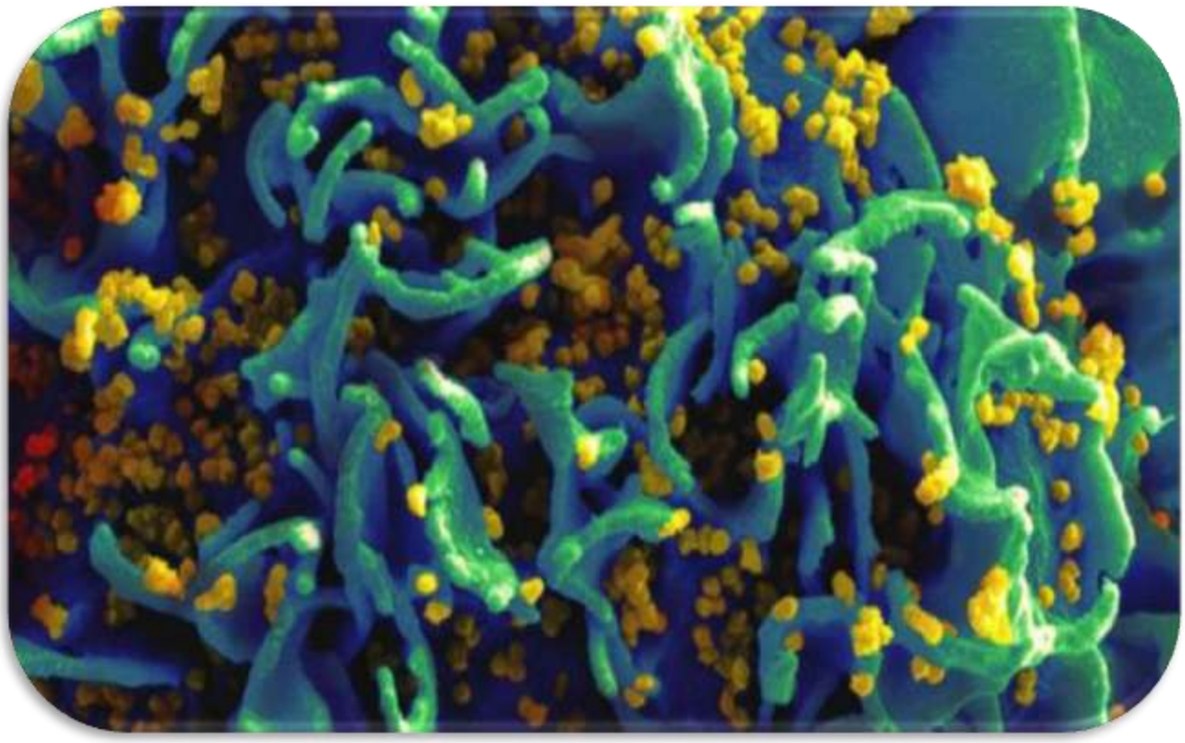
IMMUNOLOGY TEAM 431

(AIDS)



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RED ➔ Important

➔ Team's notes and explanation

Transmission(Modes of infection)

- Sexual transmission at genital or colonic mucosa
- Blood transfusion
- Mother to infant (known as vertical transmission)
- Accidental occupational exposure (with lab staff)

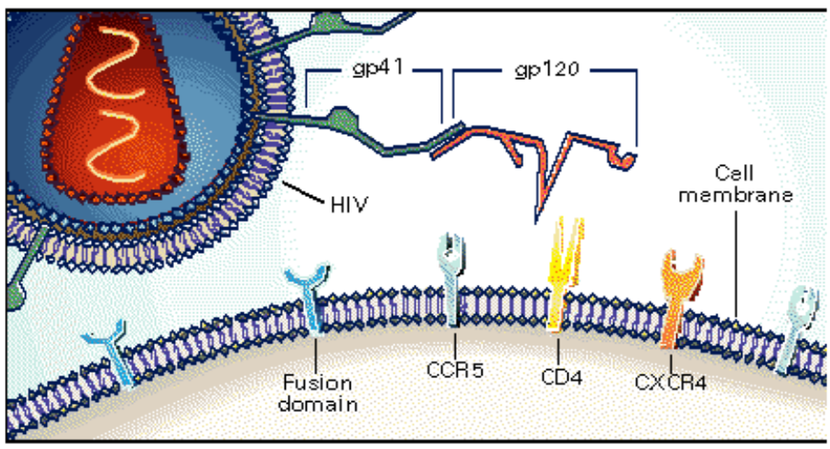
Feature of this virus:

*attacks the immune system its main target is to effect CD4+ T cell

*HIV is a virus that can't live outside the cell

Difference between HIV+ and AIDS:

Pt with AIDS, has clinical sign and symptoms with severe illness (opportunistic) and neoplasm



A

The virus contains an envelope, matrix and capsid (core) which has the RNA and enzymes: reverse transcriptase, protease and intagrase

HIV and Cellular Receptors

Infection occurs when the virus comes in contact with the surface of the target cell via the glycoprotein (120 and 41)

Why does the HIV target CD4 cells?
Because the gp120 reacts to the receptors on the surface of the CD4 cells and gp41 (stalk part of gp120) interacts with the chemokines 4 and 5(CxCR4& CCR5) which are also found on CD4 cells.

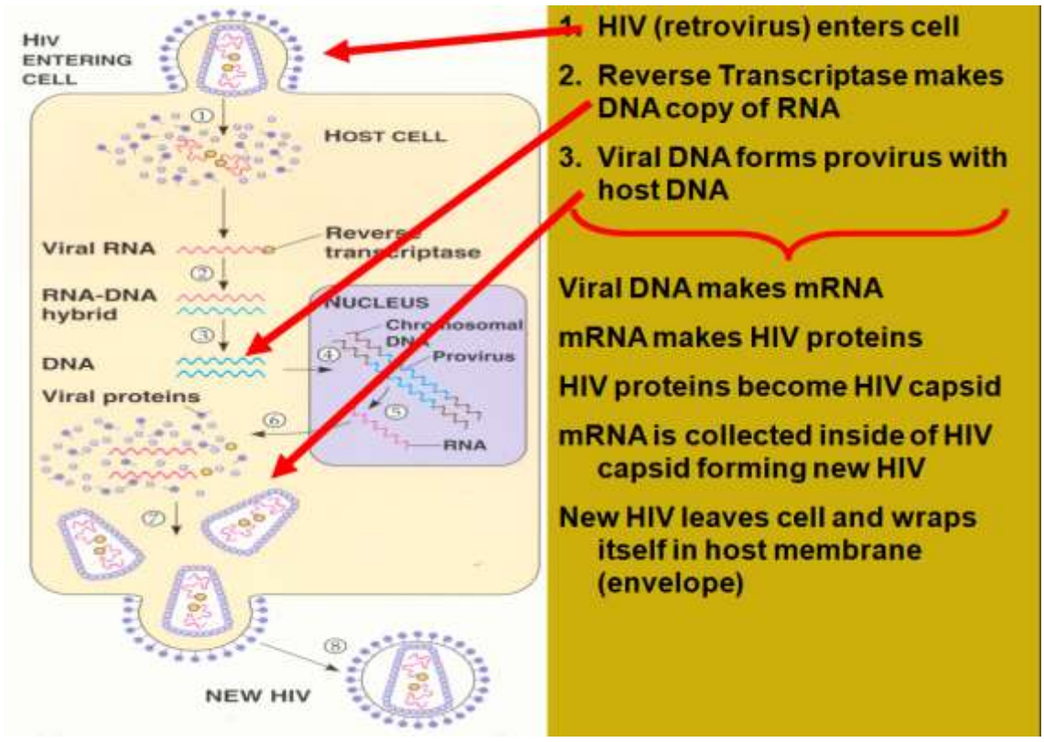
What are chemokines? A group of cytokines that are involved in cell traffaking(movement of cell from the blood into the tissues).

What does that mean? If there is infection in an area these chemokines are released leading to recruitment of further cells that contain chemokines too.(increase the mess with infiltration of more cells)

So what happens next? If the gp120 binds to the CD4 surface and the gp41 bind to the chemokines 4 and 5 the envelope of the virus will fuse together with the cell membrane of the host cell. Then the core (containing the viral RNA) will enter the host cell.

How HIV Enters Cells

- gp120env protein binds to CD4 molecule
  - CD4 found on T-cells macrophages, and microglial cells
  - Binding to CD4 is not sufficient for entry (2 parts needed for the entry)
- gp120env protein binds to co-receptor
  - Chemokine receptors:
  - CCR5 and CXCR4 receptors
- Binding of virus to cell surface results in fusion of viral envelope with cell membrane
- Viral core is released into cell cytoplasm

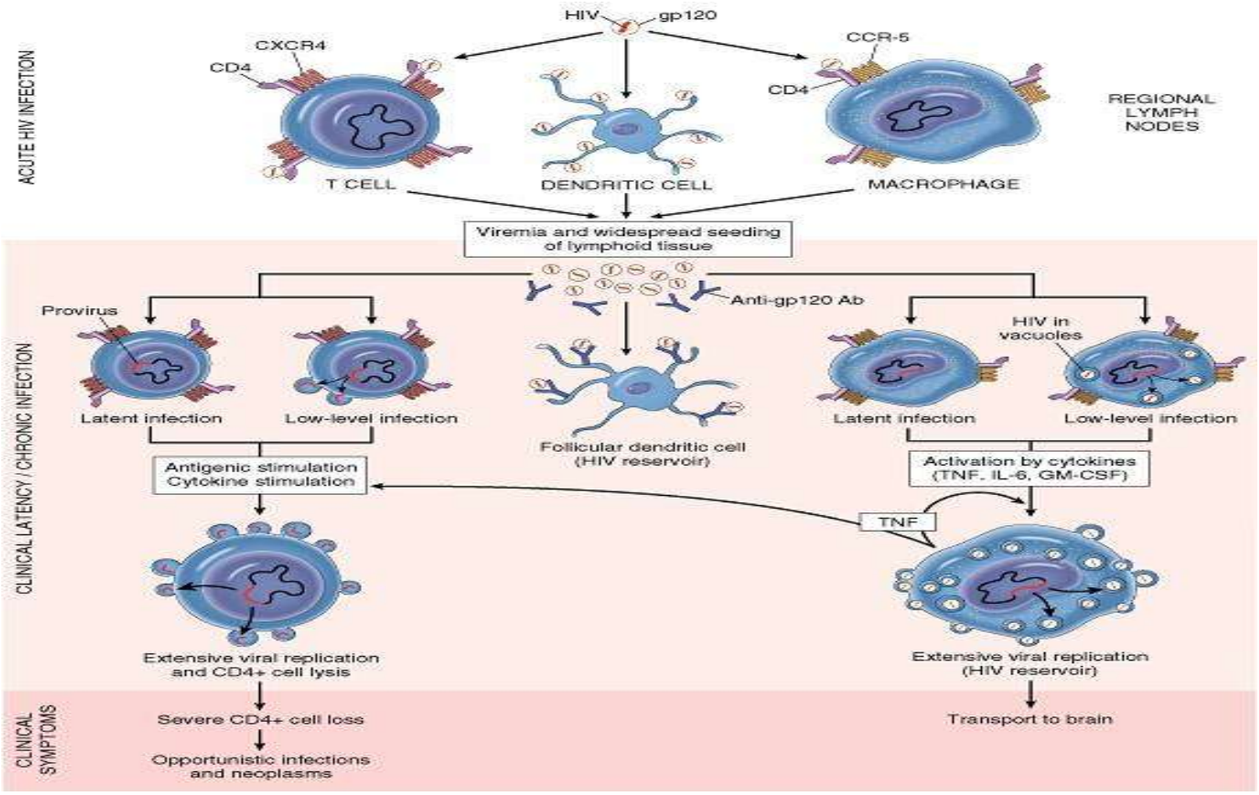


Why is HIV a retrovirus? Because it has the reverse transcriptase.

What does this enzyme do? Converts the viral RNA to DNA.

Why dose reverse transcriptase convert the viral RNA to DNA?

same concept of PCR amplification. One single copy of viral DNA will form a complimentary strand of DNA (double strand DNA) then the intagrase enzyme comes into play. It inserts this newly formed DNA into the normal host DNA. This is where the problem happens, once the viral DNA gets stuffed into the host DNA and the normal process of transcription occurs, the viral DNA will get transcribed then translated to form the viral protein along with all the other proteins that get translated normally. So the host cell is making both host and viral protein which accumulate in the host cytoplasm. The viral protein then binds with the viral RNA present in the cytoplasm, and together they form a new capsid (core) identical to the one that came into the cell. The host cells has become somewhat of a factory producing more and more viral protein and it also provides the viral envelope (its own cell membrane) when the formed core buds out of the cell.



The HIV mainly attacks the CD4 cells but dendritic cells and macrophages also become targets because their job is to 'eat foreign Ag' and macrophages have CD4 receptors.

The problem is when the HIV infects the macrophages because they have vesicles which are filled with phagocytic enzymes. What happens? The viruses grow in these vesicles then rupture them and infect the adjacent ones (this is all taking place in the cytoplasm of the macrophages). The problem is, macrophages don't die very quickly and they travel to the bone marrow and CNS where there they become a constant supply of the virus because immune cells can't reach that far do to the BBB. And the immune system fails to destroy the massive and constantly increasing number of HIV, which will eventually enter the blood.

The latent phase (when the infected person shows no symptoms) is caused by two things :

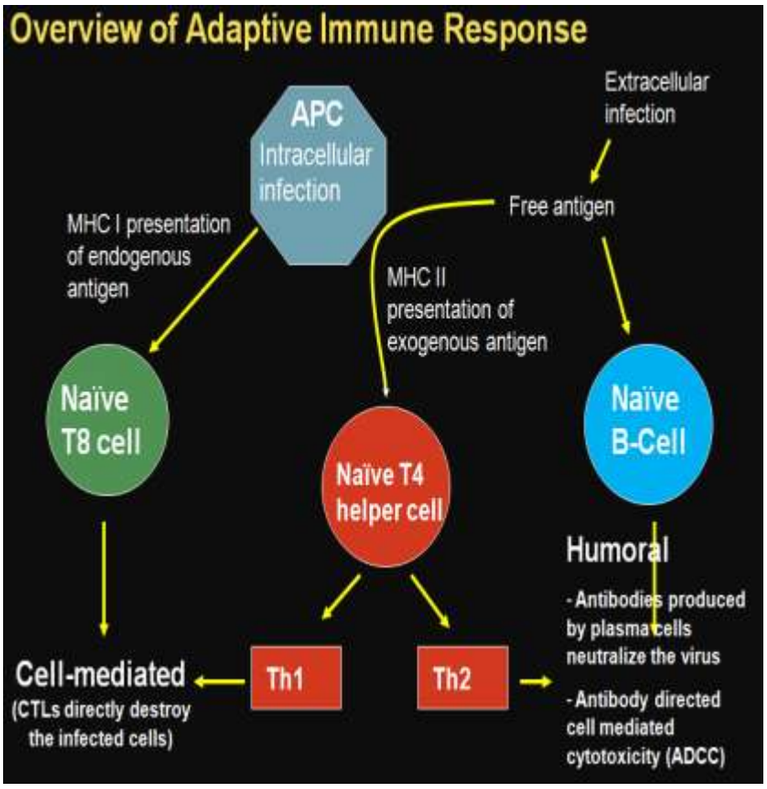
1) decreased viral load (no. of viruses)

2) the virus has very low antigenic effect.

When the viral load increases and the CD4 cell count decreases the pt. begins to develop the symptoms. When the cytokines increase they help in proliferation of the virus. The AIDS stage will soon develop (by soon I mean 10 to 15 years later!!)

Viral-host Dynamics general info

- About 1010 (10 billion) virions are produced daily
- Average life-span of an HIV virion in plasma(outside the host cell) is ~6 hours
- Average life-span of an HIV-infected CD4 lymphocytes is ~1.6 days
- HIV can lie dormant within a cell for many years, especially in resting (memory) CD4 cells, unlike other retroviruses without any manifestations



What is happening in the picture?
If the viral Ag binds to MHC1 then the CD8 cells will become activated and start killing… and if the Ag binds to MHC2 then they will activate CD4 cells which will lead to activation of T1/T2 helper cells and B cells.B cells will lead to formation of AB (and possibly get effected resulting in them forming more HIV)

General Principles of Viral-host Interactions

- Host: mounts HIV-specific immune responses
  - Cellular (cell-mediated) - most important
  - Humoral (antibody-mediated)
- Virus:subverts the immune system
  - Infects CD4 cells that control normal immune responses
  - Integrates into host DNA
  - High rate of mutation
  - Hides in tissue not readily accessible to immune system (subverts)

Subverts: means that the HIV will make the immune system either not see it, or attack elsewhere.

How?1) The HIV stays inside the cells (so immune system doesn't see it)
2) The viral infected cells no longer function normally and don't trigger immunity

Cells Infected by HIV

- Numerous organ systems are infected by HIV:
  - Brain: macrophages and glial cells
  - Lymph nodes and thymus: lymphocytes and dendritic cells
  - Blood, semen, vaginal fluids: macrophages
  - Bone marrow: lymphocytes
  - Skin: langerhans cells
  - Colon, duodenum, rectum: chromaffin cells
  - Lung: alveolar macrophages

HIV hides mostly in macrophages because they live longer, so the virus can survive for a longer time and hide there for a longer time as well

Principles of Immune Dysfunction in HIV

- All elements of immune system are affected (total destruction) after infection by HIV.
- Advanced stages of HIV are associated with substantial disruption of lymphoid tissue
  - Impaired ability to mount immune response to new antigen

What normally happens is when we are exposed to foreign Ag our body can form Ab against them. But in case if HIV the immunity is lost and there is no response to infections

  - Impaired ability to maintain memory responses

Which will lead to a state of sever immunodeficiency leading to opportunistic infections

  - Susceptibility to opportunistic infections

What are they, infections that do not normally occur. A healthy immune system has the ability to inhibit the microorganisms causing these infections. But when a sever state of immunodeficiency occurs the body can no longer prevent these infections from taking place granting them the opportunity to cause infection (as the name implies)

Mechanisms of CD4 Depletion and Dysfunction

- Direct(physical presence of the virus and it infecting the cell)
  - Elimination of HIV-infected cells by virus-specific immune responses
  - Loss of plasma membrane integrity because of viral budding (the host cell membrane become weak)
- Indirect
  - Syncytium formation (fusion of cells that are highly unstable and die quickly)
  - Apoptosis programmed cell death
  - Autoimmunity

Autoimmunity is caused by hyper activation of the B cells which will produce a large number of Ab. Some are protective and others are considered destructive (auto antibodies)

- HIV induces immune activation
  - Which may seem paradoxical(unexpected)because HIV ultimately results in severe immunosuppression and hyperactivation
- Activated T-cells support HIV replication
  - Intercurrent infections are associated with transient increases in viremia
  - Accounts for why TB worsens underlying HIV disease

In pts.already infected with TB that has been in a latent state, TB become reactivated because the CD4 cells that were keeping it under control are now severely decreased and cytokines which usually help the body react to infection, help in the viral proliferation instead

Role of Cytokine Dysregulation in Pathogenesis of HIV

- HIV is associated with increased expression of pro-inflammatory cytokines
  - TNF-alpha, IL-1,IL-6, IL-10, IFN-gamma
- HIV results in disruption and loss of immunoregulatory cytokines(they are either very high/low or not released when needed)
  - IL-2(very important for the growth lymphocytes)IL-12(controls the production of IFN-gamma)
  - Necessary for modulating effective cell-mediated immune responses (CTLs and NK cells)

Decrease in IL2/12 which are important to aid immunity and increase in the cytokines that promote immune destruction

Primary Infection

- 70-80% symptomaticflu like symptoms, 3-12 weeks after exposure
- Fever, rash, cervical lymphadenopathy, aseptic meningitis, encephalitis, myelitis, polyneuritis

usually not severely ill so they remain undiagnosed for HIV. The symptoms usually go away and the person enters a stage of latent infection that can remain for several years

- Surge in viral RNA copies to >1 million
- Fall in CD4 count to 300-400 cells/mm^3
- Recovery in 7-14 days

Every time the viral load increase the CD4 count has to decrease and vice versa

Seroconversion the time when the pt blood is (+) for Ag

- Median 8 weeks after infection
- Level of viral load post sero-conversion correlates with risk of progression of disease
- Asymptomatic Phase
- Remain well with no evidence of HIV disease except for generalized lymphadenopathy
- Fall of CD4 count by about 50-150 cells per year

CD4 T-cell Count and Progression to AIDS

- Gradual reduction in number of circulating CD4 cells is inversely correlated with the viral load
- Any depletion in numbers of CD4 cells renders the body susceptible

This is how the treatment of HIV is monitored if the no. of CD4 cells remains relatively constant throughout the years then the treatment is effective and if the no. is decreasing then the treatment is not working. When the no of CD4 cells greatly decrease leading to opportunistic infections this will be the stage of AIDS

Opportunistic infections

Candidiasis(oesophagus, bronchi, trachea, and lungs)

If white patches on the oral mucosa (oral thrush) directly think immunodeficiency

Coccidioidomycosis

Cryptococcosis, extrapulmonary

Cytomegalovirus disease

Herpes simplex: chronic ulcer(s)

Histoplasmosis, disseminated or extrapulmonary

Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)

*Pneumocystis*pneumonia

*Salmonella*septicaemia,

Toxoplasmosis of brain

AIDS – Indicator Conditions

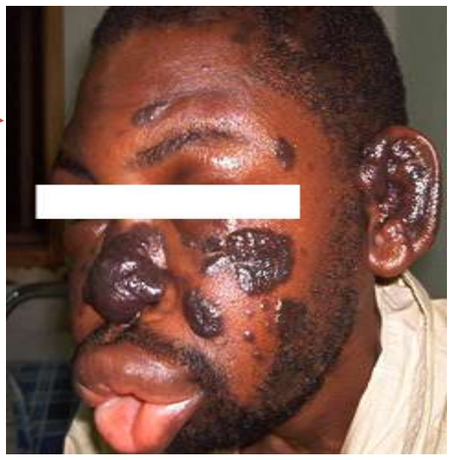
Neoplasia

Kaposi's sarcoma

Lymphoma (Burkitt's, immunoblastic, primary in brain)

Invasive cervical cancer

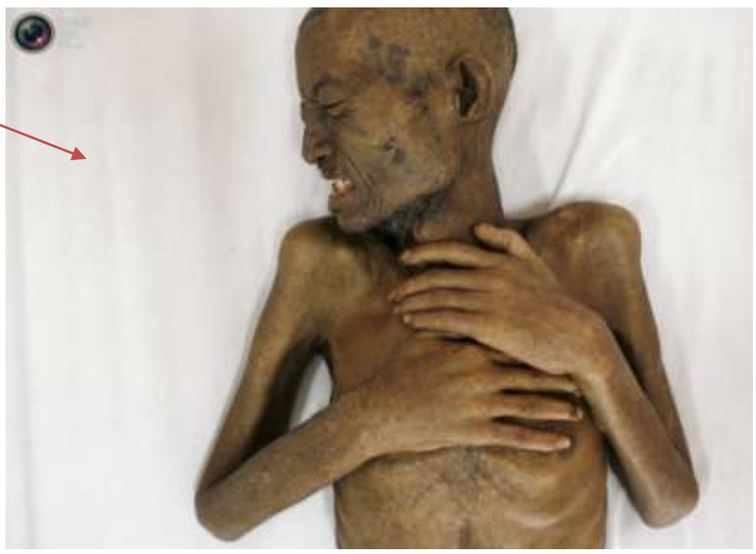
Opportunistic infections

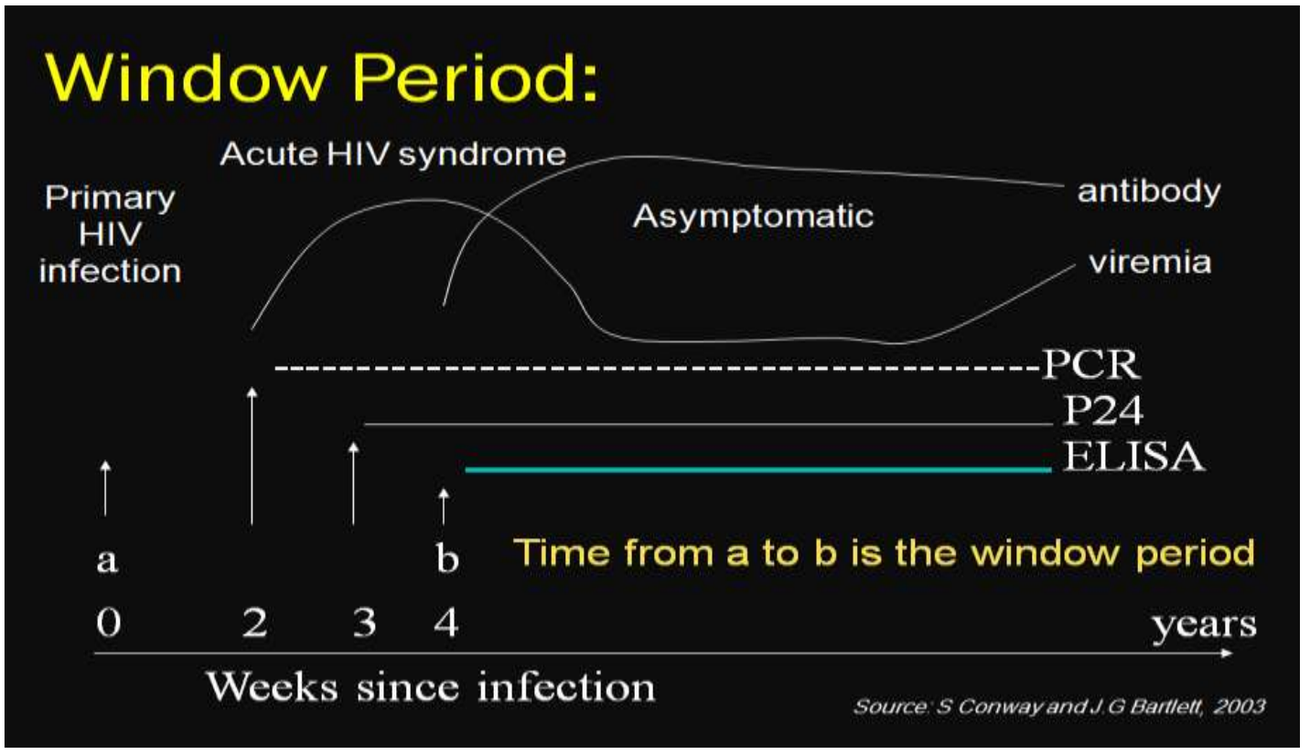


General

Wasting syndrome, HIV-related

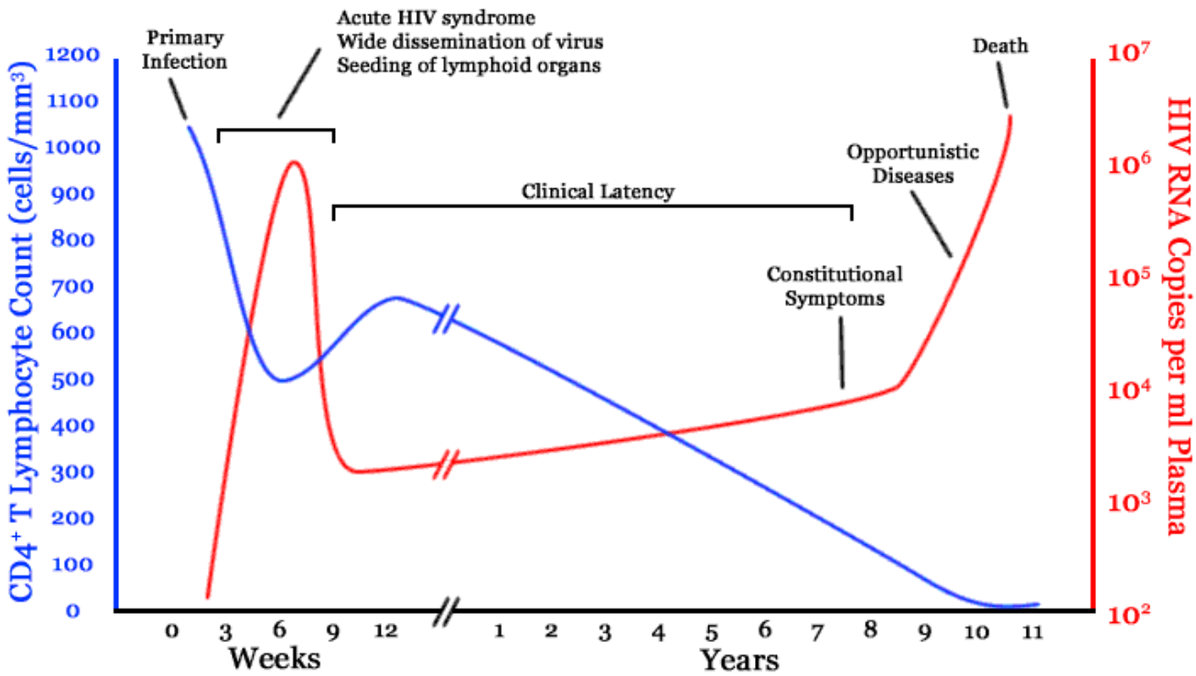
Encephalopathy, HIV-related





Window Period: Untreated Clinical Course (0 = time of infection, after 2 weeks the RNA may be detected via PCR, after 3 weeks the viral proteins may be detected via western blot test, by 4 weeks the disease may be detected by ELISA.)

Normally PCR is not used because, its expensive and time consuming. The only one of the 3 that is done on a routine basis is ELISA (used for detecting the Ab) but ELISA is only effective after about 1 month of infection. Which means that till the 4th week the blood contains HIV but undetected. (Time between week 1 to 4 is called the window period.) The time that the virus can NOT be detected.



Natural History of HIV (acute phase viral load high and CD4 low (very quickly) Atthe time of death the viral load reaches its highest peak and the CD4 are at their lowest limit. During the latent, there is a progressive increase in the viral load and a gradual decrease in the CD4 cells)

Diagnosis of HIV infection

Tests for HIV detect either antibodies or antigens associated with HIV in whole blood, saliva, or urine

A person whose blood test results show HIV infection is said to be "seropositive" or "HIV-positive"

A person whose blood test results do not show HIV infection is said to be "seronegative" or "HIV-negative"

Laboratory Markers of HIV Infection

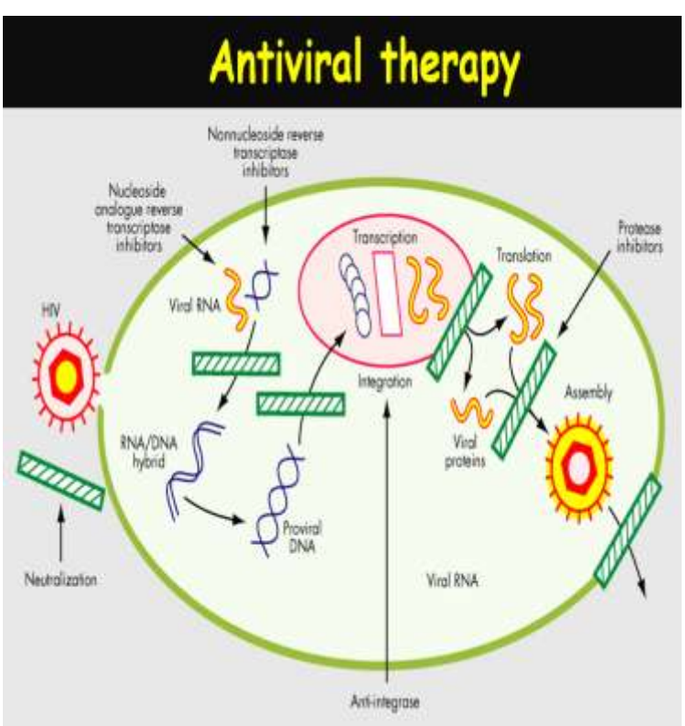
- Viral load
  - Viral load is the amount of HIV in the blood
  - It can be measured by the HIV ribonucleic acid polymerase chain reaction blood test (HIV-RNA PCR)
    - Marker of HIV replication rate
- CD4 count
  - Marker of immunologic damage

Laboratory tests for detection of HIV

- Antibody test, ELISA
- Western blot viral proteins
- HIV RNA viral load PCR

Management

- Treatment recommended when symptomatic or CD4 count below 200
- Earlier if high viral load, rapidly falling CD4 count, hepatitis C co-infection



Levels of action of Antiviral drugs

1) fusion between HIV and host cell membrane
2) reverse transcriptase
3) intagrase 4) transcription 5) protease
6) budding out of the host cell

Take Home Message

- Infection with HIV usually occurs by sexual transmission, blood transfusion, mother to infant or accidental exposure (different modes)
- HIV targets the immune system and primarily infects CD4 helper lymphocytes
- Immunodeficiency associated with HIV infections is mainly due to reduction in CD4 helper lymphocyte counts
- Increased viral load, significant reduction in CD4 lymphocytes, opportunistic infections and neoplasia are the hallmarks of progression to AIDS

Test your self ☺

Q1/ which of these cells it's the main target for HIV virus?

a) CD4+ T cell
b) CD8+ T cell
c) Macrophage

Q2/to design a vaccine against HIV infection, a logical goal would be to alter some native molecule or product of the virion in order to make it highly immunogenic.if you wished to prevent the attachment of the virus to helper T cell ,which molecule or family of molecules might best be targeted?

a) Gp120
b) P17
c) P24
d) Nucleocapsid protein

Q3/what is the function of reverse transcriptase ?

a) Convert RNA to DNA in the virus
b) Convert RNA to DNA in the host cell (target cell)
c) Integrate viral DNA with host cell DNA

1- A
2- A
3- B