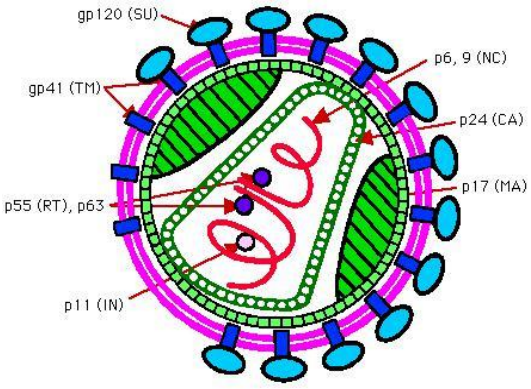
A I D S

HIV human immunodeficiency virus, a non-oncogenic retrovirus, is the primary etiologic agent of acquired immunodeficiency syndrome (AIDS). The illness was first described in 1981, and the end of 1983 was isolated the virus. Both HIV-1 and HIV-2 cause AIDS, but HIV-1 is found worldwide, HIV-2 is found primarily in West Africa.

HIV is a retrovirus, a member of the Lentivirinae subfamily, which causes "slow" infections with long incubation periods.



Structure: HIV virion is spherical, 100-200 nm in diameter. HIV has bar-shaped (D) core surrounded by an envelope containing virus specific glycolproteins (gp120 and gp41). The genome of HIV consists of two identical molecules of single-stranded, positive polarity RNA and is said to be diploid. Three structural gens: **gag, pol and env**, which encode the structural proteins. The genome RNA has six regulatory genes. Two of these **tat and rev** are required for replication, and the other four **nef, vif, vpr and vpu**, are not required for replication and are termed "accessory" genes.

The gag gene encodes the internal "core" proteins, the most important of which is **p24,** an antigen used in serologic tests. The **pol** gene encodes several proteins, including the virion "reverse transcriptase" which synthesizes DNA by using the genome RNA as a template, an integrase that integrates the viral DNA into cellular DNA, and a protease that cleaves the various viral precursor proteins. The **env** gene encodes gp160, a precursor glycoprotein that cleaved to form the two envelope (surface) glycoproteins, gp120 and gp41.

And there are three viral enzymes in nucleocapsid of the virion: **reverse transcriptase, protease, integrase.** Reverse transcriptase is the RNA-dependent DNA polymerase that is the source of the family name retroviruses. This enzyme transcribes the RNA genome into the proviral DNA. The viral protease cleaves the precursor polyproteins into functional viral polypeptides.

The essential regulatory gene is the **tat** (transactivation of transcription) gene, which encodes a protein that enhances viral (and cellular) gene transcription. **Tat** protein and another regulatory protein **Nef** repress the synthesis of class I MHC proteins, thereby reducing the ability of cytotoxic T cells to kill HIV-infected cells. **Rev** gene controls the passage of late mRNA from the nucleus into the cytoplasm.

Antigenic structure: There are several important antigens:

1. gp120 and gp41 are the type-specific envelope glycoproteins, gp120 protrudes from the surface and interacts with the **CD4 receptor** on the cell surface. Gp41 is embedded in the envelope and mediates the fusion of the viral envelope with the cell membrane at the time of infection.

2. The group specific antigen, **p24,** is located in the core and is not known to vary. Antibodies against p24 do not neutralize HIV infectivity but serve as important serologic markers of infection.

The natural host range of HIV infectivity is limited to humans, although certain primates can be infected in the laboratory. HIV is not an endogenous virus of humans; ie, no HIV sequences are found in normal cell DNA. The origin of HIV and how it enteres the human population remains uncertain. There is an evidence that chimpanzees living in West Africa were the source of HIV-1.

Replication cycle: The initial step is attachment, when the virion gp120 binds the CD4 protein of the cell surface. The virion gp120 protein then interacts with the second protein on the

cell surface, one of the chemokine receptors. Next the virion gp41 protein mediates fusion of the viral envelope with the cell membrane, and the virion enters the cell. After uncoating, the virion RNA-dependent DNA polymerase transcribes the genome RNA into double-stranded DNA, which integrates into the host cell DNA. The viral DNA can integrate at different sites in the host cell DNA, and multiple copies of viral DNA can integrate. Integration is mediated by a virus-encoded endonuclease (integrase). Viral mRNA is transcribed from the proviral DNA by host cell RNA polymerase and translated into several large polyproteins, which are then cleaved by the virus-encoded protease to form the virion structural proteins. The Gag polyprotein is cleaved to form the main core protein (p24), the matrix protein (p17), and several smaller proteins. The **Pol** polyprotein is cleaved to form the reverse transcriptase, integrase, and protease. The immature virion containing the precursor polyproteins forms in the cytoplasm, and cleavage by the viral protease occurs as the immature virion buds from the cell membrane. It is this cleavage process that results in the mature, infectious virion.

Transmission and Pathogenesis: Transmission of HIV occurs primarily by sexual contact and by transfer of infected blood. Perinatal transmission from infected mother to neonate also occurs (35-50%), either across the placenta, at birth, or via breast milk. Small amounts of virus have been found in other fluids, eg, saliva and tears, there is no evidence that they play a role in infection.

HIV infects helper T cells and kills them, resulting in suppression of cell-mediated immunity. This predisposes the host to various opportunistic infections and certain cancers such as Kaposi's sarcoma and lymphoma. However, HIV does not directly cause these tumours because HIV genes are not found in these cancer cells. The initial infection of the genital tract occurs in dendritic cells that line the mucosa (Langerhans cells), after which the local CD4 positive helper T cells become infected. HIV is first found in the blood 4-11 days after infection.

HIV also infects brain monocytes and macrophages, producing multinucleated giant cells and significant central nervous system symptoms. The fusion of HIV-infected cells in the brain and elsewhere mediated by gp41 is one of the main pathologic findings. The cells recruited into the syncytia ultimately die. The death of HIV-infected cells is also the result of immunologic attack by cytotoxic CD8 lymphocytes. Effectiveness of the cytotoxic T cells may be limited by the ability of the viral Tat and **Nef** proteins to reduce class I MHC protein synthesis.

Another mechanism which explained the death of helper T cells is that HIV acts as a "super antigen", which indiscriminately activates many helper T cells and leads to their demise.

A person infected with HIV is considered to be infected for life. This seems likely to be the result of integration of viral DNA into the DNA of infected cells.

The main immune response to HIV infection consists of cytotoxic CD8-positive lymphocytes. These cells respond to the initial infection and control it for many years Mutants of HIV, especially in the **env** gene encoding gp120, arise, but new clones of cytotoxic T cells proliferate and control the mutant strain. Cytotoxic T cells lose their effectiveness because so many CD4 helper T cells have died that the supply of lymphokines, such as IL-2, required to activate the cytotoixic T cells is no longer sufficient. There is also evidence that "escape" mutants of HIV are able to proliferate unchecked because the patient has no clone of cytotoxic T cells capable of responding to the mutant strain. Antibodies against various HIV proteins, such as p24, gp120, and gp41, are produced but they neutralize the virus poorly in vivo and appear to have little effect on the course of the disease.

HIV has three main mechanisms by which it evades the immune system:

1.Integration of viral DNA into host cell DNA, resulting in a persistent infection;

2.A high rate of mutation of the env gene;

3.The production of the Tat and Nef proteins that down-regulate class IMHC proteins required for cytotoxic T cells to recognize and kill HIV-infected cells.

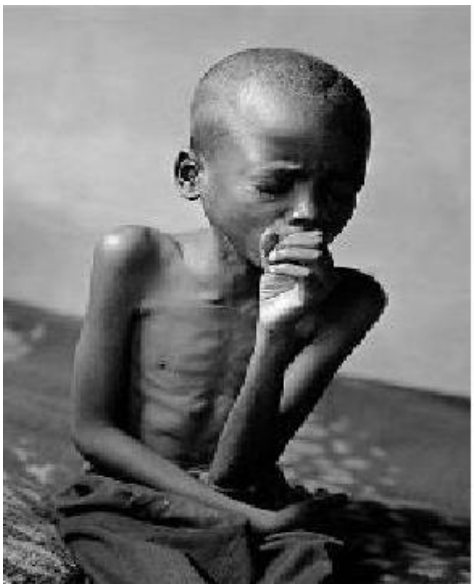
Clinical findings: The clinical picture of HIV infection can be divided into: **1.** an early, **2.** an acute stage, **3.** middle, **4.** latent stage, **5.** a late, and immunodeficiency stage. In the acute stage, which usually begins 2-4 weeks after infection, mononucleosis like picture of fever,

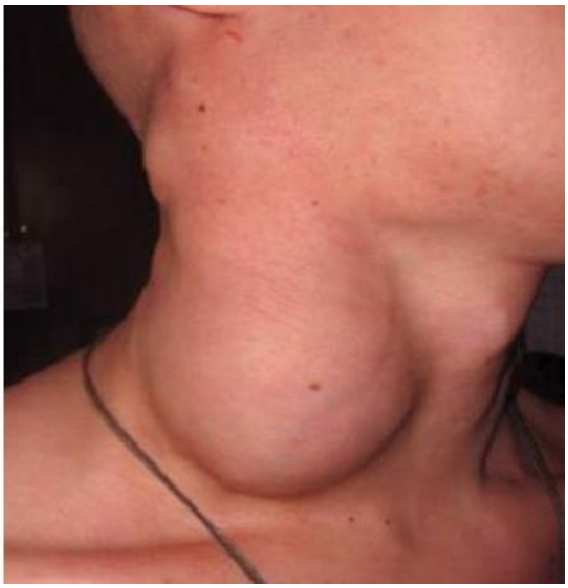
lethargy, sore throat, and generalized lymphadenopathy occurs. A maculopapular rash on the trunk appears. Leukopenia occurs, but the number of CD4 cells is usually normal. This acute phase typically resolves spontaneously in about 2 weeks. Antibodies to HIV typically appear 3-4 weeks after infection. Note that the inability to detect antibodies prior to that time can result in "false-negative" serologic tests; i.e., the person is infected, but antibodies are not detectable at the time of the test. This has important implications because HIV can be transmitted to others during this period.

After initial viremia, a viral "set point" occurs, which can differ from one person to another. The set point represents the amount of virus produced, i.e., the "viral load", and tends to remain "set" or constant, for years. The higher set point, the more likely the individual is to progress to symptomatic AIDS.

In the middle stage, a long latent period, measured in years, usually ensues. The patient is asymptomatic during this period. Although the patient is asymptomatic and viremia is low or absent, a large amount of HIV is being produced by lymph node cells but remains sequestered within the lymph nodes. This indicates that during this period of clinical latency, the virus itself does not enter a latent state.

A syndrome called AIDS-related complex (ARC) can occur during the latent period. The most frequent manifestations are persistent fevers, fatigue, weight loss, and lymphadenopathy. ARC often progresses to AIDS.





The last stage of HIV infection is AIDS, manifested by a decline in the number of CD4 cells and an increase in the frequency and severity of opportunistic infections. The two most characteristic manifestations of AIDS are Pneumo-cystis pneumonia and Kaposi's sarcoma. However, many other opportunistic infections occur too: disseminated herpes simplex, herpes zoster, cytomegalovirus infections, fungal infections, etc.

Immunity: HIV-infected persons develop both humoral and cell-mediated responses against HIV-related antigens. Antibodies to a number of viral antigens develop soon after infection, but the response pattern against specific viral antigens changes over time as patients progress to AIDS. Antibodies to the envelope glycoproteins (gp41, gp120, gp160) are maintained, but those directed against the core protein (p24) decline. The decline of anti-p24 may herald the beginning of clinical signs and other immunologic markers of progression.

Most infected individuals make neutralizing antibodies against HIV. The envelope glycoproteins appear to be the major targets for antibody neutralization. The neutralizing antibodies can be measured in vitro by inhibiting HIV infection of susceptible lymphocyte cell lines. Viral infection is quantified by **(1)** reverse transcriptase assay, which measures the enzyme activity of released HIV particles; **(2)** indirect immunofluorescence assay, which measures the percentage of infected cells; **(3)** reverse transcriptase-polymerase chain reaction (RT-PCR) or

branched-chain DNA amplification assays that measure HIV nucleic acids. Relatively low neutralizing activity is present in the sera of both asymptomatic seropositive individuals and patients with AIDS.

Treatment: Zidovudine and Lamivudine, which are nucleoside inhibitors and Indinavir a protease inhibitor. This combination is known as **HAART**, which is an acronym for "highly active antiviral therapy". It is very effective in prolonging life, improving quality of life, and reducing viral load but does not cure the chronic HIV infection. Another highly effective regimen is the combination of Zidovudine, lamivudine, and the non-nucleoside reverse transcriptase inhibitor, Efavirenz.

Azidothymidine (AZT) inhibits HIV replication by interfering with proviral DNA synthesis. Dideoxynosine (DDI), Videx is recommended for patients who are intolerant to AZT. Nevirapine (Viramune), Delaviridine, Efavirenz (Sustiva) are reverse transcriptase inhibitors. Protease inhibitors, such as Saquinavir, Ritonavir, etc., when combined with nucleoside analogues, such as Azidothymidine, are very effective in inhibiting viral replication and increasing CD4 cell counts.

Treatment for acute HIV infection with two reverse transcriptase inhibitors and protease inhibitor is recommended. With this regimen, the viral load drops below the level of detection; CD4 cell counts rise, and CD8 activity increases.

In this complex treating of opportunistic infections is included.

Laboratory diagnoses:

1. **Virus isolation:** HIV can be cultured from lymphocytes in peripheral blood (and occasionally from specimens from other sites). The number of circulating infected cells varies with the stage of disease. Higher titers of virus are found in the plasma and in peripheral blood cells of the patients with AIDS, as compared with asymptomatic individuals. The magnitude of plasma viremia appears to be a better correlate of the clinical stage of HIV infection than the presence of any antibodies. The most sensitive virus isolation technique is to cocultivate the test sample with uninfected, mitogen-stimulated peripheral blood mononuclear cells. Primary isolates of HIV grow very slowly compared with laboratory-adapted strains. Viral growth is detected by testing culture supernatant fluids after about 7-14 days for viral reverse transcriptase activity or for virus-specific antigens.

2. **Serology:** Detection of antibodies by ELISA (enzyme-linked immunosorbent assay). Because there are some false-positive results with this test, the definitive diagnosis is made by Western blot analysis, in which the viral proteins are displayed by acrylamide gel electrophoresis, transferred to nitrocellulose paper (the blot), and reacted with the patient's serum. If antibodies are present, they will be bound to the viral proteins (predominantly to the gp41 or p24 protein). Enzymatically labelled antibody to human IgG is then added. A colour reaction reveals the presence of the HIV antibody in the infected patient's serum.

3. **Detection of viral nucleic acid or antigens:** The polymerase chain reaction (PCR) is very sensitive and specific technique that can be used to detect HIV DNA (branched – chain DNA – bDNA test). The HIV RNA levels are important predictive markers of disease progression and valuable tools to monitor effectiveness of antiviral therapies. Low levels of circulating HIV-1 p24 antigen can be detected in the plasma by ELISA soon after infection. The antigen often becomes undetectable after antibodies develop and may reappear late in the course of infection, indicating a poor prognosis. The test can be used to detect antigen in supernatant fluids from virus-infected tissue culture cells.