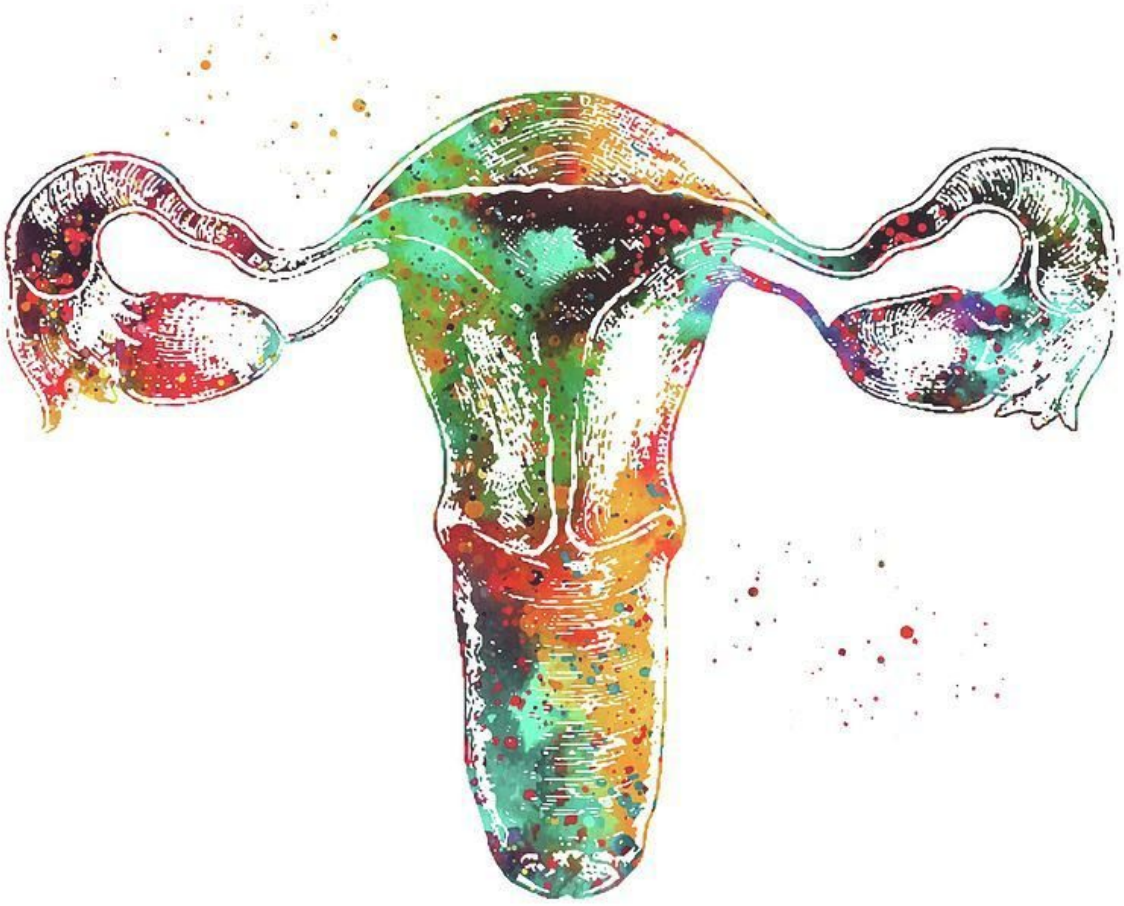


Lecture 10: AIDS

Objectives:

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

MED437
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 437

Important
Terminology
Doctor's Notes
Extra Information

Rikabi's Notes (collected by Abduljabbar Alyamani)

STD/Venereal diseases are also discussed today (they are a fashion now) associated with traveling to Bahrain (not a small number).

This lecture will cover STDs (Sexually transmitted diseases) then AIDS. We will focus on pathological features and diseases encountered. STDs are many, most importantly: chlamydia, gonorrhea, HIV, and syphilis.

Case 1: Gonorrhea

- Gonorrhea affects males and females. In females it presents **asymptomatically** (but it is still contagious to males at this point). It could present with discharge in females. The cause are gonococci (gram negative diplococci). Transmitted through sexual intercourse (usually through extramarital activity). Transmitted to male from female. Some people with long beards could have it.

Presentation:

- The patient doesn't like coming to a teaching hospital. Because many people will see him. Usually goes to private hospital (unless he's stupid or ignorant).
- The patient comes with purulent discharge from the penis. He claims it's from Indian food or an eye that did not pray on mohammad PBUH. Culture or smear of pus shows diplococci gram-.
- Symptoms appear shortly after intercourse (the patient probably travelled recently) unless the infection is chronic which causes infertility. Chronic infection could cause infertility due to blockage of epididymis from fibrosis (it causes chronic epididymitis and chronic prostatitis).
- Acute infection presents with burning on micturition and penile discharge. On his underwear you'll see yellow solid stains (Pus solidifies due to fibrin). Treated **with high dose** of penicillin. New generation (spectinomycin). **Don't be fooled by STD people they often lie** (he's referring to their recent activity and habits).

Case 2: Chlamydia

- Same symptoms. Yellowish discharge and burning on micturition (also likes Bahrain, Saudi Arabia is too dry ☹). **Culture is negative!!** He insists the infection is from Indian food. The infection is caused by chlamydia. Very difficult to culture. Obligate intracellular. Causes **non specific urethritis**. Characterized by discharge with nothing found on culture. Can also affect female and cause cervicitis or vaginitis. Important to think about and diagnose. Response to erythromycin and tetracycline is good. Common species include Chlamydia Trachomatis or Hominis. Complement fixation test is used to determine type of chlamydia. Easy to diagnose and treat.

Case 3: Syphilis

- 3 types (Primary, secondary, tertiary) Caused by Treponema pallidum. Transmitted sexually.
    - Primary presentation is like the picture (ulcer on the penis or sometimes on scrotum). Always on lower side. **Painless** with discharge.
        - Examination is through **dark field microscopy (Immunofluorescence)** look on dark field Treponema will show. This is a very specific and very sensitive test.
        - Serological test: VDRL (Venereal disease research laboratory). Good for syphilis but could give **false positive frequently**. Important to not be stupid. 90-year-old athani most likely does not have syphilis (false positive when someone has another disease or disorder). Serology positive tests must be taken **with context**.
        - Treatment is high dose of penicillin. Given by injections for a period of time. Can **transform into secondary with inadequate treatment.**
    - Secondary syphilis: is called the mimicker disease because it mimics many other conditions. Rash on palms or soles of foot (erythematous and vesicular rash). Could be generalized. If you see this rash on a suspicious man. Do serology for syphilis. Dark field microscopy can't work here. Private sector is bad at diagnosing it.
        - Typical presentation of a young patient with unexplained skin rash affecting palms and soles. Biopsy shows **plasma cell infiltrate**. Skin biopsy of plasma cells. Consider the patient's age sex and job etc.
            - Sometimes causes **flat condyloma near anus or vagina** sometimes in other areas. Also called **Condylomata lata**. Presents in **secondary syphilis**

        - **HPV causes condyloma acuminatum usually exophytic (protruding)** also seen on anus penis or vulva. Especially HPV types: 16 18 31 33. Not all serotypes are carcinogenic. Also called viral wart on penis or cervix.
    - Tertiary syphilis: very rare. Presents with cardiovascular or neurological manifestations.
        - Neurological manifestations affect the spinal cord and is called tabes dorsalis. **Sometimes affects thoracic aorta not abdominal aorta** causes aortitis and aneurysm or valve incontinence. Aneurysm of abdominal aorta is due to atherosclerosis.

AIDS (Acquired immunodeficiency syndrome)

- Epidemiology:
    - Quite common but shrinking due to treatment advances. Affects gays and africans and americans. Millions on research for AIDS. Because it affects important people (western people). Great advances in treatment. Antiretrovirals are very effective. Delay AIDS and almost eradicate it.
    - How common is aids? Before 1980 it was not known. In 1980 discovered in Puerto Rico which is full of homosexuals. Found that they have weird symptoms:
        1. Unexplained persistent fever
        2. Unexplained weight loss (wasting)
        3. Unordinary infections
        4. Severe anemia
    - HIV (retrovirus) was found to be the cause. There are two types:
        - Type 1 is common in the west.
        - Type 2 is common in Africa and Asia.
    - It is an RNA virus. It is estimated 36 million people have aids. Every year 1-2 million people die from it.
    - In certain parts of Africa 70% of the population is HIV positive. Serology is positive. He may or may not have the syndrome. High in central and west Africa. In certain areas everybody is positive. Decreases in prevalence due to antiretrovirals.

- This picture depicts the retrovirus very clearly. It is a large virus. Rich in lipids. bilayer with capsid/matrix inside. **Lipid bilayered virus.** Has RNA. External proteins determine **affinity** with CD4 cells, macrophages histiocytes, microglial cells, and dendritic cells. Dendritic cells are APCs found in lymph nodes. Modified macrophages of CNS. Histiocytes. **Most important cell affected is the CD4 cell**.

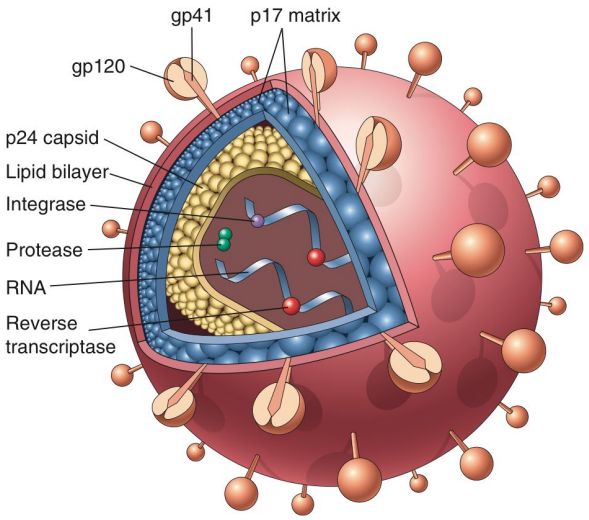


Fig. 5.37 The structure of the human immunodeficiency virus (HIV)-1 virion. The viral particle is covered by a lipid bilayer derived from the host cell and studded with viral glycoproteins gp41 and gp120.

- p41 and p120 help it to adhere to cells and helps with infectivity. Inside the virus there is RNA and some enzymes. Some important enzymes:
    1. **Reverse transcriptase** to transform RNA to DNA. Virus can manufacture its own DNA. Forms a new virion with new RNA and enzymes.
    2. Protease
    3. Integrase
- The virus lives in blood, mucosa, milk, vaginal secretions, and saliva. Based on these locations you can determine the modes of transmission. Mucosa is in the anus and vagina (homosexual intercourse leads to transmission). The receiver in the relationship is more likely to get it. The virus loves the mucosa. It can go from mother to baby through milk but infectivity here is low. It is also low for saliva. Blood to blood transmission in lab very low (Needle stick injury). In this case you give the technician antiretrovirals. Remember the commonly transmitted diseases from needle stick injuries are HCV, HBV, and HIV.
- Sequence of events in AIDS (pathogenesis):
    - A gentleman is sick of sandstorms and decided to go to Bahrain. On the way back he went to Makkah. In Bahrain he had fun and contracted HIV which is asymptomatic. **After 2-3 weeks seroconversion occurs.** At this point serology for HIV is positive. **To become definitely positive, it takes 9- 12 weeks**. First serology test is ELISA which is immune based. Cheap and simple. Positive or borderline we do PCR. Then usually nothing happens to the patient. Then he goes to donate blood at KKUH. Blood must be thoroughly checked. At this point he discovers he has HIV.
        - We used to buy blood a while ago, and then it was blocked.
- Some people infected with HIV have simple viral illness. Flu, muscle ache, fatigue, headache. He might die 50 years later without knowing he has the virus.
- Which patients present with symptoms?
    - People that are exposed to something that activated the virion. Usually a bacterial or viral infection, e.g.: CMV, EBV, flu viruses or bacterial infection. Quick replication of CD4 leads to increased CD4 destruction. Syndrome occurs when the number of CD4 cells drops below 200/microl.

- The progression of AIDS is monitored with CD4 count and CD4/8 ratio.
    - The patient obviously won't come to you saying he has a low CD4 count.
    - He will present with:
        1. Pneumonia
        2. Diarrhea
        3. Unexplained fever
        4. Unexplained weight loss
        5. Cancers
- All complications of AIDS:
    1. Tumors
    2. Opportunistic infection
    3. Neurological symptoms
- (Picture of herpes causing extensive ulceration here). Everybody has herpes. Manifestations of HSV with AIDS is worse.
- Presentations of AIDS
    1. Herpes virus causing extensive ulceration around the mouth.
    2. Interstitial pneumonia due to CMV (which causes inclusions in type 2 pneumocytes).
    3. Interstitial pneumonia due to pneumocystis jiroveci (old name pneumocystis carinii). Presents as **pneumonia without inflammatory cells.** Causes soap bubble exudate with no inflammatory cells. Organism spores detected with silver stain. Treated with erythromycin or tetracycline. If you don't treat he will die.
    4. Viral encephalitis. Histopathology shows macrophages, giant cells, and a small number of lymphocytes (because he lacks lymphocytes).
    5. TB without a granuloma (because he doesn't have CD4 cells). Reaction only has macrophages. Ziehl neelsen stain shows many Mycobacteria. TB is resurging due to AIDS.
        a. He might be able to form a granuloma if the CD4 count isn't too low. (enough IL 12 & IFNγ)
    6. Lymph nodes composed of macrophages only (again no lymphocytes).
    7. Fungal infections (Aspergillosis, chromomycosis).
    8. Toxoplasma gondii and cryptococcus neoformans cause meningitis and encephalitis in immunocompromised patients.
    9. Tumors:
        a. Kaposi sarcoma presents as **hemorrhagic erythematous skin patches** on legs or gum or skin. Biopsy shows spindle cells. With RBCs between them because the endothelial cells are forming vessels. It is a common tumor of homosexuals. Related to HHV-8 virus (human herpesvirus 8). Not all Kaposi sarcomas are from AIDS. Found in other immunocompromised patients (e.g. patients on immunosuppressants).
        b. Malignant lymphomas. Enlarged lymph nodes and subcutaneous lymph nodes. Non-Hodgkin lymphoma.
        c. Anal carcinoma

Introduction

- Human immunodeficiency virus (HIV) is the causative agent for AIDS.
- HIV is caused by a retrovirus of the lentivirus family that contains only RNA.
- It was unknown until the early 1980's, but since then it has spread around the world to infect millions of people.
- All HIV infected persons are at risk for illness and death from development of opportunistic infections and tumors and the inevitable manifestations of AIDS.
- The most common type of HIV infections 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.
- The mature virus consists of an electron dense core containing the viral genome consisting of the 2 short strands of RNA (ribonucleic acid).
- It also contains enzymes: reverse transcriptase, protease, ribonuclease, and integrase.
- All Are Encased by an outer lipid envelope.

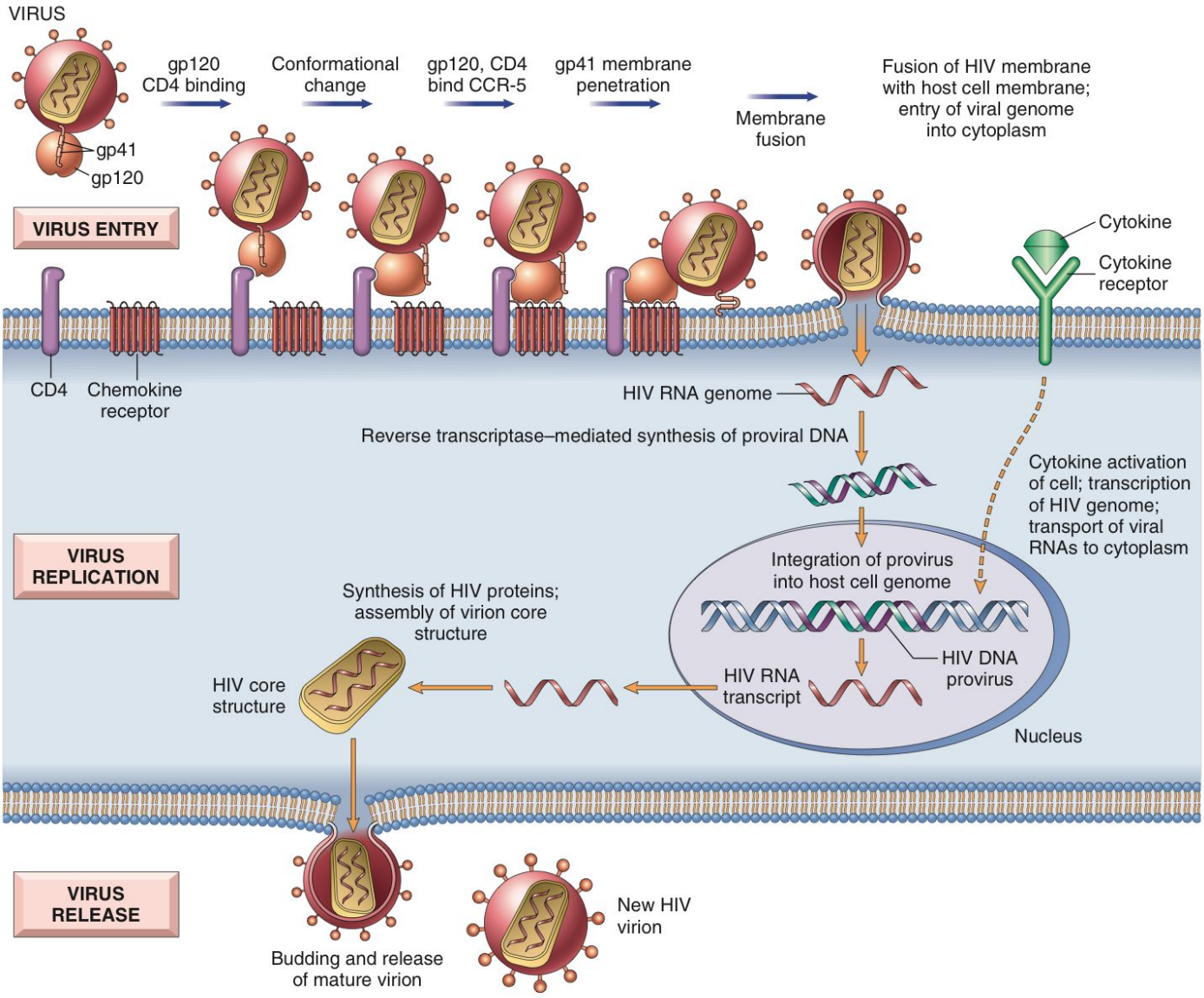
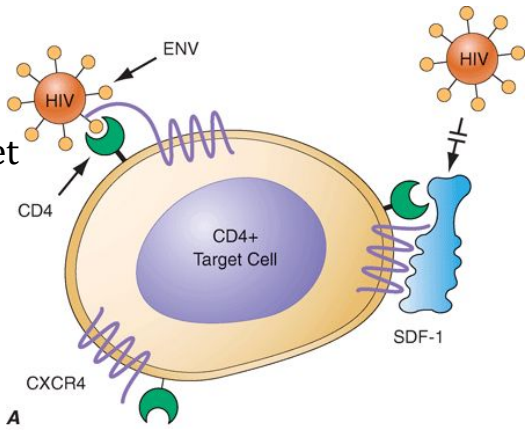


Fig. 5.38 The life cycle of HIV showing the steps from viral entry to production of infectious virions. *(Adapted from Wain-Hobson S: HIV. One on one meets two.* Nature *384:117, 1996.)*

Pathogenesis of HIV Infection

- The HIV virion expresses a cell surface protein/antigen called gp120.
- gp120 aids in the binding of the virus to the target cells. 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.
- gp120 is responsible for tropism/attraction to CD4+ receptors. This function helps in entry of HIV into the host cell.
- In addition, gp120 also 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.
- The T-lymphocytes have surface CD4 receptors (CD4+ T lymphocytes) to which HIV can attach to promote entry into the cell.



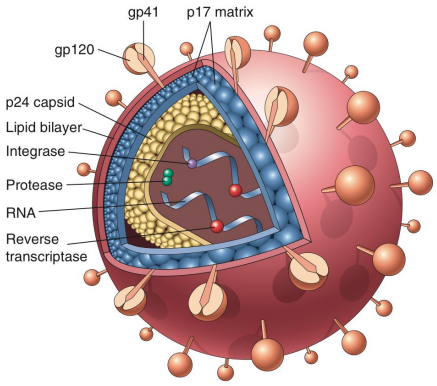
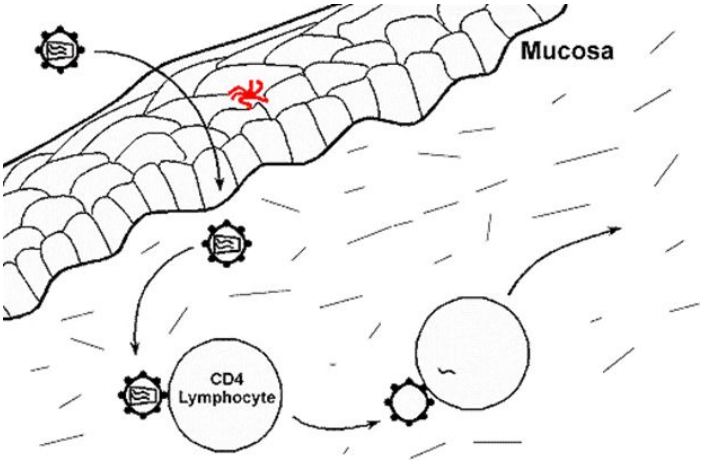


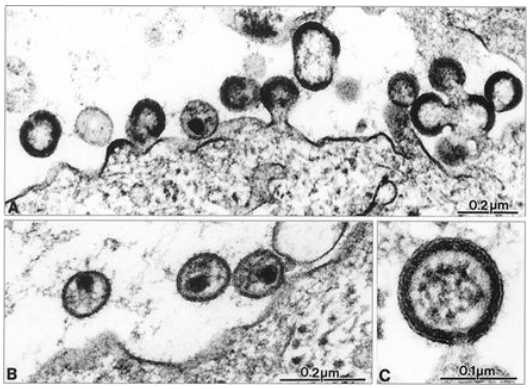
Fig. 5.37 The structure of the human immunodeficiency virus (HIV)-1 virion. The viral particle is covered by a lipid bilayer derived from the host cell and studded with viral glycoproteins gp41 and gp120.



A Langerhans cell in the epithelium is shown in red in this diagram

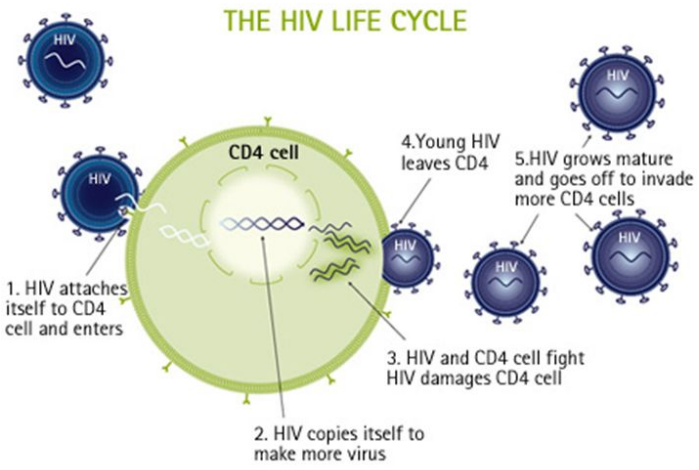
- HIV is shown crossing the mucosa of the genital tract to infect CD4+ T lymphocytes.
- The probability of infection depends on both the number of infective HIV virions in the body fluid which contacts the host as well as the number of cells with CD4 receptors available at the site of contact.

- Retroviruses are unable to replicate outside the living host cells because they only contain RNA and do not contain DNA.
- Therefore once HIV infects a cell, it must use its reverse transcriptase enzyme to transcribe/convert its RNA to host cell proviral DNA for replication.
- The enzyme, **reverse transcriptase** in the HIV helps in the reverse transcription (i.e. conversion) of **RNA to proviral DNA**. The proviral HIV DNA is then inserted into host cell genomic DNA by the **integrase** enzyme.
- Once the HIV proviral DNA is within the infected cell's genome, the HIV provirus is replicated by the host cell to produce additional HIV virions which are released by surface budding.
- Alternatively the infected cells can undergo lysis with release of new HIV virions which can then infect additional cells.



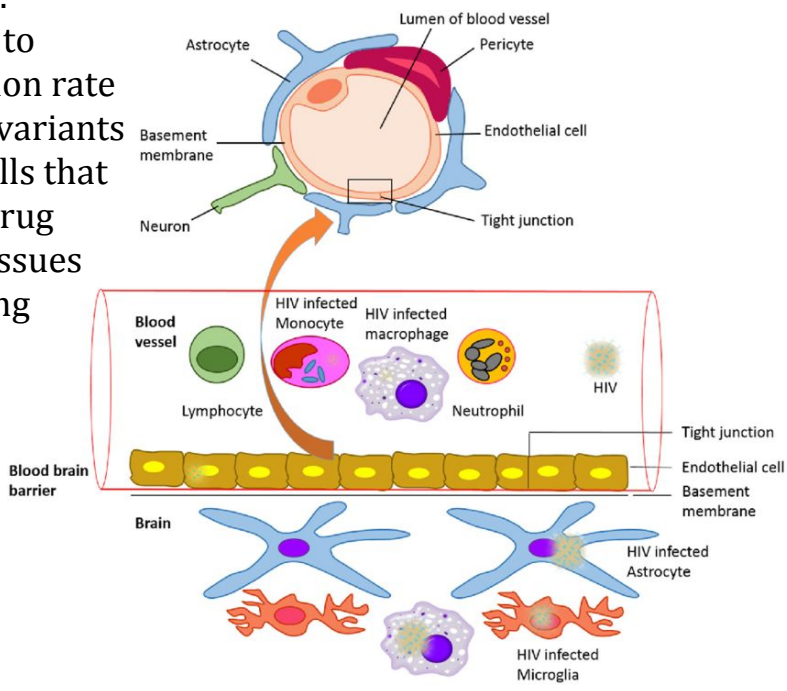
HIV viral particles are seen adjacent to the cell surface in this electron micrograph

HIV Life Cycle



HIV Infection

- Macrophages and Langerhans cells are both important as reservoirs and vectors for the spread of HIV in the body including the CNS.
- Both macrophages and Langerhans cells can be infected by HIV but are not destroyed themselves. HIV can then be carried via these cells elsewhere in the body.
- Once the infection extends to the lymph nodes, the HIV virions are trapped in the processes of follicular dendritic cells (FDC's), where they provide a reservoir and infect CD4+ T lymphocytes that are passing through the lymph node. The FDC's themselves become infected, but are not destroyed.
- The target cells are: blood monocytes and tissue macrophages, T lymphocytes, 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.
- In addition, HIV has the ability to mutate easily. This high mutation rate leads to the emergence of HIV variants within the infected person's cells that are more toxic and can resist drug therapy. Over time, different tissues of the body may harbor differing HIV variants



Modes of Transmission of HIV

- HIV can be present in a variety of body fluids and secretions. They include genital secretions, blood, breast milk, saliva, urine, tears, and sweat.
- However, saliva, urine, tears, and sweat are of no major clinical importance, as transmission of HIV through these fluids does not routinely occur because of the low concentration of HIV in these fluids.

Modes of transmission of HIV (the high risk population)

- HIV is primarily spread as a sexually transmissible disease.
- Transmission of HIV 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 routes:
    1. IV drug users sharing infected needles. Less common practices like the use of instruments such as tattoo needles that are not properly disinfected also carry a potential risk.
    2. Health care workers with percutaneous exposures (needle puncture) to HIV-containing blood.
    3. Persons receiving multiple blood transfusions e.g. hemophiliacs. Screening of blood products for HIV has significantly reduced HIV transmission by this means.
- HIV infection 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.
- 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.

Diagnosis of AIDS

- 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)
- 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 the development of the clinical signs and symptoms of AIDS.

Clinical Presentation

- Primary HIV infection may go unnoticed in at least half of cases, produce a mild disease which quickly subsides, or produce an 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.

Pathogenesis of AIDS/ Clinical AIDS

- The primary target of HIV is the immune system, which is gradually destroyed.
- 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
- Eventually, when a significant number of CD4+ T lymphocytes have been destroyed and when production of new CD4+ cells cannot match destruction, 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.**
- **The development of signs and symptoms of AIDS correlates with the CD4+ lymphocyte count.** 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.

Acquired Immunodeficiency Syndrome (AIDS)

- The stage of clinical AIDS is reached years after the initial infection and is marked by the development of one or more of the typical opportunistic infections or neoplasms common to AIDS.
- Following are some of the more common complications seen in AIDS:

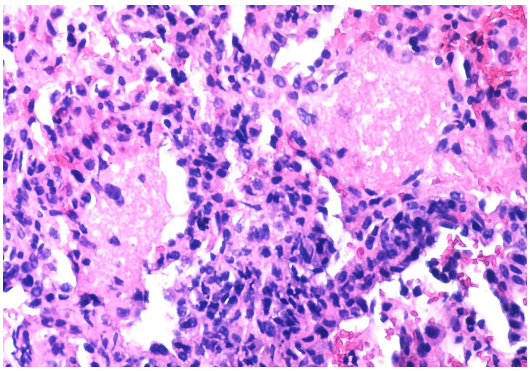
- **Infections** e.g. pneumocystis jiroveci,CMV, mycobacteria, fungi.
- **Neoplasms** (Rikabi's note: 1-Kaposi Sarcoma 2- Lymphomas 3-Carcinoma in the anal region)
- **Miscellaneous** e.g. lymphoid interstitial pneumonitis which is a condition involving the lung that can be seen in AIDS in children.

Infections

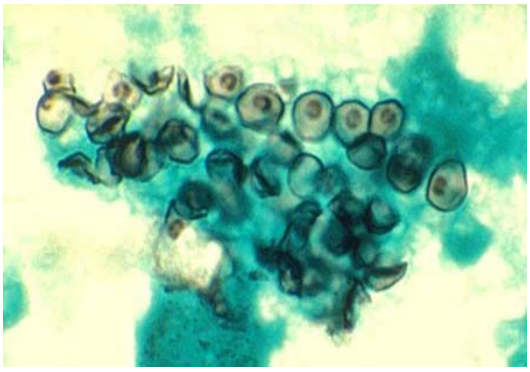
Pneumocystis Jiroveci:

- Pneumocystis jiroveci (P. carinii) is the most frequent opportunistic infection seen in AIDS. It commonly produces a pulmonary infection.
- The diagnosis is made histologically by finding the organisms in cytologic. (bronchoalveolar lavage) or biopsy (transbronchial biopsy) material from lung.
- 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.

H&E Stain



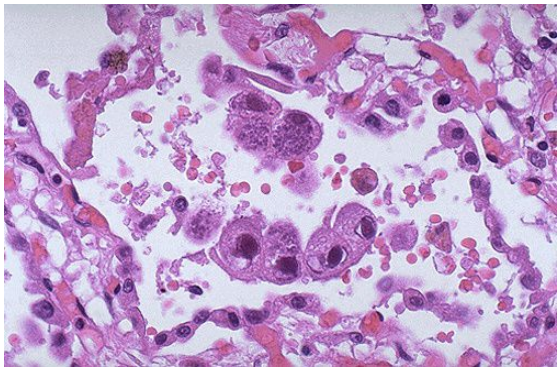
Silver Stain



Cytomegalovirus:

- CMV infection is seen in AIDS. It causes pneumonia and it can also cause serious diseases in the brain and gastrointestinal tract.
- It is also a common cause for retinitis and blindness in persons with AIDS.

Intranuclear inclusions



Infections (cont.)

Mycobacterial infections:

- Mycobacterium tuberculosis.
- Mycobacterium avium complex (MAC) infection.
- Definitive diagnosis of mycobacterial disease is made by culture and PCR.

Fungal Infections:

- Candidiasis of the esophagus, trachea, bronchi, or lungs.
- Cryptococcus neoformans (produces pneumonia and meningitis), Histoplasma capsulatum, and Coccidioides immitis.

Parasitic infection:

- 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 Microsporidia produce voluminous watery diarrhea in patients with AIDS.

Viral HIV encephalitis

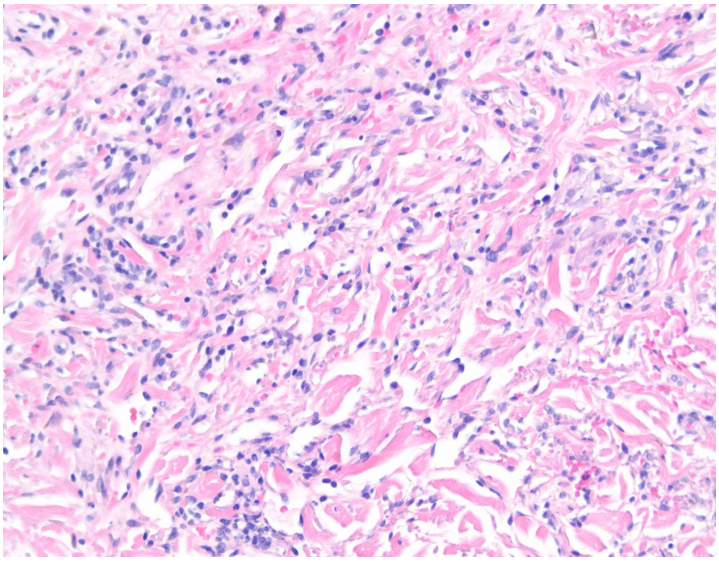
Syphilis (primary, secondary and tertiary)

Neoplasms

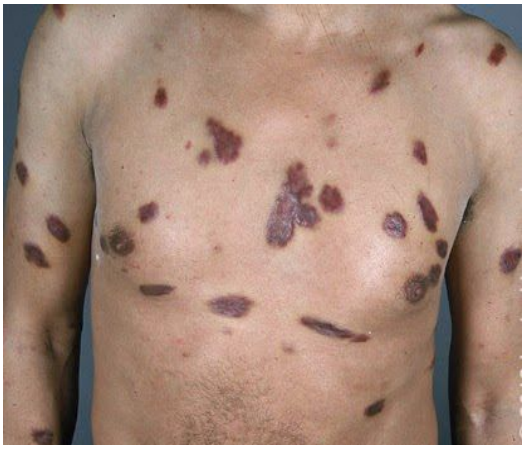
Kaposi's sarcoma (KS):

- Produces reddish purple patches or nodules over the skin and can be diagnosed with skin biopsy.
- Visceral organs can also be involved with KS.
- It is a sarcoma of the blood vessels.
- It is associated with HHV-8.
- On histology, it shows malignant spindle cells of vascular origin.

Malignant spindle cells



Reddish purple patches



Malignant lymphomas:

- Are seen with AIDS. They are commonly B-cell non-Hodgkins lymphoma.
- They are typically of high grade and often in the brain. They are very aggressive and respond poorly to therapy.

MCQ

1) When does the signs and symptoms (and infections) of AIDS begin to show?
   a) CD4 count below 200/microliter.
   b) CD4 count below 100/microliter
   c) CD8 count below 200/microliter
   d) CD4 & CD8 below 200/microliter
2) Which one of the following tests used to confirm HIV infection?
   a) ELISA
   b) Microscopic testing
   c) CD4 Count
   d) Immunofluorescence assay (IFA)
3) A patient lives in KSA, came to Pulmonary clinic complaining and showing symptoms of pneumonia. Patient won't respond to antibiotics. Radiological study shows interstitial pneumonitis. Patient's CD4 count is less than 200 mm^3. What's most likely the causative organism?
   a) M. Tuberculosis
   b) M. avium
   c) Cytomegalovirus (CMV)
   d) S.C. pneumonia
4) A patient came to the dermatology clinic with red purple patches all over his skin. Social history mentions multiple homosexual contact. CD4 count is less than 200 mm^3 What's most likely causes this condition?
   a) HIV
   b) CMV
   c) HHV-8
   d) HSV2
5) Which of the following is not a receptor for binding of HIV?
   a) CD4+ receptors
   b) CXCR4
   c) CCR5
   d) TM4SF5
6) The transition from the acute phase to a chronic phase of infection is characterized by:
   a) Viremia
   b) Fever
   c) Vomiting
   d) Bacteremia

Answers: 1A 2D 3C 4C 5D 6A

Cases From (**435**)

1. 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.

   Q1) What is the strain that is most likely responsible for the initial transmission of the virus?

2. 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.

   Q2) What is the most likely diagnosis?

Answers:

Q1) R5

Q2) Kaposi's sarcoma

“I want to congratulate all of you for finishing the pathology portion of your basic science years, it’s been a long and confusing journey but we’ve made it this far and will surely continue to excel. I want to thank every single person who has contributed to this team’s efforts including past leaders, members, and any individual who spent their time to help their brothers (and sisters) in arms.” - Fahad Alfaiz

"الحمدلله الذي بنعمته تتم الصالحات .

وانتهينا من اخر محاضرة في "علم الأمراض" وأود حقيقة أن أشكر من شارك في هذا العمل بدءًا من القادة حتى للأعضاء وجميع من بذل في هذا العمل❤️

ومن خلال هذه الرحلة البسيطة التي تعلمنا منها الكثير وواجهتنا فيها الكثير العقبات خصوصا في البدايات لتصقلنا وتوجهنا نحو الطريق السليم .

ها أنتم اليوم تملكون رسالة جميلة ناضلوا من أجلها وتذكروا أن كثرة العقبات وصعوبتها لا تصنع إلا نهاية جميلة تستحق هذا الجهد!."

-بلقيس الراجحي

The End

Team Members:

Fahad Alfaiz
Abduljabbar Alyamani
Abdullah Alomar
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