INTRODUCTION

Five cases of *pneumocystis carinii* Pneumonia (PCP), a rare opportunistic infection in immunocompromised persons, were reported in previously healthy and young gay men from Los Angeles in 1981\(^1\). Soon thereafter, another set of men were reported to have developed a rare skin cancer called Kaposi’s sarcoma (KP). Many more such cases of PCP and KP quickly emerged. U.S. Centers for Disease Control and Prevention (CDCP) formed a task force to monitor the outbreak. After recognizing a pattern of anomalous symptoms in patients, the task force named the condition Acquired Immune Deficiency Syndrome (AIDS)\(^2\).

One year later in 1983, two separate research groups led by Robert Gallo and Luc Montagnier independently declared that a novel retrovirus may have been causing AIDS patients, and published their findings in the same issue of the journal *Science*\(^3,4\). Gallo called the virus HTLV-III as its shape was similar to human T lymphotropic viruses (HTLVs). Montagnier's group isolated a virus from a patient showing lymphadenopathy of the neck and physical weakness, two classical symptoms of AIDS. Montagnier's group named their isolated virus lymphadenopathy-associated virus (LAV). In the subsequent year (1984) Robert Gallo and Jay Levy independently established the association of this virus with AIDS\(^5,6\). Later on, in 1985, an International Virus Taxonomy Consortium decided to name this virus as Human Immunodeficiency Virus type 1, or HIV-1 1985\(^7,8\). In 2008, Luc Montagnier along with his lab associate Francoise Barre-Sinoussi was awarded Nobel Prize in medicine for this discovery.

Epidemiology

An estimated 34 million people were living with HIV in 2010, indicating 17% increase in HIV infected individuals in last 10 years. 2.7 million individuals got infected with HIV in 2010. 1.76 million people have died in 2010 because of AIDS. Introduction of HAART in low and middle income countries has helped to reduce not only the number of deaths due to AIDS in patients but also infection in children. Subsaharan Africa region is still heavily affected by HIV epidemic. Proportion of women living with HIV remained stable to 50% of total infected population\(^9\).
AIDS prevalence in India:
More than 60% of the world’s population resides in Asia and it has the second highest number of people living with HIV/AIDS after the sub-Saharan African region. Demographically, India is the second largest country in the world. It has the third largest number of people living with HIV/AIDS, and accounts for roughly half of Asia’s HIV prevalence. There are 23.95 lakhs of people living with HIV infection in India. It is estimated that India had approximately 1.2 lakh new HIV infections in 2009, as against 2.7 lakh in 2000. Children under 15 yrs account for 3.5 percent of all infections, while 83 percent are in the age group 15-49 years. Of all HIV infections, 39 percent (9.3 lakhs) are among women. The four high prevalence states of South India (Andhra Pradesh – 5 lakhs, Maharashtra – 4.2 lakhs, Karnataka – 2.5 lakhs, Tamil Nadu – 1.5 lakhs) account for 55 percent of all HIV infections in the country. West Bengal, Gujarat, Bihar and Uttar Pradesh are estimated to have more than one lakh PLHA each and together account for another 22 percent of HIV infections in India. The states of Punjab, Odisha, Rajasthan & Madhya Pradesh have 50,000–1 lakh HIV infections each and together account for another 12 percent of HIV infections. Analysis of epidemic projections revealed that the number of new annual HIV infections has declined by more than 50 percent during the last decade. The primary drivers of HIV transmission are female sex workers, men who have unprotected sex with men and injected drug users.

HIV taxanomy and classification
HIV belongs to Family Retroviridae, subfamily Lentivirinae and genus Lentivirus in primate lentivirus group. Lentiviruses (lenti, Latin for slow) are characterized by slow growth and long asymptomatic incubation period. HIV-1 is the result of zoonotic transmission of SIVcpz in Chimpanzees in West Central Africa. HIV is classified as HIV-1 and HIV-2 on the basis of sequence deviation exceeding 50% and on the presence of vpx gene in HIV-2. HIV-2 has 40-60% homology with HIV-1 and was isolated from some AIDS patients of West Africa in 1986. HIV-2 is less predominant than HIV-1, which is found across the world. HIV-2 is mainly concentrated in West African part of the globe, with some cases also identified in America and Western
Europe. The clinical manifestation associated with both etiological agents of AIDS is indistinguishable. However, epidemiology studies suggest that the incubation period of disease development is longer for HIV-2 than HIV-1. In addition, HIV-2 maintains low level of viremia and shows lower rates of transmission and thereby remains geographically localized compared to HIV-1.

HIV-1 can be classified into three groups based upon differences in envelope gene (env). These three groups are the “major” group M, the “outlier” group O and the “new or non-M and non-O” group N. Recently, a new human immunodeficiency virus has been identified in a Cameroonian woman. It is closely related to gorilla simian immunodeficiency virus (SIVgor) and shows no evidence of recombination with other HIV-1 lineages. This new virus seems to be the prototype of a new HIV-1 lineage that is distinct from other HIV-1 groups M, N and O, hence it was designated as HIV-1 group P. Within HIV-1 groups, M accounts for more than 90% infections worldwide. Group M is further subclassified into nine genetically distinct subtypes (clades): A, B, C, D, F, G, H, J and K. These subtypes show 25-30% amino acid differences in their env sequence due to the error prone reverse transcriptase activity. Within A and F subtypes, subclusters have been identified and designated as sub-subtypes A1, A2 and F1, F2 respectively which are more closer to each other than to other subtypes.

Further, there are circulating recombinant forms of HIV, generated by mixing of genetic material of two subtypes in cells of infected individual. CRFs were first identified by full length sequence analysis of virus isolated from Thailand and Central Africa. The HIV-1 subtypes and CRFs are very unevenly distributed throughout the world, with subtypes A and C being widespread, subtype A predominates in West and Central Africa. Subtype C is the major cause of AIDS in Southern and East Africa, India and other Asian countries. It has caused the world’s worst HIV epidemic and is responsible for around half of all infections. Historically, subtype B has been the most common subtype in Europe, America, Japan and Australia. Subtype D is generally limited to East and Central Africa. CRF A/E is prevalent in South-East Asia, but originated in Central Africa. Subtype F has been found in Central Africa, South America and Eastern Europe. Subtype G and CRF A/G have been observed in West
and East Africa and Central Europe. Subtype H has only been found in central Africa while J only in Central America. Subtype K is restricted in Democratic Republic of Congo and Cameroon. Many unique recombinant forms (URFs) also exist among HIV isolates. These arise in a similar way as the CRFs, when two or more strains undergo recombination within an individual host to form a mosaic genome. These URFs globally occur at a very high frequency. However, in contrast to CRF’s they have not spread beyond their initial host. These genetically diverse populations which have evolved in the absence of selection pressure in the HIV-1 infected individuals are also called quasispecies”.

**HIV and its pathogenesis**

HIV-1 is an enveloped positive strand RNA virus belonging to the lentivirus family of retroviruses. It contains two linked copies of a single stranded RNA (each ~ 9 kb long), each of which contains the genetic information necessary to encode all 15 viral proteins. During the replication cycle, viral RNA is reverse transcribed into double stranded DNA which then integrates into the host cell genome, where it is referred to as the “proviral DNA” containing 9 ORFs. The three large open reading frames gag, pol, and env are common to all retroviruses. The gag gene encodes the Gag precursor polyprotein, pr55 which is cleaved by viral protease to produce the structural proteins-matrix (p17), capsid (p24), nucleocapsid (p7) and p6. Env (gp160) is cleaved to form gp120 surface and gp41 transmembrane glycoproteins. The pol encoded region is then cleaved by the viral protease to liberate the viral enzymes- protease, reverse transcriptase and integrase; which are essential proteins for viral replication. Nef, Vif, Vpu and Vpr are the accessory proteins. Tat and Rev are the regulatory proteins.

The HIV-1 long terminal repeat (LTR) is approximately 640 bp in length and is segmented into the U3, R, U5 region. It is present at either end of the proviral DNA. The U3 region is further subdivided according to transcription factor sites that populate the LTR and their impact on LTR activity and viral gene expression. The ends of the LTRs participate in the integration of the provirus into the host genome. Once the provirus has been integrated, the LTR on the 5’ end serves as the promoter.
for the entire retroviral genome, while the LTR at the 3’ end provides for the nascent viral RNA polyadenylation and encodes the accessory protein, Nef. Regulatory viral and cellular proteins modulate LTR mediated expression of HIV-1 proviral genome. Integrated 5’ LTR is always precisely organized into two distinct nucleosomes termed Nuc-0 and Nuc-1.

The envelope protein (Env) of HIV-1 binds to CD4 first, undergoes a conformational change and then binds to one of the chemokine receptors CCR5 or CXCR4, which is followed by fusion of the virion and plasma membranes allowing entry of the virus into the cell. Uncoating of virus takes place in the cytoplasm, and involves partial dissociation of capsid in order for reverse transcription to take place to form double stranded complementary DNA. This DNA is then transported into the nucleus and integrated into host genome with the help of Vpr and integrase protein of virus. During viral expression, this proviral DNA is transcribed to produce new viral genomes and spliced and unspliced mRNAs, which are in turn translated to produce various viral proteins. Components of the virion are then transported to the plasma membrane where virion assembly occurs. After budding and release from plasma membrane these virion particles mature into fully infectious virions. HIV-1 causes loss of CD4 T cells by direct viral killing of the cells or indirectly by impairing function of uninfected bystander cells consequently leading to the cell destruction by apoptosis.

HIV-1 infection is characterized by slow and progressive deterioration of the integrity and function of the immune system. Although the clinical manifestation of HIV-1-associated immune system dysfunction varies from individual to individual, the natural course of HIV-1 infection generally involves three phases: acute phase, chronic phase and clinical apparent disease. Acute phase, lasting for 6-12 weeks, is characterized by flu like symptoms, peak virus load and decline in number of CD4+ cells within the peripheral circulation. Chronic asymptomatic phase, lasting for an average seven to ten years, is characterized by a slow but steady decline in the number of CD4+ T lymphocytes and in general integrity of the immune system. During this period, HIV-1 replication reaches a steady level known as set point. Clinically apparent disease or AIDS onset is characterized by drastic reduction in CD4+ cells to
200 cells per mm3 from the normal level of 800-1200 cells per mm3. The CD4+ T cell depletion is associated with high viral turnover and is continued by the progressive loss of T-cell mediated immunity\textsuperscript{19,20}. According to the CDC, twenty six known clinical conditions affect people with AIDS; most are infections that do not usually affect healthy individuals. These include yeast infections of the esophagus, bronchi, and lungs; \textit{Pneumocystis} pneumonia, toxoplasmosis, Kaposi’s sarcoma, cytomegalovirus (CMV), \textit{Salmonella} infections and tuberculosis. In addition, individuals who have been affected by HIV are more likely to become seriously ill or die than other members of the population during outbreaks of infections such as cryptosporidium and coccidiomycosis. Time of AIDS onset varies from individual to individual from 2-15 years\textsuperscript{21,22}.\n