MEDICINE

432 Team

56 HIV and AIDS

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

Not Given!

Definition:

Infection with Human immunodeficiency Virus (HIV). and if left without treatment, is usually a fatal infection.
Characterized by:

- Progressive immunodeficiency: irreversible
- Long latency period: stays alive for a long period and after that period passes by, the complications of immunodeficiency will manifest
- Opportunistic infection: only in poor immune system: toxoplasma, pneumocystis pneumonia, fatal diseases, TB reactivation and other diseases.

It is an RNA virus that belongs to the family Retroviredae. It is called — Retrovirus —, and that is why we call the medications anti-retro viral drugs.

Retrovirus: information in the form of RNA is transcribed into DNA in the host cell.

There are two viruses:

HIV1 and HIV2.
- It causes diseases by disrupting the immune system function as measured by CD4 cell depletion called:
AIDS=Acquired Immune Deficiency Syndrome.

- ✓ HIV1: Predominate worldwide
- ✓ HIV2: Predominate in western Africa

✓The hallmark of HIV Disease:

Infection and viral replication within T-lymphocyte expressing the CD4 antigen resulting in:

- ❖ **Qualitative and quantitativedefect in CD4 responsiveness**, and that's why immune deficiency occurs.
- ❖ **Progressive depletion in CD4 cell counts:** AND This effect on helper-inducer lymphocytewill increase the risk of:

1) Opportunistic infections such as Pneumocystis Jiroveci and toxoplasma
2) Neoplasm such as Lymphoma (such as non-Hodgkin)and Kaposi sarcoma

✓ History:

1st recognized in USA 1981
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...later on, Pneumocystis pneumonia and Kaposi sarcoma are diseases that appear in immune deficient patients only
3) The disease became recognized in both male and female with (IUDs)(they now call it recreational drugs) as well as
4) Recipients of blood transfusion and hemophiliacs

Epidemiology:

- HIV infection/AIDS is a global pandemic
- Cases reported everywhere.
- Ranging 30—36 million.
- More than 95% reside in low and middle –income countries
- 50% are females
- 2.5 million are children (less than 13)
- Epidemic was first recognized in USA and shortly thereafter in Western Europe.
- More than 2/3rd (95%) of all people with HIV live in sub-Saharan Africa.

Global summary of the AIDS epidemic | 2010

Number of people living with HIV	Total	34.0 million [31.6 million–35.2 million]
	Adults	30.1 million [28.4 million–31.5 million]
	Women	16.8 million [15.8 million–17.6 million]
	Children (<15 years)	3.4 million [3.0 million–3.8 million]
People newly infected with HIV in 2010	Total	2.7 million [2.4 million–2.9 million]
	Adults	2.3 million [2.1 million–2.5 million]
	Children (<15 years)	390 000 [340 000–450 000]
AIDS deaths in 2010	Total	1.8 million [1.6 million–1.9 million]
	Adults	1.5 million [1.4 million–1.6 million]
	Children (<15 years)	250 000 [220 000–290 000]

World Health Organization UNAIDS

✓Asia:

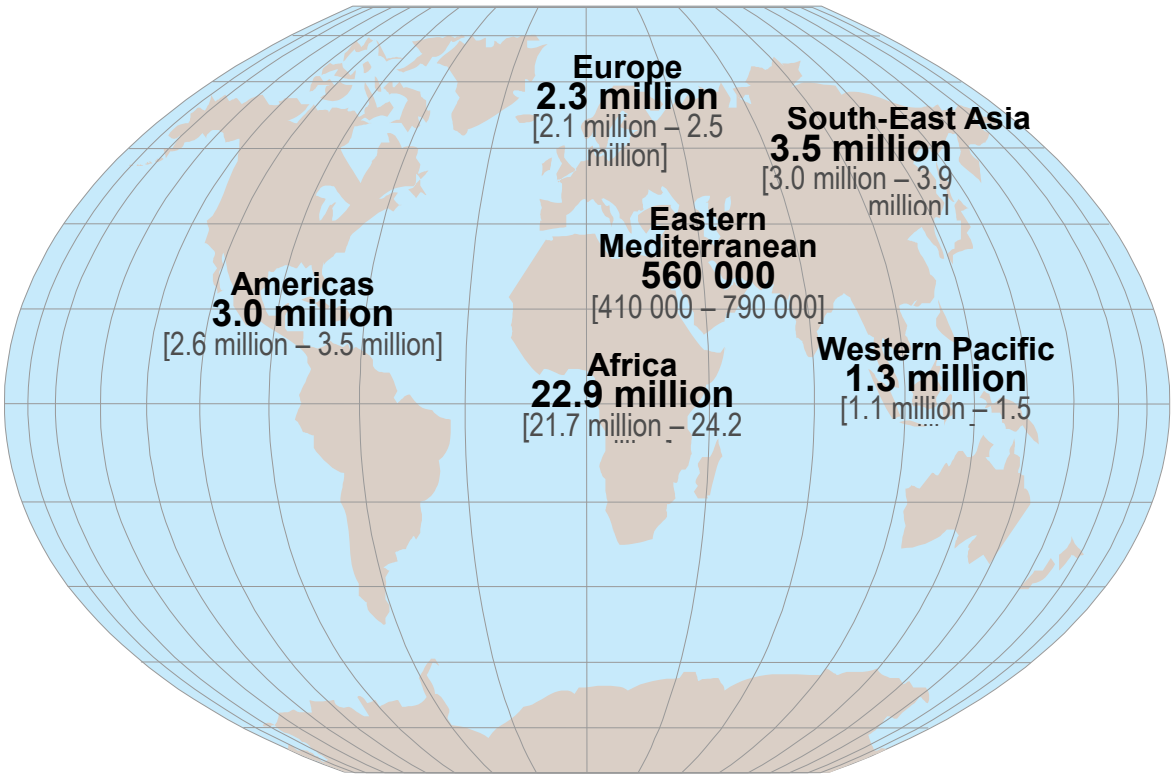
- 4.9 million People living with HIV.
- National HIV prevalence is highest in Southeast Asia 4.0 million.
- HIV prevalence is increasing in Indonesia and Vietnam.

World Health Organization UNAIDS

Global summary of the AIDS epidemic, December 2007

Number of people living with HIV in 2007	Total	33 million [30 – 36 million]
	Adults	30.8 million [28.2 – 34.0 million]
	Women	15.5 million [14.2 – 16.9 million]
	Children under 15 years	2.0 million [1.9 – 2.3 million]
People newly infected with HIV in 2007	Total	2.7 million [2.2 – 3.2 million]
	Adults	2.3 million [1.9 – 2.8 million]
	Children under 15 years	370 000 [330 000 – 410 000]
AIDS deaths in 2007	Total	2.0 million [1.8 – 2.3 million]
	Adults	1.8 million [1.6 – 2.1 million]
	Children under 15 years	270 000 [250 000 – 290 000]

Adults and children estimated to be living with HIV, by WHO Region, 2010



Total: 34.0 million

✓HIV is primarily found in the:

- Blood,
- Semen, or
- Vaginal fluid of an infected person.

Transmission:

❖ Sexual (heterosexual, msm, others)

❖ Heterosexual is the most common mode of transmission worldwide.

❖ Vertical transmission from pregnant woman to the newborn (MTCT) is the main mode of transmission worldwide.

✓Infection in children.

- Blood and body fluid the incidence in Saudi Arabia is rare because we no longer export blood from abroad, and we have very sensitive tests.
- IVDU (Intravenous Drug Abusers)
- No evidence of spread by: casual contact or by insects such as by mosquito

Structure:

- It is an RNA virus

It is an icosahedral متعددالسطوح structure of:

1) Lipid Envelope: derived from infected cell, containing numerous external spikes formed

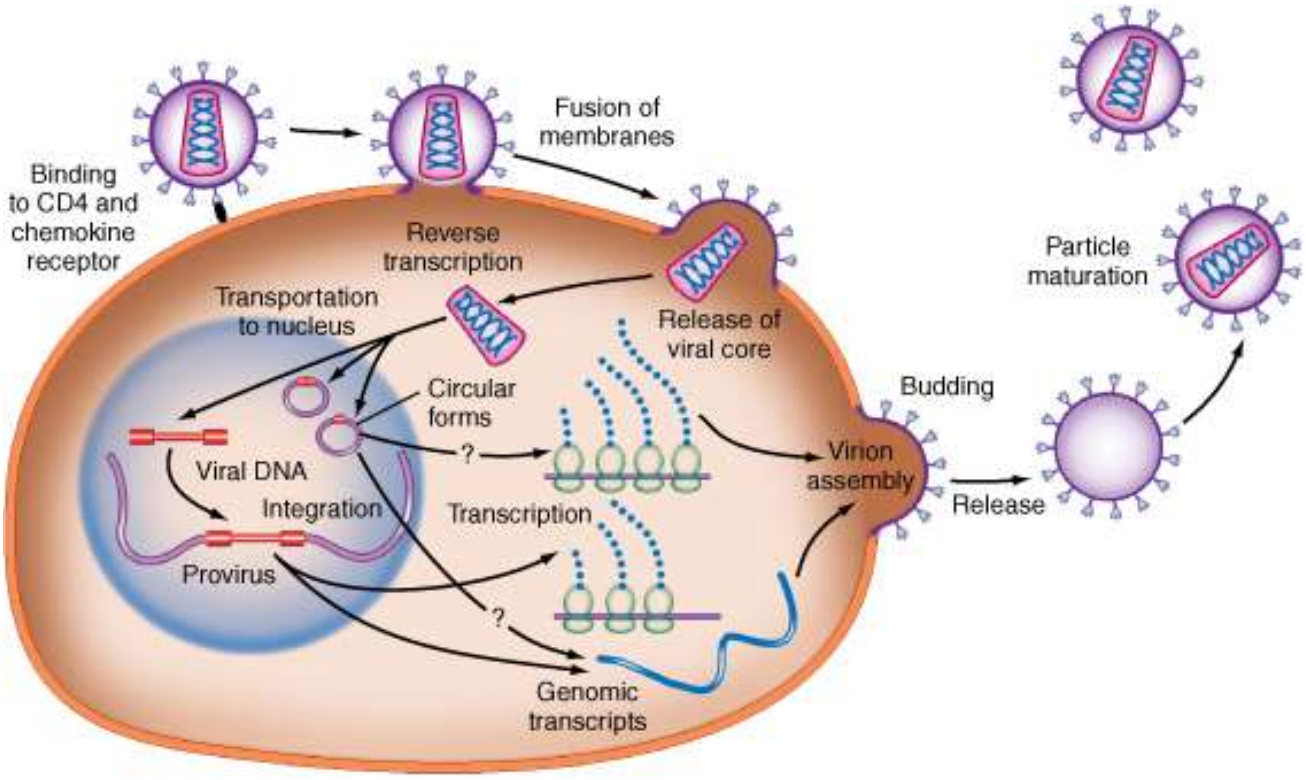
By two major envelope proteins:

a) The external gp 120

b) The transmembranegp 41

2) Nucleocapsid (gag) with P24 major core protein and RNA, which will become DNA in the host cell.

3) Polymerase (pol)



✓HIV life cycle and replication:

1) Attachment:

This takes place through receptor specific:

A) CD4---gp120

B) CO-receptor: 1) CCXR5

2) CXCR4

2) Penetration

3) Upcoating, to reveal its RNA

4) Reverse transcription: Formation of cDNA

5) Integration

6) Transcription of proviral DNA

a) Formation of genomic RNA

b) Formation of structural mRNA

7) Translation of structural m RNA

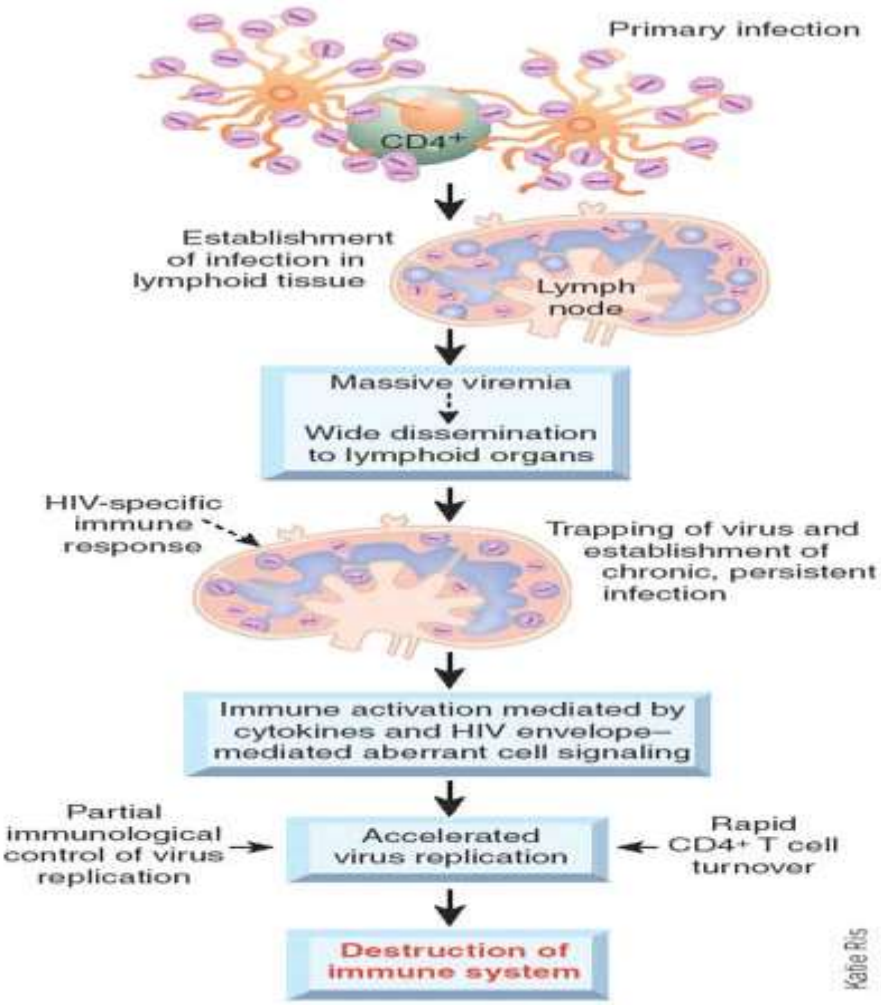
a) Formation of viral structural protein.

b) Packaging of genomic RNA of structuralprotein.

8) Final assembly

a) Insertion of viral specific glycoprotein into plasma membrane

b) Budding
c) Release of mature virions
9) Final maturation BY cleavage of gag and pol by polymerase enzyme, and then it leaves the cell and move to the blood stream.



Pathogenesis of HIV virus:

Suppose someone was infected through sexual contact, the virus will first attach to the wall of the genital tract and attack the CD4, then it will move to the lymphoid tissue draining the affected organ (in this case the genitals). In the lymph nodes, it replicates and causes massive viremia that goes to the whole body and spreads everywhere.

Diagnosis:

- 1984: Rapid development of screening test
- 1985: blood donors were routinely screened for antibodies and also for Hepatitis B/C
- 1996: blood banks added thep24 antigen capture assay to detect early cases.

When screening the blood we look for antibodies first, but it usually takes about 2-6 weeks to appear; hence, scientists developed the detection of the p24 antigen.

- ELISA: is the screening test used to screen blood products and patients.

Sensitivity of more than 99.5%

- **The fourth generation test:**

EIA test: combine detection of antibody to HIV and detection of p24 antigen.

Extremely sensitive but specificity is not optimal, low risk. Only 10% who are positive by
thistest turned to be real positive.

- **Western blot: confirmatory test**: It might miss the cases in EARLY stage especially since this is the most contagious period in all of HIV infection.

There is a problem with the indeterminate cases.(Window period).

- Western blots, or protein immunoblots, are used to detect specific proteins in a sample. The test involves sorting proteins by length on a gel and then probing the gel with antibodies that react to the proteins that are being searched for.
- For HIV testing: labs work with prepared protein samples, and look to see if there are any antibodies in a person's blood that stick to them

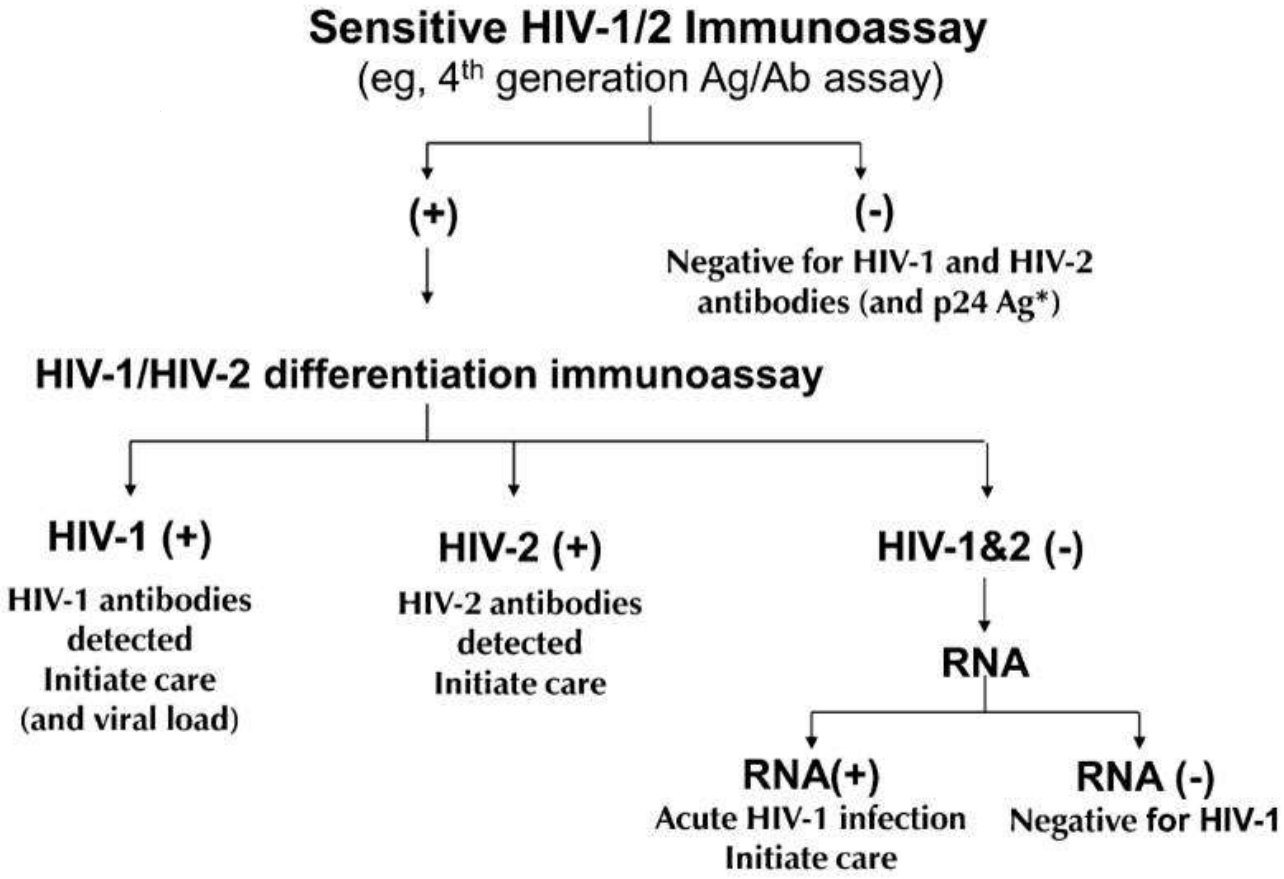
- **PCR: (polymerase chain reaction) quantitative RNA assay used as:**

1) Confirmatory test and
2) To assess the viral load
3) Babies born to HIV-positive mothers, because their blood contains their mother's HIV antibodies for several months.
4) Blood supplies

- Not for routine testing:

a) Decreased sensitivity and specificity at lower viral load
b) Significant cost.

Algorithm testing for HIV



Staging (WHO):

Acute HIV infection

- Clinical stage1: Asymptomatic infection
- Clinical stage2: Mild symptoms, lymphadenopathy, and mild splenomegaly.
- Clinical stage3: Moderate symptoms: diarrhea, weight loss, hair loss, fatigability… etc.
- Clinical stage4: Sever symptoms, advanced immune deficiency

✓Clinical stage 1:

- Asymptomatic
- Persistent generalized lymphadenopathy

✓Clinical stage 2:

- Moderate and unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections (such as Sinusitis, bronchitis, otitis media and pharyngitis)
- Herpes Zoster.

- Recurrent oral ulcerations
- Papular pruritic eruptions
- Angular cheilitis and Seborrhoeic dermatitis

✓Clinical stage 3:

- Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month) Severe weight loss (>10% of presumed or measured body weight)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g. pneumonia, empyema, meningitis, bacteraemia, pyomyositis, bone or joint infection)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Conditions where confirmatory diagnostic testing is necessary
- Unexplained anaemia (< 80 g/l), and or neutropenia (<500/µl) and or thrombocytopenia (<50 000/ µl) for more than one month

✓Clinical stage 4:

- Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis
- Extrapulmonary Tuberculosis
- Kaposi's sarcoma
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Conditions where confirmatory diagnostic testing is necessary
- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy

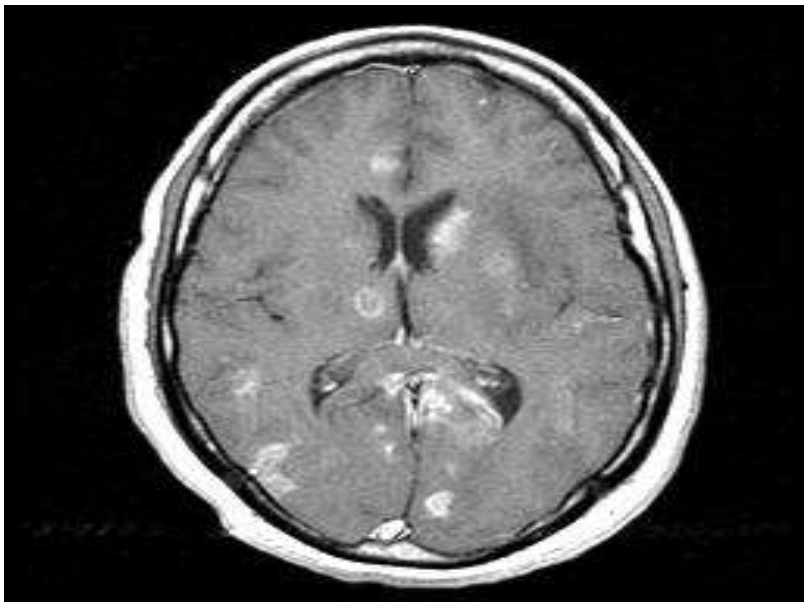
- Candida of trachea, bronchi or lungs
- Cryptosporidiosis
- Visceral herpes simplex infection
- Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
- Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
- Recurrent non-typhoidal salmonella septicaemia
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Visceral leishmaniasis

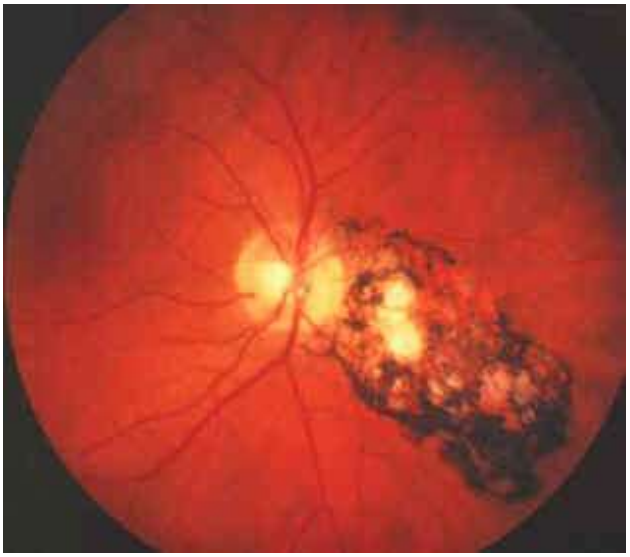
Immunological staging:

CD4 positive T lymphocytes level is the main method of assessing the immune status of the HIV positive patient.

1. >500 cells/mm³ normal immunity.
2. 350-500 cells/mm³ mild deficiency.
3. 200-350 cells/mm³ moderate immune deficiency.
4. <200 cells/mm³ sever immune deficiency

TOXOPLASMOSIS in AIDS patient





KOPOSI SARCOMA

ORAL HAIRY LEUKOPLAKIA

CANDIDAISIS

Natural history:

The average time from acquisition of HIV to an AIDS- defining illness: Is about 10 years, and then the survival average is 1-2 years. The common scenario BUT

- There is tremendous individual variability in these time intervals: Patient scan progress from acute HIV infection to death within 1-2 years, and others don't manifest HIV- related immunosuppression for 20 years

Stages of HIV infections:

A] Viral Transmission:

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

B] Acute HIV infection:

Acute HIV occurs 1-4 wks after transmission and accompanied by Burst HIV replication with a decline in CD4 cell count.

Most patient manifest a symptomatic mononucleosis like-syndrom that is usually overlooked.

C] Seroconversion:

Development of a positive HIV antibody test usually occurs within 4 wks and invariably by 6 months.

D] Asymptomatic HIV infection

It lasts variable amount of time (average 8-10 yrs) and is accompanied by a gradual decline in CD4 counts with relatively stable HIV RNA level. (The viral 'set point')

Goals of antiretroviral therapy (ART):

- Eradication of HIV is not possible with currently available antiretroviral medications.
- Improvement of quality of life
- Reduction of HIV-related morbidity and mortality
- Restoration and/or preservation of immunologic function. Improve the CD4 count.
- Maximal and durable suppression of viral loadto prevent opportunistic infections and decrease the chances of transmission.

✓Medications:

Nucleoside Analogue RTI;

Abacavir (ABC)
Didanosine (ddi)
Emtricitabine (FTC)
Lamivudine (3TC)
Stavudine (d4T)
Tenofovire DF
Zalcitabine (ddC)
Zidovudine (AZT, ZDV)

Non-nucleoside RTIs;

Delavirdine
Efavirenz
Nevirapine

Protease Inhibitors (PIs);

Amprenavir
Atazanavir
Darunavir
Fosamprenavir
Indinavir
Lopinavir/Ritonavir (Kaletra)
Nelfinavir
Ritonavir
Saquinavir
Tipranavir

Fusion Inhibitors;

Enfuvirtide (Fuseon)

✓Indication of initiation of antiretroviral drugs

- Chronic infection

a) Symptomatic disease
b) A symptomatic disease with
    1) CD4 count less than 350
    2) Pregnancy

- Post exposure prophylaxis.

✓Prevention:

- The only absolute way to prevent sexual transmission of HIV infection is:

Abstinence from sexual relation the most important!

- Safer sexual contact: Use of condom...10% failure rate.
- Circumcision: results in 50% reduction of HIV acquisition. An area in Africa had low Prevalence of HIV and when investigated, it was foundthat Muslims live in it and all males had been circumcised.
- Stop using IDUs
- Screen all blood and blood products.

✓ The corner stone of an HIV prevention strategy is :

- ❖ Education
- ❖ Counseling
- ❖ Behaviour modification

Prgnancy and HIV infection

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 :
    1) Established infection 14%
    2) Primary infection 29%

Current evidence suggests most transmission occur during the intrapartum period.

Overall risk for mother to child transmission (MTCT) IS 16 – 25 % (without antiretroviral Rx)

Perinatal hiv transmission

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

- Effective antiretroviral therapy (ART)
- Elective caesarean section when appropriate
- Formula feeding

SUMMARY

-Human immunodeficiency virus (HIV) is an RNA virus, icosahedral structure that belongs to Retroviredae family .it cause a chronic and -if left without treatment- a fatal infection.

- It characterized by progressive irreversible immunodeficiency, long latency period, and opportunistic infection.
- The most common virus associated with HIV is HIV 1
- Pathophysiology: the virus attaches to the surface of CD4+ T lymphocytes, enters the cell and uncoats, then its RNA will transcribed to DNA by reverse transcriptase. When the virus enters the lytic stage of infection, CD4 cells are destroyed and this will cause depletion of CD4 number and will result in weakens of the cellular immunity of the host.
- HIV is found in blood, semen, vaginal fluid of an infected person, but remember, HIV is a fragile virus. It cannot live for very long outside the body.
- Mood of transmission: sexual (heterosexual, msm, others), vertical transmission, blood and body fluid transfusion, IV drug abusers.
- Diagnostic tests are ELISA, p24 antigen, EAI test, western blot and PCR.
- PCR is used to detect viral load, so it use to assess the effectiveness of therapy.
- P24 antigen used to detect viral load, but it is less sensitive.
- ELISA is the screening test used to screen blood products and patients, it sensitivity is >99.5 %
- Western blot is the confirmatory test for positive result on ELISA test.
- Clinical manifestations: it is divided into 3 stages: stage 1 asymptomatic, stage 2 with weight loss, recurrent infections, oral ulcerations, herpes zoster… etc., stage 3 with chronic diarrhea, and sever weight loss, unexplained persistent fever, oral candidiasis, and oral hairy leukoplakia.
- Opportunistic infections will occur if the CD4 count is <200,
- Treatment with antiretroviral therapy. Indications are symptomatic patient regardless of

CD4 count, or asymptomatic patient with CD4 count < 500
- Prevention by education, counseling and behavior modification.

Questions

1) Which of the following viruses is associated with Kaposi Sarcoma?
A) Herpes Simplex Virus type 1 (HSV-1)
B) Cytomegalovirus (CMV)
C) Epstein-Barr Virus (EBV)
D) Human Herpes Virus 8 (HHV-8)

2) The decision to begin antiretroviral therapy is based on:
A) The CD4 cell count
B) The plasma viral load
C) The intensity of the patient's clinical symptoms
D) All of the above

3) Effectiveness of antiretroviral therapy is measured by:
A) A fall in the plasma viral load and an increase in theCD4 count.
B) A rise in red blood cell count and hemoglobin level.
C) A rise in plasma HIV antibodies level.
D) A reduction in opportunistic infections.

4) A 27 years old man has fever, macular rash and lymphadenopathy. He has unprotected sex with a male partner 2 weeks before the onset of these symptoms and has just learned that the partner is infected with HIV. The patient's rapid test is negative. What is the best test to evaluate this patient for HIV infection?

A) ELISA
B) PCR for HIV RNA
C) Western blot testing
D) Glycoprotein 120 using ELISA
E) PCR for HIV DNA

Q1: Indications are symptomatic patient regardless of CD4 count, or asymptomatic patient with CD4 count < 500 + The urgency for ART increases when a person's viral load is greater than 100, 000 copies/mL.

Q3: HIV infection usually diagnosed by ELISA or rapid test, but when acute retroviral syndrome is highly susceptible in-patient with high risk behavior a plasma RNA PCR should be used in conjunction with HIV antibody test (rapid test) to diagnose acute HIV infection.

432 Medicine Team Leaders

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Answers:

1st Questions: D

2nd Questions: D

3rd Questions: A

4th Questions: B