cause for retinitis and blindness in persons with AIDS.
Fungal Infections	• Candidiasis of the esophagus, trachea, bronchi, or lungs. • Cryptococcus neoformans (produces pneumonia and meningitis), Histoplasma capsulatum, and Coccidioides immitis. Make sure that you remember the names and make sure that you know about Pneumocystis jiroveci.
Mycobacterial infections	• Definitive diagnosis of mycobacterial disease is made by culture and PCR. • Mycobacterium tuberculosis & Mycobacterium avium complex (MAC) infection.
Other Infections	• 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) **just know the names of these infection no one will ask you how you diagnose it**

Malignant neoplasms Seen With AIDS:

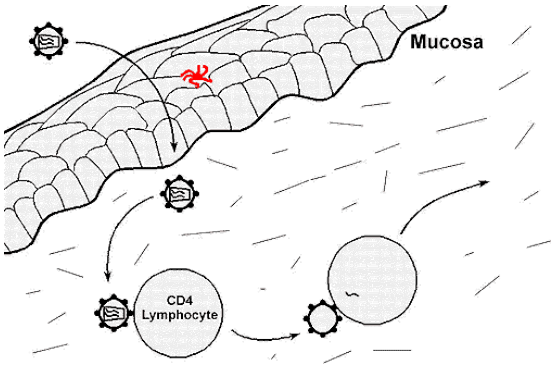
- **Kaposi's sarcoma (KS):**
  - It is a sarcoma of the blood vessels & produces reddish purple patches or nodules over the skin and can be diagnosed with skin biopsy.
  - Visceral organ can also be involved with KS. It is associated with HHV-8 and on histology, it shows malignant spindle cells of vascular origin.
    What are the names of blood vessel tumors? meningioma and angiosarcoma, so kaopsi's sarcoma is the sister of angiosarcoma.

- **Malignant lymphomas**:
  - Commonly it is B-cell Non Hodgkins Lymphoma.
  - They are typically of a high grade and often in the brain. They are very aggressive and respond poorly to therapy.
    -Lymphoma: tumor of the cells that is coming from the lymph nodes.
    -What about leukemia? tumor of the cells that arising from the bone marrow.
    -If we give you story and we ask you whether it is kaposi's or lymphoma you should be able to distinguish it.

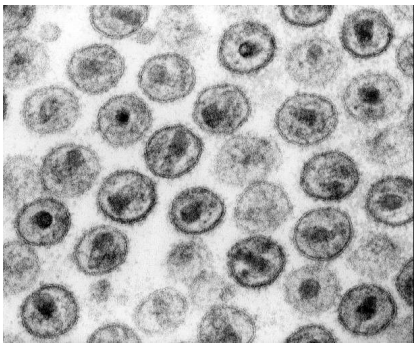
Extra Summaries, Pictures and helpful explanations



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.
The higher the number of HIV that enter and the higher the number of CD4 positive cells present, the higher the chances of developing infection, but if there is only have one virus and one lymphocyte we should not probably develop HIV infection



Human immunodeficiency virus is shown crossing the mucosa of the genital tract to infect CD4+ T-lymphocytes. A Langerhans cell in the epithelium is shown in red in this diagram



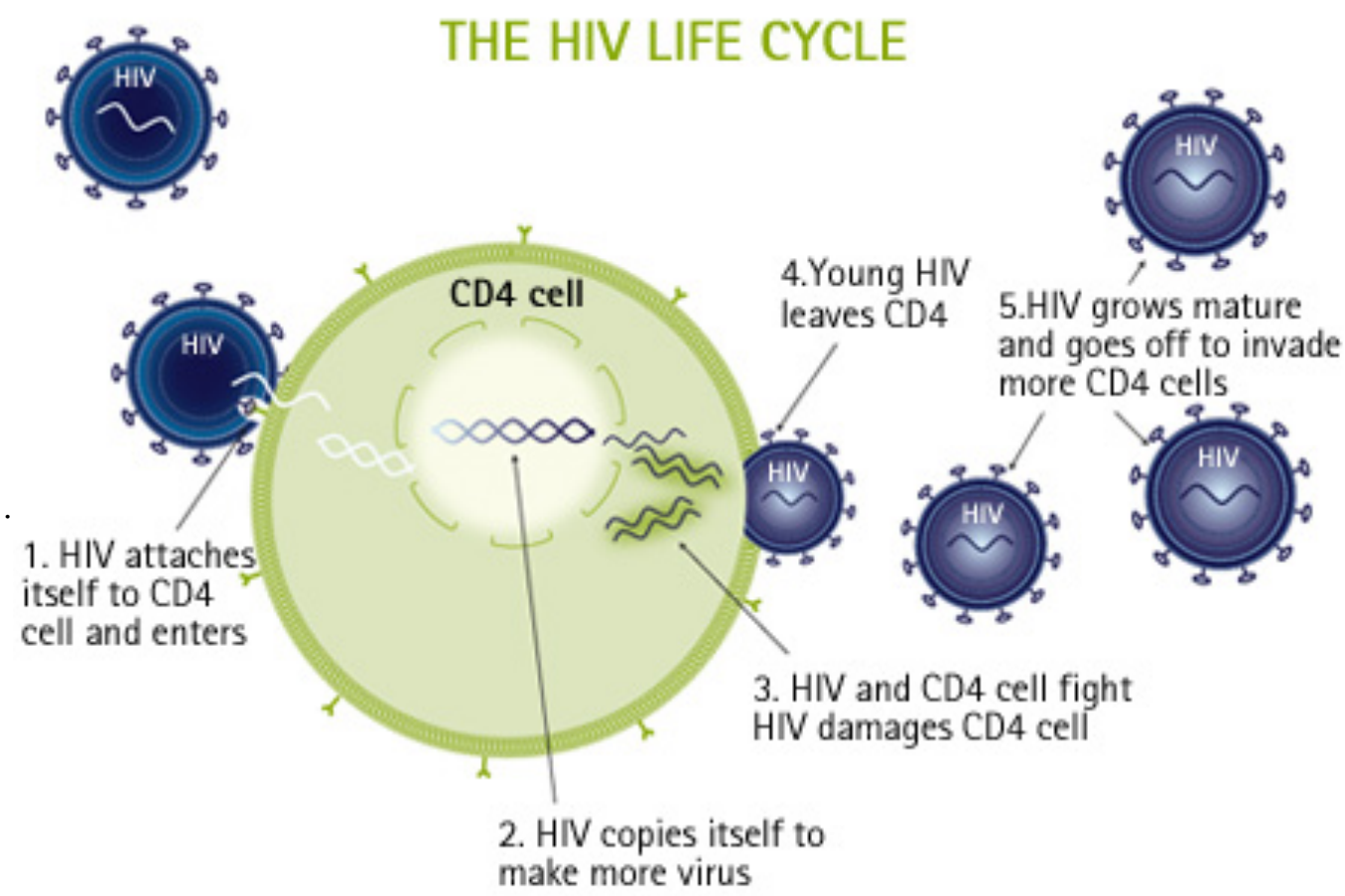
HIV viral particles are seen adjacent to the cell surface in this electron micrograph

Progression of HIV Infection:

1. acute infection.
Within days after the first exposure to HIV, viral replication can be detected in the lymph nodes. This replication leads to viremia, accompanied by an acute HIV syndrome that includes a variety of nonspecific signs and symptoms. The virus disseminates throughout the body and infects helper T cells, macrophages, and DCs in peripheral lymphoid tissues. As the infection spreads, the immune system mounts both humoral and cell-mediated immune responses directed at viral antigens. These immune responses partially control the infection and viral production, and such control is reflected by a drop in viremia to low but detectable levels by about **12 weeks** after the primary exposure.

***2. chronic progressive infection of peripheral lymphoid tissues*.**
The transition from the acute phase to a chronic phase of infection is characterized by dissemination of the virus (viremia), and the development of host immune responses.

During this period of the disease, the immune system remains competent at handling most infections with opportunistic microbes, and few or no clinical manifestations of the HIV infection are present. Therefore, this phase of HIV disease is called the *clinical latency period*.
Early in the course of the disease, the body may continue to make new CD4+ T cells, so CD4+ T cells can be replaced almost as quickly as they are destroyed.
Eventually, over a period of years, (& Although a majority of peripheral blood T cells do not harbor the virus) the continuous cycle of virus infection and T cell death leads to a steady decline in the number of CD4+ T cells in the lymphoid tissues (*lymph nodes and the spleen)* and the circulation.



Now Check Your Understanding!

MCQs:

1. **A person who is HIV positive, coming to the hospital with a lesion on his ankle which is hemorrhagic, bleeding and a mass, on histology it shows malignant spindle cells of vascular origin, what is the most likely diagnosis:**
   A. Kaposi's sarcoma
   B. Lymphoma
   C. CMV infection

2. **HIV virus genome contains which of the following?**
   A. DNA
   B. RNA
   C. both

3. **Endemic AIDS is caused by?**
   A. HIV1
   B. HIV2
   C. Both

4. **Once the virus enters the human body it attaches itself to the target via:**
   A. CD4
   B. CD8
   C. CD3

5. **The conversion of RNA to proviral DNA by which enzyme?**
   A. Reverse transcriptase
   B. Protease
   C. Ribonuclease

6. **What are the target cells for HIV**
   A. Monocytes
   B. Macrophages
   C. T and B lymphocytes
   D. All

7. **Which of the following is not a receptor for binding of HIV?**
   A. CD4+ receptors
   B. CXCR4
   C. CCR5
   D. TM4SF5

MCQs:
1: A 2: B 3: B 4: A
5: A 6: D 7: D

8. **The transition from the acute phase to a chronic phase of infection is characterized by:**
   A. Viremia
   B. Fever
   C. Vomiting
   D. Bacteremia

9. **The major mechanism of loss of CD4+ T cells is**
   A. Lysis
   B. Direct infection of thymic progenitor cells
   C. Chronic activation of uninfected cells
   D. Formation of syncytia

10. **Partial control of the infection and viral production is a characteristic of**
   A. acute infection
   B. chronic infection
   C. resolved infection
   D. latent infection

11. **5. A 32-year-old male taxi driver was hospitalised for a pneumonic illness. History obtained from the patient confirmed some months of fever, generalized lymphadenopathy, pharyngitis, rash, arthralgia and diarrhea. which viral strain is most likely responsible for the initial transmission of the virus.**
   A. X4
   B. R5
   C. CXCR4
   D. CCR5

MCQs:
8: A 9: A 10: A 11: B

Thanks for checking our work! Good Luck.

Done by:

نوف التويجري & عمر آل سليمان

مي العقيل

لولوة الصغير

بدور جليدان

دانيا الهنداوي

نورة الطويل

{ قال صلى الله عليه وسلم: من سلك طريقًا يلتمس فيه علمًا سهّل الله له به طريقًا إلى الجنّة }

قادة الفريق:
نوف التويجري & عمر آل سليمان

تم إنجاز هذا العمل بفضل الله وتوفيقه ثم بفضل المجموعة المتميزة التي شاركت في إنجازه فلهم كل الشكر والتقدير.

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لا تنسوهم من دعواتكم.