Team Medicine

28#

HIV/AIDS

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431 Teams

Definition:

Infection with Human immunodeficiency Virus (HIV)

Compared to spontaneously resolved infections; for example, brucella, the treatment here is to prevent complications and make the recovery faster, but if not treated, patients will ultimately recover. There are many Bedouins in the desert that don't know they are infected, they get a febrile illness and then recover, and that is applicable for most of the intracellular organisms, but HIV has no spontaneous recovery and is not like other viruses, such as the common cold. Everyone gets the common cold for few days and then it resolves but HIV usually leads to chronic and if left without treatment, is usually a fatal infection.

Characterized by:

A} Progressive immunodeficiency→ irreversible

B} Long latency period→ stays alive for a long period and after that period passes by, the complications of immunodeficiency will manifest

C} 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.

The virus goes into the human body as RNA and then changes into DNA, it benefits from the DNA and the cell division to divide its self and return to RNA

1 million viruses inter the cell → billions come out.

There are two viruses:

HIV1 andHIV2.

- 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

The HIV virus affects the cell-mediated immunity.
T-cells control viruses and fungi (CD4 helper cells and CD8 suppressor cells), while B-cells (immunoglobulins) control bacteria.

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

The prevalence in India is now increasing because they are legalizing same-sex marriage.

- 1983: HIV was isolated from patient with lymphadenopathy
- 1984: HIV was demonstrated to be the causative agent of AIDS
- 1985: ELISA test was developed

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 WesternEurope.
- More than 2/3rd(95%)of all people with HIV live in sub-Saharan Africa. In Zimbabwe a ratio of 1:3 are affected with HIV.

- 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.
  - Epidemic is expanding in Eastern Europe and central Asia: 1.6 million
  - HIV prevalence is decreasing in certain areas because they are taking care of drug abusers by supplying them with sterile syringes to prevent HIV, hepatitis and other diseases.

The graphs are only to be read:

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]

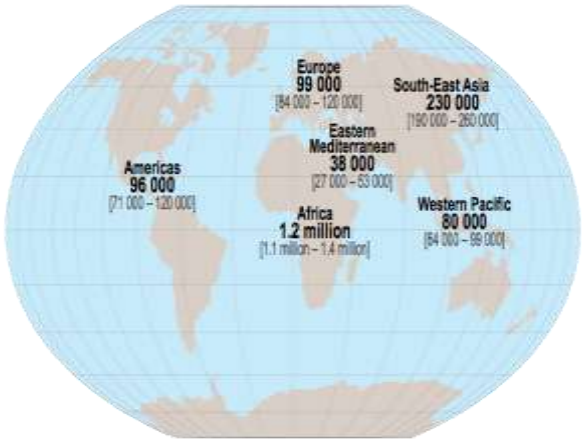
World Health Organization UNAIDS

Regional HIV and AIDS statistics and features | 2010

	Adults and children living with HIV	Adults and children newly infected with HIV	Adult prevalence (15–49) [%]	Adult & child deaths due to AIDS
Sub-Saharan Africa	22.9 million [21.6 million – 24.1 million]	1.9 million [1.7 million – 2.1 million]	5.0% [4.7% – 5.2%]	1.2 million [1.1 million – 1.4 million]
Middle East and North Africa	470 000 [350 000 – 570 000]	59 000 [40 000 – 73 000]	0.2% [0.2% – 0.3%]	35 000 [25 000 – 42 000]
South and South-East Asia	4.0 million [3.6 million – 4.5 million]	270 000 [230 000 – 340 000]	0.3% [0.3% – 0.3%]	250 000 [210 000 – 280 000]
East Asia	790 000 [580 000 – 1.1 million]	88 000 [48 000 – 160 000]	0.1% [0.1% – 0.1%]	56 000 [40 000 – 76 000]
Latin America	1.5 million [1.2 million – 1.7 million]	100 000 [73 000 – 140 000]	0.4% [0.3% – 0.5%]	67 000 [45 000 – 92 000]
Caribbean	200 000 [170 000 – 220 000]	12 000 [9400 – 17 000]	0.9% [0.8% – 1.0%]	9000 [6900 – 12 000]
Eastern Europe and Central Asia	1.5 million [1.3 million – 1.7 million]	160 000 [110 000 – 200 000]	0.9% [0.8% – 1.1%]	90 000 [74 000 – 110 000]
Western and Central Europe	840 000 [770 000 – 930 000]	30 000 [22 000 – 39 000]	0.2% [0.2% – 0.2%]	9900 [8900 – 11 000]
North America	1.3 million [1.0 million – 1.9 million]	58 000 [24 000 – 130 000]	0.6% [0.5% – 0.9%]	20 000 [16 000 – 27 000]
Oceania	54 000 [46 000 – 62 000]	3300 [2400 – 4200]	0.3% [0.2% – 0.3%]	1600 [1200 – 2000]
TOTAL	34.0 million [31.6 million – 35.2 million]	2.7 million [2.4 million – 2.9 million]	0.8% [0.8% - 0.8%]	1.8 million [1.6 million – 1.9 million]

The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information.

Estimated adult and child deaths from AIDS, by WHO Region, 2010



Total: 1.8 million [1.6 million – 1.9 million]

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

Total: 34.0 million

Estimated number of adults and children newly infected with HIV, by WHO Region, 2010

Total: 2.7 million [2.4 million – 2.9 million]

- 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 of an infected person.

Transmission:

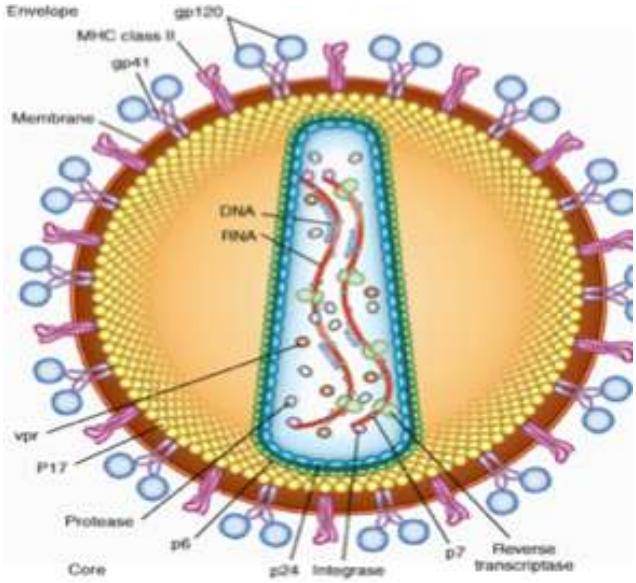
- ❖ Sexual(heterosexual, msm, others)
- ❖ Heterosexual is the most common mode of transmission worldwide.
- ❖ Vertical transmissionfrom pregnant woman to the newborn (MTCT) is the main mode of infection in children.
- ❖ Blood and body fluid, the incidence in Saudi Arabia is rare because we no longer 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 متعددالسطوحstructure of:

1) Lipid Envelope(env) 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

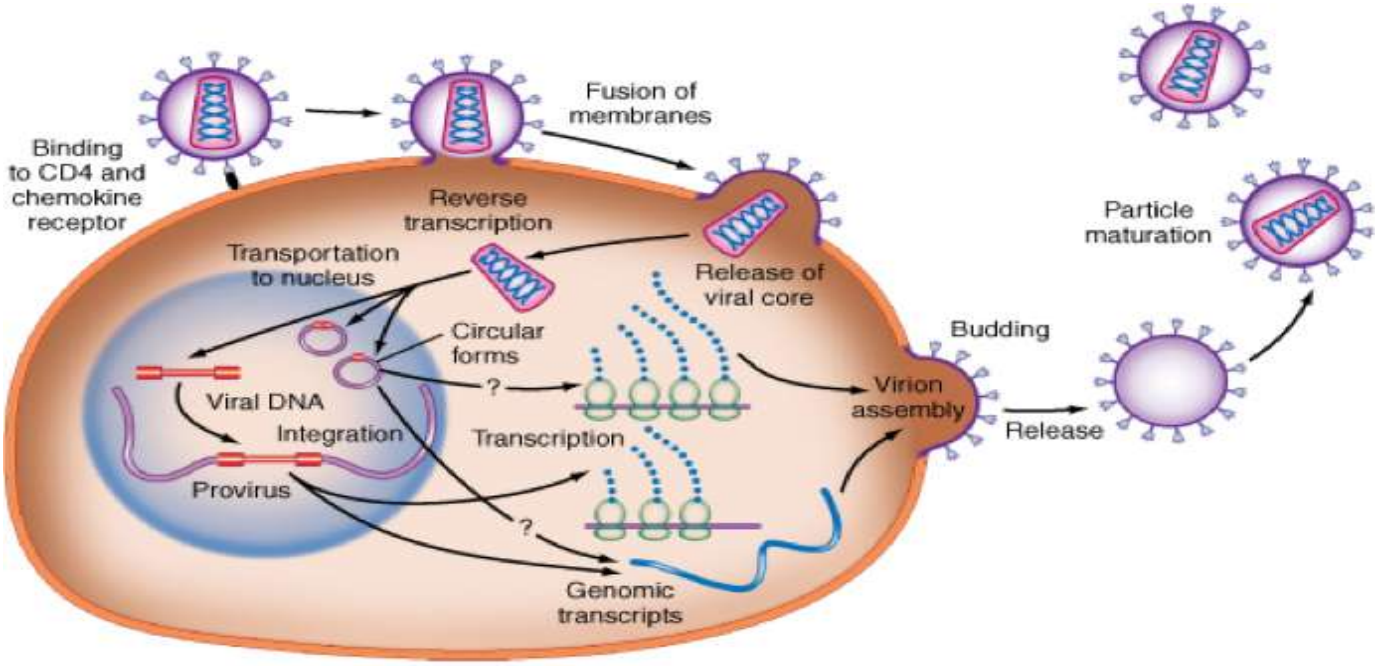
a) Insertion of viral specific glycoprotein into plasma membrane

b) Budding

c) Release of mature virions

9) Final maturation

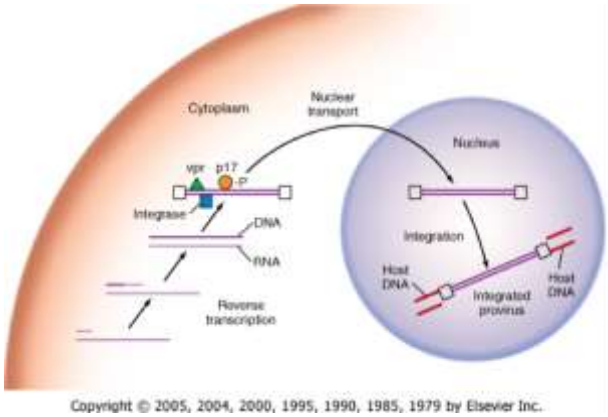
BY cleavage of gag and pol by polymerase enzyme, and then it leaves the cell and move to the blood stream.



If you remember in the biochemistry, it is irreversible when the DNA is transformed to RNA and then to protein, but the HIV virus reverses this cascade to produce RNA from the cell's DNA using the enzyme reverse transcriptase. Medications are used to inhibit this enzyme. The virus integrates its self in the sequence of the DNA in the host cell, replicates, detaches and become RNA and then leaves the cell in millions.

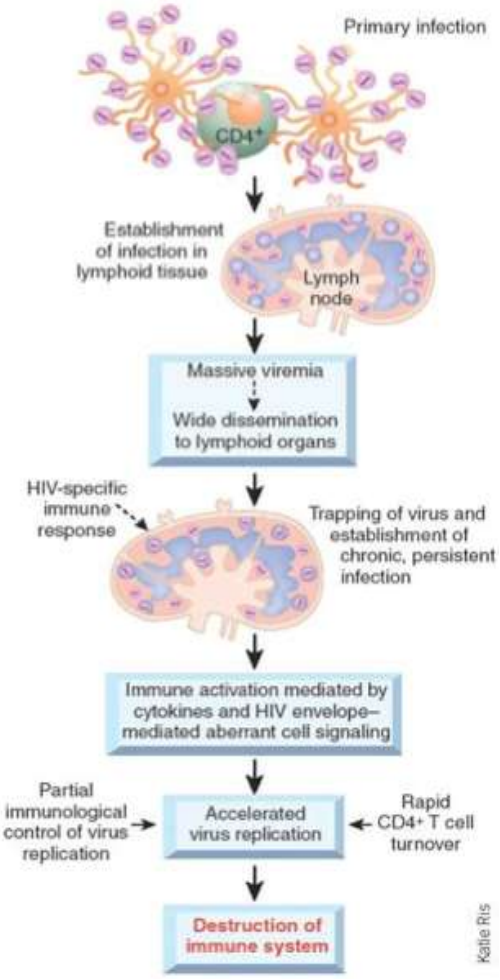
It is very difficult to control HIV and stop this disease once it's in the body.

For those who are interested in Genetics (extra information) →



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.

P24 antigen was added to the ELISA test and is now called a combined test.

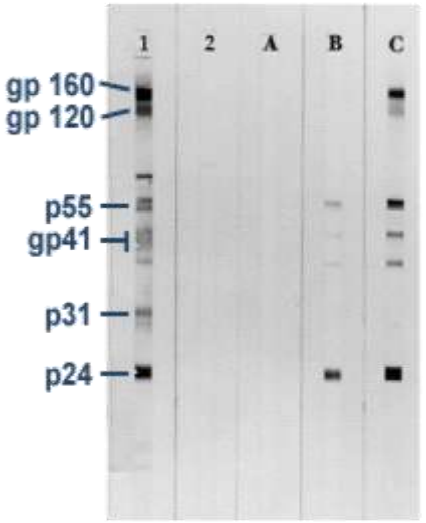
Infectious diseases physicians should always check that p24 antigen test is applied beforeapproving and signing the marriage-screening certificate.

❖**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).

1 is positive in Western blot test



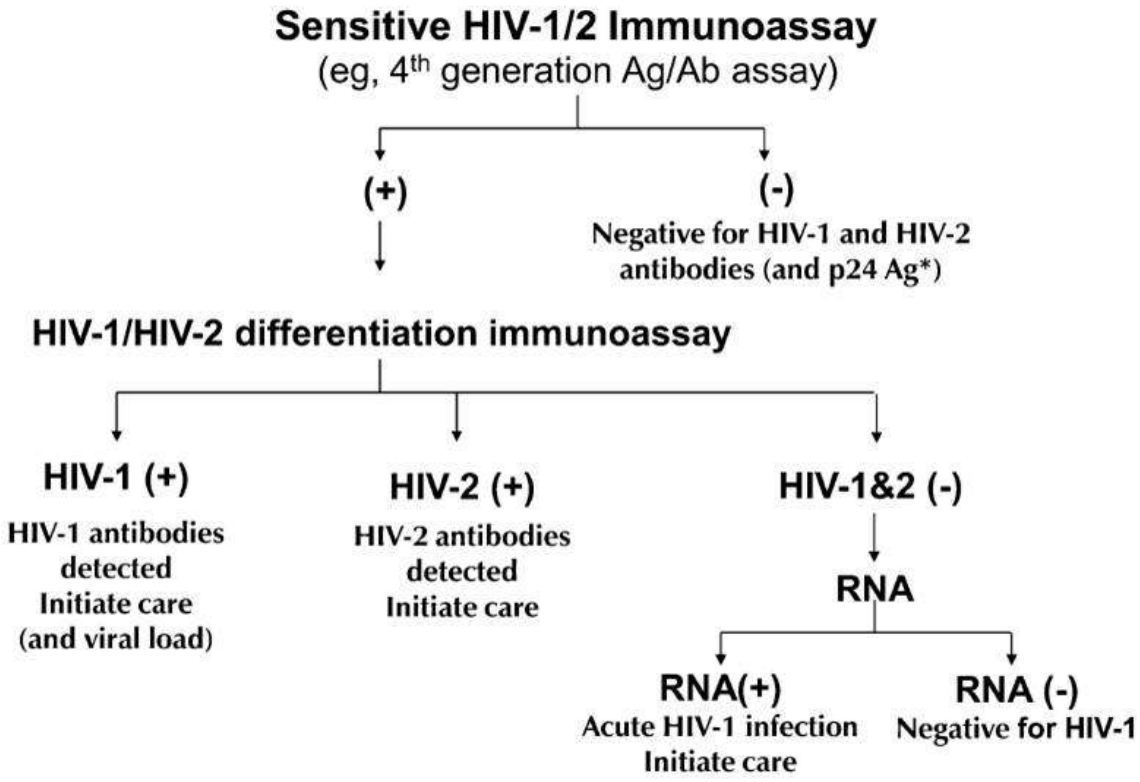
- Western blots, or protein immunoblots, are used to detect specific proteins in a sample. The test involves sorting proteins by length on a gel and then probing the gel with antibodies that react to the proteins that are being searched for.
- For HIV testing : labs work with prepared protein samples,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

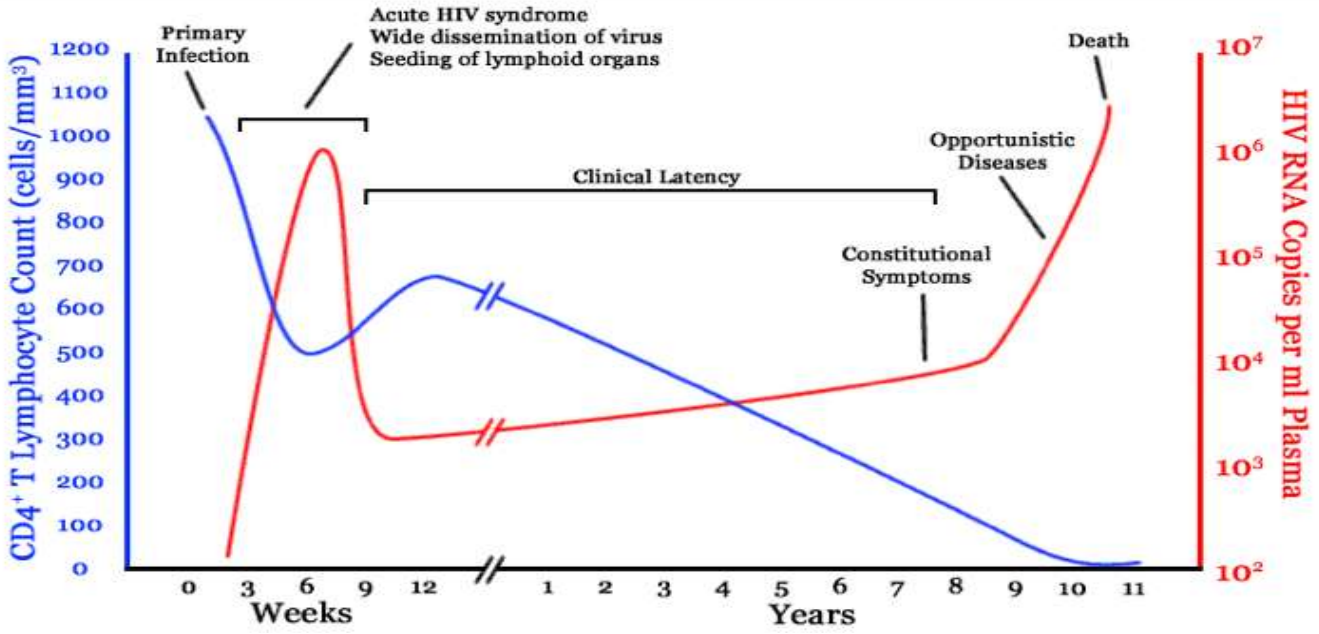
1) Confirmatory test and
2) To assess the viral load
3)Babies born to HIV-positive mothers, because their blood contains their mother's HIV antibodies for several months.
4)Blood supplies

When the combined test results are undetermined, the patient will be referred to the infectious disease unit where they will first repeat the combined test and then do a PCR. PCR measures the RNA itself whether it was present or not and it is also used to assess the viral load when someone is on treatment, in order to decide whether the medication is enough or not. The PCR is only done for undetermined cases. It is time-consuming and expensive compared to other tests.

❖ **Algorithm testing for HIV**



HIV Progression



Blue: CD4 count

Red: viral load

You can see from day 1 that the patient is infected.

Normal individuals have a CD4 count that ranges between 500 to 1400. There's a dramatic drop of CD4 because the HIV virus uses CD4 cells for replication and then kills the cells afterwards. When the viral load increases→ the immunity decreases. In the past, it was called a case of AIDS when there were opportunistic infections with HIV (pneumocystis or toxoplasmosis) but that is not true, AIDS is when the CD4 count drops below 200 (damaged immune system). HIV usually causes problems after 8-10 years because the CD4 count reaches below 200 in the period, meaning that there are many people that don't know they are infected. That's why nowadays they have counseling clinics where people can pop in and ask for screening.

Case:

A man complained about a hospital claiming that it infected his 70-year old mother with HIV following a cancer surgery (she was tested positive for HIV after the surgery). The surgery was operated on the mother a year before the doctor received the case, and when he checked her tests he found that the platelets count was low before the operation along with other signs that she had the infection before the surgery. The patient's husband was dead and they don't know the cause of death, so it is more likely that she got the infection from other sources.

- **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

READ CAREFULLY:

❖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
- Seborrhoeic dermatitis

❖Clinical stage 3:

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations:where physicians who do the screening discover that the patient has HIV.

- Unexplained chronic diarrhea 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), if the patient is not dieting, → alarming symptom. Most of the times, these patients turn out to be not infected with HIV because its prevalence in KSA is rare, but the screening must be done when exhausting all the investigations without reaching a diagnosis.
- Oral candidiasisnot in neonates, pregnant women, cancer patients or taking antibiotics but in a young, healthy and fit patient that presents with oral thrush or a diabetic that presents with deep candidiasis (esophagus) is a worrying sign. Some times when you give a child antibiotic he may develop oral thrush and that shouldn't frighten you.
- Oral hairy leukoplakia

Stage 3 is usually done using simple investigations, but it can still go undiscovered.
Simple infections cause diarrhea but only for 2-3 days so if a young man got diarrhea for more than 4 months for example, and antibiotics are not helping, an HIV test must be done, and if it was positive, you rely on the test.
You do not screen for HIV unless there were risk factors and you should ask for them, such as extramarital sexual contact and drug abuse, especially that nowadays it's easier to ask and people are willing to talk about their habits because it's for their sake. You should always suspect HIV in stage 3 because it goes on for sometime.

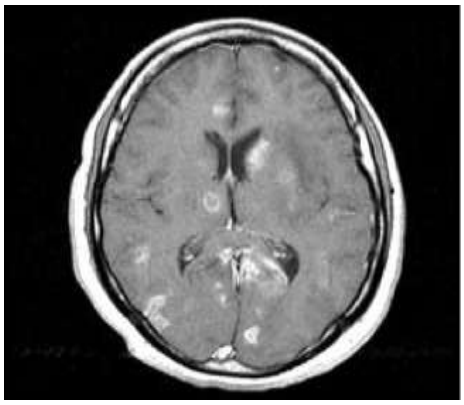
➢ **Immunological staging:**

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→ opportunistic infections occur. We should give prophylaxis to increase the CD4 count. Toxoplasmosis does not develop when the CD4 count is above 200.**IMPORTANT! AREA OF TESTING!!**

Toxoplasmosis in AIDS patients:



(A) (B)

(A) Ring- enhancing lesion in the brain caused by toxoplasmosis
(B) Toxoplasma in the retina. Some patients are referred from the ophthalmology department and then infectious diseases physicians discover that they have HIV.

Kaposi Sarcoma in AIDS patients:

(A) (B)

(B) The Kaposi Sarcoma seen in the US in 1981that turned out to be HIV-related. Kaposi Sarcoma is much more common in HIV but it can occur with other immune suppression incidents.

Candidiasis in AIDS patientsOral Hairy Leukoplakia in AIDS patients

Oral thrush

White patches at the lateral aspect of the tongue

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 scenarioBUT
- There is tremendous individual variability in these time intervals:

  Patientscan progress from acute HIV infection to death within 1-2 years, and others don't manifest HIV- related immunosuppression for 20 years

There are people who go from infection to AIDS directly because their immune system is very damaged, but these cases are rare.

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 weeks after transmission and accompanied by Burst HIV replication with a decline in CD4 cell count.

Most patientsmanifest a symptomatic mononucleosis like-syndrome, which is usually overlooked.

The manifestation of acute HIV infection is like any other viral infection: fever, fatigue, sometimes skin rashes and mild splenomegaly; therfore, it might be mistaken for another viral infection and overlooked. If the symptoms remain for 4 weeks than the patient might go to the hospital and get told that he has HIV after the screening; if not, he may infect others during that stage and that's what makes it a serious condition. The most important thing in these cases is to find them and control the disease transmission.

C. Seroconversion:

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

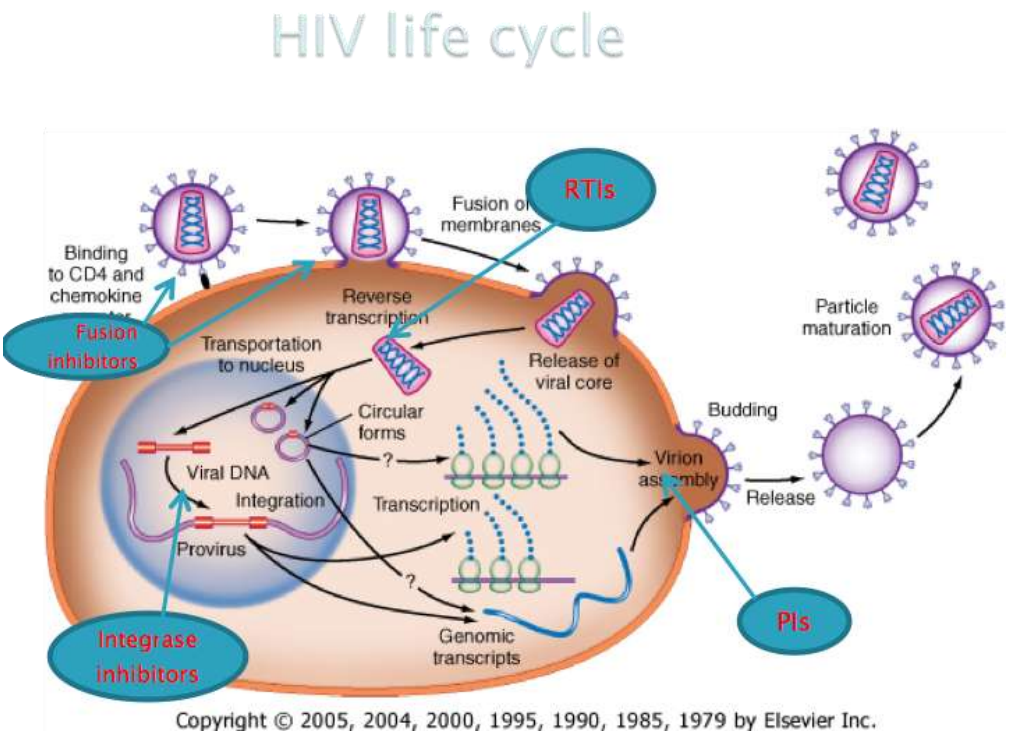
D. Asymptomatic HIV infection:

It lasts for variable amount of time (average 8-10 yrs) and is accompanied by a gradual decline inCD4 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 when the CD4 count is high and the viral load is low. After the treatment, the viral load may become undetected even by PCR, but that doesn't mean that the patient is cured but that it is no longer circulating in the blood and is now hiding in the lymphoid tissue, so no transmission will occur sexually.

Medications:the doctor said not to bother yourselves with names!



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) Asymptomatic disease with

  1) CD4 counts less than 350

  2) Pregnancyis important because of the transmission chance from mother to fetus, but if the viral load is undetected than the transmission from mother to fetus is less likely to happen. Transmission risk used to be 25 – 40% but now it's < 1%.

- Post exposure prophylaxis, for example: after a sexual encounter, give a triple-therapy prophylaxis for 6 weeks.

The corner stone of an HIV prevention strategy is:

- Education
- Counseling
- Behavior modification

The problem is that there are more than 25% of infected patients that do not know.

- Routine testing between 13 and 64 years (CDC recommendation without written consent).

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.

Pregnancy and HIV infection:

Overall risk: 16 – 25 %

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

A. In utero: 25-40%
B. Intrapartum: 60-75%
C. Breast feeding: 1) Established infection 14%

2) Primary infection 29%

Females are advised not to breast feed their babies because of the chance of transmission, but in poor areas where malnutrition is present and antiviral medications are absent,females with HIV are allowed to do so.

- Current evidence suggests most transmissions occur during the intrapartum period.

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, sever weight loss , unexplained persistent fever, oral candidiasis, oral hairy leukoplakia.
- Opportunistic infections will occur if the CD4 count is <200 , examples are : toxoplasmosis, pneumocystis pneumonia, TB reactivation and others.
- 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.

MCQs

1- 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 Answer: D

Explanation: 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.

2- 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.

Answer: A

3- 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

Answer: B

Explanation: 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.