2nd Year

Reproductive Block

Immunology

HIV
(Human Immunodeficiency Virus)
&
AIDS
Acquired Immune Deficiency Syndrome

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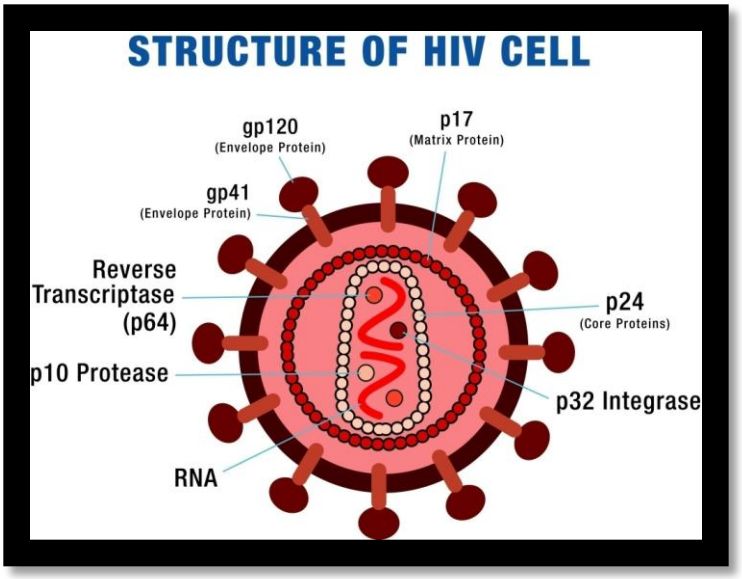
The phenotype (or physical appearance/structure) of HIV



Note: AIDS is the end stage of HIV

HIV is an enveloped virus.
Gp 120, Gp 41 → Envelope proteins

Transmission

Modes of infection

- Sexual transmission at genital or colonic mucosa
- Blood transfusion
- Mother to infant
- Accidental occupational exposure (For instance, doctors, nurses..etc..)

Study of HIV "exposed uninfected" individuals revealed the presence of a mutated CCR5 receptor in some people. Patients homozygous for this mutation are relatively resistant to the virus.

How HIV Enters Cells

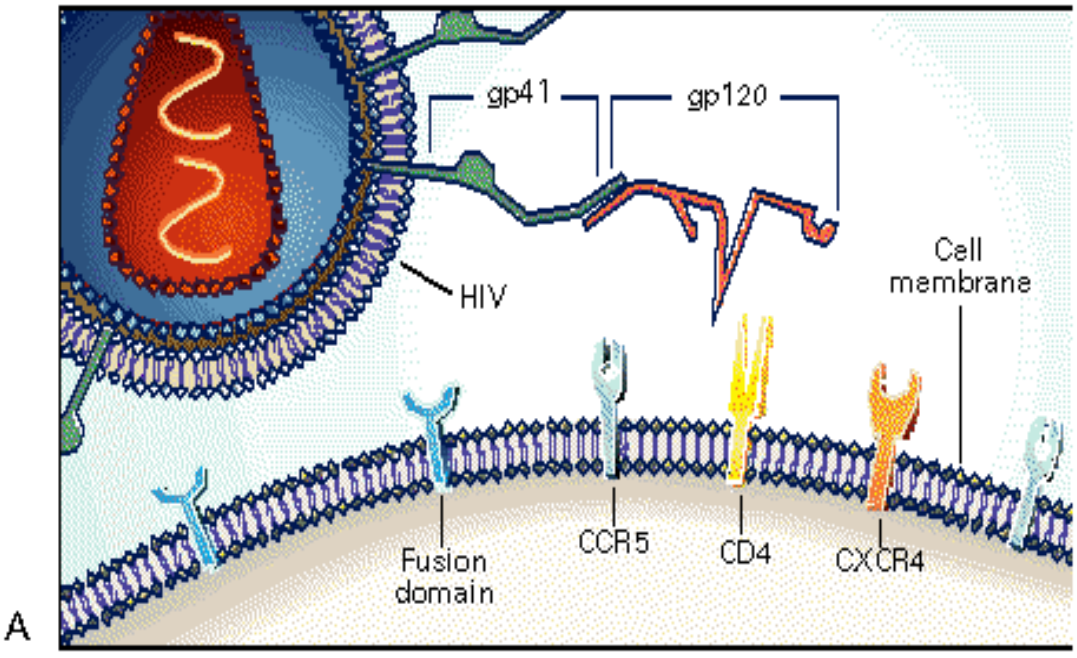
- gp120 env protein binds to CD4 molecule
  - CD4 found on T-cells macrophages, and microglial cells
  - Binding to CD4 is not sufficient for entry
- gp120 env protein binds to co-receptor
  - Chemokine receptors:
  - CCR5 and CXCR4 receptors
- Binding of virus to cell surface results in fusion of viral envelope with cell membrane
- Viral core is released into cell cytoplasm

In order for HIV to actually enter a cell it needs to bind to both CD4 cells and to Co-receptors (CCR5 & CXCR4)

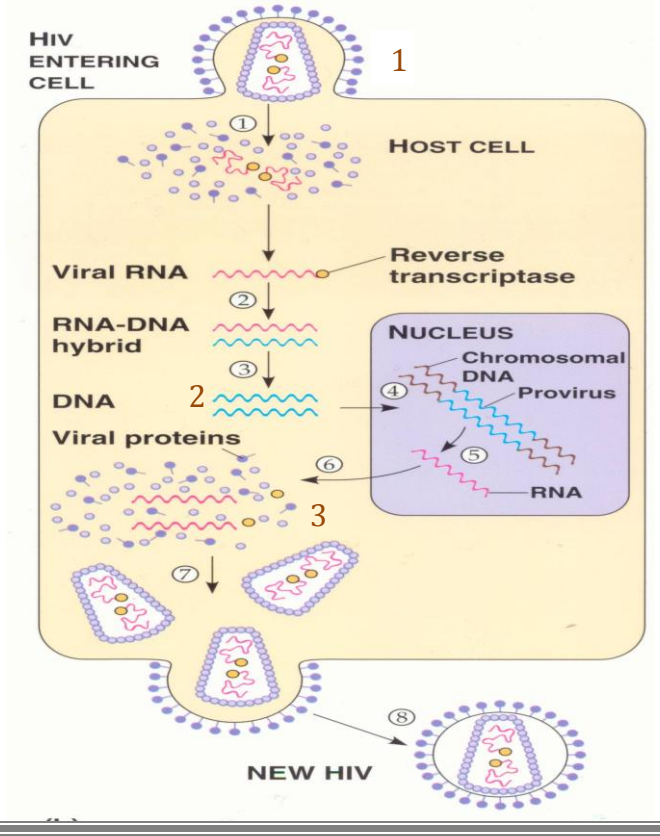
- Now a review of the lifecycle steps in more detail: For attachment and entry into the human cells, HIV use normal proteins on the surface of human cells.

1. HIV attaches to the CD4 cell protein. These receptors occur on CD4 cells, monocyte, and macrophages
2. As second step in entry, HIV binds to co-receptors, which are normally receptors for chemokines. A mutant CCR5 receptor gene that prevents the virus from binding to the cell has been discovered. Homozygosity for this mutant gene is strongly protective against HIV infection. Heterozygous people are not protected from infection but the disease may take longer to develop.

HIV and Cellular Receptors



This picture shows HIV's attachment and entry into a host cell. The gp-120 protein attaches to a CD4 receptor. The gp-41 is exposed for attachment to the host cell, and fusion of the cell membrane with the viral envelope starts.

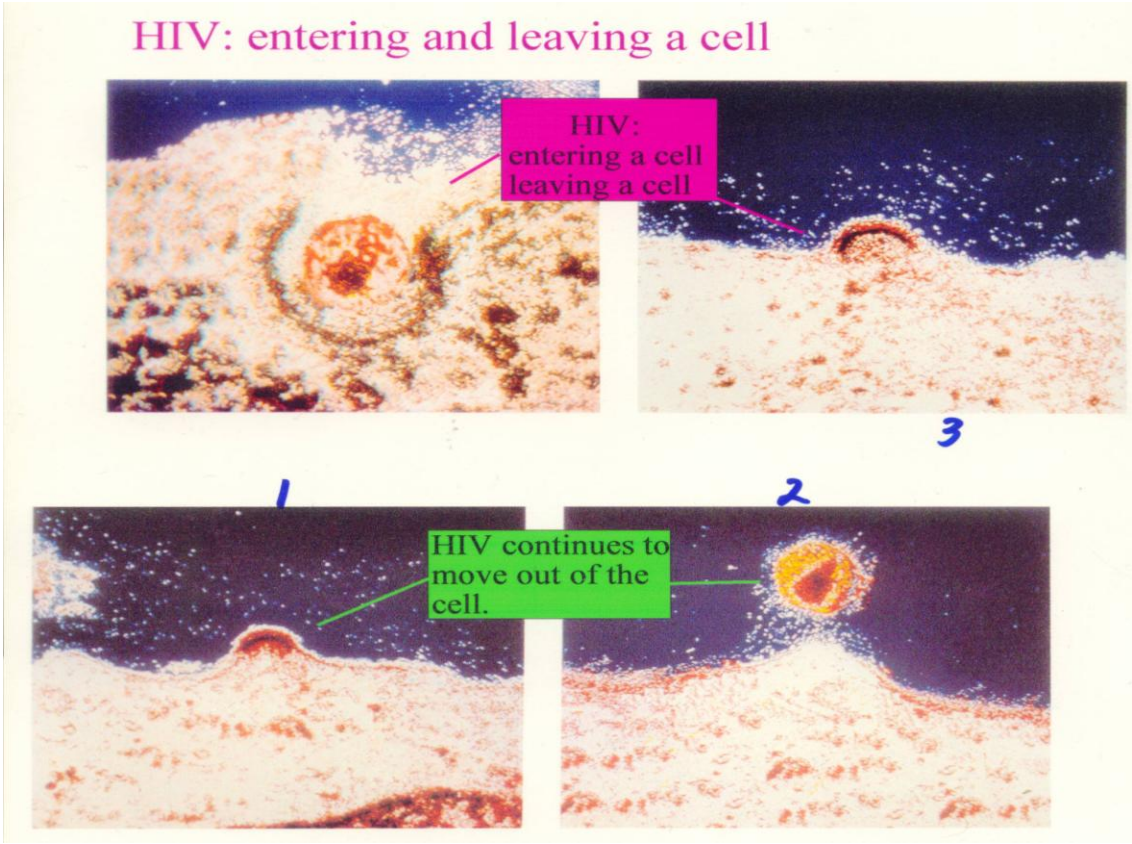


1. HIV (retrovirus) enters cell
2. Reverse Transcriptase makes DNA copy of RNA
3. Viral DNA forms provirus with host DNA
   (Look at the numbers on the image)

<u>After entering the cell:</u>

- Viral DNA makes mRNA
- mRNA makes HIV proteins
- HIV proteins become HIV capsid
- mRNA is collected inside of HIV capsid forming new HIV
- New HIV leaves cell and wraps itself in host membrane (envelope)

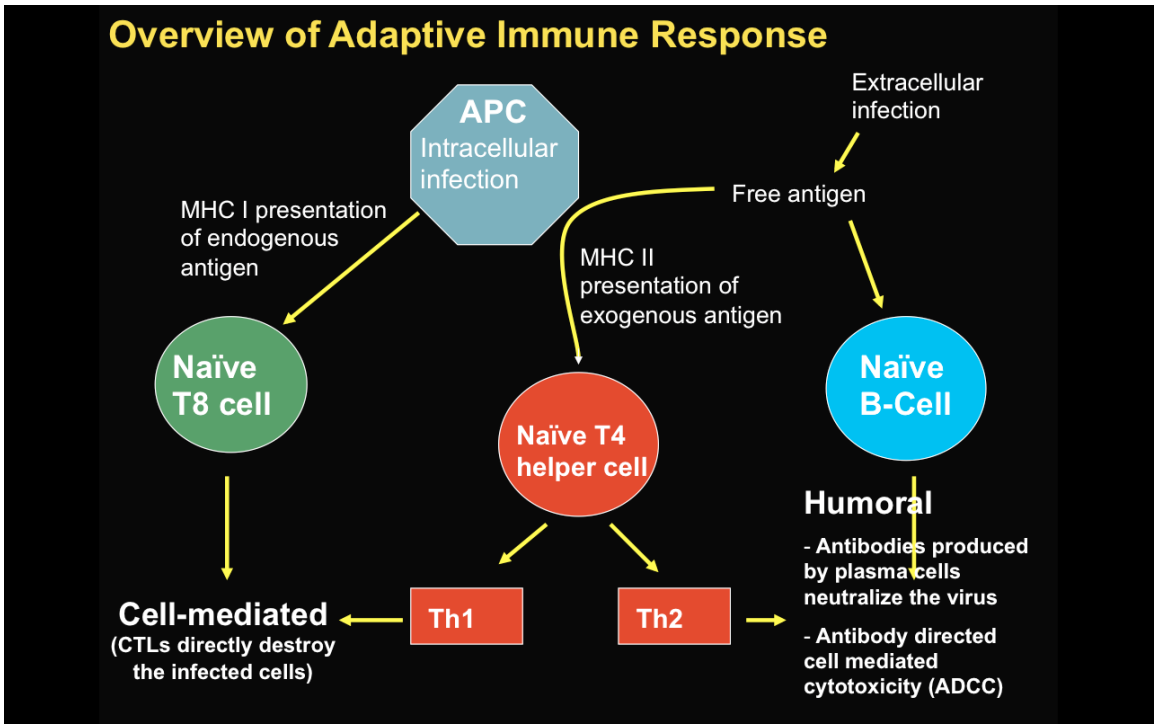
(HIV takes its capsule from the membrane of CD4 cells)



Viral-host Dynamics

- About 1010 (10 billion) virions are produced daily
- Average life-span of an HIV virion in plasma 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

The extremely high rates of viral replication results in every possible point mutation in the viral genome arising daily. In any given patient, the virus usually varies by 1-6% in the env gene, for example.



- This is an important slide representing the adaptive immune response, which is the main response to HIV (as opposed to the innate immune response).
- The adaptive immune response is divided into two types: the cell-mediated (cytotoxic t-cell) type and the humoral (antibody-mediated) type. In general, the location of the infection (intracellular or extracellular) determines the type of adaptive immune response.
- Intracellular infections stimulate a cell-mediated response that will ultimately kill the infected cell. This is mediated by T8 cells, and utilizes the MHC I system.
- Extracellular infections stimulate a humoral response that will help contain these free antigens. Some extracellular antigens will be picked up by APC (antigen presenting cell) and be presented by way of MHCII to the Thc (T Helper Cells), which will further differentiate into either TH1 or TH2.
- TH1 in turn will augment the cell-mediated response and Th2 augments the humoral.
- CENTRAL TO THE ADAPTIVE IMMUNE RESPONSE IS THE TH4 CELL. BECAUSE HIV DEPLETES AND DISTRUPTS THE FUNCTION OF THIS CELL, ADAPTIVE IMMUNITY IS IMPAIRED.

Main response to HIV → Adaptive Immune Response.
HIV attacks the adaptive immunity causing its impairment.
So HIV basically destroys the response needed to destroy it, Eventually leaving the patient with little or no immunity.

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

While the host mounts an immune response, the virus employs mechanisms to evade the host's response.

The virus infects CD4 cells, which are the most important component in our cell-mediated immunity.

The virus utilizes the host's DNA to replicate; it uses reverse transcriptase to make RNA copies from the host's DNA thus making more copies of itself.

The virus then takes it's envelope from CD4 cells when it destroys them.

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

General Principles of Immune Dysfunction in HIV

⦿ All elements of immune system are affected
⦿ Advanced stages of HIV are associated with substantial disruption of lymphoid tissue

- Impaired ability to mount immune response to new antigen
- Impaired ability to maintain memory responses
- Susceptibility to opportunistic infections

The effects of HIV on the human immune system are extensive and complex, resulting in both depletion and dysfunction of all elements of the immune system.

The virus impairs memory responses → No memory cells formed against virus → No long-term protection.

Mechanisms of CD4 Depletion and Dysfunction (Decrease in CD4 cells)

⦿ Direct

Elimination of HIV-infected cells by virus-specific immune responses
Loss of plasma membrane integrity because of viral budding

⦿ Indirect

Syncytium formation (fusion of cells that are highly unstable and die quickly)
Apoptosis
Autoimmunity

Role of Cellular Activation in Pathogenesis of HIV

Not only does the virus destroy and disrupt the immune system, the virus can manipulate the immune system to its own replicative advantage. This is achieved by immune activation. Clinically, this is demonstrated by the observation that viral load transiently increases in the presence of undercurrent illnesses, such as TB.

<u>HIV induces immune activation</u>
Which may seem paradoxical because HIV ultimately results in severe immunosuppression

<u>Activated T-cells support HIV replication</u>
Intercurrent infections are associated with transient increases in viremia
Accounts for why TB worsens underlying HIV disease

Role of Cytokine Dysregulation in Pathogenesis of HIV

The immune system activation (and disruption) by HIV is mediated by various cytokines

- 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
  - IL-2, IL-12
  - Necessary for modulating effective cell-mediated immune responses (CTLs and NK cells)

Primary Infection

- 70-80% symptomatic, 3-12 weeks after exposure
- Fever, rash, cervical lymphadenopathy, aseptic meningitis, encephalitis, myelitis, polyneuritis
- Surge in viral RNA copies to >1 million
- Fall in CD4 count to 300-400 cells/mm^3
- Recovery in 7-14 days

Seroconversion

Seroconversion → to undergo a change from a seronegative to a seropositive condition (To become HIV positive)

- Median 8 weeks after infection
- Level of viral load post sero-conversion correlates with risk of progression of disease

Asymptomatic Phase

As the CD4 number falls and the viral load increases the patient becomes more prone to opportunistic infections, so he/she will start getting infections that healthy people usually do not get.

- 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 to opportunistic infections

Opportunistic Infections

- Candidiasis (oesophagus, bronchi, trachea, and lungs)
- Coccidioidomycosis
- Cryptococcosis, extrapulmonary
- Cytomegalovirus disease
- Herpes simplex: chronic ulcer(s)
- Histoplasmosis, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Pneumocystis pneumonia (Most common, most important opportunistic infection)
- Salmonella septicaemia
- Toxoplasmosis of brain

Aids- Indicator conditions

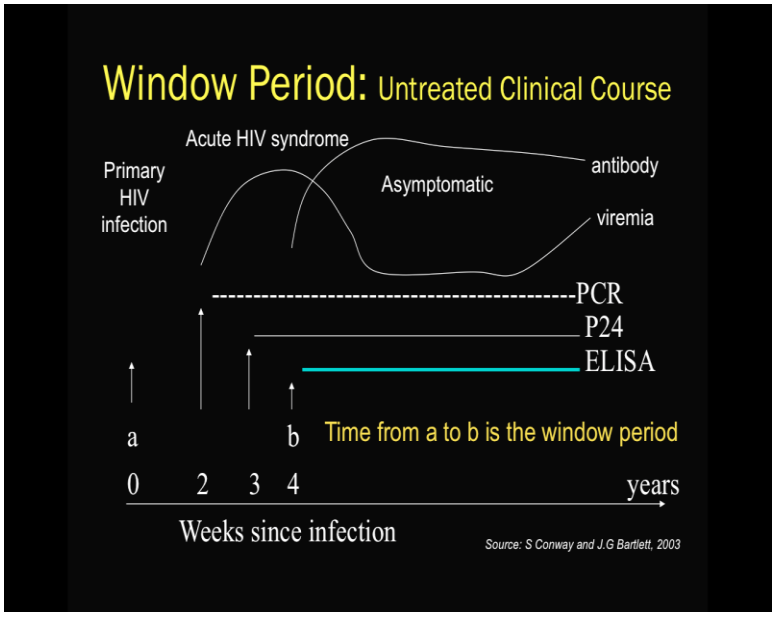
Neoplasia

- Kaposi's sarcoma
- Lymphoma (Burkitt's, immunoblastic, primary in brain)
- Invasive cervical cancer

Opportunistic infections

General

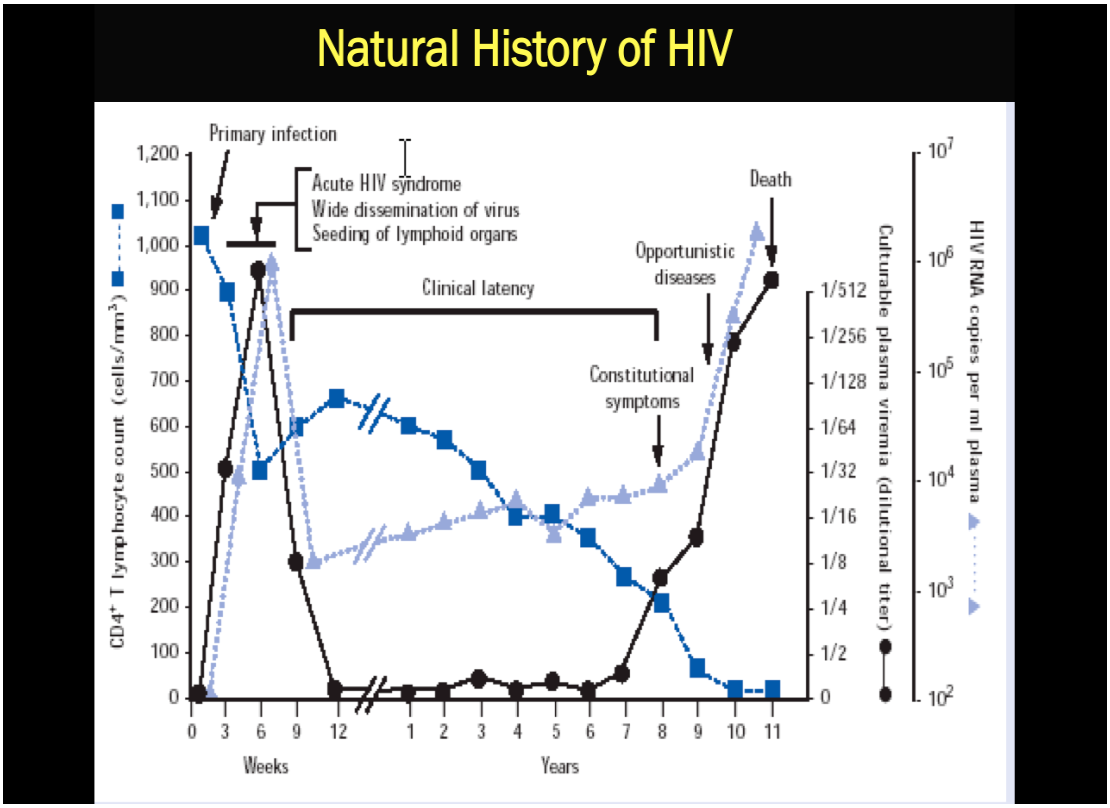
- Wasting syndrome, HIV-related
- Encephalopathy, HIV-related



- The window period begins at the time of infection and can last 4 to 8 weeks.
- During this period, a person is infected, infectious and viremic, with a high viral load and a **negative** HIV antibody test.
- The point when the HIV antibody test becomes positive is called the point of seroconversion.

An HIV patient goes through:

- A window period → Negative HIV antibody test
- Seroconversion → The test goes from negative to positive.



- Acute (primary) retroviral syndrome is the initial event after infection, which is characterized by a rapid decline in CD4 cell count and high plasma viremia.
- Development of cytotoxic T-cell (CTL) response results in clinical recovery of acute infection and a reduction in plasma viremia. The virus reaches "set point" as a result of this immune response. The viral load at this "set point" correlates with the rate of CD4 decline and disease progression. Overtime, HIV RNA levels gradually increase.
- In parallel, the CD4 cell count gradually declines over several years, but rapidly drops 1.5 to 2 years before an AIDS-defining diagnosis.
- When the CD4 count falls below 200, patients develop opportunistic infections, tumors, and neurological complications. The median survival after the CD4 count has fallen to <200 is 3.7 years, if untreated.

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

The average CD4 T cell count in HIV-1 uninfected Ethiopians reportedly ranged from 591 × 10*6 to 775 × 10*6 cells/L

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

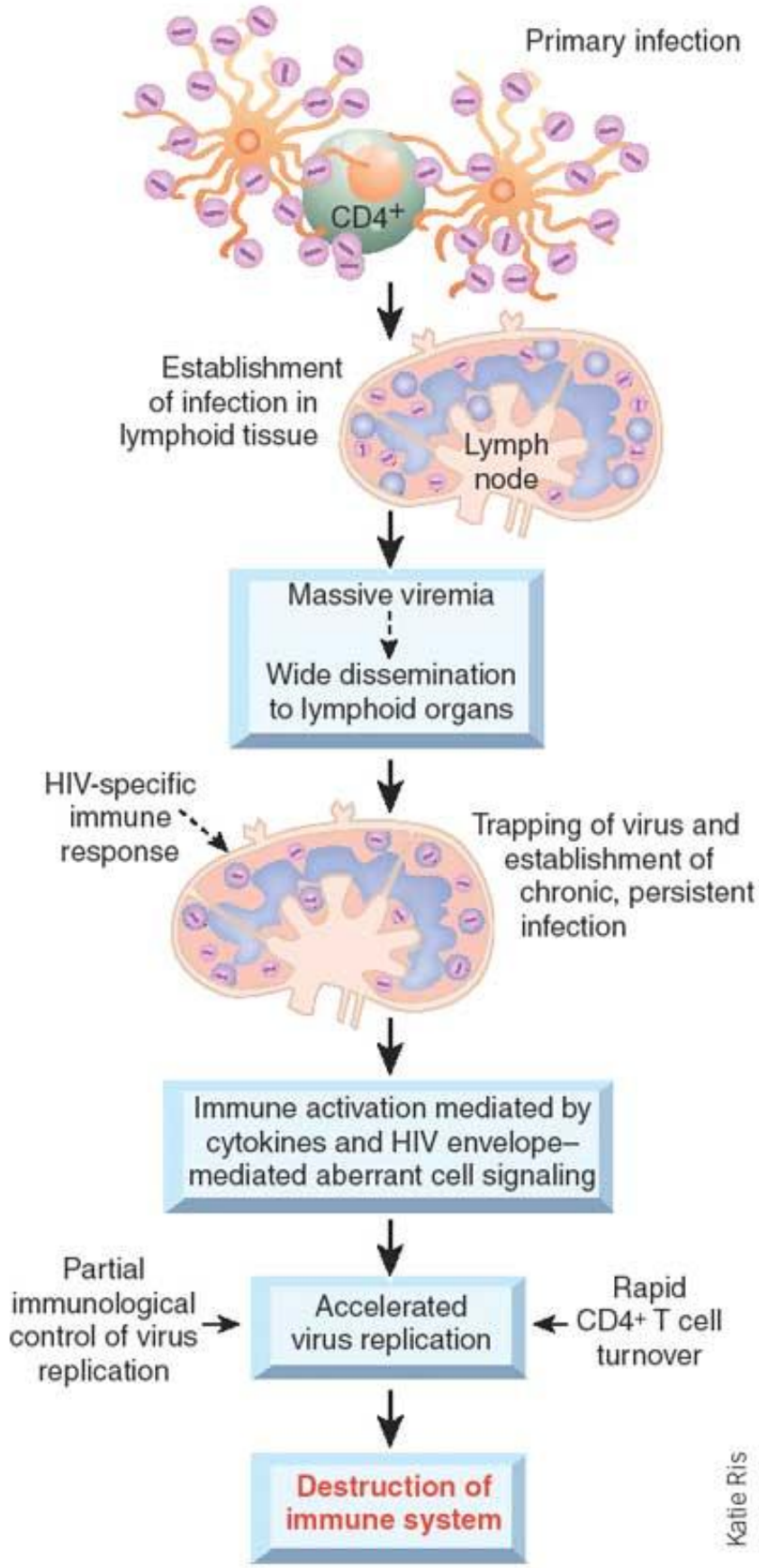
- Antibody test, ELISA
- Western blot (Detects Antigens)
- HIV RNA viral load (Replicating Markers)
- RNA is detected using PCR

Management

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

- Antiviral therapy
  - Reverse transcriptase inhibitors
  - Protease inhibitors
  - Fusion inhibitors

- Infection with HIV usually occurs by sexual transmission, blood transfusion, and mother to infant or accidental exposure
- 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


Primary infection
CD4+
Establishment of infection in lymphoid tissue
Lymph node
Massive viremia
Wide dissemination to lymphoid organs
HIV-specific immune response
Trapping of virus and establishment of chronic, persistent infection
Immune activation mediated by cytokines and HIV envelope–mediated aberrant cell signaling
Partial immunological control of virus replication
Accelerated virus replication
Rapid CD4+ T cell turnover
Destruction of immune system
Katie Ris