

# Challenges to Cure: Transmission, Virulence and Pathogenesis of HIV Infection

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**ABSTRACT-** Human immunodeficiency virus (HIV) is a major contributor to the global burden of the disease, opportunistic infections, and tumors follow. HIV also directly attacks the immune system and affects certain body's system (like Central Nervous System, Respiratory and Cardiovascular Systems, Digestive System etc). HIV transmission is complex and depends on the number of behavioral and biological co-factors. The hallmark of HIV infection is the progressive depletion of CD4 helper T cells because of reduced production and increased destruction. Although the typical HIV infected patient shows a sustained CD4 cell increase, a remarkable number of subjects never achieve normal ranges of CD4. HIV infection is also characterized by a marked increase in immune activation, which includes both the adaptive and innate immune systems and abnormalities in coagulation. Extraordinary efforts in the fields of clinical, pharmacology, and biology care have contributed to progressively turn HIV infection from an unavoidably fatal condition into a chronic manageable disease, at least in the countries where HIV infected people have full access to the potent anti-retroviral (ARV) drug combinations that permit a marked and sustained control of viral replication. Although their pathogenesis is still under-discussed, they are likely to originate from immune dysfunction associated with HIV infection and chronic inflammation. The last consideration regards the dis-homogenous pattern of HIV disease worldwide.

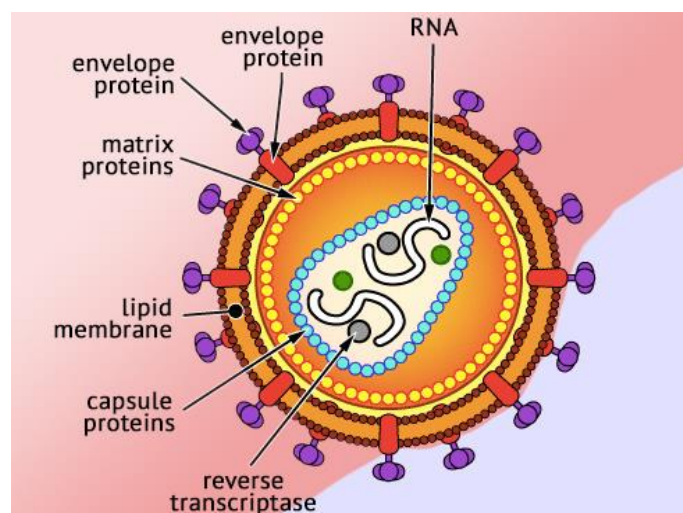
**Key-words-** Human immunodeficiency virus (HIV), simian immunodeficiency viruses (SIV), Antiretroviral (ARV) therapy, Acquired immunodeficiency syndrome (AIDS), Cell mediated immunity (CMI), Anti-retroviral agents

## INTRODUCTION

HIV virus is the harmful mediator of Acquired Immunodeficiency Syndrome (AIDS), was identified in 1983 following the first reported cases of AIDS in 1981-1982. HIV is a member of a class known as Retroviruses. These viruses store their genetic information as ribonucleic acid (RNA), unlike most viruses which store their genetic information as deoxyribonucleic acid (DNA). Previous to viral replication can obtain place, the RNA must be converted to DNA by the reverse transcription enzyme, hence the Latin term Retro, meaning 'turning back' <sup>[1]</sup>.

HIV comprises an outer envelope consisting of a lipid bilayer with spikes of glycoproteins (gp), gp41 and gp120 encoded by *env* gene. These glycoproteins (gp) are associated in such a manner that glycoproteins 120 protrude from the surface of the HIV virus. The envelope is inside membrane made of nucleocapsid (p 17, matrix protein), which surrounds a central core of protein, p24 (capsid protein) encoded by *gag* gene.

Within this core, are 2 copies of single-stranded RNA (ssRNA) (the virus genome). Proteins, p7 and p9, are bound to the RNA and are believed to be involved in regulation of gene expression. Multiple molecules of the enzyme, like reverse transcriptase (RT), integrase (IN) and protease (PR) are also present in the center encoded by *pol* gene. This enzyme is responsible for converting the viral RNA into pro-viral DNA <sup>[1]</sup>.

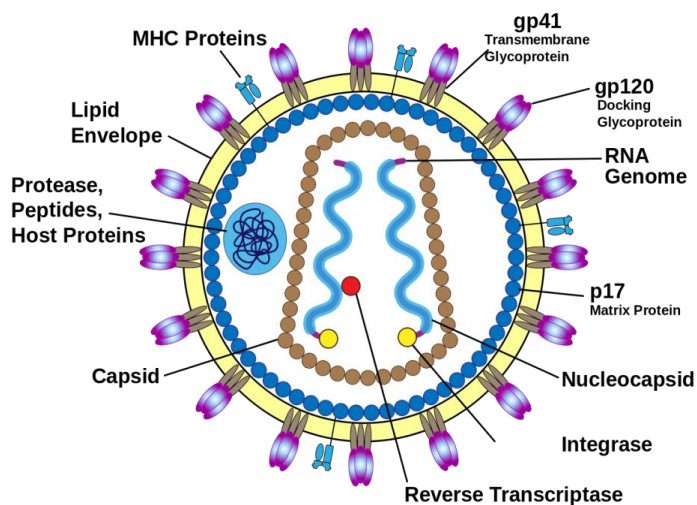


**Fig. 1:** Structure of the Human immunodeficiency virus (HIV)

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**Fig. 2:** Genome Structure of the Human immunodeficiency virus (HIV)

Source: <https://mappingignorance.org/tx/media/2013/01/fig1.png>

HIV virus was unknown until the early 1980's however while then has infected millions of persons in a worldwide pandemic. The consequence of HIV infection is the relentless destruction of the immune system leading to the onset of the acquired immunodeficiency Syndrome (AIDS). The AIDS pandemic has already resulted in the deaths of over half its victims. Almost HIV viral infected people are at danger for disease and death from opportunistic infections and neoplastic complications because of the inevitable manifestations of AIDS<sup>[2]</sup>. AIDS, the Acquired Immunodeficiency Syndrome, is the disease known to be scourge for our century has had an impact like no other disease. Human Immunodeficiency Virus (HIV) affects the human Helper T lymphocytes and macrophages, which are important in maintaining cell mediated immunity (CMI). The CMI is essential in protecting persons from many diseases including tuberculosis. HIV virus is the more significant known risk factor that promotes progression to active tuberculosis in people with *Mycobacterium tuberculosis* infection<sup>[3]</sup>. Bamisaye *et al.*<sup>[4]</sup> validated the that ABO/Rh antigens and Haemoglobin electrophoretic patterns are not associated with HIV infection but CD4 T-cells level is significantly associated with ABO blood groups in HIV

infection with blood group A and AB having increased CD4 cell count thereby contributing to increased immune resistance in such individuals. There is therefore, need to determine the mechanism and substances responsible for this immune protective action<sup>[4]</sup>.

Yasmin and Nandan<sup>[5]</sup> had emphasized that co-infection of tuberculosis in HIV/AIDS patient is a concern. There is direct relationship among CD4 counts depletion with Pulmonary Tuberculosis in HIV/AIDS patients. Tuberculosis remains an important public health problem and has been exacerbated by the HIV epidemic, resulting in increased morbidity and mortality worldwide<sup>[5]</sup>. HIV/AIDS disease leads to immune suppression and is a strongest of all known risk factors for the development of Tuberculosis disease and there is need for constant monitoring of HIV positive patients for acquisition of Tuberculosis, an assessment the type of prevalent mycobacteria in the region and information on the resistance pattern obtained in the prevalent strains. Therefore, adequate knowledge is absolutely necessary for optimum management and to reduce mortality and morbidity<sup>[5]</sup>.

At begin of the 21<sup>st</sup> century, the incidence of HIV infection stabilized at about 0.8%. The age group of 15 to 24 years young individuals were the most affected, accounted for 45% of new HIV infections. Globally, over half the victims of AIDS are women and a consequence of this is perinatal infection resulting in a significant number of children born with HIV infection. The capacity of the AIDS pandemic has already led to complicated consequences, not only for healthiness care systems of countries unable to cope with many AIDS victims but also for the national economies of those countries due to the loss on young to middle aged individual who are economically most productive<sup>[6]</sup>.

Costs for detection, diagnosis, and treatment are considerable when efficient therapies for persons with complications of HIV infection are instituted to prolong survival. In the 1990's in the U.S., the average cost for medical care of an HIV-infected patient was double the average income for half of all such patients<sup>[7]</sup>. Although the therapies of the pharmacologic exist for prolonging the life of HIV viral infected people, such therapies are expensive and out-of-reach for many persons worldwide. The years of useful life lost by the predominantly younger population infected with HIV virus has a serious economic impact<sup>[8]</sup>. In the era of antiretroviral therapy in the U.S. the average life expectancy for persons diagnosed with HIV infection increased from 10.5 years in 1996 to 22.5 years in 2005<sup>[9]</sup>.

Targeting high risk groups with educational campaigns, increasing condom use, male circumcision, reducing sexually transmitted diseases, increasing the availability of antiretroviral drugs, and needle-exchange programs for injection drug users have shown success in reducing or stabilizing rates of HIV infection<sup>[6,10]</sup>. Treatment programs for those with AIDS are expensive and difficult to administer. Brazil has had success in reducing health care costs of HIV infection with use of more widely available antiretroviral drugs.

A few pharmaceutical manufacturers have decided to subsidize the expenses, or allowed generic manufacture of antiretroviral agents, lessening therapy to about 1\$ USD/ day, but the numbers of infected persons make treatment an expensive option for many countries. Lack of resources for health care has limited budgets to deal with HIV when other health problems loomed large<sup>[6,10]</sup>.

**Acute HIV infection-** Acute HIV infection is the period of time immediately following infection with HIV virus. The HIV virus in the blood during this time is often the highest it will ever be since the body's defenses have not had enough time to respond to the virus. Initially,

HIV appears to establish a localized infection via the vaginal or anal canals, with the transmitted/founder virus being highly homogeneous<sup>[11]</sup>. As the quantity of HIV virus increase in the body, a big number of WBC, called CD4 cells, are damaged. Over time, HIV infection causes a dramatic decrease in the number of CD4 cells that considerably weakens the immune system. During the first weeks after HIV transmission, severe losses of CD4 cells occur, particularly in the gastro-intestinal mucosa, as a 'cytokine storm' ensues and plasma viral loads reach very high levels<sup>[12,13]</sup>.

**Table 1:** Summary of HIV types and groups

S. No	Type	Group	Origin	Isolates <sup>1</sup> (%)	Epidemiology	Comments
1	HIV-1	M	SIVcpz	259,678 (98.2%)	All continents with exception of Antarctica	Major group responsible for the AIDS pandemic; fit than HIV-1 group O and HIV-2
		O	SIVgor or SIVcpz	1,095 (0.4%)	Majorly found in Central and West Africa	Naturally resistant to NNRTI; less fit than group HIV-1 M and HIV-2
		N	Recombinant group M ancestor / SIVcpz	22 (<0.001%)	Only found in Cameroon	Very rare epidemically; few studies on drug resistance published
		P	SIVgor	Single case	Undetermined	Described in 2009 in a Cameroonian woman. The actual number of infections is unknown.
2	HIV-2	-	SIVsm	3,593 (1.4%)	Mainly found in Western and Central Africa; some cases in Western Europe, India, United States, Brazil and Japan	Apparently slower progression to AIDS; less susceptible to some anti-HIV-1 drugs; naturally resistant to NNRTI

<sup>1</sup>Isolates sequenced and available at the Los Alamos HIV Sequence Database as of 18 July 2009

**Genetic Diversity (GD) of HIV-** Genetic diversity is probably one of the most important concepts in biology. In its most simple definition, GD refers to any and every kind of genetic variation at the individual, population, inter-population or species level. Genetic diversity has a large impact on conservation biology<sup>[14]</sup> and the study of human origins,<sup>[15]</sup> as well as molecular epidemiology<sup>[16]</sup>, domestication,<sup>[17]</sup> fitness<sup>[18]</sup> and disease.<sup>[19]</sup> In HIV-1, higher levels of Genetic diversity have been associated with clinical outcomes such as immune escape of selected variants,<sup>[20]</sup> emergence of drug resistance mutations and the consequent therapy failure<sup>[21]</sup> and even with disease progression.<sup>[22,23]</sup> Genetic diversity has also been used to study the geographic and temporal spread of HIV-1, shedding light on global and regional population dynamics. HIV-1 GD stems from at least three different sources: multiple introductions of HIV-1 into the human population,<sup>[24-26]</sup> the low fidelity and high recombinogenic

power<sup>[27,28]</sup> of its reverse transcriptase<sup>[29]</sup> and its high virus turnover.<sup>[30]</sup>

**Transmission of HIV-** HIV can be transmitted from one person to another through sexual contact, and in a limited number of other ways. HIV can also be transmitted by sharing blood, needles and other injecting equipment. If any lady is pregnant then it's possible to transmit the virus in the baby body before or during birth, or by breastfeeding<sup>[31,32]</sup>. HIV infection can acquire from kissing, coughs, saliva, hugging, sharing baths, sneezes, or towels, from swimming pools, toilet seats or from sharing toothbrushes, razors, cups, plates or cutlery<sup>[31,32]</sup>. It is unable to acquire HIV from any animals or insects, including mosquitoes. HIV isn't transmitted through biting. For HIV infection acquisition, the virus must induce optimal conditions for the infection to occur, as indicated by the low transmission rate and the existence of individuals who remain uninfected despite being

repeatedly exposed [31,32]. In fact, during the initial steps of viral infection the virus needs to overcome the mucosal barrier and to find proper target cells such as Dendritic cell (DCs), macrophages, activated CD4 T cells, to rapidly replicate and spread [33,34].

**Pathogenesis of HIV Infection-** CD4 cells are the main target cells for HIV. CD4 lymphocyte (a type of WBC) is keys in both humoral and cell-mediated immune responses. Their number decreases during HIV infection. The pathogenesis of AIDS disease has proven to be quite complex and dynamic, with most of the critical events (e.g., transmission, CD4 (+) T cell destruction) occurring in tissues that are not easily accessible for analysis. The non-human primate model of AIDS has been used extensively to fill these gaps in our understanding of AIDS pathogenesis. Recent data suggest that CD4 down-modulation plays an important role in HIV pathogenesis and replication *in vivo* condition. Disease succession association among enhanced virus-induced CD4 down-modulation and a subset of long-term non-progressor is infected with viruses defective in this function [35-37].

**Virulence of HIV Infection-** Uncovering the factors behind this variation in HIV virulence (rate of disease progression) might provide important clues for the understanding and management of the disease. In current years, a huge effort has been put into elucidating as well as quantifying the function of host genetic factors [38,39]; however, systematic studies on the contribution of viral genetic factors had remained scarce. Hints for the role of viral factors included differences in virulence based on viral subtype [40,41], co-receptor use [42,43], or the presence of deleterious mutations in the virus [44,45]. The description of the chronic virus load may influence heritability estimates depending on the nature of the within-host evolution of HIV. Given the great evolutionary capacity of the virus, if genetic factors affect virulence, these might also change during the course of an infection [46,47].

## CONCLUSIONS

Acquired immunodeficiency syndrome (AIDS) is the last phase of HIV viral infection. At the final stage, the immune system is severely weakened, and the risk of contracting opportunistic infections is much greater. The innate immune response to HIV is largely mediated by natural killer cells and is also crucial for virus control. HIV-associated inflammation, which isn't completely inverted by the Anti-retroviral (ARV) therapy, might be a contributing factor, but again it doesn't fully explain the apparent acceleration of aging process found in HIV infected population. In addition to biological mechanisms, we need to consider behavioral and psycho-social factors such as stress, depression, and coping that may affect adherence to medications as well as the immunology and virology of the disease. The number of older people living with HIV and those with co-infections such as Hepatitis B and C is also increasing. Successful long-term antiretroviral therapy is capable to

decrease, but not to eradicate, the burden of swelling, which is likely to be causative, associated to some troubling complications of HIV infection, such as cardiovascular diseases, tuberculosis, an emerging problem in HIV infected population. Toxicity from the anti-HIV drugs affects many organs. Organ damage patterns differ between the various drugs, and their effects reverse when therapy is stopped.

While CD4 cell decline is the most specific feature of HIV infection; its mechanism has not been totally clarified. Several questions in this decade are still under mysterious like Does HIV infection accelerates the normal aging process?, Does antiretroviral therapy have a role in declining the transmission at individuality and society level? Can HIV infection be cured?, In the absence of an effective vaccine, HIV eradication becomes a major goal for global health. When is the best time to start antiretroviral therapy?, Which is the best ARV combination to start with?, How long an individual should be treated with ARV therapy?, These "classic" questions are still unlocked, and they are likely to stay scientists very hectic for at least one more decade. Further research is still needed to clarify the above some questions.

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