HIV & AIDS

Objectives :

- ★ Have an overview of the epidemiology of HIV worldwide and in Saudi Arabia.
- ★ Understand the risk factors for HIV.
- ★ Know the life cycle of HIV and have a brief overview of antiretroviral therapy.
- ★ Describe the infections and opportunistic diseases expected to occur in AIDS.

Editing file

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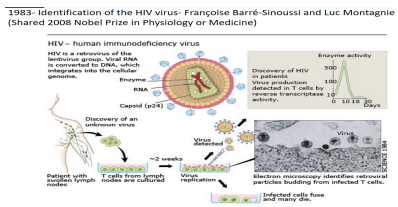
Important
Golden notes
Extra

History and Epidemiology

◀ History of HIV

1983

Luc Montagnier and Françoise Barré-Sinoussi reported the discovery of a new virus (later called HIV) that is the cause of AIDS.



01

1981

HIV **started** in Human in **USA** (1981) and then spread rapidly to all over the world. 2**70 reported cases** of severe immune deficiency among gay men, and 121 of those individuals had died.

02

03

1984

Blood test was developed.

- **CDC (Center of Disease Control) reported the occurrence of:**

1 Unexplained occurrence of pneumocystis pneumonia in 5 healthy homosexual in LA.

2 Kaposi sarcoma in 25 healthy homosexual men in NY and LA.

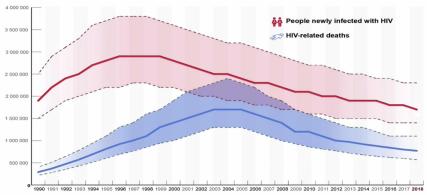
3 The disease became recognised in both male and female with (IUDs).

4 Recipients of blood transfusion and haemophiliacs.

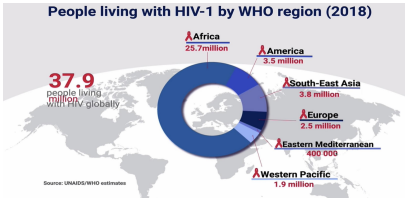
◀ Epidemiology of HIV

- HIV: the worst epidemic of the twentieth century and has reached every country . With more than **35 million fatalities.**
- The AIDS epidemic now ranks alongside the:
  A] Bubonic Plague of the 14th century : (1347 to 1352) 75 to 100 million death
  [Flea-borne zoonosis caused by the bacterium Yersinia pestis.].
  April 1, 2015, a total of 11 cases of human plague have been reported IN Western USA. (3 Patients died).
  B] Influenza pandemic (1957–1958) 20 to 50 million death
- In some countries in sub-Saharan Africa, the AIDS epidemic had caused a dramatic decline on life expectancy.
- **Worldwide statistics:**
  - 38.0 million people globally were living with HIV, with Africa having the highest number of infected patients .
  - 1.5 million people became newly infected.
  - 680 000 people died from AIDS-related illnesses.
  - 100 million people have become infected with HIV since the start of the epidemic.
  - 36 million people have died from AIDS-related illnesses since the start of the epidemic.
  - **An estimated 0.7% of adults aged 15–49 years worldwide are living with HIV.**

Decline in HIV-1 incidence and mortality over time



People living with HIV-1 by WHO region (2018)



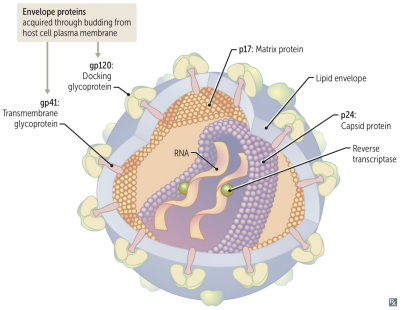
Global summary of the HIV-1 pandemic (2018)

	People living with HIV in 2018	People newly infected with HIV in 2018	HIV-related deaths 2018
Total	37.9 million [32.7 million – 44.0 million]	1.7 million [1.4 million – 2.3 million]	770 000 [570 000 – 1.1 million]
Adults	36.2 million [31.3 million – 42.0 million]	1.6 million [1.2 million – 2.1 million]	670 000 [500 000 – 920 000]
Women	18.8 million [16.4 million – 21.7 million]	–	–
Men	17.4 million [14.8 million – 20.5 million]	–	–
Children (<15 years)	1.7 million [1.3 million – 2.2 million]	160 000 [110 000 – 260 000]	100 000 [64 000 – 160 000]

Human Immunodeficiency Virus (HIV)

فيروس نقص المناعة البشرية

HIV Structure



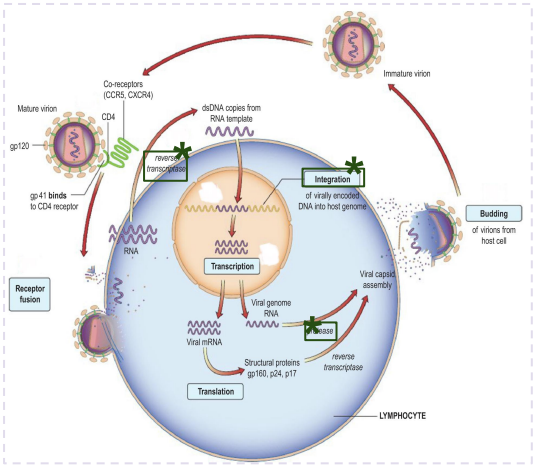
- HIV Is a member of the lentivirus family, a subgroup of **retroviruses**, and it is an **RNA viruses** that replicate via a DNA intermediate.
- **It is made of:**

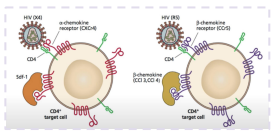
1) The core: contain the genetic material [RNA] and Reverse transcriptase [enzyme]
2) The capsid: outer protein coat. (p24)
3) Lipid envelope (env): It's derived from infected cell, containing numerous external spikes formed by two major envelope proteins:
A- The external **gp120** which attaches to host CD4+ T-cell.
B- The transmembrane **gp41**
4) Polymerase (pol)

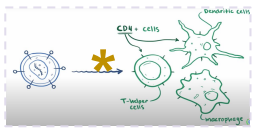
Retroviruses: a virus that uses RNA as its genetic material and it makes a DNA copy of its genome that is inserted into the DNA of the host cell.

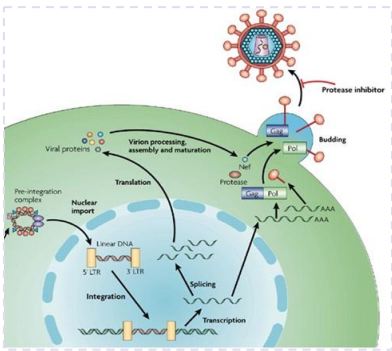
HIV Life Cycle & Replication

why is it more dangerous than other viruses? because it suppresses the immunity. Because HIV infects immune cells. Activation of cellular immunity helps the virus paradoxically to further replicate and ensures chronicity









01 Binding of Viral gp120 protein to CD4 receptor containing cells: CD4+ T cells, dendritic cells, and macrophages.

02 Viral entry into these cells is mediated by different receptors. GP-120 must bind to CD4+ receptor as well as to the chemokine receptor CCR5 (On macrophages, dendritic cells, T-cells) and CXCR4 (On T-cells). Viral entry into macrophages via CCR5 mainly occurs during the early stages of infection, while entry via CXCR4 occurs in later stages. people who are deficient in CCR5 don't develop the infection.

03 Fusion between cell membrane and the virion, Penetration & Up-coating.

04 Reverse transcription by Reverse transcriptase enzyme which synthesizes dsDNA from genomic RNA; dsDNA integrates into host genome by integrase .

05 Transcription of pro-viral DNA by formation of genomic RNA & formation of structural mRNA.

06 Translation of structural m RNA by formation of viral structural protein & packaging of genomic RNA of structural protein.

07 Final assembly by insertion of viral specific glycoprotein into plasma membrane, Budding & Release of mature virions.

08 Final maturation by cleavage of gag and pol by polymerase enzyme. by Protease

"**Pol**ly is a **R**eally **I**mportant **P**erson.": the proteins coded by the **pol** gene are **R**everse transcriptase, **I**ntegrase, and **P**rotease.

We have **3 important enzymes**:
-**Reverse transcriptase**: converts viral RNA to dsDNA

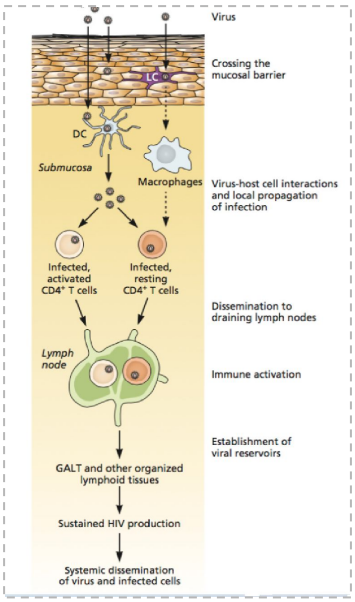
-**Protease:** cleavage of gag and gag-pol proteins during maturation of the virion

-**Integrase:** helps insert the viral genes into the host genome

these enzymes are targeted in treatment

Pathogenesis and Types of HIV

◀ Pathogenesis



- HIV-1 most often enters the host through the anogenital mucosa.
- Viral penetration of mucosal epithelium, followed by infection of submucosal **CD4+ T cells**, **dendritic cells**, **macrophages** and microglial cells in the CNS with subsequent spread to lymph nodes and ultimately Viremia (5 to 30 days).
- Once virus enters the blood, there is widespread dissemination to organs such as the brain, spleen, and lymph nodes
- During the initial period, the effector memory CD4+ T cells in the gut mucosa are preferentially depleted, followed by the progressive generalized loss of naïve T cells.
- The intestinal mucosa is also a primary target during initial infection which can lead to an early and disproportionate loss of CD4+ T cells in the gastrointestinal compartment, compared to peripheral blood.
- HIV RNA levels rapidly increase from the earliest quantifiable measure to a peak level that usually **coincides** with seroconversion.
- **Cellular immune response:**

Early

- At the time of initial infection with HIV, patients have a large number of susceptible CD4+ T cells and no HIV-specific immune response.
- Therefore Viral replication is rapid; plasma HIV RNA levels may climb to more than 10(7) copies/mL.

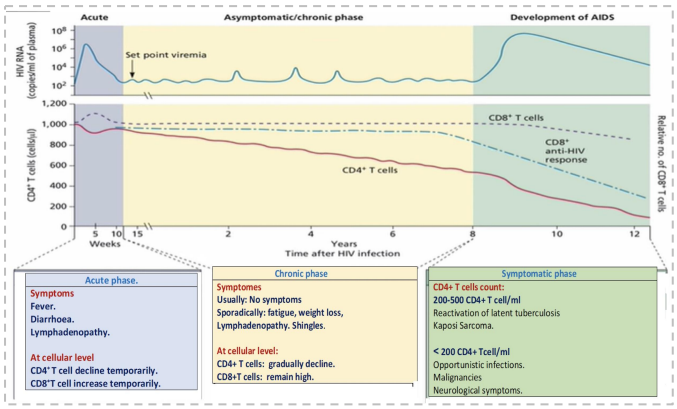
Late

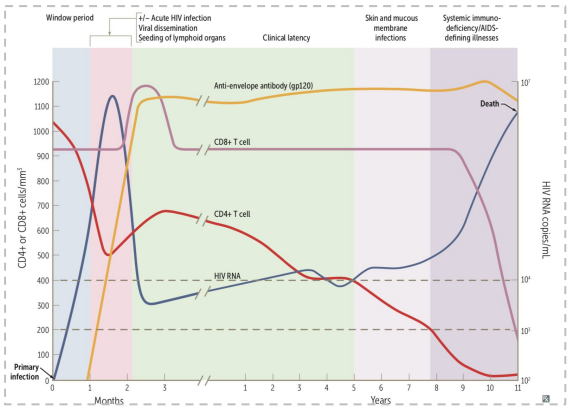
- Concomitant with the evolution of HIV specific immunity (virus-specific CD8+ cytotoxic T lymphocytes).
- This will lead to a fall in plasma RNA levels precipitously by 2 to 3 logs, and symptoms of the acute retroviral syndrome resolve.

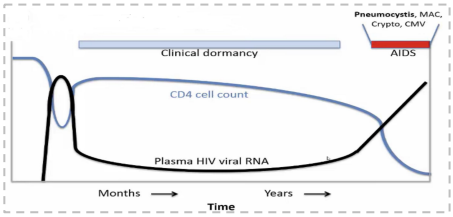
◀ Types of HIVs[1]

HIV-1	HIV-2
Predominate **worldwide**	Predominates in **western Africa and Southern Asia**.Closely resemble HIV-1 but is a much **slower** **progression** to AIDS.

◀ Natural history of HIV infection







Natural history of HIV

◀ Natural history of HIV infection cont.

- A latent HIV reservoir is a group of immune system cells in the body that are infected with HIV but are not actively producing new HIV.
- Finding ways to target and destroy latent reservoirs is a major challenge facing HIV researchers who are exploring different strategies for clearing out reservoirs.
- HIV medicines prevent HIV from multiplying, which reduces the amount of the virus in the body (called the viral load). Because the HIV-infected cells in a latent reservoir are not producing new copies of the virus, HIV medicines have no effect on them.

Progression to chronic immunodeficiency EXTRA

- HIV infects CD4+ lymphocytes, then reproduces and spreads to other CD4+ lymphocytes near the original site of infection → infection of CD4+ lymphocytes concentrated in specialized lymphoid tissue (e.g., lymph nodes or gut-associated lymphatic tissue (GALT)) → explosive growth and dissemination → acute HIV syndrome with high viral load
- Window period: The time between infection and detectability of HIV antibodies
- After the acute stage, viral load decreases and remains at roughly that level for approximately 8–10 years (clinical latency stage).
- During the clinical latency phase, the virus mainly replicates inside the lymph nodes
- Increasing loss of CD4+ lymphocytes (especially T cells) impairs immune function and, thereby, facilitates opportunistic infections and development of malignancies (AIDS). These secondary diseases are usually the cause of death in individuals with HIV.
- Increased viral load generally leads to a decreased number of CD4+ lymphocytes and vice versa, but the relation is not linear.
- Viral load predicts the rate of disease progression and CD4 count correlates with immune function.

1 Acute HIV infection (2-4 weeks after exposure)

- **Flu – like infection OR no symptoms. Large viral load / highly contagious.**
- The **2-4 weeks** immediately following infection may be silent, both clinically and serologically.
- Acute HIV infection may present as a **Mononucleosis type of syndrome/Glandular fever:**
  - Diagnosis can frequently be missed by clinicians.
  - **Fever, fatigue**, and myalgia/arthralgia are the most common
  - Gastrointestinal symptoms (nausea, diarrhea, weight loss)
  - Oropharyngeal symptoms (sore throat, ulcerations, painful swallowing)
  - Neurological symptoms are common, including headache, photophobia, myelopathy, neuropathy and, in rare cases, encephalopathy.
  - Other symptoms: lymphadenopathy, **maculopapular rash**.
  - **NONE of these symptoms is specific, but:**
    - Prolonged duration of symptoms
    - Presence of mucocutaneous ulcers are suggestive of the diagnosis
- The illness lasts **up to 3 weeks and recovery is usually complete**
- **Lab & Serology:**
  - CD4 lymphocytes may be markedly depleted and the **CD4:CD8 ratio reversed**.
  - **Antibodies** to HIV may be **absent** during this early stage of infection
  - **High viral load**
  - p24 may be detectable

Note: An estimated **10 to 60 percent** of individuals with early HIV infection **will not experience symptoms**.

Natural history of HIV cont.

◀ Natural history of HIV infection *cont.*

2 Chronic phase (Clinical latency)

- **Clinical latency / asymptomatic Viral load increases a lot and CD4 cell count decreases.**
  When CD4+ count is below 500 cells/mm^3
- It lasts variable amount of time average **8-10 yrs** and is accompanied by a **gradual decline in CD4 counts.** Viraemia peaks during primary infection and then drops as the immune response develops, to reach a plateau about 3 months later.
- Older age is associated with more rapid progression.
- Gender and pregnancy per se do not appear to influence the rate of progression
- Most are asymptomatic. However, the virus continues to replicate and the person is **infectious**.
- A subgroup of patients have **persistent generalized lymphadenopathy (PGL)** defined as **lymphadenopathy (>1 cm) at two or more extra-inguinal sites for more than 3 months** in the absence of causes other than HIV infection.
- There may be splenomegaly.

3 Symptomatic HIV infection

- **Immune system is seriously damaged**
- As HIV infection progresses, the viral load rises, the **CD4 count falls** and the patient develops an array of symptoms and signs
- In an individual patient, the clinical consequences of HIV-related immune dysfunction will depend on at least **three factors:**
  - **The microbial exposure of the patient throughout life:** Many clinical episodes represent reactivation of previously acquired infection, which has been latent.
  - **The pathogenicity of organisms encountered**
  - **The degree of immunosuppression of the host:** When patients are profoundly immunocompromised (CD4 count <100 cells/mm^3) disseminated infections with organisms of very low virulence such as M. avium-intracellulare and Cryptosporidium are able to establish themselves.

Genetic susceptibility

- **Elite controllers:**
  - HIV positive subjects who are able to control **HIV** without ever progressing to **AIDS**
  - A few individuals with HIV may, even in the absence of antiretroviral therapy, retain normal CD4 counts and low or undetectable plasma viremia.
  - The most extensively studied of these genetic factors is the C-C chemokine receptor 5 (CCR5), a major receptor for HIV.
  - **CCR5 (delta) 32 homozygotes genotype:** people who inherited the **Delta 32 mutation**, resulting in the genetic deletion of a portion of the CCR5 gene are **highly resistant to HIV infection.**
  - **Heterozygous CCR5 mutation → Slower course**

Transmission of HIV

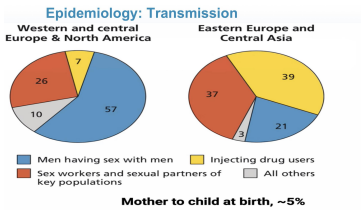
◄ Routes of Transmission

- HIV is a fragile virus. It cannot live for very long outside the body.
- HIV is primarily found in the blood, semen, or vaginal fluid, breastmilk of an infected person, so it is transmitted through:
- The virus can enter the blood via:
  1] the lining of the male/female genital tract (sexual activity).
  2] The lining of the mouth (breast feeding from infected mother).
  3] Broken skin

★ Sexual intercourse (most common)	Mother to child	Blood, blood products	Contaminated needles
World-wide, **heterosexual** (most common all over the world) l **and homosexual** (common in north america) **intercourse** accounts for the **vast majority of infections**. Repeated exposure increases the risk Coexistent STIs are alerting, especially those causing genital ulceration, enhance transmission	Can occur in **utero (30%),** although the majority of infections takes place **perinatally (60%)**. It also can transmitted through **breast milk (10%)**	Blood product recipients. The risk of Infectious diseases is minimal in developed countries since the introduction of screening blood products. Be careful with broken skin "wound" always wear gloves.	This is a major route of transmission of HIV among intravenous drug addicts who share needles and syringes. Health care workers with a needle-stick exposure are at high risk as well.

- **Is HIV transmitted by casual, ordinary social or household contact?** No
- **What factors increase the risk of HIV transmission?**
  1) High viral load. (Acutely infected "sky high viral load" or chronically untreated patient)
  2) Certain sexual behaviours (MSM is more) MSM: men who have sex with men افعال قوم لوط
  3) Presence of ulcerative sexually transmitted infections.
  4) lack of circumcision.
  5) Certain other host and genetic factors.

Risk of transmission can be lowered significantly if HIV infection is treated consistently and viral load is below the limit of detection.



◄ Epidemiology of Transmission

1) Sexual transmission:

- Heterosexual transmission : More than 80 percent of infections worldwide. (Transmission is more from man to women).
- **Sub-Saharan Africa** houses the majority of the world's HIV-infected population and heterosexual transmission is the main contributor to the HIV epidemic…BUT IN OTHER PART OF THE WORLD (especially USA): more men than women are infected with HIV.
- United States, the number of newly diagnosed HIV infections attributed to MSM sexual contact increased from 2009 to 2015, while those attributed to injection drug use and heterosexual contact decreased. 68% of newly diagnosed HIV in USA are among men (Homosexuality).

Clinical features of HIV

◄ Epidemiology of Transmission cont.

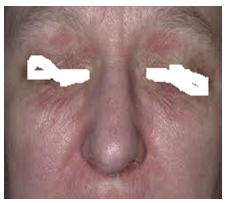
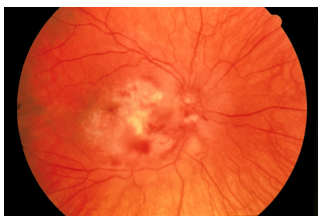
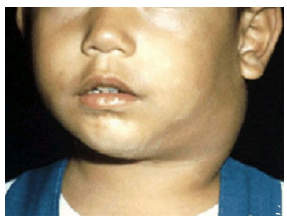
2) Injection drug use:

- Outside of sub-Saharan Africa, injection drug use (IDU) accounts for approximately 30 percent of new HIV infections in Central and Eastern Europe and in some countries of Asia.
- Needle exchange programs has resulted in reducing the number of new HIV infections by up to 70 percent like in Australia. They gave them clean syringes instead of sharing with others
- Unfortunately, 40 percent of countries with documented injecting drug use do not have needle-syringe programmes in place.

3) Mother to child transmission:

- Over two million infants are born to HIV-infected women annually.
- Without antiretroviral preventive interventions, the risk of perinatal HIV transmission has varied between 15 and 45 percent.
- Mother-to-child transmission accounts for 90% of HIV infections among children worldwide.
- Certain countries in sub-Saharan Africa, 20 to 40 % of pregnant women are HIV-infected, and one-third of their babies become infected.
- A mother with HIV should not breastfeed her baby

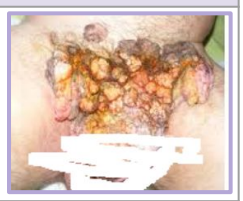
◄ Clinical features (Click here for a nice Summary)

Skin	Eyes (Fundoscopy)	Lymph node
Seborrheic dermatitis 	**CMV retinitis** (CD4 less than 50) 	Generalized lymphadenopathy (TB, Lymphoma) 

Genital Exam

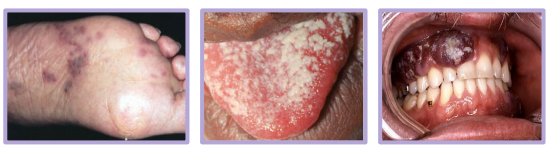
Ulcers, Condylomatous lesions:

1) **Condyloma Acuminatum** (Genital Wart): A wart, found on the genitals caused by **human papilloma virus** (an STD).
2) **Condyloma latum:** wart-like lesions on the genitals due to syphilis (STD).



Oropharynx

1) **Oral thrush** a young, healthy man/women with candida in the mouth is suspicious
2) **Hairy leukoplakia** if you see hairy leukoplakia it's HIV until proven otherwise
3) **Mucosal kaposi sarcoma**
4) **Odynophagia**



Complications of HIV

◄ Complications of HIV infection

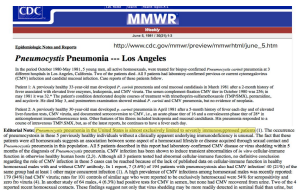
You develop AIDS when you get opportunistic infections or have low number of CD4 cells **<200 cell/mm^3**

Progressive depletion in CD4 cell counts with increased risk of:

1. **Opportunistic infections** (OIs) such as Pneumocystis Jiroveci, CMV,TB, fungal infection...etc
2. **Malignancy** such as Lymphoma(non hodgkin lymphoma) and Kaposi sarcoma

1- Opportunistic Infections

They do not occur in normal people


CDC MMWR

Pneumocystis Pneumonia — Los Angeles

Pneumocystis jirovecii Pneumonia

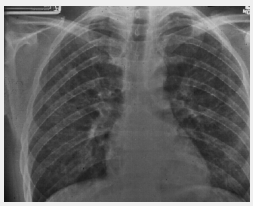
- One of the **leading causes of opportunistic infections among persons with HIV** and low CD4 cell counts **(<200 cell/mm3)**. It causes lower respiratory tract infection in severely immunosuppressed patients, In the past it used to be an infection in leukaemia patient.
- Occurs in those who are unaware of their HIV diagnoses or are not receiving medical care.
- Pneumocystis is currently recognized as a **fungus** (atypical fungi). based upon ribosomal RNA and other gene sequence homologies.
- **X-ray:** typically shows bilateral perihilar interstitial infiltrates.
- **HRCT:** ground glass appearance
- **transmission: airborne route**.

◄ Case study:

❖ 22 years old young male who presented with progressive shortness of breath, dry cough and dyspnea for 2 wks. Examination; looks in respiratory distress with RR : 28/m, No focal lung findings, Oral thrush, Decreased oxygen saturation.

❖ Investigations:

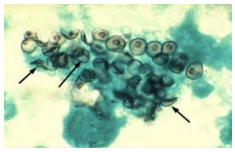
- **Chest x-ray:** diffuse lung infiltrate,
- **HIV antibody:** Reactive .
- **CD4:** 27 cells/microL.
- **Elevated LDH**.



Q1: What's the most likely diagnosis? AIDS with Pneumonia..likely to be Pneumocystis jirovecii Pneumonia. If a patient presents with pneumonia that's not responding to meds, this should raise suspicion of Pneumocystis pneumonia

Q2: When to consider Pneumocystis jirovecii Pneumonia?

1. AIDS with CD4 <200 cells
2. Organ transplant
3. High dose of corticosteroids


Pneumocystis cysts

Q3: How to confirm the diagnosis?

Definitive diagnosis of PCP requires visualization of the cystic or trophic forms in respiratory secretions by methenamine silver stain

Q4: What's the most appropriate treatment?

Trimethoprim-sulfamethoxazole.

Q5: How to prevent such disease?

By prophylaxis: TMP/SMX in patients with CD4+ T-cell count < 200 cells/µL

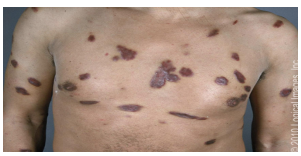
Complications of HIV cont.

◄ Complications of HIV infection cont.

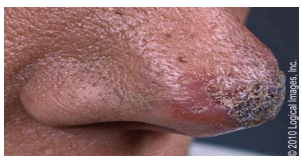
2- Malignancy (AIDS-defining cancers)

A- Kaposi sarcoma

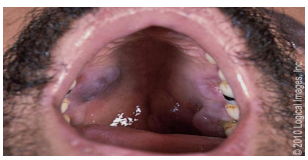
- HIV is 500 times more likely to be diagnosed with KS.
- a vascular tumour that is etiologically associated with **human herpesvirus 8 (HHV-8).** "انتبهولها"
- the most common tumour arising in HIV-infected persons (CD4 <500 cells/mm^3).
- It is **most common in homosexual or bisexual men**, and is much less common among injection drug users, transfusion recipients, women or children, and haemophiliacs.
- KS is considered an **AIDS-defining illness** (any kaposi patient must be screened for HIV) and is predominantly a disease of men that is characterized by vascular proliferation on skin and mucosae (initially particularly face/oral cavity and chest).
- **Diagnosis:** Skin biopsy: spindle-shaped cells, leukocyte infiltration, and angiogenesis
- Management:
  - **Incidence** has declined substantially since widespread use of potent **antiretroviral therapy (ART).**
  - **Chemotherapy:** should be reserved for those patients who fail to remit on ART, or be given together with ART if there are poor prognostic features such as visceral involvement, oedema, ulcerated lesions and B symptoms.



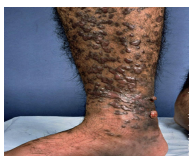
Kaposi sarcoma



An erythematous to violaceous plaque on the nose



Nodules of Kaposi sarcoma on the palate



Multiple violaceous papules on the lower leg

B- Non-Hodgkin lymphoma

- HIV is 12 times more likely to be diagnosed with Non-Hodgkin lymphoma (when CD4 <500 cells/mm^3).
- S&S:
  - Painless lymphadenopathy
  - Constitutional symptoms: weight loss, fever, night sweats
  - Other: Splenomegaly, hepatomegaly, Fatigue Anemia, bleeding, increased susceptibility to infections
  - Extranodal disease: most commonly involves the gastrointestinal tract, skin, thyroid, and CNS
- **Diagnosis:**
  - Immunohistochemistry
    - B-cell lymphomas: CD20 positive
    - T-cell lymphomas: CD3 positive
  - Lumbar puncture with CSF examination (cytology; detection of **EBV** DNA) in case of:
    - Primary CNS lymphoma, Neurologic signs and symptoms, HIV-positive.
- **Treatment:** Click here

C- Cervical cancer

- HIV is 3 times more likely to be diagnosed with Cervical cancer. Related to **HPV**.

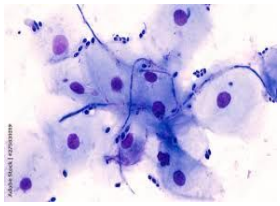
Complications of HIV cont.

Other Complications of HIV infection

1- Candidiasis:

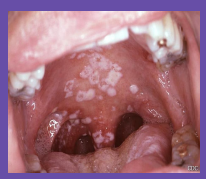
The infection can be :
Mucosal and disseminated

- Mucosal candidiasis, in the form of oral, esophageal or vaginal:
  -Thrush or oropharyngeal candidiasis.
  -Candida esophagitis.



12.9 CD4 count and risk of common HIV-associated diseases

<500 cells/mm³	
• Tuberculosis	• Kaposi's sarcoma
• Bacterial pneumonia	• Non-Hodgkin lymphoma
• Herpes zoster	• HIV-associated idiopathic thrombocytopenic purpura
• Oropharyngeal candidiasis	
• Non-typhoid salmonellosis	
<200 cells/mm³	
• *Pneumocystis jirovecii* pneumonia	• HIV wasting syndrome
• Chronic herpes simplex ulcers	• HIV-associated dementia
• Oesophageal candidiasis	• Peripheral neuropathy
• *Cystoisospora belli* (syn. *Isospora belli*) diarrhoea	• Endemic mycoses
<100 cells/mm	
• Cerebral toxoplasmosis	• Cytomegalovirus
• Cryptococcal meningitis	• Disseminated *Mycobacterium avium* complex (MAC)
• Cryptosporidiosis and microsporidiosis	• Progressive multifocal leucoencephalopathy
• Primary CNS lymphoma	

Disease	Clinical features/diagnosis	Management
CD4 <500 cells/mm³		
(Thrush) Oropharyngeal candidiasis (in the 439 slides) 	• **White patches** on the inner cheeks, tongue, roof of the mouth, and throat. • Oropharyngeal candidiasis is very common. It is nearly always caused by **C. albicans** • Pseudomembranous candidiasis is the most common manifestation, **Scrapable** white plaque • ones we see it not in neonate ,not in pregnant lady, not in somebody on steroid (i will screen him)	• Topical antifungals are usually effective. **Antifungal lozenges** are more effective than antifungal solutions. • Systemic azole therapy, usually **fluconazole**, should be given if topical therapy fails or if there are oesophageal symptoms.
Oral hairy leukoplakia	• **Unscrapable** white plaque on lateral tongue • It is usually asymptomatic and is due to **EBV**.	-
CD4 <200 cells/mm³		
Candida esophagitis **(in the 439 slides)** **Esophageal Candidiasis: is AIDS defining even if CD4 more than 200**	• One of the most common infections in people living with HIV/AIDS • the most present with dysphagia, pain on swallowing (**odynophagia**), regurgitation and **retrosternal pain.** **Diagnosis**: Endoscopy shows white-yellow plaques. **Confirmation**: Histologic examination using Hematoxylin and eosin stain of biopsies or brushing of esophageal plaques showing pseudohyphae.	• Antifungal : Oral **fluconazole**.

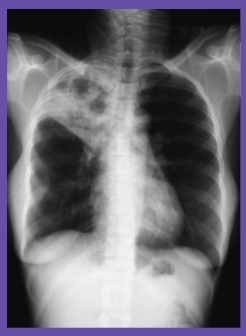
Complications of HIV cont.

◄ Other Complications of HIV infection *(cont.)*

CD4 <200 cells/mm^3

2-Tuberculosis (in the 439 slides)

CD4 below 200



what reactivate TB : (HIV)

- Among people with latent TB infection, HIV infection is the strongest known risk factor for progressing to TB disease.
- Patient infected with both HIV and TB is at least 10 times more likely to develop active TB, **especially when their CD4 count is under 200.**
- Worldwide, TB is a leading cause of death for people with HIV.
- It can be : 1]Pulmonary or 2]Extrapulmonary

Night sweats, fever, weight loss

- Abdominal pains, diarrhea
- Anemia, leukocytosis
- Diagnosis: **Acid-fast bacilli**

- **Macrolide (clarithromycin or azithromycin) plus ethambutol**
- **Prophylaxis**: azithromycin, clarithromycin, or, in select cases, rifabutin

Chronic herpes simplex virus

Unusual manifestations of infection, including:

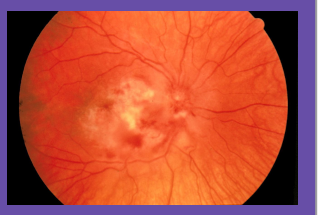
- **Chronic ulcers** (> 1 month)
- **Esophagitis** (onset at age > 1 month)
- Bronchitis or pneumonitis

- **Acyclovir**, valacyclovir, or famciclovir

CD4 <100 cells/mm^3

3-Cytomegalovirus (in the 439 slides)

only occurs when the immune system is down



we call HIV -> AIDS when CD4 is below 200

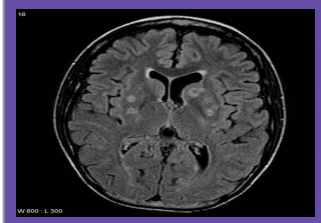
but CMV usually when below 100 or even below 50

- Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpesvirus family that can cause disseminated or localized end-organ disease in people with HIV with advanced immunosuppression.
- Most clinical disease occurs in individuals previously infected with CMV experiencing **reactivation of latent infection.**
- End-organ disease occurs in patients with advanced immunosuppression, typically those with CD4+ T lymphocyte cell (CD4) counts **<50** cells/mm. **(IMP)**
- **CMV retinitis** is the **most common CMV end-organ disease in HIV patients**. (30% without ART), fundoscopy shows cotton-wool spots.
- **CMV Colitis**. The most frequent clinical manifestations are weight loss, fever, anorexia, abdominal pain, diarrhea, and malaise, endoscopy shows linear ulcers.
- **CMV Esophagitis** occurs in a **small percentage** of patients with AIDS and causes **odynophagia**, nausea, and occasionally fever.
- Biopsy: intracellular inclusions (**"owl's eye"**)

- It Can be treated with Antiviral drugs : **Ganciclovir** (IV) OR Valganciclovir (Orally).

Complications of HIV cont.

◀ Other Complications of HIV infection *(cont.)*

Disease	Clinical features/diagnosis	Management
CD4 <100 cells/mm^3		
4- Cerebral toxoplasmosis (in the 439 slides)  **commonest site of toxoplasmosis is: Brain**	• Toxoplasma gondii is an obligate intracellular protozoan parasite presenting as a zoonotic infection distributed worldwide. • Symptomatic disease most often occurs as a complication of reactivation of latent infection. • It causes severe opportunistic infections as a result of reactivation of the parasite if the CD4 counts **fall below 100 cells/µl.** • The most common site of reactivation is the **central nervous system.** • CNS toxoplasmosis begins with encephalitis : Headache. Later, confusion and drowsiness, seizures, focal weakness. Fever is usually but not always present. • Most common cause of **cerebral abscess** in HIV patients. • CT-SCAN or MRI : Single or multiple hypodense or hypointense lesions in white matter and basal ganglia. • Impaired vigilance, **focal neurologic deficits**, seizures, fever • **Contrast CT/MRI:** multiple contrast-enhanced lesions • Toxoplasma **chorioretinitis** is also possible.	• Standard therapy consists of: pyrimethamine, sulfadiazine. or Trimethoprim-sulfamethoxazole an alternative regimen.
Primary CNS lymphoma	• **High-grade B-cell lymphomas associated with EBV infection**. • **Imaging (Contrast CT):** Single homogeneously enhancing, periventricular lesion with surrounding oedema • Lumbar puncture, PCR for EBV DNA in the CSF has a high sensitivity and specificity for PCNSL.	• Prognosis is poor • High dose **methotrexate** with/without whole brain radiotherapy • Oral/IV corticosteroids: after histological diagnosis; to control symptoms of raised ICP
Cryptosporidium spp	• **Chronic watery diarrhea** with nausea and abdominal pain • Stool examination: **Acid-fast oocysts** in stool	• Antiparasitic therapy (e.g., nitazoxanide)
Aspergillus fumigatus	• Invasive fungal pneumonia characterized by **cough ± hemoptysis**, **pleuritic pain** and fevers. • Imaging: **Cavitating consolidation, 'tree-in-bud',** nodules with ground glass halo and, in later stages, air-crescent sign (caused by lung necrosis)	-
Bacillary angiomatosis 	• Bacillary angiomatosis is a bacterial infection caused by **Bartonella henselae or B. quintana** • Skin lesions range from solitary superficial **red–purple lesions** resembling KS or **pyogenic granuloma**, to multiple **subcutaneous nodules or plaques**. Lesions are **painful** and may bleed or ulcerate. • Diagnosis is made by **biopsy** of a lesion and **Warthin–Starry silver staining**, which reveals aggregates of bacilli.	• Treatment with **doxycycline** or **azithromycin** is effective.

Diagnosis of HIV

◀ Diagnosis

Nearly 15 percent of HIV-infected persons in the United States remain unaware of their HIV infection.

- **Whom to test?**

1 **Symptoms of HIV infection:**
Signs and symptoms of acute or chronic HIV infection should be tested. Testing for HIV RNA may be needed.

2 **Possible HIV exposure:**
Patients after a known high-risk exposure to HIV (eg, sexual or percutaneous).

3 **Patient with sexually transmitted disease (STD).**

4 **Pregnant women** should be tested for HIV early in each pregnancy (Screening).

- **What is the definition of Acquired Immunodeficiency syndrome (AIDS)?(IMP)**

1. It is defined by a loss of CD4 T lymphocytes **(< 200 cell) OR**
2. The occurrence of **opportunistic infections or cancers** in HIV infected Patient.

Note: Not all those infected with HIV have AIDS. AIDS is the last stage of HIV infection.

Test	Purpose
HIV antibody tests	• Only look for **antibodies** to HIV. Detect HIV infection **23 to 90 days** after an exposure.
HIV Antibody/Antigen immunoassay	• Is the **screening test**, used to screen blood products and patients. • A positive antibody test from **two different immunoassays** is sufficient to confirm infection. • It detect both HIV **antigen (p24) and antibody IgG (gp120)**. • Detects HIV infection after **18 to 45 days** after exposure.
The INNO-LIA™ (HIV I/II) Score is a Line Immunoassay (LIA®)	• To confirm antibodies against the human (HIV-1) and (HIV-2) • **Differentiates between HIV-1 and HIV-2**, Sensitivity 100%, Specificity: 96%
Nucleic acid amplification test (NAT)-PCR (polymerase chain reaction) PCR is done for every blood donation we don't rely on antigen/antibody	• Diagnose HIV about **10-33 days** after exposure: • **Confirmatory test** for undetermined cases. • Looks for the actual virus in the blood, to assess the viral load (viraemia). • PCR is more sensitive than p24 antigen detection for diagnosing primary infection. • The viral load is the **best indicator of long-term prognosis.** • **Used to diagnose babies born to HIV-positive mothers**, because their blood contains their mother's HIV antibodies for **several months** (Up to 15 months).
CD4+ count	• Correlates with overall immune function (Normal is over 500 cells/mm^3) • CD4+ counts increase in response to successful ART therapy • performed every 3–6 months in patients on ART, together with viral load. • Critical measurement for initiating opportunistic infection prophylaxis
Rapid tests	1) The rapid antigen/antibody test with a finger prick and takes 30min. 2) The oral fluid antibody self-test provides results with 20min

Diagnosis of HIV cont.

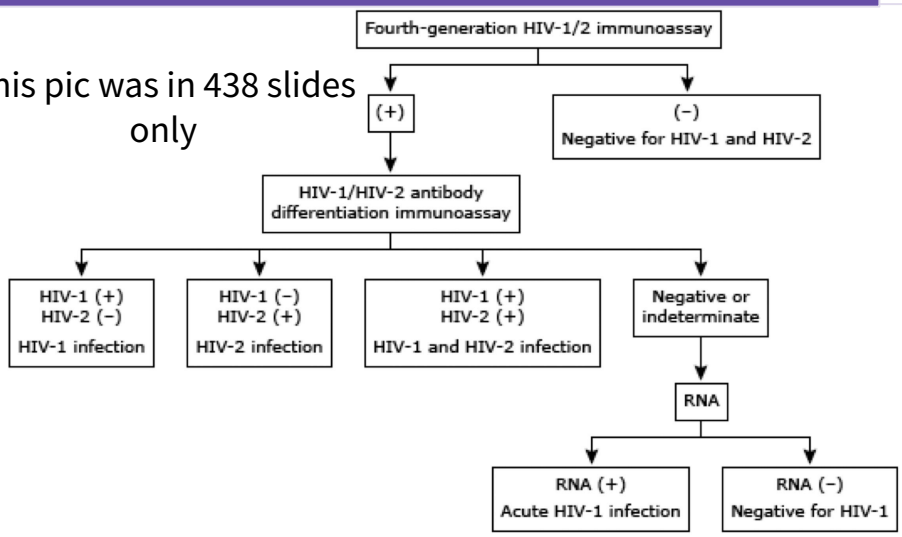
◀ Diagnosis cont.

Test	Target of detection	Time to positivity (day)
Enzyme-linked immunoassay		
First generation	IgG antibody	35-45
Second generation	IgG antibody	25-35
Third generation	IgM and IgG antibody	20-30
Fourth generation	IgM and IgG antibody and p24 antigen	15-20
Western blot		
	IgM and IgG antibody	35-50 (Indeterminate) 45-60 (Positive)
HIV viral load test		
Sensitivity cutoff 50 copies/mL	RNA	10-15
Ultrasensitive cutoff 1-5 copies/mL	RNA	5

Positive result with **Third-(HIV- antibody only)** and/or **Fourth-generation (HIV antigen and antibody)** HIV serologic assays **should be confirmed by** confirmatory **HIV-1/HIV-2 antibody differentiation immunoassay**.

Recommended algorithm for HIV diagnosis

This pic was in 438 slides only



Box 12.9 Summary of the Centers for Disease Control (CDC) classification of HIV infection

Absolute CD4 count (/mm³)	A *Asymptomatic or persistent generalized lymphadenopathy or acute seroconversion illness*	B *HIV-related conditions,[a] not A or C*	C *Clinical conditions listed in AIDS surveillance case definition (see Box 12.10)*
>500	A1	B1	C1
200–499	A2	B2	C2
<200	A3	B3	C3

[a]Examples of category B conditions include: bacillary angiomatosis, candidiasis (oropharyngeal), constitutional symptoms, oral hairy leukoplakia, herpes zoster involving more than one dermatome, idiopathic thrombocytopenic purpura, listeriosis, pelvic inflammatory disease, especially if complicated by tubo-ovarian abscess, peripheral neuropathy.

Diagnosis of HIV cont.

Baseline investigations

Baseline assessment for a newly diagnosed asymptomatic patient with HIV infection	
Haematology	• Full blood count, differential count and film
Biochemistry	• Serum, liver and renal function including eGFR • Fasting serum lipid profile, total cholesterol, HDL cholesterol • Fasting blood glucose • Serum bone profile including 25 OH vitamin D • Urinalysis • Dipstick for blood, protein and glucose • Urine protein/creatinine ratio
Immunology	• Lymphocyte subsets (repeat to confirm baseline within 1–3 months) • HLA B*5701 status
Virology	• HIV antibody (confirmatory) • HIV viral load • HIV genotype and subtype determination • Hepatitis A IgG • Hepatitis B surface antigen and full profile • Hepatitis C antibody (followed by hepatitis C RNA testing if antibody positive and confirmation of antibody positive status if RNA negative)
Microbiology	• Toxoplasmosis serology • Syphilis serology • Screen for other sexually transmitted infections
Other	• Cervical cytology • Chest X-ray if indicated • 10-year cardiovascular risk assessment • Fracture risk assessment

Approaching sick HIV-positive patients

Potential problems

- Adverse drug reactions
- Acute opportunistic infections
- Presentation or complication of malignancy
- Immune reconstitution phenomenon
- Infection in an immunocompromised host
- Organic or functional brain disorders
- Non-HIV-related pathology must not be forgotten

Full medical history

Remember:

- Antiretroviral drugs, prophylaxis, travel, previous HIV-related pathology, potential source of infectious agents (food hygiene, pets, contacts with acute infections, contact with TB, sexually transmitted infections)
- Secure confidentiality. Check with patient who is aware of HIV diagnosis

Full physical examination

Remember:

- Signs of adverse drug reactions, e.g. skin rashes, oral ulceration
- Signs of disseminated sepsis
- Clinical evidence of immunosuppression, e.g. oral candida, oral hairy leucoplakia
- Focal neurological signs and/or meningism
- Evidence of altered mental state – organic or functional
- Examine:
    - The genitalia, e.g. herpes simplex, syphilis, gonorrhoea
    - The fundi, e.g. CMV retinitis
    - The mouth
- Lymphadenopathy

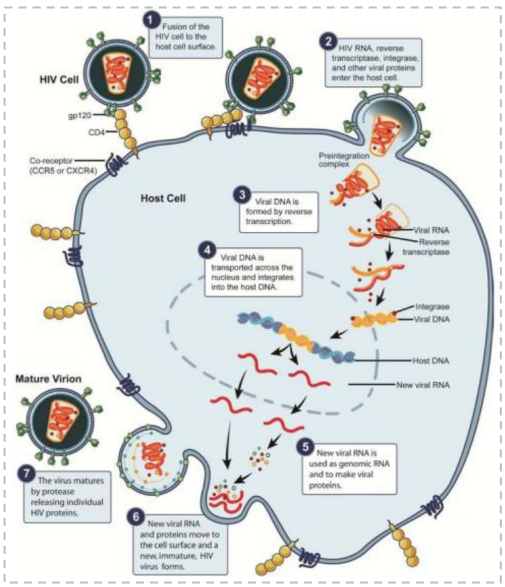
Immediate investigations

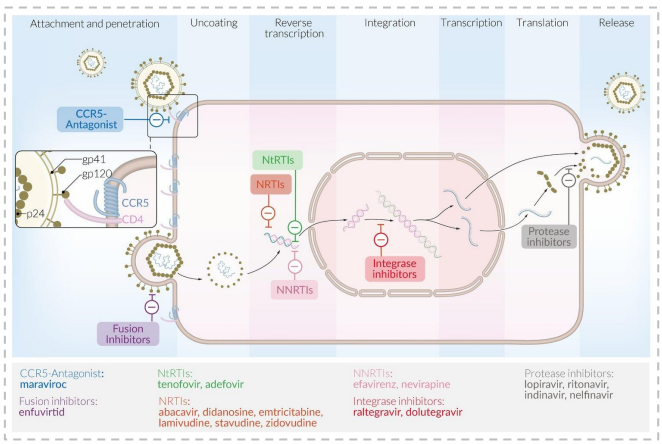
- Full blood count and differential count
- Liver and renal function tests
- Plasma glucose
- Blood gases including acid–base balance
- Blood cultures, including specimens for mycobacterial culture
- Microscopy and culture of available/appropriate specimens: stool, sputum, urine, CSF
- Malaria screen in recent travellers from malaria areas
- Serological tests for cryptococcal antigen, toxoplasmosis: save serum for viral studies
- Chest X-ray
- CT/MRI scan of brain if focal neurological signs and **ALWAYS before lumbar puncture**

Treatment of HIV

◀ Treatment ★

- HIV/AIDS has become a manageable chronic health condition, enabling people living with HIV to lead long and healthy lives.
- HIV can be suppressed by treatment regimens
- Current ART **does not cure HIV infection** but highly suppresses viral replication and allows an individual's immune system recovery to strengthen and regain the capacity to fight off infections.
- Combination antiretroviral therapy (ART) regimens have led to remarkable declines in morbidity and mortality among persons with HIV.
- The standard of care today is to treat nearly all HIV-infected individuals with ART, regardless of CD4 count. But most countries **start treatment if:**
  - **CD4 count ≤350 :** Initiating ART results in a significant decline in the risk of AIDS-related morbidity and mortality .
  - **CD4 count <200 cells [AIDS] :** ART improves survival and delays disease progression.
- **Why is treatment not given to everyone?** you cannot provide for everyone (cost effectiveness), toxicity, and to not induce viral resistance in the community.
- **Rationale for universal treatment**:
  - Reduce HIV infection–related morbidity and prolong duration and quality of life
  - Restore and preserve immunologic function.
  - Maximally and durably suppress viral load (plasma HIV RNA)
  - Prevent HIV transmission.
- Treatment is initiated with **three drugs: two NRTIs in combination,** with a third agent - either an **NNRTI**, a boosted **PI** or an **integrase inhibitor** (Patients may need to change therapy because of drug **resistance** (indicated by a **rise in viral load and falling CD4 count**)





don't focus on names of drugs just know the 3 mechanisms which is related to the 3 enzymes:
-reverse transcriptase
-protease
-integrase

(imp) we should use (compaination) multiple antiretroviral therapy to slow the progression of the disease.

Prevention of HIV

◀ Treatment (cont.)

don't focus on names of drugs just know the 3 mechanisms which is related to the 3 enzymes.

Drug name	MOA	Side-effects
Reverse transcriptase inhibitors (-INE,-VIR)		
1) Nucleoside Analogue RTI (NRTI):		
• **Abacavir (ABC)**[1] • **Emtricitabine(FTC)** • **Lamivudine(3TC)** • **Tenofovir**	Inhibit synthesis of DNA by reverse transcription and also act as DNA chain terminators	Nausea, mitochondrial dysfunction and lactic acidosis, polyneuropathy, pancreatitis (didanosine), myelosuppression (lamivudine, zidovudine), lipodystrophy (stavidudine, zidovudine)
2) Non-nucleoside RTI (NNRTI)		
• **Delavirdine** • **Efavirenz** • **Nevirapine**	Bind directly to, and inhibit reverse transcriptase	Rash, toxic epidermal necrolysis, elevation of liver enzymes, central nervous system effects (dreams, hallucinations, depression) with efavirenz
Protease inhibitors (-NAVIR)		
• **Atazanavir** • **Darunavir**	Act competitively on HIV aspartyl protease enzyme, which is involved in production of functional viral proteins and enzymes → stop the assembly of the virus	Lipodystrophy, hyperlipidaemia, gastrointestinal intolerance, peri-oral paraesthesia (ritonavir), intracranial bleeding (tipranavir)
Integrase inhibitors		
• **Raltegravir** • **Dolutegravir**	Prevents insertion of HIV DNA into the human genome, stop the replication of the virus	Gastrointestinal side-effects, headache, myopathy, rhabdomyolysis

◀ Prevention

- The only absolute way to prevent sexual transmission of HIV infection is "**Following religious teachings**" { وَلَا تَقْرَبُوا الزِّنَى إِنَّهُ كَانَ فَاحِشَةً وَسَاءَ سَبِيلًا }.
- Abstinence from sexual relation completely.
- **Safer sexual contact**: Correct and consistent use of condoms during sexual contact have an **85%** or greater protective effect against HIV and other STIs **(10 – 15 % failure rate) .**
- **Circumcision**: Results in 50-60% reduction of HIV acquisition and other STDs.
- Stop using IDUs.* Longitudinal studies among HIV discordant couples suggest that male circumcision.
- Needle exchange programs has resulted in reducing the number of new HIV infections by up to 70 percent like in Australia.
- Screen all blood and blood products.

1- You must test for the **HLA B5701 before using abacavir** (usually abacavir is co-formulated with lamivudine and it's called Kivexa). Those with the HLA-B5701 mutations are at risk for life-threatening skin reactions such as Stevens-Johnson syndrome

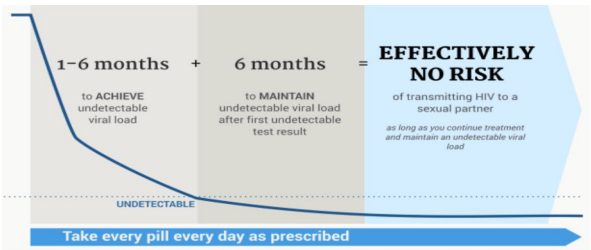
Prevention of HIV

◀ Prevention (cont.)

Use of ARVs for prevention	
Secondary prevention benefits of ART • Several studies confirmed that if an HIV-positive person is taking ART and is virally suppressed [**Durably undetected]** they do not transmit HIV to other partner.	
Pre-exposure prophylaxis for HIV-negative partner	• Oral PrEP of HIV is the daily use of ARVs by HIV-negative people to protect themselves from high-risk sexual and needle-sharing practices with potentially HIV-infected contacts. Its effective in reducing HIV transmission.

Post-exposure prophylaxis	• **Indicated in case of:**
	  ○ Sexual contact (unprotected)
	  ○ Health care associated percutaneous exposure. (Needle-stick)
	• PEP may be useful up to 72 hours after possible exposure.
	• PEP is **not recommended when care is sought > 72 hours after potential exposure.**
	• PEP is given for 1 month as a combination therapy

◀ Treatment as Prevention



◀ How to eliminate Mother to child transmission?

- Pregnant women infected with HIV infection caries risk to infect her baby by:
  1) In utero: 25-40%
  2) Intrapartum: 60-75%
  3) Breast feeding : Established infection 14% or Primary infection 29%
- In the absence of any interventions during these stages, rates of HIV transmission from mother-to-child can be between 15% and 45%
- Today the risk of perinatal transmission is less than 2% with:
  - Effective antiretroviral therapy (ART)
  - Formula feeding
- HIV-positive women are **advised against breast-feeding**, which doubles the risk of vertical transmission.
- Delivery by **caesarean section reduced the risk** of vertical transmission in the pre-highly active antiretroviral therapy (HAART) era, but if the woman is on effective ART and the labour is uncomplicated, vaginal delivery carries no additional risk.
- Women conceiving on an effective **ART regimen should continue** on their medication. For women naive to therapy who require treatment of their own HIV, whether pregnant or not, **triple therapy is the regimen of choice.**
- After delivery the **baby should receive zidovudine** for 4 weeks postpartum and the mother should remain on ARVs with appropriate monitoring and support.

Summary

◀ Acute HIV Infection

- Exposure to symptoms: **2-4 wks.**
- It resemble infectious mononucleosis with:

01	02	03	04	05	06	07	08	09
Fever	**Pharyngitis**	**Adenopathy**	**Rash**	**Myalgia**	**Fatigue**	**Oral Ulcer**	**Diarrhea**	**Anorexia**

- Then HIV RNA level falls and the symptoms resolve.
  - CD4 cell count **rebounds but remains below the bassline.**

◀ Chronic HIV Infection

- **Asymptomatic** chronic phase:
  - Active viral replication is ongoing and **progressive**.
- Patient with high HIV RNA may progress to symptomatic disease than those with low HIV RNA level.
- Chronic immune activation lead to increase in various inflammatory markers.
- This increase the risk of Non-AIDS related comorbidities:
  - CVD, Renal dysfunction and cancer.

- **What is the definition of Acquired Immunodeficiency syndrome (AIDS)?**

1. It is defined by a loss of CD4 T lymphocytes **(< 200 cell) OR**
2. The occurrence of **opportunistic infections or cancers** in HIV infected Patient.

Test	Purpose
HIV antibody tests	• Only look for **antibodies** to HIV. Detect HIV infection 23 to 90 days after an exposure.
HIV Antibody/Antigen immunoassay	• Is the **screening test**, used to screen blood products and patients. • It detect both HIV **antigen (p24) and antibody IgG (gp120)**. • Detects HIV infection after 18 to 45 days after exposure.
The INNO-LIA™ (HIV I/II) Score is a Line Immunoassay (LIA®)	• To confirm antibodies against the human (HIV-1) and (HIV-2) • **Differentiates between HIV-1 and HIV-2**, Sensitivity 100%, Specificity: 96%
Nucleic acid amplification test (NAT)-PCR (polymerase chain reaction)	• Diagnose HIV about 10-33 days after exposure: • **Confirmatory test** for undetermined cases. • Looks for the actual virus in the blood, to assess the viral load (viraemia). • **The viral load is the best indicator of long-term prognosis.** • Babies born to HIV-positive mothers, because their blood contains their mother's HIV antibodies for **several months** (Up to 15 months).

Treatment:

- Initiated with three drugs: **two NRTIs in combination, with a third agent** - either an NNRTI, a boosted PI or an integrase inhibitor

Take home Messages

- HIV is a subgroup of retroviruses, and it is an RNA viruses that replicate via a DNA intermediate.
- CD4 receptor containing cells: CD4+ T cells, dendritic cells, and macrophages.
- GP-120 must bind to CD4+ receptor as well as to the chemokine receptor CCR5 (On macrophages, dendritic cells, T-cells) and CXCR4 (On T-cells).
- We have 3 important enzymes(these enzymes are targeted in treatment):
  -Reverse transcriptase,-Protease,, -Integrase
- There is 3 phases for HIV infection :
  -Acute HIV infection (2-4 weeks after exposure): Flu – like infection OR no symptoms. Large viral load / highly contagious.
  -Chronic phase (Clinical latency):Clinical latency / asymptomatic Viral load increases a lot and CD4 cell count decreases.
  -Symptomatic HIV infection: Immune system is seriously damaged, the viral load rises, the CD4 count falls and the patient develops an array of symptoms and signs.
- Most common Route of Transmission: World-wide, heterosexual (most common all over the world) and homosexual intercourse accounts for the vast majority of infections.
- Progressive depletion in CD4 cell counts with increased risk of:
  -Opportunistic infections (OIs) such as: Pneumocystis Jiroveci, CMV,TB, fungal infection...etc
  -Malignancy such as: Lymphoma(non hodgkin lymphoma) and Kaposi sarcoma
- Pneumocystis jirovecii Pneumonia:One of the leading causes of opportunistic infections among persons with HIV and low CD4 cell counts (<200 cell/mm3), and on X-RAY its typically shows: bilateral perihilar interstitial infiltrates.
- Kaposi sarcoma: a vascular tumour that is etiologically associated with human herpesvirus 8 (HHV-8). (KS is considered an AIDS-defining illness).
- Definition of Acquired Immunodeficiency syndrome (AIDS): loss of CD4 T lymphocytes (less than 200 cell).
- Esophageal Candidiasis: is AIDS defining even if CD4 more than 200
- TB :especially when their CD4 count is less than 200 cells.
- Cerebral toxoplasmosis :CD4 counts fall less than 100 cells.
- Cytomegalovirus: CD4+ T lymphocyte cell (CD4) counts less than 50 cells.
- we should use (compaination) multiple antiretroviral therapy to slow the progression of the disease.
- PEP is not recommended when care is sought > 72 hours after potential exposure.

Lecture Quiz

Q1: A 42-year-old man presents to accident and emergency with a 3-week history of shortness of breath, dry cough, fevers and malaise. He has presented as his exercise tolerance has deteriorated. He mentions that he has been HIV positive for ten years. On examination, there are fine crackles throughout both lung fields. Chest x-ray demonstrates bilateral perihilar interstitial shadowing. What is the most likely causative organism?

A. Pneumocystis jirovecii
B. Herpes simplex virus type 1
C. Herpes simplex virus type 2
D. Streptococcus pneumoniae
E. Mycoplasma pneumoniae

Q2: A 42-year-old man presents to accident and emergency with a 3-week history of retrosternal discomfort after swallowing. He mentions that he has been unable to keep any food down at all. He has been HIV positive for ten years. He is admitted and endoscopy shows areas of ulceration throughout the oesophagus. What is the most likely causative organism?

A. Staphylococcus aureus
B. Cryptosporidium parvum
C. Candida albicans
D. Pneumocystis jirovecii
E. Cryptococcus neoformans

Q3: A 42-year-old man presents to his GP with 'blotches' over his legs. He has been HIV positive for ten years. On examination, there are multiple purple and brown papules over his legs and his gums. What is the most likely diagnosis?

A. Malignant melanoma
B. Squamous cell carcinoma
C. Basal cell carcinoma
D. Kaposi's sarcoma
E. Toxoplasmosis

Q4: A 42-year-old man presents to his GP complaining of deterioration in his vision in the right eye and the presence of floaters. The change in his vision has been causing him to suffer from headaches. He has been HIV positive for ten years. Fundoscopy reveals haemorrhages and exudates on the retina. What is the most likely diagnosis?

A. Retinal detachment
B. CMV retinitis
C. Kaposi's sarcoma
D. Optic atrophy
E. Diabetic retinopathy

Q5: A 42-year-old man presents to accident and emergency with a 1-day history of headache and fevers. He presents with his partner who says he has been becoming increasingly confused and disorientated. On examination, his temperature is 38.5°C. On cranial nerve examination there is a right-sided superior quadrantanopia. An urgent CT scan of the head is organized which shows multiple ring enhancing lesions. What is the most likely diagnosis?

A. Toxoplasmosis
B. Meningitis
C. Cryptosporidiosis
D. CMV encephalitis
E. Histoplasmosis

Answers: Q1:A | Q2:C | Q3:D | Q4:B | Q5:AB

Answers Explanation File!

GOOD LUCK !

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