HIV & AIDS

435 medicine teamwork

[Important | Notes | Extra | Editing file]

lecture 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

The Doctor said: in this lecture you're not required to memorize the epidemiology & drugs

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HIV and AIDS

General Characteristics:

Definition of HIV:

- Infection with (Human Immunodeficiency Virus), which leads to chronic and without treatment usually fatal infection, characterized by :
  A. Long latency period
  B. Progressive immunodeficiency and this will lead to:
  C. Opportunistic infection يعني انتهازية ما تحصل بالإنسان الطبيعي لان جهازنا المناعي كويس، examples of opportunistic infections that happen in HIV pt.: pneumocystis pneumonia & Toxoplasmosis
- HIV cause diseases by disrupting the immune system function as measured by CD4 cell depletion called : AIDS (Acquired Immune Deficiency Syndrome). So we don't call someone AIDS pt. unless he really has the stage of immune Deficiency that usually takes about 5-10 years.

Types of HIV:

- **HIV1:** Predominate world wide, ↑virulent &↑susceptible to mutation.
- **HIV2:** predominate (in specific regions) in western Africa. closely resemble HIV-1 BUT is a much slower progression to AIDS, ↓virulent & ↓ susceptible to mutation.

The hallmark of HIV Disease:

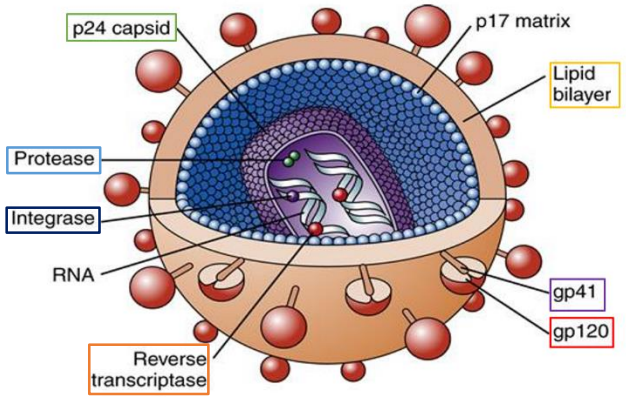
- Infection and viral replication within T-lymphocyte expressing the CD4 antigen resulting in **Progressive depletion in CD4 cell counts**
  →This effect on helper-inducer lymphocyte will increase the risk of:
  1- Opportunistic infections such as Pneumocystis Jiroveci
  2- Neoplasma such as lymphoma especially NON Hodgkin lymphoma(extremely imp)& Kaposi Sarcoma.

I'm sure that u know there are two systems in the immune system: 1)humoral: antibodies & Igs which's for the bacteria 2) cell mediated immunity which's for viruses, fungal & TB. So,HIV damage the cell mediated immunity particularly CD4 (T helper cells)

Virus Morphology:

- **It is an RNA Lentivirus virus**. lentivirus means slow virus, it goes inside the body & does not produce the disease, if u exposed to influenza virus today you'll be sick tomorrow but if somebody exposed to HIV he'll have many years before developing the disease.
- belong to **retrovirus family**:
  - Information in the form of RNA is transcribed into DNA in the host cell. retro means back, normally in the transcription process RNa transcribed into DNA then DNA translate into Protein! Here the virus has the capability inside it to get back to RNA after transcription into DNA.

- **It is an icosahedral[1] structure of :**
  - Lipid Envelope (env) derived from infected cell, containing numerous external spikes formed by two major envelope proteins:
    - The external **gp 120** it's the most imp. one bc. this is the one who cheat when hook to the cell لو تنسون كل التراكيب الا هذا
    - The transmembrane **gp 41**
  - **Nucleocapsid (gag)** with **P24** major core protein, the core contains two single strands of RNA.
  - **Polymearse(pol)**(*pol* codes for the enzymes reverse transcriptase,integrase and protease)



[1] متعدد السطوح

History:

First recognized in USA 1981, CDC reported the occurrence of :

1. Unexplained occurrence of pneumocystis pneumonia in 5 healthy **homosexuals** in Los Angeles
2. Kaposi sarcoma in 25 healthy homosexual men in NY and LA
3. Later on the disease became recognized in both male and female with IV drug users 'IVDU'.
4. As well as recipients of blood transfusion and hemophiliacs (factor A)

1983
HIV was isolated from patient with lymphadenopathy

1984
HIV was demonstrated to be the causative agent of AIDS

1985
ELISA test was developed

✵The massage here is, there are two important things associated with the transmission; sexual & IVDUs

HIV life cycle & replication:

Recall from 435 microbiology team:اقروه و بيسهل عليكم حياتكم
HIV needs CD4 receptors to enter the cell, it will leave the envelope outside and enter as ssRNA, after entering the cell, reverse transcriptase will convert the viral RNA into DNA. So, if we do anti-reverse transcriptase in the treatment we will prevent this step. Then the pro DNA (viral DNA) enter the nucleus to integrate with the host DNA by the enzyme which will make them dsDna, after that it will multiply inside the cell making the cell produce large amount of the provirus (millions) which will use the protease enzyme to convert it back to RNA then it will release and infect other cells

①**Binding:** the virus binds to host CD4 receptor containing cells (T cell, macrophages, and microglial cells)via the envelope glycoprotein gp 120 and co-receptors CCR5 and CXCR4.

↓

②**Fusion** (between cell membrane and the virion)→**Penetration**→**Upcoating**.

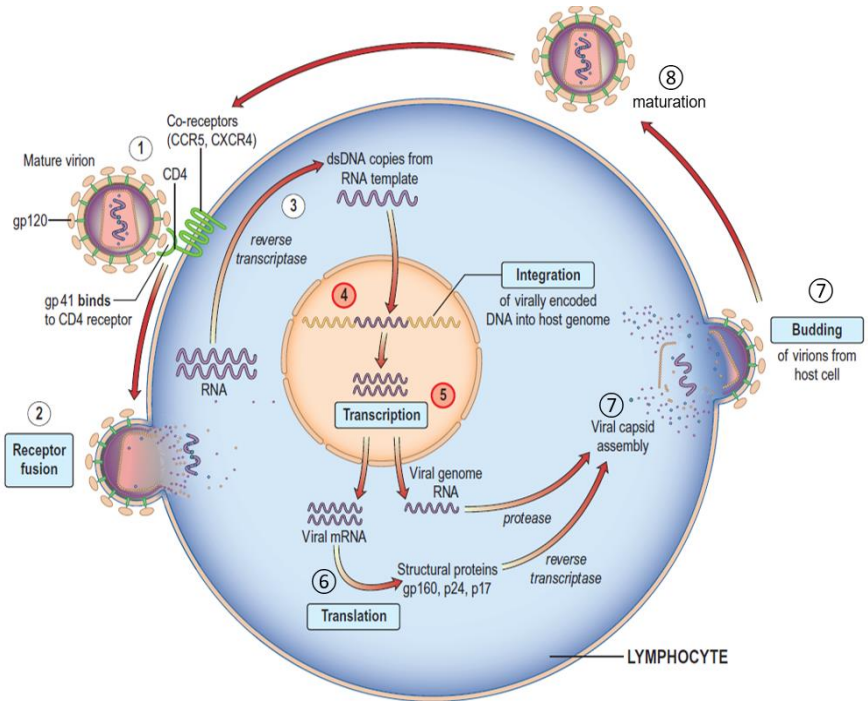
↓

③**Reverse transcription**, Formation of cDNA

↓

④**Integration:** it goes inside the nucleus & Integrate with the host DNA by the enzyme integrase (in the nucleus, virally encoded DNA is inserted into the host genome)

↓



⑤**Transcription** of proviral DNA - formation of genomic RNA - formation of structural mRNA (an RNA molecule is now synthesized from the DNA template!!!). now it well replicate using host's DNA, once it replicate into large number it well be back to RNA by an enzyme called protease	→	⑥**Translation** of structural m RNA: -Formation of viral structural protein - Packaging of genomic RNA of structural protein	→	⑦**Final assembly:** a)Insertion of viral specific glycoprotein into plasma membrane b) Budding c)Release of mature virions	→	⑧**Final maturation:** by cleavage of gag and pol by polymerase enzyme.

لماذا لا نستطيع ان نتخلص من الفيروس؟ لانه داخل في جيناتنا لازم نقتل كل الجينات عشان نتخلص منه وهالشي مستحيل حاليا

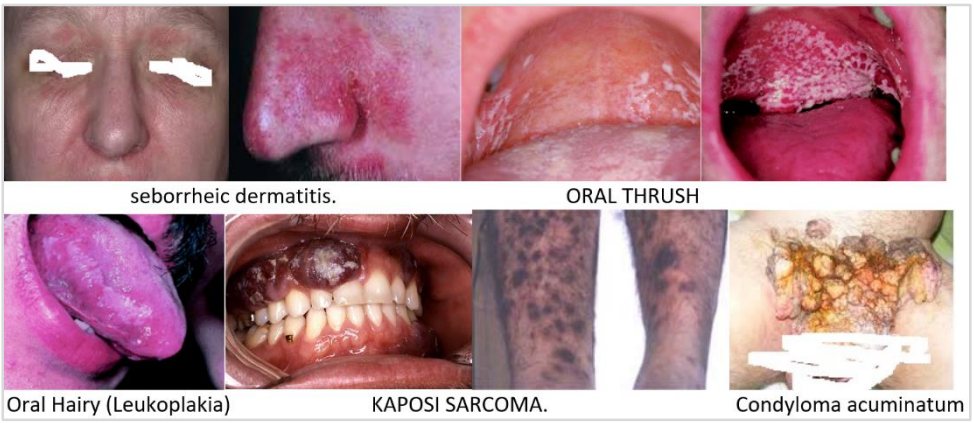
Transmission:

- HIV is a fragile virus(It cannot live for very long outside the body) if u compare HIV with Hep B, it's much better for example if someone has Hep B and bleed upon this table & the blood stay here for a week, the virus will not die and it will stays alive if u come & touch the blood u may be infected but this is not happening with HIV, it's very fragile that die immediately after leaving the human body.
- HIV is primarily found in the blood,semen,or vaginal fluid of an infected person (it does occur in the saliva, sweat & other body fluid but in small amount that are not infectious)
- **it is transmitted through:** (arranged by most common to least common)
    1) Sexual (heterosexual ,men who sex with men ,others): Heterosexual is the most common mode of transmission worldwide.
    2) Vertical transmission:from pregnant woman to the newborn (MTCT)is the main mode of infection in children. we're able now to reduce the incidence of infection from 25-40% to 1% , I've about 10 women in my clinic who deliverd normal child with appropriate treatment!
    3) Blood and body fluid:it's less common now with the new screening techniques
    4) IV Drug Users:Possibility of transmission of these infections by needle prick: Hep B: 30%, Hep C: 3%, HIV: 0.3%

No evidence of spread by : casual contact or by insects such as by mosquito.

Clinical presentation:

1-Acute HIV infection (primary infection) nothing special	- Acute HIV occurs 2-4 wks after transmission . - Most patient manifest a symptomatic **mononucleosis like-syndrome** which is usually overlooked: o Fever, sweats, Pharyngitis, lymphadenopathy. o truncal maculopapular rash, malaise, lethargy, headache, arthralgias/myalgia, fatigue, oral ulcer. o Diarrhea, anorexia. - duration of illness is brief 3 days to 2 weeks. **→THEN:** o HIV RNA level falls and the symptoms resolve. o CD4 cell count rebounds but remains below the basline
2-Asymptomatic chronic phase	- Asymptomatic chronic phase (seropositive but no clinical evidence of HIV infection) - during which the infected individual remains well with no evidence of disease, **except** for persistent generalized lymphadenopathy(defined as enlarged glands at ≥2 extrainguinal sites). - CD4 counts are normal>500/ mm^3 But by time there's a gradual decline in CD4 counts. - Longest phase (lasts **variable** amount of time average 8-10 yrs). - Active viral replication is ongoing and progressive→Chronic immune activation lead to increase in various inflammatory markers→This increases the **risk** of non-AIDS related comorbidities: **CVD**, **Renal dysfunction,** and **cancer** Patient with high HIV RNA may progress to symptomatic disease THAN those with low HIV RNA level.
3-Symptomatic HIV infection (pre-AIDS)	- first evidence of immune system dysfunction. - without treatment, this phase lasts about 1-3 years. - **the following frequently appear:**(wide range of disorders indicating some impairment of cellular immunity) 1. **Skin:** condition associated with HIV, seborrheic dermatitis إلتهاب الجلد الدهني. 2. **Oropharynx:** oral thrush it's oral candida & when it's happen it usually means the pt is immune compromise, u can see it in pregnant women, newborn, diabetic pt but if u see it in young healthy pt it's AIDS, hairy leukoplakia it's always indicate AIDS, mucosal kaposi sarcoma.

	⚠ **Note:** Careful examination of the mouth is important, as oral candidiasis and oral hairy leucoplakia are common and important conditions that require the initiation of antiretroviral therapy and prophylaxis against opportunistic infections, irrespective of the CD4 count. 3. **Lymph node:** Generalized lymphadenopathy (TB , Lymphoma). 4. **Eyes: Fundoscopy:** CMV retinitis. (CD4 less than 50). 5. **Genital exam:** ulcers, condylomatous lesions (genital warts) a. Condyloma acuminatum: A pointed papilloma typically found on the skin or mucous membranes of the anus and external genitalia. i. **caused by:** human papillomavirus (HPV) ii. **Transmitted through:** sexual contact. 6. **constitutional symptoms:** night sweats, weight loss and diarrhea.  seborrheic dermatitis. ORAL THRUSH Oral Hairy (Leukoplakia) KAPOSI SARCOMA. Condyloma acuminatum
4-AIDS	1. marked immune suppression leads to disseminated opportunistic infections and malignancies. 2. CD4 count is < 200 cells/mm^3 3. pulmonary, GI, neurologic, cutaneous and systemic systems are common.

▶ **Notes in The Natural History:**

The average time from HIV to an AIDS is about 10 years→then survival averages 1-2 years.

BUT!!!

There is tremendous individual variability in these time intervals:Patients progress from acute HIV infection to death within 1-2 years and others not manifesting HIV- related immunosuppression for 20 years

✵The mode of transmission does not affect the natural history of HIV disease

To sum up stages of HIV infection:

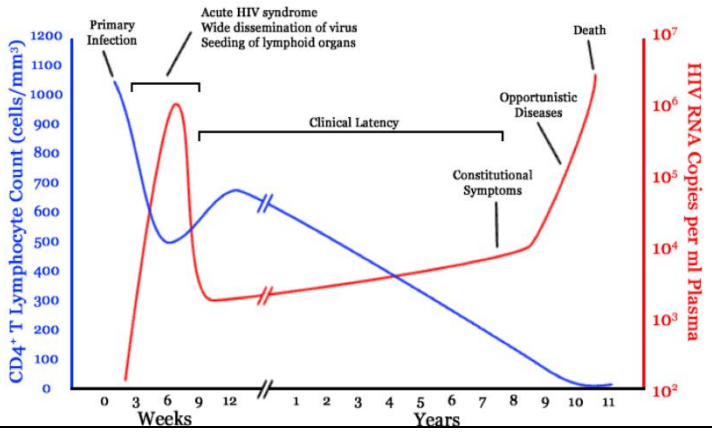
Viral Transmission→Acute HIV infection(occurs 2-4 wks after transmission)→Seroconversion[2] (occurs 2-12 weeks after the development of symptoms) →Asymptomatic HIV infection (last 8-10 yrs) → symptomatic HIV infection(last 1-3 yrs) →AIDS(Average survival 1-2 yrs)

[2] **Seroconversion** is the period of time during which HIV antibodies develop and become detectable.

HIV Serology:

CD4 Cell Count	Viral Load (HIV-1 RNA Levels)
✓ CD4 positive T lymphocytes level is the main method of assessing the immune status of the HIV positive patient. ✓ It is used to determine when to initiate antiretroviral therapy and PCP prophylaxis. It is also useful in assessing the response to antiretroviral therapy. **Immunological staging:** 1. >500 cells/mm³ normal immunity. 2. 350-500 cells/mm³ mild deficiency. 3. 200-350 cells/mm³ moderate immune deficiency. Start treatment here 4. <200 cells/mm³ severe immune deficiency. this is the time when he develop AIDS, cancer & opportunistic infections	- Used to assess response to and adequacy of antiretroviral therapy: ○ If the viral load is still >50 after about 4 months of treatment, modification in the regimen may be needed. ○ Do not stop antiretroviral therapy even if viral loads are undetectable for years;Latently infected cells can lead to reappearance of viral RNA once therapy is stopped.
❋Measure the plasma HIV RNA levels and the CD4-cell count at the time of diagnosis and every 3 to 4 months thereafter.	

HIV progression:



basically the CD4 will sharply drop bc when the virus finish entering the cell & replicate it will destruct the cell such a قليل خاتمة! So, most of infected CD4 will be damaged or become non-function then the immune system try to overcome it the CD4 count will slightly increase and the viral load decrease (9-12 weeks). then the pt. will be a carrier for 5-10 years then when the immune system will be completely damaged, DEATH gonna happen! so, the virus won't leave the human without killing him unless if he's on treatment! he can live like anyone

⚠ **Note:** in the past we used to use ELISA test but it only detects antibody, the problem is that antibodies take time to develop. so, if u screen someone who's in the window area u can miss the case! so wt we do? now we added something in the virus itself in the core, p24, so we're not only test the antibodies we're testing the core and we'll be able to detect the infection bc. we're able to detect the antigen of the antibody "Combo test"

Diagnostic Investigations:

Screening Tests (initial tests):

1- **Combo test:**(combo= combination: antibodies+antigens)
   - will detect HIV1 and HIV2 and P24 antigen:Sensitivity of more than 99.5%.

2- **ELISA:**(were used in the past)
   - Screening test for detecting antibody to HIV; becomes positive 1 to 12 weeks after infection

Confirmatory Tests:

1- **The INNO-LIA™ HIV I/II Score is a Line Immuno Assay (LIA®)***to confirm :*
   - The presence of antibodies against the human immunodeficiency virus type(HIV-1) and (HIV-2) in human serum or plasma.
   - Also differentiates between HIV-1 and HIV-2 —infections
   - Sensitivity: 100%, specificity : 96%

2- **Western blot assays:**
   - can also be used to confirm infection, but they are expensive and sometimes yield indeterminate results.

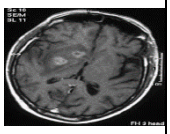
3- **PCR(polymerase chain reaction):** *for quantitative RNA assay*

❋NOT routine testing we've to leave it only for: confirmatory of undetermined cases, asses viral load & baby born to HIV

used as :
   - Confirmatory test for undetermined cases.
   - To asses the viral load .
   - Babies born to HIV-positive mothers, because their blood contains their mother's HIV antibodies for several months.

Why it's Not for routine testing:
   - Decreased sensitivity at lower viral load
   - Significant cost& time consumer

Complications of HIV/AIDS:

Tuberculosis:	Candidiasis:	Toxoplasmosis:
TB is the most common opportunistic infection and a leading cause of death	It causes inflammation and a thick, white coating on the mucous membranes of the mouth, tongue, esophagus or vagina.	Just know that it can happen in the brain "go through it" This potentially deadly infection is caused by Toxoplasma gondii, a parasite spread primarily by cats. It causes meningoenchephalitis. ○ **DX:** Serology and MRI. ○ **Treatment:** Combination of (pyrimethamine+sulfadiazine) Respond very well. 

Cancers common to HIV/AIDS:	
Kaposi's sarcoma: A tumor of the blood vessel walls, common in HIV-positive patients. Rare in none. i. Kaposi's sarcoma usually appears as pink, red or purple lesions on the skin and mouth and can also affect the internal organs, including the digestive tract and lungs.	**non-hodgkin lymphoma.**

Antiretroviral Therapy (ART):

Goals of Antiretroviral Therapy (ART):

▶ **NOTE:** Eradication of HIV? Not possible with currently available antiretroviral medications. we're able to treat them but not able to cure them!

- ✓ Improvement of quality of life.
- ✓ Reduction of HIV-related morbidity and mortality.
- ✓ Restoration and/or preservation of immunologic function.
- ✓ Maximal and durable suppression of viral load.
- ✓ stop the transmission.

Indications of initiation of antiretroviral drugs:

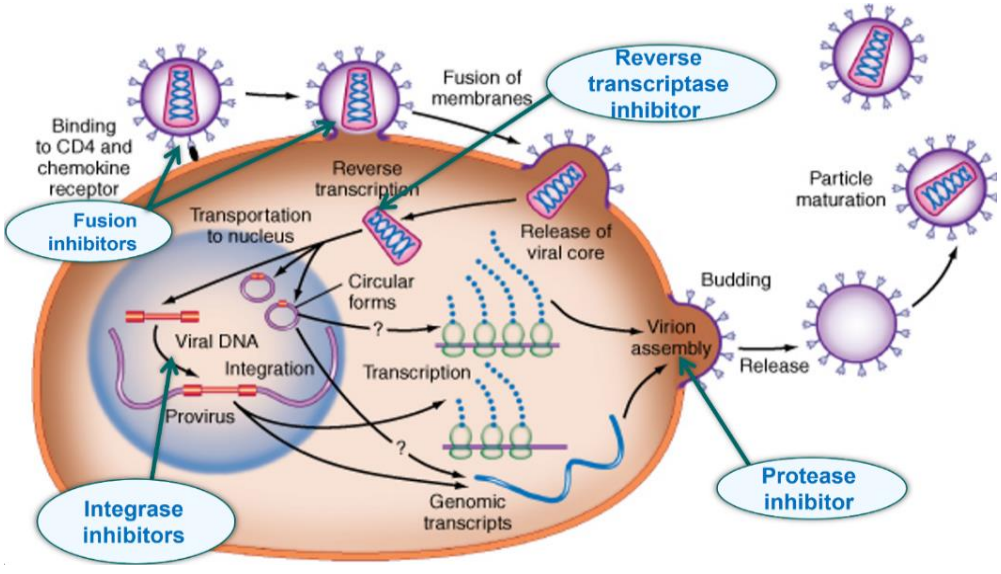
- Symptomatic HIV patients regardless of CD4 count.
- Asymptomatic HIV patients with:
  - CD4 count less than 350.
  - Pregnancy

- Post exposure prophylaxis:
  - healthcare worker
  - someone who practice sex

antiretroviral drugs:

first line medications:			second-line agents:	
RTI's	non-nucleoside RTI's	protease inhibitors	Entry (fusion) inhibitors	Integrase inhibitors

there was a drug which works upon fusion but it's injectable so they don't use it anymore, other drug works on transcription and stop it here, also there is drug works on integration and stop it here, & the last one is protease inhibitor. we don't block one at a time we block two at the same time so the virus has no chance to develop resistance.



Chemoprophylaxis:

chemoprophylaxis:

- **What is it:**Chemoprophylaxis is the use of antimicrobial agents to prevent infections.
- **Types of prophylaxis:**
  - Primary prophylaxis is used to prevent opportunistic infections that have not yet occurred. الفكره هنا من مبدأ الوقاية خير من العلاج فيما ان مريض الايدز عرضه لانفكشن كثيره فهنا نعطي مضاد للمايكروبز قبل ماتصير عندهم الانفكشن
  - Secondary prophylaxis is used to prevent recurrence of opportunistic infections because many may recur after an initial response to therapy. Secondary prophylaxis can be discontinued when ART results in immune reconstitution, with CD4 counts increasing to over 200 cells/mm3, but for CMV and MAC, prophylaxis can be stopped if CD4 counts increase to more than 100 cells/mm3

Indications of Opportunistic infection chemoprophylaxis:

In HIV patients It's recommended to prevent Pneumocystis jirovecii when their CD4 count below 200 cells/mm3

- **Prophylaxis:** co-trimoxazole 1 ds OD
- Pneumocystis jirovecii:can Cause Pneumonia

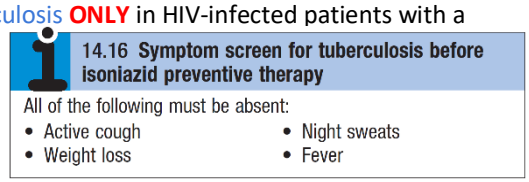
(my aim is to treat him until he become above 200 so I give him co-trimoxazole & clarithromycin as a prophlaxis until their CD4 above 200 for 3 months then I stop it and say u r fine & have no problem!)

In HIV patients It's recommended to prevent Mycobacterium Avium-Intracellulare when their CD4 count below 50 cells/mm3

- **Prophylaxis:** clarithromycin 500 mg orally twice a day.

Read it just in case(Isoniazid preventive therapy (IPT):

- Isoniazid preventive therapy (IPT) has been shown to reduce the risk of tuberculosis **ONLY** in HIV-infected patients with a positive tuberculin skin test(induration of 5 mm or more)
- Screen all patients with a yearly tuberculin skin test is require.
- There is no CD4 count or clinical threshold for starting or stopping IPT.
- It is important to rule out active tuberculosis before starting IPT(see the fig→)



Prevention:

1. The only absolute way to Prevent sexual transmission of HIV infection is :اتباع قول الله تعالى
   { وَلَا تَقْرَبُوا الزِّنَى إِنَّهُ كَانَ فَاحِشَةً وَسَاءَ سَبِيلًا }
2. **Abstinence** from sexual relation completely
3. Safer sexual contact: Use of condom, 10% failure rate.
4. Circumcision: results in 50% reduction of HIV acquisition
5. Stop using IDUs
6. Screen all blood and blood products.
7. The **corner stone** of an HIV prevention strategy is:
   - Education
   - Counseling
   - Behavior modification
8. If more than 25% of infected patient does not know, What to do? Routine testing between 13 and 64 years. (CDC recommendations without written consent)

Mother to child transmission:

Pregnancy and HIV infection:

Pregnant women infected with HIV infection caries risk to infect her baby by:

In utero,25-40%	Intrapartum, 60-75%	Breast feeding:
	Current evidence suggests **most transmission** occur during the intrapartum period. Bc it mixes with blood	○ Established infection 14% ○ Primary infection 29% HIV lady should not breastfeed

✓ Overall risk for mother to child transmission (MTCT) is 16%-25% (without antiretroviral Rx)
✓ HIV woman who want to get pregnant has to plan with her physician before conceive pregnancy

Perinatal HIV transmission:

Today the risk of perinatal transmission is: Less than 2% with:

1. Effective antiretroviral therapy (ART)
2. Elective caesarean section when appropriate
3. Formula feeding

MCQS

1)A 25 years old pregnant women at 20th week of gestation presented to the clinic and was diagnosis to have HIV. Laboratory revealed viral load of 100,000 copies, and CD4 count of 450 cells/mm2. She is on No medication and get warred about her fetus contacting the infection.
Which one of the following is most appropriate next step?
A. testing for her husband and other children
B. Induction for abortion
C. Initiation of antiretroviral therapy
D. Reassurance and follow up after 4 weeks

2)A 39 year old man IV drug abuser came complaining of fever, night sweats and hemoptysis.
AFB stain was positive. Also blood test revealed that he is positive to HIV with 50 cell CD4+. What is your next step in management?
A. Start antiretroviral then after that start TB medications.
B. Start antiretroviral till CD4+ become 350 cell then start anti TB.
C. Now treat only the HIV infection
D. Start anti TB medication at the same time with antiretroviral therapy

3)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

4)HIV is spread in Saudi Arabia through which one of the following routes?
A. Drug abusers
B. Sexual
C. Blood products
D. Vertical

Answer key:

1 (C) | 2 (D)| 3(B) | 4 (B)

SUMMARY