***CHAPTER***

***BIOLOGY AND PATHOGENESIS OF HIV INFECTION***

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**ASTRACT:**

**One of the most totally global diseases has always been HIV/AIDS. The lent virus known as the human immunodeficiency virus (HIV) is what causes AIDS and HIV infection. In people with AIDS, the immune system gradually fails, which promotes the growth of malignancies and infections that can be fatal. HIV can be transmitted through the exchange of blood, semen, vaginal fluid, and breast milk. HIV can be found in these physiological fluids as both free virus particles and as a virus inside infected immune cells. Important immune system components including helper CD4 T cells and macrophages are infected by HIV. HIV infection causes decreased T cell counts through a variety of processes, including infected T cells' pyroptosis.** **The majority of AIDS symptoms are caused by illnesses that don't typically arise in people with strong immune systems. The majority of these illnesses are opportunistic infections brought on by bacteria, viruses, fungi, parasites, and other microorganisms that are often controlled by immune system components that HIV weakens. When a couple with one infected member continuously uses condoms, the annual rate of HIV infection is less than 1%. Female condoms may offer a comparable amount of protection, according to some data.**

**Keywords:** HIV,CD4 T Cells,AIDS,Macrophage.

**INTRODUCTION:**

Before the early 1980s, no one knew that the human immunodeficiency virus (HIV) was responsible for an increasing number of cases of uncommon opportunistic infections and Kaposi sarcoma in people with lymphadenopathy and compromised cell-mediated immunity. [1,2] Since then, a global epidemic of HIV infection has affected millions of people. HIV infection causes the immune system to continually deteriorate, which triggers the establishment of the acquired immunodeficiency syndrome (AIDS).

Over half of the victims of the AIDS pandemic have already died. Because of the unavoidable symptoms of AIDS and long-term HIV treatment, all HIV-infected people are at risk for disease and mortality from opportunistic infections, neoplastic complications, and comorbidities. [3,4] Multiple factors have influenced HIV transmission since human HIV infection became widespread. A method of dissemination not seen in earlier human pandemics was made possible by the development of swift air travel in the 20th century. People at risk are now more prevalent nearby as a result of urbanisation. Promiscuity in human sexual practises has become more widespread among communities all over the world. In the 20th century, injectable delivery of illicit narcotics became a more common and feasible method of administration. [3]

The AIDS pandemic has gone through four major phases of evolution over time. Initially, HIV spread rapidly among urban populations after emerging from endemic rural areas. Dissemination took place during the second phase, which involved identifiable risk categories. Sexual promiscuity and injection drug use were two behaviours in these risk categories that contributed to the third phase of escalation, which lasted until the 1980s. In some areas, including western Europe, North America, and Australia, where control efforts seem to be working, there has been a fourth phase of stabilisation. The pandemic did, however, continue to spread in some areas, such as central Africa and Asia, well into the 1990s and into the twenty-first century. [5,6] Although the number of Americans living with HIV climbed significantly in the 1980s, reached a high in the 1990s, and has since decreased, the number of HIV-infected people who go on to acquire AIDS and need treatment increased throughout the 1990s and into the new millennium. In the United States, there were 1.19 million people living with HIV as of the end of 2019, including 0.159 million people whose infection had not yet been identified. [7,8]

The number of new HIV infections presumably peaked in 1997 on a global scale. Over 34 million people worldwide had HIV infection at the end of the 20th century, over 21 million people had died from AIDS, and over 95% of HIV-positive people lived in developing countries. With 2% of the world's population, nine southern African nations were home to a third of all HIV-positive people. [9] Beginning in the year 2000, the frequency of HIV infection worldwide stabilised at 0.8%. Young people between the ages of 15 and 24 were the age group most affected, accounting for 45% of new HIV infections.

Over half of AIDS victims worldwide are women, and as a result, prenatal infection causes infants to be born infected with HIV. The scope of the AIDS pandemic has already had serious ramifications for the national economies of those countries due to the loss of young to middle-aged people, who are economically most productive, as well as for the health care systems of those countries, which are unable to handle many AIDS victims. [10] The impact of HIV infection was lessened by three developments. The creation and implementation of efficient multi-drug antiretroviral therapy (ART) at the turn of the 20th century was the first. The second was the realisation that HIV transmission might be stopped by using ART to lower viremia. The third involved starting ART as soon as HIV infection began, regardless of CD4 cell numbers, to lessen subsequent immunologic damage and increase infected people's longevity. The test-and-treat approach is this. Thus, a crucial component of this strategy is widespread testing to identify HIV-positive individuals. The stigma associated with HIV infection and potential sanctions against infected people continue to act as obstacles to widespread testing, nevertheless. [11] From 3.3 million in 2002 to 2.3 million in 2012, there were fewer new HIV infections in the world. An estimated 300,000 people died from AIDS in 1990. In 2005, there were 2.3 million AIDS-related deaths worldwide; by 2012, that number had dropped to 1.6 million. By 2012, an estimated 9.7 million individuals in low- and middle-income nations had begun antiretroviral medication. Of the 52.8 million deaths that occurred globally in 2010, the projected 1.5 million deaths from AIDS accounted for 2.8%. In 2010, AIDS ranked as the sixth most common reason for years of useful life lost (YLL) globally. [4,12]

Significant effort has been made to educate people who could be at risk of contracting HIV. [19] Prior to making decisions about the distribution of healthcare resources and control measures, it is important to have a thorough grasp of AIDS challenges, particularly the nature of HIV and its methods of transmission. [20] Despite widespread belief that AIDS is a minor threat that doesn't necessitate lifestyle adjustments, particularly among young people, prevention methods for HIV will necessitate constant education. [21] Political coalitions are necessary for the implementation of preventative measures across international borders in the fight against AIDS. For every venue, a different approach should be used. Every person on earth is impacted by the AIDS epidemic in some way due to the size of the reservoir of infected people, the scope of global human connection, and the tremendous expenses of the disease. [22] A few examples of prevention techniques are as follows: [23]

* Make HIV testing a routine part of medical care.

 • Implement new models for diagnosing HIV infections outside medical settings.

 • Prevent new infections by working with persons diagnosed with HIV and their partners.

 • Provide antiretroviral drugs to infected persons who need them.

 • Further decrease perinatal HIV transmission.



 Fig: HIV Infection Fig:HIV Skin Lesions

**PATHOGENESIS OF HIV INFECTION:**

RELEASE.— HIV is released from the host cell throughout the course of numerous processes. The nucleocapsid (NC) protein interacts with the RNA inside the capsid, the matrix (MA) protein surrounds the capsid and is located just below the viral envelope, and all of these proteins are formed under the control of the HIV p55 protein. The MA, CA, and NC proteins are created by the cleavage of the big precursor proteins by a protease enzyme that is encoded by the HIV pol gene. The host cell membrane is used by budding virions to help produce the outer virion envelope required for the generation of infectious particles. Cellular endosomal sorting complexes required for transport (ESCRT), which sort proteins and create multivesicular bodies (MVBs), are necessary for the process of viral budding from the surface of the infected host cell. MVBs are intermediates in the production of secretory lysosomes. [24,25,26]

Dendritic cells are important in the transmission of HIV. DCs can be divided into myeloid (mDC) and plasmacytoid (pDC) DCs. While pDCs are CD11c+HLA-DR+ cells distinguished by surface expression of the C-type lectin BDCA2, high levels of the alpha chain of the receptor for interleukin-3 (CD123), and the immunoglobulin superfamily receptor immunoglobulin-like transcript 7, mDCs exhibit high surface levels of CD11c and HLA-DR (ILT7). Because of the specific distribution of pattern recognition receptors (PRRs), including as toll-like receptors, C-type lectins, and intracellular nucleic acid sensors, they are experts in recognising various pathogen-associated molecular patterns (PAMPs). Both mDCs and pDCs can activate CD4+ and CD8+ T cells to fight various pathogen types. Natural killer (NK) cells, which are crucial in viral infections in particular, can interact with both mDCs and pDCs. As a result, it appears that various DC subtypes contribute differently to immune responses against microbial infections and are affected by context- and pathogen-dependent variables. [27]

A "founder" virus or a small number of viral genetic variants are most likely where most HIV infections start, from which subsequent clones grow. Due to the virus's limited environmental persistence and need to swiftly find a host cell, the initial infectious phase is ineffective, and the majority of virions die. The antiviral apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like-3G (APOBEC3G) that host cells produce inhibits virus multiplication by acting as a cytidine deaminase. The HIV gene that codes for reverse transcriptase also has a high mutation rate and a high rate of transcription errors. As a result, the majority of early HIV contacts with host cells do not lead to persistent infections. [28]

**HUMAN IMMUNODEFICIENCY VIRUS SUBTYPES:**

According to phylogenetic study, there are four main subgroups of HIV-1, which most likely developed as a result of several historical transmission events involving humans, chimpanzees, and gorillas. The terms M (major), N (nonmajor and non-outlier), O (outlier), and P are used to describe these groups. The simian immunodeficiency viruses SIVcpz (M and N) and SIVgor share many similarities with these groups (O and P). [29] The simian immunodeficiency virus (SIV), which is prevalent in the chimpanzee Pan troglodytes troglodytes, appears to be a source of Groups M and N. The SIV seen in lowland gorillas is more closely connected to groups O and P. (Gorilla gorilla). Most HIV-1 infections have been found in people in group M. Less than 2% of all HIV infections are caused by Groups N, O, and P, which have the highest prevalence in West and Central Africa, with Cameroon as the epicentre. Group N and P infections are still uncommon, and there have only been roughly 100,000 group O infections. [30,31] Genetic diversity in HIV-1 subtypes can range from 8 to 17% on average to 30% on occasion; amongst subtypes, it ranges from 17 to 35% on occasion to 42%. Although people travel between populations, different subtypes of HIV-1 that have emerged and will continue to emerge during the AIDS pandemic have been discovered with specific geographic distributions. over time increases variability HIV subtype variation may additionally complicate testing methods because not all subtypes of HIV may exhibit the same diagnostic sensitivity and specificity of laboratory tests. [32] HIV-1 is becoming more diverse as a result of subtype recombination. Circulating recombinant forms (CRFs), or recombinants between subtypes, have nearly 100 documented examples. The term "unique recombinant form" (URF) is applied to HIV1 strains that do not fit these requirements. CRFs A-G (CRF02 AG), which are most prevalent in West Africa, and A-E (CRF01 AE), which are mostly observed in East Asia and Southeast Asia, are the most prevalent CRFs. Both the percentage of CRFs and the number of recombinants have increased globally. Africa has the widest variety of subtypes and recombinants. [33] Some subtypes and CRFs have had their migration routes tracked. While subtypes A and D later spread epidemics in eastern Africa, they seem to have started in central Africa. The majority of subtype C cases are found in southern Africa, from where they have spread to India and other Asian nations. The majority of HIV-1 infections in Europe and the Americas are caused by subtype B, which appears to have originated from a single African strain that initially moved to Haiti in the 1960s before moving on to the US and other western nations. [34]

**OTHER HUMAN RETROVIRUSES HIV-2:-**

The multiple HIV-1 strains that have been discovered in different parts of the world are all immunologically similar and just slightly different in their DNA sequences. Senegal provided the first report of a potential HIV-1 variation in 1985. [35] This second retrovirus, known as HIV-2, was first discovered in Portuguese patients in 1986, although it is now most prevalent in West African nations, with a smaller prevalence in Western European countries and other regions where migration from West Africa has taken place. [36,37] It's thought that HIV-2 first appeared in Africa in the 1940s. HIV-2, which resembles the simian immunodeficiency virus (SIV) more closely than HIV-1, is thought to have spread to humans through zoonotic infections from the primate reservoir of sooty mangabeys (Cercocebus atys atys), which is where SIVsmm originated. [38] According to serologic research, HIV-2 has been present in West Africa since 1966. HIV-2 subtypes A to I are probably the result of zoonotic transmission, however only subtypes A and B experienced an epidemic. West African countries are the main sites of HIV-2 infection, with Guinea-Bissau, Guinea, The Gambia, Senegal, Sierra Leone, Cape Verde, Angola, Mozambique, and Cote d'Ivoire having the highest subgroup A prevalence rates. Ghana, Burkina Faso, Mali, and Cote d'Ivoire may be the countries where subtype B is most common. Portugal and France are the only non-African nations with up to 5% of all HIV infections as HIV-2, and the incidence elsewhere is partially a result of connections to former colonies. There are up to 2 million infected individuals, some of whom also have HIV-1. Similar to how HIV-1 spreads, so does HIV-2. Although HIV-2 infections peak at a younger age than HIV-1 infections do, there doesn't seem to be a gender difference in infection rates. [38, 39] Greater CD4 lymphocyte counts, lower plasma viral RNA levels, a slower development to AIDS, and decreased mortality are all characteristics of HIV-2 infection patients compared to those with HIV-1 infection. While heterosexual transmission and maternal-to-child transmission are less effective, the risk factors for transmission are the same as for HIV-1. Plasma viral RNA may not even be detectable in people not taking antiretroviral medication. Despite having a higher mutation rate than HIV-1, HIV-2 does not benefit from this in terms of selection. Instead, the immune response with broadly neutralising antibodies, which are uncommon in HIV-1 infection, are present with HIV-2 infection and their presence is equivalent to a vaccine response to stop viral replication. [39]

**EPIDEMIOLOGY OF HIV/AIDS:**

In-depth epidemiologic and clinical research has been done to better understand how HIV spreads from one person to another. Human travel aids in the spread of AIDS, as it has in previous outbreaks. Aside from influenza, other endemic diseases that spread from localised foci include syphilis in the 16th century, bubonic plague in the 17th century, and influenza in the early 20th century. The easy access to modern jet aircraft for transportation that many people enjoy creates a pathway for the spread of AIDS from one area or population to another. [40] But unlike most infections in previous epidemics, AIDS is characterised by a very long latent period before any outward symptoms of infection appear in those who are infected. The typical HIV-infected person may experience an acute, self-limited sickness in the beginning, require several weeks to become seropositive, and then survive up to 8 or 10 years without therapy on average before showing clinical signs and symptoms of AIDS. Infected individuals were quickly and easily identified in almost all previous infectious disease epidemics, allowing for the quick implementation of preventative measures. However, HIV-positive individuals cannot be identified just by appearance, are not motivated to seek medical care, and frequently are not aware that they may be infecting others. [41,42,43] Where the virus manifests in the body and how it is excreted are important factors in how HIV spreads. HIV can be found in a wide range of bodily fluids and secretions, although its propagation is significantly aided by its presence in blood, vaginal secretions, and, to a lesser extent, breast milk. However, the presence of HIV in saliva, urine, tears, and sweat has little clinical or societal significance because HIV is not frequently transmitted by these fluids, primarily due to the low concentration of HIV in these fluids. [44] Because saliva exposure carries a lower risk than blood exposure due to saliva's HIV inhibitory properties, oral-genital sexual practises carry a significantly lower risk of HIV transmission than genital-genital or genital-anal practises. HIV transmission could be made more likely by oral ulcers, bleeding, and inflammation. [45] Cerebrospinal fluid contains many infectious HIV particles, but daily contact with this fluid is extremely uncommon. [46] Male to male, male to female, and female to male transmission of HIV are all possible. Even though women with same-sex contact are frequently bisexual and have additional risk factors for HIV infection, female to female transmission of the virus is still quite uncommon. [47,48] The scope and rate of HIV transmission may be slowed down, even to a small level, by altering sexual behaviour habits. In the 1990s, the prevalence of HIV infection among men who had sex with men in the United States remained high (7.2%), and 41% of men reported having unprotected anal sex within the previous six months. [49]

**PATTERNS FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION :**

There are three ways that the HIV infection spreads globally. Early in the pandemic, pattern 1 largely afflicted metropolitan regions in the Americas and Western Europe, where the bulk of HIV infections occurred in men who had sex with other men (gay and bisexual men), followed by infections in people who used injectable drugs. Initial observations among heterosexuals showed fewer cases. In regions where HIV had been around longer and there were more people living with the virus, Pattern 2 manifested itself. Equal numbers of men and women contracted HIV, and heterosexual relationships were the main method of transmission. These regions included sub-Saharan Africa and portions of the Caribbean, where heterosexual people were infected with HIV and congenital AIDS was a serious issue. In regions of the world where HIV has only recently been introduced, no well defined risk groups have established, and only sporadic cases are reported, Pattern 3 has been seen. Campaigns for treatment, prevention, and education have altered and slowed the spread of HIV in the twenty-first century. [50]

**Methods to Reduce Rates of HIV Transmission:**

 • Treat HIV infection as an illness, not as a social stigma

• Reduce levels of poverty in society that lead to increased risks through drug abuse and promiscuity

 • Provide HIV testing and counseling to identify infected persons who can reduce their risk to others

• Provide educational programs for children and adults which describe how to avoid sexually transmitted diseases

• Promote sexual barrier precautions among high risk commercial sex workers and clients

• Provide clean needles for injection drug users

• Offer male circumcision

• Create health care programs with ongoing support to provide antiretroviral therapy for all persons living with HIV to extend life and reduce HIV transmission rates 60

• Give HIV-infected pregnant women antiretroviral therapy to reduce perinatal HIV transmission

 • Consider pre-exposure prophylaxis with antiretroviral drugs for at risk persons

• Provide antiretroviral therapy suppressing viral load to undetectable levels

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