Abstract: HIV (human immunodeficiency virus) is the virus that causes AIDS. This virus may be passed from one person to another when infected blood, semen, or vaginal secretions come in contact with an uninfected person’s broken skin or mucous membrane. In addition, infected pregnant women can pass HIV to their baby during pregnancy or delivery, as well as through breast-feeding. HIV symptoms associate with confusion and forgetfulness, nausea, stomach cramps, diarrhea, vomiting, vision loss, rapid weight loss, dry cough. The center for control of diseases estimates 70% of the annual infections transmitted by persons who are unaware of infection. The immune dysfunction progresses to AIDS, development of infections from months to years. The initial findings include leucopenia, ulcers, lymphadenopathy, hepatosplenomegaly, neurological exams. The HIV is diagnosis by serology test, Elisa test, western Blot, PCR test, NAT test. The anti viral drugs such as zidovudine, didanosine, nelfinavir, lamivudine, Comvivir, abacavir used to treat the disease. The combination of doses and immunization therapy is used to prevent the aids. The prevention of the disease is through media. Establishing the counseling centers, rehabilitation centers in the country.

Keywords: HIV, Pcr, Nat, Western Blot, Leucopenia, Infection, Cramps, Lymphadenopathy
INTRODUCTION
Acquired immunodeficiency syndrome (AIDS) is defined in terms of either a CD4+ T cell count below 200 cells per µL or the occurrence of specific diseases\(^{(1)}\) in association with an HIV infection. In the absence of specific treatment, around half of people infected with HIV develop AIDS within ten years. The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia (40%), cachexia in the form of HIV wasting syndrome (20%) and esophageal candidiasis. Other common signs include recurring respiratory tract infections.

Infections caused by various species that are normally controlled by the immune system. Which infections occur partly depends on what organisms are common in the person's environment. These infections may affect nearly every organ system.

The infected persons can develop various cancers including Kaposi's sarcoma, Burkitt's lymphoma, primary central nervous system lymphoma, and cervical cancer. Kaposi's sarcoma is the most common cancer occurring in 10 to 20% of people with HIV. The second most common cancer is lymphoma which is the cause of death of nearly 16% of people with AIDS and is the initial sign of AIDS in 3 to 4%. Both these cancers are associated with human herpesvirus. Cervical cancer occurs more frequently in those with AIDS due to its association with human papillomavirus (HPV). Additionally, people with AIDS frequently have systemic symptoms such as prolonged fevers, swollen lymph nodes, chills, weakness, and weight loss. Diarrhea is another common symptom present in about 90% of people with AIDS. They can also be affected by diverse psychiatric and neurological symptoms independent of opportunistic infections and cancers.\(^{(2)}\)

HOW DOES HIV CAUSE AIDS
HIV destroys a certain kind of blood cell (CD4+ T cells) which is crucial to the normal function of the human immune system. In fact, loss of these cells in people with HIV is an extremely powerful predictor of the development of AIDS\(^{(3)}\). Studies of thousands of people have revealed that most people infected with HIV carry the virus for years before enough damage is done to the immune system for AIDS to develop. However, sensitive tests have shown a strong connection between the amount of HIV in the blood and the decline in CD4+ T cells and the development of AIDS. Reducing the amount of virus in the body with anti-retroviral therapies can dramatically slow the destruction of a person's immune system.

PATHOPHYSIOLOGY

- The depletion of helper T lymphocytes (CD4+ cells). The loss of CD4+ cells results in the development of opportunistic infections and neoplastic processes.
• After the virus enters the body there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood.

• During primary infection, the level of HIV may reach several million virus particles per milliliter of blood66. This response is accompanied by a marked drop in the number of circulating CD4+ T cells.[4]

• The acute viremia is almost invariably associated with activation of CD8+ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion.[17]

• The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts recover.

• A good CD8+ T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus67. Ultimately, HIV causes AIDS by depleting CD4+ T cells.

• This weakens the immune system and allows opportunistic infections. T cells are essential to the immune response and without them; the body cannot fight infections or kill cancerous cells. The mechanism of CD4+ T cell depletion differs in the acute and chronic phases.[5]

• During the acute phase, [18] HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis may also be a factor.

• During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.

Fig: Pathophysiology of HIV -AIDS
HIV - AIDS SIGNS AND SYMPTOMS

- large lymph nodes or "swollen glands" that may be enlarged for more than three months frequent fevers and sweats. \(^7\)
- skin rashes or flaky skin that does not go away
- short-term memory loss
- slow growth or frequent illness in children cough and shortness of breath
- seizures and lack of coordination difficult
- painful swallowing
- confusion and forget fullness
- nausea, stomach cramps
- diarrhea,
- vomiting
- vision loss
- unexplained weight loss
- fatigue
- unusual tiredness

The following may be warning signs of infection with HIV:

- Rapid weight loss
- Dry cough
- recurring fever or profuse night sweats
- profound and unexplained fatigue
- Swollen lymph glands in the armpits, groin, or neck
- Diarrhea that lasts for more than a week
- White spots or unusual blemishes on the tongue, in the mouth, or in the throat
- Pneumonia

- Red, brown, pink, or purplish blotches on or under the skin or inside the mouth, nose, or eyelids

- Memory loss, depression, and other neurological disorders

**PHASES OF HIV INFECTION**
THE ORIGIN OF AIDS

Simian Immunodeficiency Viruses (SIVs) are closely related to HIV and HIV-2, for instance, has an almost exact counterpart in a virus of the sooty-mangabey, a type of African monkey. The HIV-2's connection to the sooty mangabey is probably the most compelling evidence for animal to man transfer of HIV. A likely source of HIV-1 has been more difficult to pin down. The closest simian virus to HIV-1 discovered to date exists in certain chimpanzees. Scientists have long recognized the ability of certain viruses and other diseases to pass from animals to humans. This process is referred to as zoonosis. Once an animal disease has infected people, it may then be passed from human to human. By early 1982 the group of disease entities was named the acquired immune deficiency syndrome (AIDS) by the Center for Disease Control (CDC).[6]

EPIDEMIOLOGY

According to the Centers for Disease Control and Prevention (CDC), in 2009 the estimated rate of diagnoses of HIV infection in the 40 states that have confidential name-based reporting was 17.4 per 100,000 populations. From 2006 to 2009, the estimated number and rate of annual diagnoses of HIV infection in those states remained stable. The CDC estimated that at the end of 2006, the most recent year for which national prevalence estimates are available, there were 1,106,400 adults and adolescents living with HIV infection in the United States. This represents an increase of approximately 11% from the previous estimate in 2003; the increase may reflect a higher proportion of HIV-infected people knowing their status and seeking care, and/or increased Survival among people infected with HIV. In 2009, the estimated rate of AIDS diagnoses in the US was 11.2 per 100,000 populations. More than 1 million persons were diagnosed with AIDS from 1981 to 2008, and more than 600,000 people died with AIDS.[7]

CLASSIFICATION

The CDC classification of HIV disease was first put forth as a categorization of HIV related symptoms into four groups and was explicitly for "public health purposes" and not "intended as a staging system," (9) although it was frequently treated as if it were a staging system in the AIDS literature. Staging is disease classification that aims primarily to make groupings that have different prognosis and can be used in guiding treatment decisions. Stages attempt to classify disease in a progressive sequence from least to most severe, each higher stage having a poorer prognosis or different medical management than the preceding stage. The current CDC classification system from the revision in 1993 combines three categories of the CD4 count with three symptom categories and is closer to a staging system but is still not described as such. The CDC, however, proposed that it be used to "guide clinical and therapeutic actions in the management of HIV infected adolescents and adults." This description of its intended use is close to the use of a staging system.
CD4+ T-lymphocyte categories:

Category 1: > 500 cells/mm³ (or CD4% > 28%)  Category 2: 200-499 cells/mm³ (or CD4% 14% - 28%)  Category 3: < 200 cells/mm³ (or CD4% < 14%)

Categories of clinical conditions:

Category A:

Asymptomatic HIV infection, persistent generalized lymphadenopathy acute (primary) HIV infection with accompanying illness or history of acute HIV infection in an adolescent (>13 years) with documented HIV infections. Conditions listed in categories B and C have not occurred.

Category B:

Consists of symptomatic conditions in an HIV infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: (a) the conditions are attributed to HIV infection or are indicative of a defect in cell mediated immunity; or (b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. (30)

Category C:

Includes the clinical conditions listed in 1993 AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

Transmission

<table>
<thead>
<tr>
<th>Exposure route</th>
<th>Chance of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>90%</td>
</tr>
<tr>
<td>Childbirth (to child)</td>
<td>25%</td>
</tr>
<tr>
<td>Needle-sharing injection drug use</td>
<td>0.67%</td>
</tr>
<tr>
<td>Percutaneous needle stick</td>
<td>0.30%</td>
</tr>
<tr>
<td>Receptive anal intercourse*</td>
<td>0.04–3.0%</td>
</tr>
<tr>
<td>Insertive anal intercourse*</td>
<td>0.03%</td>
</tr>
<tr>
<td>Receptive penile-vaginal intercourse*</td>
<td>0.05–0.30%</td>
</tr>
<tr>
<td>Insertive penile-vaginal intercourse*</td>
<td>0.01–0.38%</td>
</tr>
<tr>
<td>Receptive oral intercourse*§</td>
<td>0–0.04%</td>
</tr>
<tr>
<td>Insertive oral intercourse*§</td>
<td>0–0.005%</td>
</tr>
</tbody>
</table>
SEXUAL TRANSMISSION

- HIV is commonly transmitted sexually by penile anal intercourse and penile vaginal intercourse and infrequently by fellatio. Vaginal intercourse can transmit HIV to either the male or the female partner, but a number of studies have shown that the risk is higher to the female partner. Studies of homosexual men have shown consistently that the receptive partner in anal intercourse is at the highest risk of HIV infection and that risk is strongly related to the number of male sexual partners.

- Anal intercourse has also been shown to be a risk factor for the female partner in heterosexual studies. Presumably, fellatio would pose the same risk to the female partner as to the receptive oral partner in male homosexual couples, but data are lacking on the risk in heterosexuals.\(^8\)

VERTICAL TRANSMISSION

- One proposed scheme for differentiating these 2 modes of transmission suggests that the virus was transmitted early or in utero if HIV is detected in the infant within the first 48 hours of life. Late or intrapartum transmission is said to have occurred if virologic evaluations are negative during the first week of life but there is subsequent HIV detection between 7 and 90 days of age.

- Applying these admittedly speculative definitions to published studies suggest that 50% to 70% of HIV vertical transmission occurs intrapartum. If true, this finding has important implications for designing strategies to interrupt transmission.\(^{31}\)

- Breast feeding substantially increases the risk of HIV vertical transmission, therefore bottle feeding is currently recommended for all infants born to HIV infected mothers.

THE REPLICATION CYCLE OF HIV-1

![Diagram of the replication cycle of HIV-1](image-url)
Virus entry

Several independent lines of evidence demonstrated that CD4 serves as a binding receptor for HIV-1, which bind with high affinity to gp120. Gp120 is a viral surface envelope protein. The post binding events required for HIV-1 and cell membrane fusion are not well understood. HIV-1, like most other retroviruses, infects cells in a pH-independent manner that is consistent with direct fusion between viral and cell surface membranes.\[9\]

REVERSE TRANSCRIPTION

- The reverse transcription pathway generates a linear DNA copy of the viral RNA genome. This step takes place within a viral nucleoprotein complex and requires the coordinated activities of reverse transcriptase, an RNA- and DNA dependent DNA polymerase, and RNaseH, which degrades the RNA component of RNA-DNA hybrid molecules. Because the viral nucleoprotein complexes are rapidly transported to the host cell nucleus, the majority of viral DNA synthesis occurs within the nuclear compartment.\(^{32}\)

- Integration of the viral DNA into cellular genomic DNA the nuclear viral complexes serve as the machines that integrate viral DNA into host cell chromosomal DNA to form a provirus. This step is critically dependent on the activity of the viral integrase protein and is essential for viral gene expression.

Viral protein expression

- The expression of viral genes requires the collaborative activities of the host cell transcription machinery (RNA polymerase and transcription factors Sp1 and NFkB) and viral regulatory proteins (tat and rev).

Virus assembly

- The MA gag protein seems to specify the site of viral assembly. Membrane attachment of viral gag and gag-pol precursor proteins requires N-terminal cotranslational addition of myristic acid to viral MA proteins.

Although MA contains the membrane binding domain and can induce membrane budding, the incorporation of gag and gag-pol precursor proteins into functional viral particles requires the presence of interaction domains of gag and a late acting L-domain of the p6 gag protein. In retroviruses, viral genomic RNA is selectively taken up from the pool of cytoplasmic RNAs because the NC gag protein recognizes specific cis-acting RNA packaging signals.\[10\]
STRUCTURE OF THE HIV VIRUS

STRUCTURAL PROTEINS

Gag proteins:
The gag gene gives rise to the 55 kilodalton Gag precursor protein, also called p55, which is expressed from the unspliced viral mRNA. After budding, p55 is cleaved by the virally encoded protease during the process of viral maturation into four smaller proteins designated MA (matrix).

Most MA molecules remain attached to the inner surface of the virion lipid bilayer, stabilizing the particle. A small percentage of MA, however, binds integrase, and is thereby recruited inside the deeper layers of the virion. These MA molecules subsequently facilitate the nuclear transport of the viral genome because a karyophillic signal on MA is recognized by the cellular nuclear import machinery. This phenomenon allows HIV to infect non dividing cells, an unusual property for a retrovirus.

The p24 (CA) protein forms the conical core of viral particles. Cyclophilin A has been demonstrated to interact with the p24 region of p55 leading to its incorporation into HIV particles. The NC region of Gag is responsible for specifically recognizing the so-called packaging signal of HIV. The packaging signal consists of four stem loop structures located near the 5' end of the viral RNA, and is sufficient to mediate the incorporation of a heterologous RNA into HIV-1 virions. CNC also facilitates reverse transcription.

Gag-Pol precursor:
The viral protease, integrase, RNAse H, and reverse transcriptase are always expressed within the context of a Gag-Pol fusion protein. During viral maturation, the virally encoded protease cleaves the Pol polypeptide away from Gag and further digests it to separate the protease (p10), RT (p50), RNAse H (p15), and integrase (p31) activities. \[^{[32]}\]
HIV-1 protease:

The HIV-1 protease is an aspartyl protease that acts as a dimer. Protease activity is required for cleavage of the Gag and Gag-Pol polyprotein precursors during virion maturation.

Reverse transcriptase:

The pol gene encodes reverse transcriptase. During the process of reverse transcription, the polymerase makes a double stranded DNA copy of the dimer of single stranded genomic RNA present in the virion.

Integrase:

The integrase protein mediates the insertion of the HIV proviral DNA into the genomic DNA of an infected cell.

Envelope proteins:

The 160 KD Env (gp160) is expressed from singly spliced mRNA. A cellular protease cleaves gp160 to generate gp41 and gp120. Gp41 contains the transmembrane domain of Env, while gp120 is located on the surface of the infected cell and of the virion through non covalent interactions with gp41. Env exists as a multimer, most likely a trimer, on the surface of the cell of the virion. Interactions between HIV and the virion receptor, CD4, are mediated through specific domains of gp120.

Regulator proteins

Tat:

Tat is a transcriptional transactivator that is essential for HIV-1 replication. Tat is an RNA binding protein, unlike conventional transcription factors that interact with DNA. The mechanism of Tat function remains controversial. From some studies, it appears that Tat acts principally to promote the elongation phase of HIV-1 transcription, other studies indicate that Tat may be involved in the phosphorylation of the carboxyl terminal domain (CTD) of RNA polymerase II.

Rev:

Rev is a 13-kD sequence-specific RNA binding protein. Rev acts to induce the transition from the early to the late phase of HIV gene expression.

Accessory proteins

Nef:

Nef has been shown to have multiple activities, including the down regulation of the cell
surface expression of CD4, the perturbation of T-cell activation, and the stimulation of HIV infectivity.

The Vpr protein is incorporated into viral particles. Vpr plays a role in the ability of HIV to infect non dividing cells by facilitating the nuclear localization of the preintegration complex. Vpr can also block cell division.\(^{11}\)

**Vpu:**

HIV-2 does not contain vpu, but instead harbors another gene, vpx. The 16-kD Vpu polypeptide is an integral membrane phosphoprotein that is primarily localized in the internal membranes of the cell. In HIV infected cells, complexes are formed between the viral receptor, CD4, and the viral envelope protein in the endoplasmic reticulum causing the trapping of both proteins to within this compartment. The formation of intracellular Env-CD4 complexes thus interferes with virion assembly. Vpu liberates the viral envelope by triggering the degradation of CD4 molecules complexed with Env. Vpu also increases the release of HIV from the surface of an infected cell.

**Vif:**

Vif is a 23-kD polypeptide that is essential for the replication of HIV in peripheral blood lymphocytes, macrophages, and certain cell lines.

**HIV SCREENING TESTS**

**ELISA**

The enzyme-linked immunosorbent assay (ELISA), or enzyme immunoassay (EIA), was the first screening test commonly employed for HIV. It has a high sensitivity.\(^{48}\)

In an ELISA test, a person's serum is diluted 400-fold and applied to a plate to which HIV antigens have been attached. If antibodies to HIV are present in the serum, they may bind to these HIV antigens. The plate is then washed to remove all other components of the serum. A specially prepared "secondary antibody" — an antibody that binds to human antibodies — is then applied to the plate, followed by another wash.

This secondary antibody is chemically linked in advance to an enzyme. Thus the plate will contain enzyme in proportion to the amount of secondary antibody bound to the plate. A substrate for the enzyme is applied, and catalysis by the enzyme leads to a change in color or fluorescence. ELISA results are reported as a number; the most controversial aspect of this test is determining the "cut-off" point between a positive and negative result.
WESTERN BLOT

Like the ELISA procedure, the western blot is an antibody detection test. However, unlike the ELISA method, the viral proteins are separated first and immobilized. In subsequent steps, the binding of serum antibodies to specific HIV proteins is visualized.

Specifically, cells that may be HIV-infected are opened and the proteins within are placed into a slab of gel, to which an electrical current is applied. Different proteins will move with different velocities in this field, depending on their size, while their electrical charge is leveled by a surfactant called sodium lauryl sulfate. Some commercially prepared Western blot test kits contain the HIV proteins already on a cellulose acetate strip. Once the proteins are well-separated, they are transferred to a membrane and the procedure continues similar to an ELISA: the person's diluted serum is applied to the membrane and antibodies in the serum may attach to some of the HIV proteins. Antibodies that do not attach are washed away, and enzyme-linked antibodies with the capability to attach to the person's antibodies determine to which HIV proteins the person has antibodies.

There are no universal criteria for interpreting the western blot test: The number of viral bands that must be present may vary. If no viral bands are detected, the result is negative. If at least one viral band for each of the GAG, POL, and ENV gene-product groups is present, the result is positive. The three-gene-product approach to western blot interpretation has not been adopted for public health or clinical practice. Tests in which less than the required numbers of viral bands are detected are reported as indeterminate: a person who has an indeterminate result should be retested, as later tests may be more conclusive. Almost all HIV-infected persons with indeterminate western blot results will develop a positive result when tested in one month; persistently indeterminate results over a period of six months suggest the results are not due to HIV infection. In a generally healthy low-risk population, indeterminate results on western blot occur on the order of 1 in 5,000 patients. However for those individuals that have had high-risk exposures to individuals where HIV-2 is most prevalent, Western Africa, an inconclusive western blot test may prove infection with HIV-2.

NUCLEIC ACID-BASED TESTS (NAT)

Nucleic-acid-based tests amplify and detect one or more of several target sequences located in specific HIV genes, such as HIV-I GAG, HIV-II GAG, HIV-env, or the HIV-pol. Since these tests are relatively expensive, the blood is screened by first pooling some 8-24 samples and testing these together; if the pool tests positive, each sample is retested individually. Although this results in a dramatic decrease in cost, the dilution of the virus in the pooled samples decreases the effective sensitivity of the test, lengthening the window period by 4 days (assuming a 20-fold dilution, ~20hr virus doubling time, detection limit 50 copies/ml, making limit of detection...
1,000 copies/ml). Since 2001, donated blood in the United States has been screened with nucleic-acid-based tests, shortening the window period between infection and detectability of disease to a median of 17 days (95% CI, 13-28 Days, assumes pooling of samples. A different version of this test is intended for use in conjunction with clinical presentation and other laboratory markers of disease progress for the management of HIV-1-infected patients.\cite{15}

**RT-PCR Test**

- In the RT-PCR test, viral RNA is extracted from the patient's plasma and is treated with reverse transcriptase (RT) to convert the viral RNA into cDNA.

- The polymerase chain reaction (PCR) process is then applied, using two primers unique to the virus's genome. After PCR amplification is complete, the resulting DNA products are hybridized to specific oligonucleotides bound to the vessel wall, and is then made visible with a probe bound to an enzyme. The amount of virus in the sample can be quantified with sufficient accuracy to detect threefold changes.\cite{13}

- In the Quantiplex b DNA or branched DNA test, plasma is centrifuged to concentrate the virus, which is then opened to release its RNA. Special oligonucleotides that bind to viral RNA and to certain oligonucleotides bound to the wall of the vessel are added. In this way, viral RNA is fastened to the wall.

- Then new oligonucleotides that bind at several locations to this RNA are added and other oligonucleotides that bind at several locations to those oligonucleotides.

- This is done to amplify the signal. Finally, oligonucleotides that bind to the last set of oligonucleotides and that are bound to an enzyme are added; the enzyme action causes a color reaction, which allows quantification of the viral RNA in the original sample.\cite{14}

**Antiviral Therapy Known as Antiretroviral Drugs**

**Nucleoside Reverse Transcriptase Inhibitors (NRTIs) such as**

- zidovudine (AZT)
- didanosine (ddl)
- zalcitabine (ddC)
- stavudine (d4T)
- lamivudine (3TC)
• Comvivir (AZT+ 3TC)
• abvacavir (Ziagen)

Protease Inhibitors (PIs) such as
• saquinavir (Invirase and Fortovase)
• ritonavir (Norvir)
• indinavir (Crixivan)
• nelfinavir (Viracept)

Non-Nucleoside Reverse Transcriptase Inhibitors such as
• nevirapine (Viramune)
• delavirdine (Rescriptor)
• efavirenz (Sustiva)

MECHANISM OF ANTI HIV –AIDS DRUGS

SIDE EFFECTS OF HIV DRUGS
• Hepatotoxicity
• Hyperglycemia
• Hyperlipidemia
• Lactic Acidosis
• Lipodystrophy
• Osteonecrosis
• Osteoporosis
• Osteopenia
• Skin Rash
• Fever and infection
• Nausea, diarrhea and vomiting
• Fatigue or tiredness
• Headaches

ANTI HIV DRUGS DOSSAGE FORMS

NAME OF THE DRUG DOSSAGE
DRUG INTERACTIONS

- Didanosine With Allopurinol, Gancyclovir
- Acyclovir With Probenecid, Alcohol
- Efavirenz With Hormonal contraceptives
- Indinavir With Antacids
- Ritonavir With Phenobarbital
- Nelfinavir With Antacids
CONCLUSION

HIV/AIDS is a Preventable disease using Pharmacological and non pharmacological therapy. using sterile needles and blood prevents the vertical transmission of the disease that is mother to child. using contraceptive methods reduce the disease progression and Promote quality of life to the Patient. Proper awareness of the society through Media, Journals, Magazines, Newspapers, Awareness Programmes Reduce the disease progression. Establishing HIV/AIDS screening centers promote early diagnosis of disease and Promote world Peace and society becomes disease free.

REFERENCES


