Sys Rev Pharm 2023; 14(4): 219-225
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453 / DOI: 10.31858/0975-8453.14.4.219-225

Review Article

Literature Review on Acquired Immunodeficiency Syndrome (AIDS)

Rutuja B Sonawane[1*] Ganesh D Barkade[2]

[1]Department of Pharmacy, Dr. Vitthalrao Vikhe Patil Foundation's College of Pharmacy, Maharashtra, India
[2]Department of Pharmaceutical Chemistry, Dr. Vitthalrao Vikhe Patil Foundation's College of Pharmacy, Maharashtra, India

Article History: *Submitted: 20.03.2023* *Accepted: 04.04.2023* *Published: 11.04.2023*

ABSTRACT

AIDS is one of the worst diseases in the world. Human Immunodeficiency Virus (HIV) is a type of lentivirus that causes HIV and AIDS. AIDS is usually caused by an infection by viruses. Bacteria, fungi, and viruses are usually controlled by the body's immune system while, HIV weakens the immune system. Thus, prevention is the only strategy available to treat HIV/AIDS. So it is important to raise awareness about this among young people. In this study, we report about HIV analyzed detailed information on biology, pathology, signs and symptoms, problems, diagnosis, treatment, types of interacting infections, and vaccine.

Keywords: AIDS, Antiretroviral drugs, HIV, Retrovirus

***Correspondence:** Rutuja B Sonawane, Department of Pharmacy, Dr. Vitthalrao Vikhe Patil Foundation's College of Pharmacy, Maharashtra, India, E-mail: sonawanerutuja121@gmail.com

INTRODUCTION

HIV stands for Human Immunodeficiency Virus. AIDS stands for Acquired Immunodeficiency Syndrome. It is contagious only to humans and can spread from one person to another, not just animals. It is not spread by mosquitoes, bats or other animals. The body's task is to protect our body from bacteria, viruses, etc. using an immune system but people with HIV cannot fight the virus. Bacteria are the smallest, simplest things that don't work outside the body while work inside the body. It is not hereditary, meaning that it cannot be passed from one generation to the next. It can be transmitted from a sick person to a healthy person. It weakens the body and causes $CD4^+$ cell deficiency in the immune system. HIV is the virus that causes AIDS and $CD4^+$ cells, also known as white blood cells, helper cells or T cells that protect us from infection (Kapila A, *et al*., 2016).

HIV's interaction with the immune system is complex and includes mainly Cytotoxic T Lymphocytes (CTL, $CD8^+$ T cells) and $CD4^+$ helper lymphocytes ($CD4^+$ cells). Although other immune cells also include blocking organisms such as macrophages, harmful cells and NK cell state responsibility, but the host produces antibodies against many types of HIV. It is the action of CTLs and $CD4^+$ cells that initiates protection against HIV (Rang HP, *et al*., 2011).

HIV interferes with the body's ability to fight disease-causing bacteria. This can lead to certain cancers and diseases such as pneumonia and meningitis. Physical barriers such as latex condoms are recommended to reduce sexual transmission of HIV. Spermicides, when used alone or in combination with condoms such as a diaphragm, increase male-to-female transmission of genital infections (Kaushik M, 2017). Bacteria can be isolated from body fluids, blood, semen, genitals, saliva, breast milk, tears, urine, cerebrospinal fluid and peritoneal fluid. Mosquitoes are not responsible for the transmission of HIV (Jangame CM, *et al*., 2021).

AIDS is an infectious disease in which $CD4^+$ count is less than 200/μL (or $CD4^+$ cells are less than 14% of lymphocytes). HIV seems to have changed its structure over a period of time and at a various places. Currently, HIV-1 is commonly known as causative virus of AIDS. However a variant of HIV-1 (more prevalent in West-Africa) has been isolated. HIV-2 is less virulent than HIV-1 and disease (Immunodeficiency state) produced by HIV-2 is less severe compared to HIV-1. HIV genome has at least eight genes of which three (gag, pol, env) governs the viral structure while rest of five namely, *TST*, rev, *VIF*, nef, *VPU* (HIV-1) and *VPX* (HIV-2) are regulatory genes (Bodhankar SL and Vyawahare NS, 2012).

By the end of 2002, more than 900,000 cases had infected 60 million people worldwide, and nearly 20 million adults and children had died from the disease. There are currently about 42 million people living with HIV/AIDS, 70 percent of whom are in Africa and 15 percent in Asia; the majority of adults in sub-Saharan Africa are greater than 8 percent. AIDS is currently reported in more than 193 countries worldwide, and the number of people living with HIV in Africa and Asia is high and is growing rapidly (Cotran RS, 1994) (*Table 1*).

LITERATURE REVIEW

Etiology

The symptoms of HIV and AIDS vary according to the stage of the infection. One may not have any symptoms when infected with HIV for the first time, but one might develop flu-like illness 2 to 6 weeks after infection. The main signs and symptoms of the disease include-fever, headache, sore throat, swelling and redness, other illnesses if HIV persists. The virus multiplies in the lymph nodes and gradually begins to destroy the T group ($CD4^+$ lymphocytes) and then white blood cells that make up the immune system of the whole body. There may be no symptoms for eight or nine years or more (*Figure 1*).

But as the virus continues to spread and destroy the immune system, it can cause chronic symptoms such as swollen lymph nodes, diarrhea, weight loss, fever, cough and difficulty breathing. The final stage of HIV, which occurs 10 years or more after initial infection, will begin with some more severe symptoms before the disease meets the definition of AIDS. In 1993, the Centers for Disease Control and prevention (CDC) redefined AIDS as an HIV infection characterized by positive antibodies to one of the following-

- Contagious disease exposure test
- One $CD4^+$ lymphocyte count is 200 or less the normal range is 600 to 1000 (Kaushik M, 2017).

Table 1: Global and Indian statistics

Year	Worldwide		India	
	Cases	Deaths	Cases	Deaths
2018	37.9 million	7,70,000	23,93,672	21,571
	(32.7 million-44.0 million)	(5,70,000-1.1 million)	(19,85,744-28,97,558)	(17,141-27,586)
2019	38.0 million	6,90,000	23,92,008	21,252
	(31.6 million-44.5 million)	(5,00,000-9,70,000)	(19,84,364-28,95,545)	(16,888-27,178)
2020	37.7 million	6,80,000	23,97,884	21,084
	(30.2 million-45.1 million)	(4,80,000-1million)	(19,89,239-29,02,658)	(16,755-26,964)
2021	38.4million	6,50,000	24,01,284	20,612
	(33.9 million-43.8 million)	(5,10,000-8,60,000)	(19,92,058-29,06,772)	(16,379-26,359)

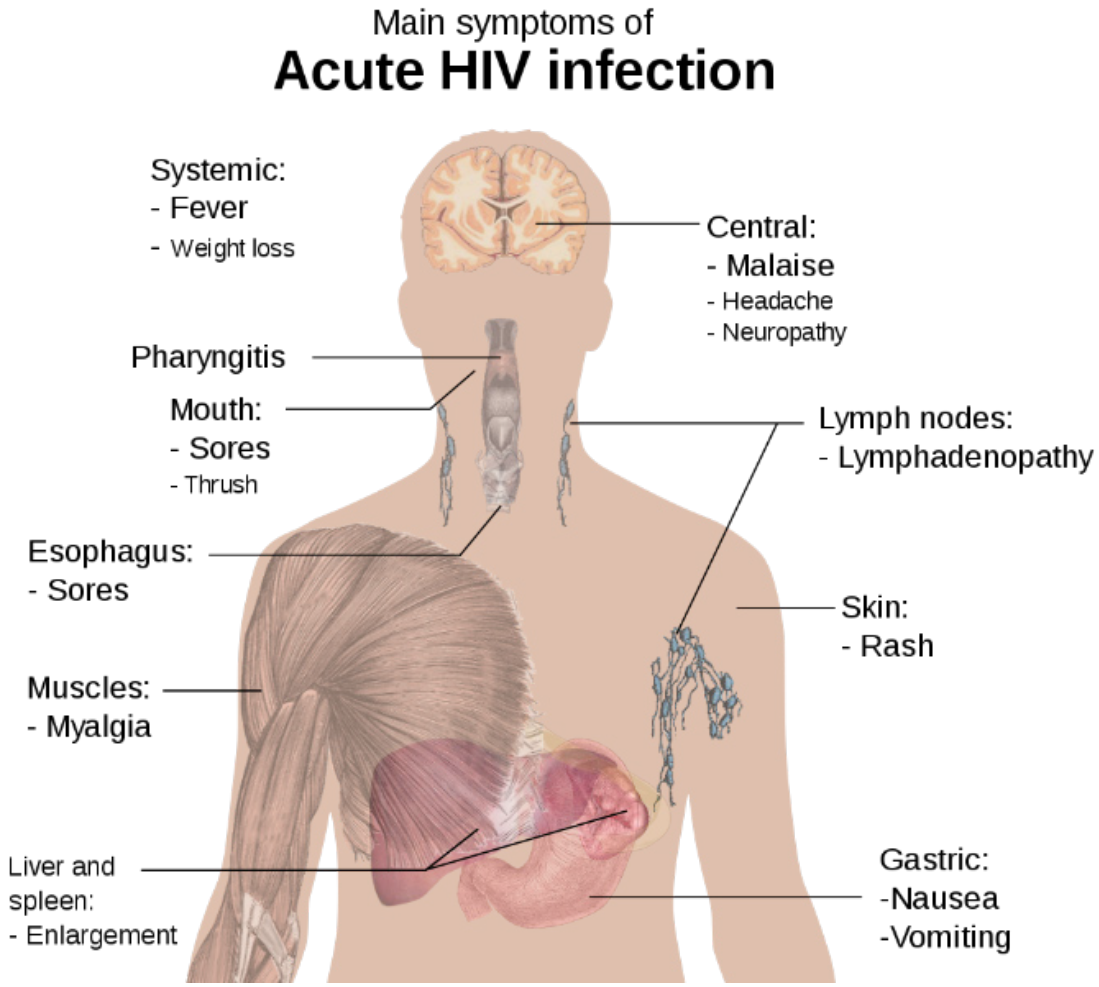

Figure 1: Main symptoms of acute HIV infection

Pathogenesis

When infected with HIV, the virus replicates in the peripheral blood. HIV, a retrovirus which has RNA genome inserted into the host cell's DNA. Where it reproduce continously leading to cell death. HIV attaches to the lymphocytes by binding with a receptor protein $CD4^+$ using the viral surface membrane envelope glycoprotein (GP120). Cells with the $CD4^+$ receptor are often called $CD4^+$ cells or T helper lymphocytes, and these cells are the main targets of the disease. These helper T lymphocytes are used to activate and regulate other cells of the immune system, such as beta lymphocytes (antibody-producing), macrophages, and cytotoxic (CD 8^+) T lymphocytes. The gradual reduction in $CD4^+$ cell population results in failure of immune function, especially cell mediated immunity. The impaired cell mediated immunity, which typically protects against intracellular parasites like viruses, protozoa and mycobacteria result in infection with capsulated bacteria.

Transmission

Humans are the only known reservoir of HIV and transmission of infection which essentially requires exchange of various body fluids like semen, vaginal secretions, milk or blood.

The well-established routes are-

Sexual contact: This is considered to be the best route, especially among young people (age of 15-24) who have about half or all of the new HIV infections worldwide. The presence of HIV in blood or semen helps the spread of the infection by intimate sexual contact including homosexual, bisexual and heterosexual contacts. The torn, damage to genital skin or mucous membrane, presence of other sexually transmitted diseases (e.g. syphilis), lack of circumcision in male and vigorous sexual activity facilitates the spread of infection.

Blood transmission: Transmission *via* whole blood and isolated blood product is the second most frequent route. The rapid spread of infection is seen in hemophiliacs, as they regularly require blood or blood products. Intravenous drug abusers may have HIV infection as a result of the practice of "needle sharing". These people are major reason, for heterosexual transmission too.

Mother to child: Mother-to-child HIV transmission (materno-foetal transmission) can take place during pregnancy (*in utero*), delivery or breast feeding. The organ donation by the infected person may lead to transmission of the disease (Bodhankar SL and Vyawahare NS, 2019).

In the absence of treatment, the transmission rate between mother and child is 25%. However, if there is treatment, this rate can be reduced to 1%. Breastfeeding is also a risk factor for the baby. HIV-2 is less likely to be transmitted through Mother-To-Child Transmission (MTCT) and sexually than HIV-1 (Bodhankar SL and Vyawahare NS, 2019).

Transplantation of infected tissue or organ: The risk of transplant-related HIV infection is low. All organ and tissue donors are screened for risk factors and tested for HIV and other infectious diseases that can be transmitted through transplantation.

Use of contaminated clotting factors by hemophiliacs: Hemophilia patients receiving untested and unscreened clotting factors are at extreme risk for HIV *via* the blood products (Jangame CM, *et al*., 2021).

Clinical manifestations

The unique feature of AIDS is that the clinical manifestations are not directly caused by the causative agent but are the result of suppressed immune system. Most of the symptoms are due to secondary opportunistic infections. The appearance and severity of clinical features is variable from person to person based upon stage of the infection. Initially, infected person may be in latent period for few months, followed by development of certain manifestations like fever, tender lymphadenopathy, etc. The person in latent period can become contagious and transmit the infection. These symptoms may disappear after few days and person is symptom-free for specific duration. Some patients develop certain persistent manifestations like long lasting fever, weight loss, continuous diarrhea, oral candidiasis, multi-deramtomal herpes zoster, viral hairy leukoplakia of tongue, anemia, swollen lymph nodes and unwell feeling, later which is termed as AIDS related complex (Bodhankar SL and Vyawahare NS, 2012).

HIV infection and Acquired Immunodeficiency Syndrome (HIV/AIDS) are a group of conditions caused by retrovirus (Krämer A, 2010; Kripke C, 2007). HIV/AIDS is considered a contagious disease (Kallings LO, 2008) and studies show that HIV can be transmitted through unprotected sex. (Rodger AJ, *et al*., 2019). HIV is usually transmitted from mother to child through unprotected sexual intercourse (including anal and genital sex), contaminated blood, hypodermic needles, and from mother to child during pregnancy, childbirth or breastfeeding (Rom WN and Markowitz SB, 2007). Some bodily fluids, such as saliva, sweat, and tears, are not contagious. Oral sex carries a small risk of transmission (Kirti YK, *et al*., 2015).

Without specific treatment, about half of all people will get AIDS within ten years. The most common complications are pneumocystis pneumonia (40%), cachexia as HIV wasting syndrome (20%), and esophageal candidiasis. Other symptoms include recurrent respiratory distress (Jangame CM, *et al*., 2021).

Symptoms

Symptoms vary according to the stage of the disease.

Primary/Acute HIV: People infected with HIV develop flu-like symptoms 2 to 4 weeks after the virus enters the body. This infection is called as initial HIV infection (infection) and it can last for several weeks.

Clinical latent/Chronic HIV: HIV remains in the body and in the white blood cells during this infection period. This phase can last for years with Antiretroviral Therapy (ART).

As the virus continues to spread and destroy the immune system, cells that help fight infection, one may have a mild infection or might experience symptoms for a long time, which is generally termed as symptomatic HIV (*Figure 2*).

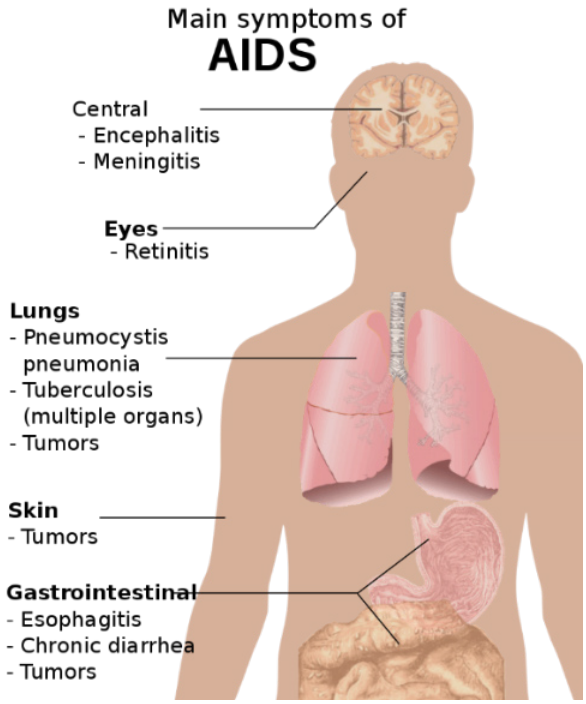

Figure 2: Main symptoms of AIDS

AIDS progression

Better access to ART reduces deaths. When AIDS occurs, the immune system is severely compromised, making the infected person more susceptible to infections that normally do not affect people with healthy immune systems (Chu C and Selwyn PA, 2010).

Structure of virus

It is around 100 nm to 120 nm in diameter and roughly spherical. Retrovirus is a 20 enveloped virus of the lentiviral subfamily. HIV is different from other retroviruses. There are two viral RNA strands in the nucleus surrounded by a protein sheath. The outer envelope contains a lipid matrix into which specific glycoproteins are embedded which are responsible for attachment to the cells. The outer shell of this virus contains a protein known as the envelope (env), which consists of an outer layer containing glycoprotein (gp) 120 and root gp41. The virus envelope contains HIV virus called p17 (substrate), the viral core, or the capsid, which contains another viral protein, p24 (core antigen) (*Figures 3 and 4*). The three main structural genes are-

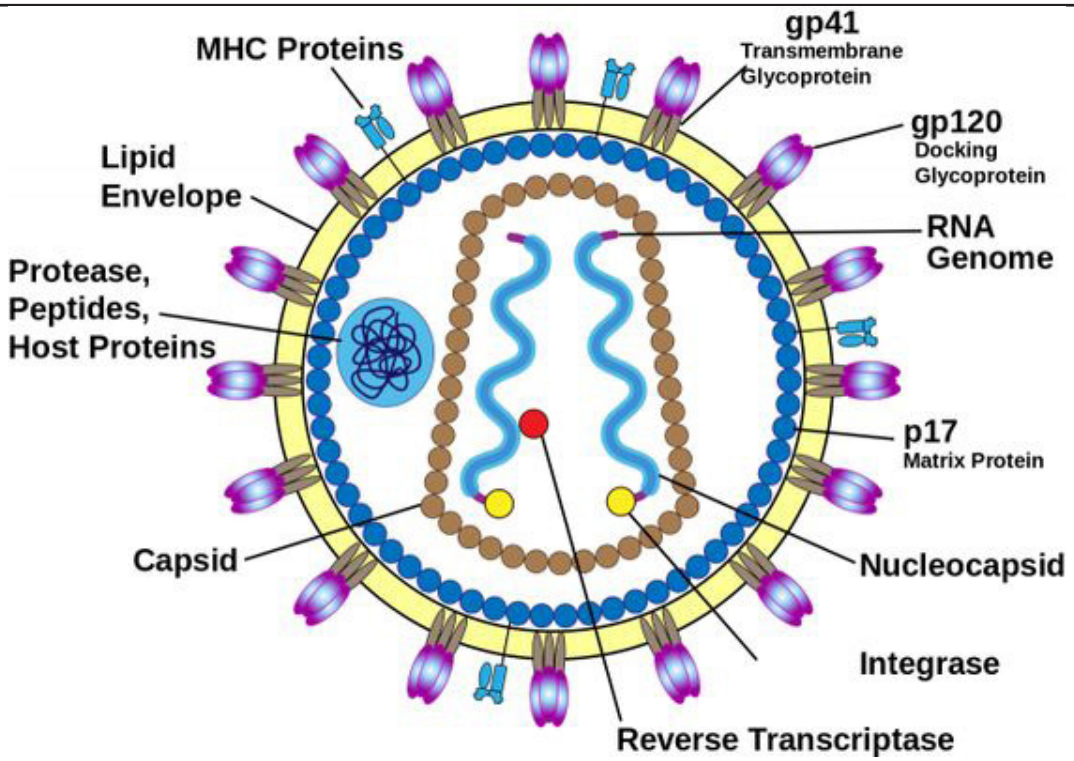

Figure 3: Structure of HIV

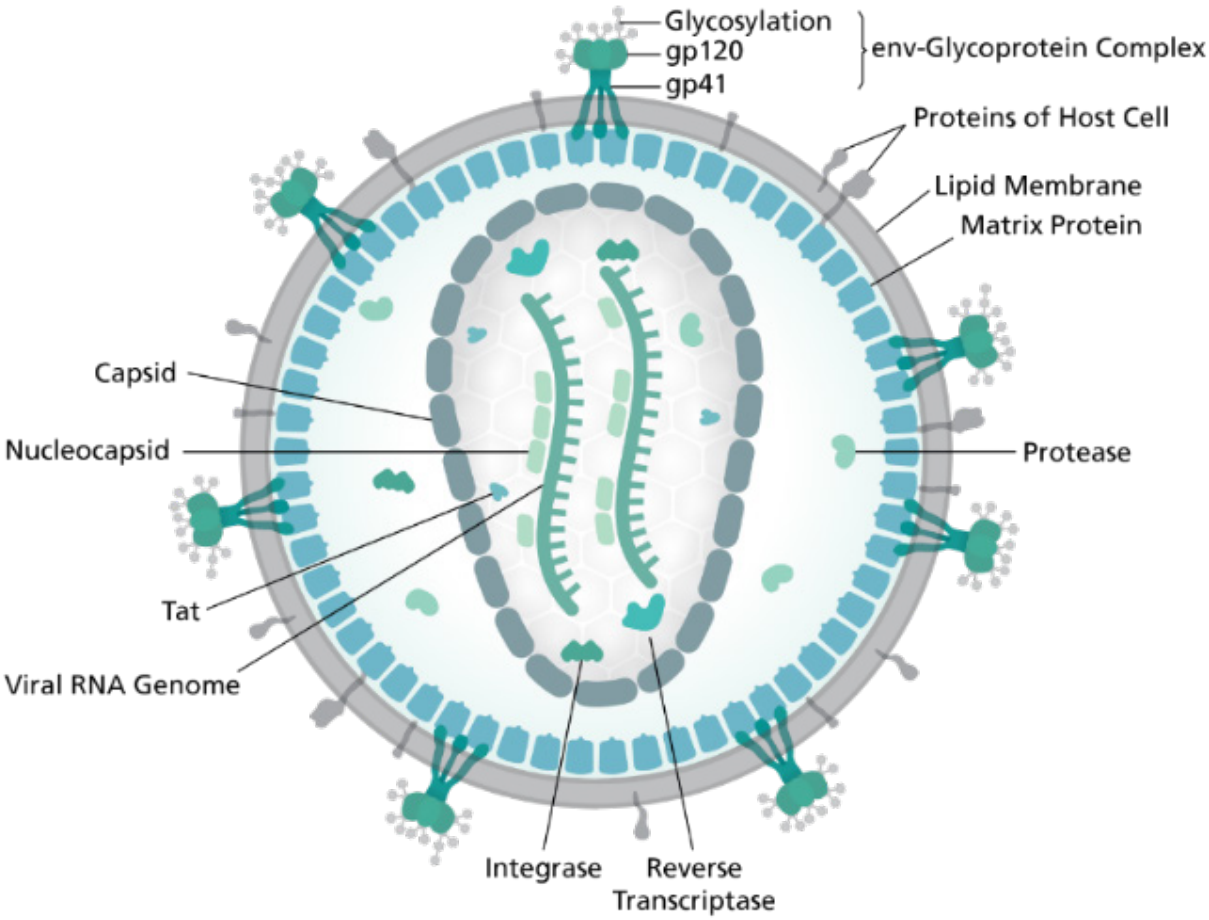

Figure 4: HIV virion structure

Group-specific antigen (Gag): The Gag protein encoded by the *GAG* gene provides the structure of the virus.

Envelope (Env): This gene encodes the envelope proteins gp160 and gp41. These polyproteins are cleaved by proteases into the envelope glycoproteins gp120 and gp41. Gp41 is a transmembrane glycoprotein antigen that binds to gp120, which is involved in both fusion and binding of HIV to the host's $CD4^+$ antigen.

Polymerase (Pol): Pol encodes the p66 and p51 subunits of reverse transcriptase and p31 encodes an endonuclease. They are responsible for converting RNA to DNA, integrating DNA into the cell's DNA, and removing protein precursors. In the first step, HIV binds to an infected cell where the binding site is $CD4^+$ antigen.

Diagnosis

There are several types of tests to test blood for HIV. This new test detects the presence of HIV antigen (a protein) up to 20 days before the test. The effectiveness of the diagnosis is described as follows-

Sensitivity test: It is the percentage of positive results in the presence of HIV infection.

Specificity test: It is the percentage of negative results in the absence of HIV and all diagnoses have limitations.

False positive test: Positive test indicates the presence of HIV in an uninfected person.

False negative test: This test indicates that the patient does not have HIV. Tests should be sensitive and specific.

Antibody tests

Enzyme-Linked Immunosorbent Assay (ELISA): The Enzyme-Linked Immunosorbent Assay (ELISA) was the first screening test which uses blood, oral fluid or urine to detect HIV antibodies. If result from either of these tests is positive, one will need to take another test called a Western blot test, which can take upto two weeks to confirm a positive result.

Western blot test: The western blot is an antibody detection test. The viral proteins are separated first, immobilized and the binding of serum antibodies to specific HIV proteins are visualized.

Antigen tests: These tests can be used to diagnose HIV infection earlier from 1-3 weeks after first infected with HIV.

Polymerase Chain Reaction (PCR): This test detects the genetic material of HIV in the blood within 2-3 weeks of infection. Babies born to HIV-positive mothers are tested with a special PCR test to determine whether the babies have HIV themselves (Jangame CM, *et al*., 2021).

Therapeutic approaches to HIV infection

Exposure to HIV infection does not always lead to HIV infection and some people remain healthy throughout their life even after HIV infection. The chance of development of AIDS is lesser in initial years after infection and gradually increases. Hence appropriate drug therapy as early as possible can delay the onset of AIDS and simultaneously can impart quality life to the patient. The current management strategy can be summarized under the following heads-

- Evaluation and staging
- Patient's counseling
- Pharmacotherapy
- Prophylaxis
- Prevention of transmission (Bodhankar SL and Vyawahare NS, 2019)

Treatment of HIV/AIDS usually involves the use of multiple antiretroviral drugs to prevent HIV infection (Arachchige ASPMA, 2022). The use of multiple drugs targeting different types of viruses, known as Highly Active Antiretroviral Therapy (HAART), which can reduce the overall HIV burden in patients, control the immune system, and prevent infections that often lead to death (Moore RD and Chaisson RE, 1999). HAART also prevents HIV infection between sero-incompatible homosexual and heterosexual couples as long as the HIV-positive partner keeps the virus under control (Eisinger RW, *et al*., 2019).

Combination therapy: The life cycle of HIV is about 1.5 days from the moment the virus enters a cell by multiplying, releasing more virus and spreading to other cells (Perelson AS, *et al*., 1996). When HIV converts its RNA into DNA by reverse transcription, it does not have an enzyme. Its short lifespan and high error rate causes the virus to mutate very quickly, resulting in a high genetic mutation rate. Most mutations are benign or negative for the parent's disease. The higher the copy number of the virus, the more likely it is to respond to the drug (Smyth RP, *et al*., 2012).

The combination usually includes three drugs from two different classes (US department of health and human services federal panel on community water fluoridation, 2015). This combination of the three drugs is often called a triple cocktail (Merrill RM, *et al*., 1999). Because HIV is mutated, patients who start regular antiretroviral therapy can take precautions. Patients using medication can follow their controls (Bangsberg DR, *et al*., 2007).

In recent years, pharmaceutical companies have combined this process into one tablet at a time. This makes taking the drug easy and consistent (adaptive) (Schmit JC, *et al*., 1996), thereby producing the long-term effects of the drug.

Highly Active Antiretroviral Therapy (HAART): Currently, more than twenty-five drugs, including combination drugs, are used for the treatment of HIV-1 in clinical practice. This particular HIV treatment gives people the chance to live a better life by improving quality and prolonging life. Ensuring and maintaining immunity against the disease and recovery are the main goals of treatment. In addition, reduction in pill burden, dosing frequency and adverse effects of the drug in advanced therapy leads to simplification of therapy. However drug-drug interaction, viral resistance, immunologic failures are some important limitations. The decision of early or delayed therapy to get maximum output clinically with minimum side effect is usually based upon potential benefits and risks associated with the therapy. Discussing the pros and cons with the patient and/or family members can make it easier (Bodhankar SL and Vyawahare NS, 2012).

Prevention

Abstain: Not having genital, anal or oral sex is the surest way to prevent HIV transmission. Ignoring or delaying sexual intercourse can reduce the risk of transmission, especially among young people who have not yet started having sex.

Drug use and needle sharing: Injecting drug use is an important factor in the spread of HIV. So, needle replacement programs are used to reduce the number of drug-related illnesses.

Exposure to body fluids: HIV infection can be controlled by taking precautions to prevent blood contamination. Medical personnel should use restraints. Regular and thorough skin cleansing can reduce the risk of infection.

Pregnancy: Anti-HIV drugs can harm the unborn child, but good treatment can prevent mother-to-child transmission of HIV. Bottle feeding if the mother is infected can be beneficial (Jangame CM, *et al*., 2021).

Classification of antiretroviral drugs

A combination regimen includes two Nucleoside Reverse Transcriptase Inhibitors (NRTI) and a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), Protease Inhibitor (PI) or integrase inhibitor (also Enzyme Nuclear Chain Transfer Inhibitor or INSTI) as the "core" (Panel on clinical

practices for treatment of HIV infection, 2000).

Entry inhibitors/Fusion inhibitors: Entry inhibitors interfere with HIV-1 binding, fusion, and entry into the brain by blocking one of several targets. Maraviroc works by targeting the co-receptor CCR5. In rare cases, individuals may develop mutations in the *CCR5* delta gene for drug resistance or disease delay and may be overcome if the *CXCR4* type HIV variant becomes dominant (Bai Y, *et al*., 2013). eg., Maraviroc, Enfuvirtide, etc.

Nucleoside Reverse Transcriptase Inhibitors (NRTI): NRTIs are nucleoside and nucleotide analogues that inhibit reverse transcriptase and act as competitive substrate inhibitors. NRTIs are incorporated into DNA strands. This prevents other nucleosides from binding due to the absence of a 3' OH group. eg., Azvudine.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI): NNRTIs inhibit reverse transcriptase by binding to the allosteric site of the enzyme, acting as non-competitive inhibitors of reverse transcriptase thereby affecting substrate reverse transcriptase (nucleoside reverse transcriptase) connects near active site (Das K and Arnold E, 2013). HIV-2 is inherently resistant to NNRTIs (Sabin C, 2006) eg., Nevirapine, Efavirenz, Loviride, Delavirdine, etc.

Integrase inhibitors: Integrase inhibitors (also called integrase nuclear helix transfer inhibitors or INSTIs) inhibit the bacterial enzyme integrase, which is responsible for the integration of bacterial DNA into bacterial DNA (Métifiot M, *et al*., 2013). eg., Raltegravir.

Protease inhibitors: Protease inhibitor blocks viral proteases required for the production of mature virions after budding from the host membrane. These drugs prevent the degradation of *GAG* and gag/pol precursor proteins. Resistance to some protease inhibitors is high and thus investigators developed second drug as effective as other anti-HIV drugs (Wensing AM, *et al*., 2010). eg., Amprenavir, Lopinavir, Indinavir, Saquinavir, Ritonavir, etc.

DISCUSSION AND CONCLUSION

AIDS has a profound long-term impact on society, social institutions, and cultural structures. Treatment mainly concerns with the use of antiretroviral therapy, safer sex practices, infusion of screened blood and avoidance of contact with infected articles.

As the number of people living with HIV on ART continues to increase, so does the pressure to tailor lifelong prevention strategies for them. Most HIV prevention (and condom use) guidelines developed by international organizations that provide guidance to national governments, nonprofits, and the private sector. This study reported about HIV infection and analyzed detailed information on biology, pathology, signs and symptoms, complications, diagnosis, disease treatment, type of infection, and antibiotics of HIV.

REFERENCES

1. Kapila A, Chaudhary S, Sharma RB, Vashist H, Sisodia SS, Gupta A. A review on: HIV AIDS. Indian J Pharm Biol Res. 2016; 4(3): 69-73.
2. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's pharmacology. Elsevier Health Sciences. 2011.
3. Kaushik M. A text book of pathophysiology. Jalandhar (Punjab). PV Publication. 2017.
4. Jangame CM, Wadulkar RD, Ladde SS, Poul BN. A text book of pathophysiology. Nirali Prakashan. 2021.
5. Bodhankar SL, Vyawahare NS. A text book of pathophysiology. Nirali Prakashan. 2012.
6. Cotran RS. Robbins pathologic basis of disease, WB Saunders. Philadelphia. 1994.
7. Bodhankar SL, Vyawahare NS. A text book of pathophysiology. Nirali Prakashan. 2019.
8. Jangame CM, Wadulkar RD, Ladde SS, Poul BN. A text book of pathophysiology. Nirali Prakashan. 2021.
9. Krämer A, Kretzschmar M, Krickeberg K. Modern infectious disease epidemiology: Concepts, methods, mathematical models, and public health. Springer Science and Business Media. 2010.
10. Kripke C. Antiretroviral prophylaxis for occupational exposure to HIV. Am Fam Physician. 2007; 76(3): 375.
11. Kallings LO. The first postmodern pandemic: 25 years of HIV/AIDS. J Intern Med. 2008; 263(3): 218-243.
12. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Degen O, *et al*. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): Final results of a multicentre, prospective, observational study. Lancet. 2019; 393(10189): 2428-2438.
13. Rom WN, Markowitz SB. Environmental and occupational medicine. Lippincott Williams and Wilkins. 2007.
14. Kirti YK, Yashveer JK, Poorey VK. Changing trends of HIV/AIDS in otorhinolaryngology with CD 4^{+} count correlation. Indian J Otolaryngol Head Neck Surg. 2015; 67: 12-15.
15. Chu C, Selwyn PA. Diagnosis and initial management of acute HIV infection. Am Fam Physician. 2010; 81(10): 1239-1244.
16. Bodhankar SL, Vyawahare NS. A text book of pathophysiology. Nirali Prakashan. 2019.
17. Arachchige ASPMA. NK cell-based therapies for HIV infection: Investigating current advances and future possibilities. J Leukoc Biol. 2022; 111(4): 921-931.
18. Moore RD, Chaisson RE. Natural history of HIV infection in the_era of combination antiretroviral therapy. AIDS. 1999; 13(14): 1933-1942.
19. Eisinger RW, Dieffenbach CW, Fauci AS. HIV viral load and transmissibility of HIV infection: Undetectable equals untransmittable. JAMA. 2019; 321(5): 451-452.
20. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics *in vivo*: Virion clearance rate, infected cell life-span, and viral generation time. Science. 1996; 271(5255): 1582-1586.
21. Smyth RP, Davenport MP, Mak J. The origin of genetic diversity in HIV-1. Virus Res. 2012; 169(2): 415-429.
22. US department of health and human services federal panel on community water fluoridation. US Public Health Service recommendation for fluoride concentration in drinking water for the prevention of dental caries. Public Health Rep. 2015; 130(4): 318-331.
23. Merrill RM, Feuer EJ, Warren JL, Schussler N, Stephenson RA. Role of transurethral resection of the prostate in population-based prostate cancer incidence rates. Am J Epidemiol. 1999; 150(8): 848-860.
24. Bangsberg DR, Kroetz DL, Deeks SG. Adherence-resistance relationships to combination HIV antiretroviral therapy. Curr HIV/AIDS Rep. 2007; 2: 65.
25. Schmit JC, Cogniaux J, Hermans P, van Vaeck C, Sprecher S, van Remoortel B, *et al*. Multiple drug resistance to nucleoside analogues and nonnucleoside reverse transcriptase inhibitors in an efficiently replicating human immunodeficiency virus type 1 patient strain. J Infect Dis. 1996; 174(5): 962-968.
26. Panel on clinical practices for treatment of HIV infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents, January 28, 2000. HIV Clin Trials. 2000; 1(1): 60-110.

27. Bai Y, Xue H, Wang K, Cai L, Qiu J, Bi S, *et al*. Covalent fusion inhibitors targeting HIV-1 gp41 deep pocket. Amino Acids. 2013; 44: 701-713.
28. Das K, Arnold E. HIV-1 reverse transcriptase and antiviral drug resistance. Part 1. Curr Opin Virol. 2013; 3(2): 111-118.
29. Sabin C. Database analyses of predictors of resistance. Antiretroviral Resistance in Clinical Practice. 2006.
30. Métifiot M, Marchand C, Pommier Y. HIV integrase inhibitors: 20-year landmark and challenges. Adv Pharmacol. 2013; 67: 75-105.
31. Wensing AM, van Maarseveen NM, Nijhuis M. Fifteen years of HIV protease inhibitors: Raising the barrier to resistance. Antiviral Res. 2010; 85(1): 59-74.