**CASE STUDY: Pandemics in History: A Study in Loss of Homeostasis.**

Epidemic of HIV started in a critical setting in late 1970s, when many people used to think that the epidemic diseases are caused by microbes, such as viruses. Some other predominant believes were that viruses do not cause any human infection and things like retroviruses those infect human, do not exist (Hutchinson, 2001). And human immunodeficiency virus (HIV) infection spread from non-human primates to humans throughout the 1900s (Paiardini & Müller‐Trutwin, 2013). However, story of unfolds of Human Immunodeficiency virus (HIV) began in 1981 when US Centres for Disease Control and Prevention (CDC) released a report of Pneumocystis carinii pneumonia (PCP) in five homosexual men. All those five patients had biopsy confirmed cytomegalovirus (CMV) infection and candida mucosal infection. Originally this virus was designated as human T lymphotropic virus (HTLV-III, AIDA associated retrovirus (ARV), or lymphadenopathy-associated virus (LAV) (Hutchinson, 2001). This infection first came in Central Africa from a type of chimpanzee in humans. Infection transferred from chimpanzee to human by a process named as zoonosis. Chimpanzee version of the virus is called simian immunodeficiency virus. Evidence show that HIV first crossed the simian-human species barrier much earlier made its way to Caribbean (Keele et al., 2006). HIV is a spherical virus of about ten-thousandth of a millimetre (Hutchinson, 2001). HIV virus belongs to the class of retrovirus and subgroup named as lentivirus, also called as slow viruses because of the long intervals between infection and the clinical symptoms to be appeared (Evans, 1993). Members of lentivirus class causes chronic infection in host and gradually damages the host’s immune system. Like all other viruses, HIV replicates inside its host and use host mechanism for its reproduction. Since HIV belongs to retrovirus class of viruses that’s why, its genes are composed of ribo-nucleic acid (RNA). However inside the host this virus uses the host’s machinery to convert its RNA into DNA by the mechanism of reverse transcription by using enzyme reverse transcriptase (Smith & Daniel, 2006) (Kilmas MD et al., 2008).

HIV primarily attacks the specific type of immune system of the body which are basically CD4 helper cells. Since this infection weakens the immunity due to which body starts losing fight against other infections as well. Excessive replication of HIV inside the host with no use of antiretroviral drugs can cause escalating decrease in CD4+ T cell count, immunodeficiency and AIDS in humans (Deeks et al., 2013; Freiberg et al., 2013).

HIV infection has also been reported to cause excessive risk of liver, cardiovascular, bone, neurological, and kidney diseases (Deeks et al., 2015). And it has been studied that these organ impairments are more prevalent in people with HIV than those without HIV infection. It has also been observed in a conceptual model of HIV infection that HIV causes harm to the mucosal and lymphoid tissues, that eventually leads to cause the progressive immunodeficiency, inflammation, and surplus intensities of pathogens. This virus also causes microbial translocation by damaging mucosal tissues of the gut. Apart from these damages, through a number of mechanisms, HIV infection itself and treatments for this infection affect liver functions too. This hepatic damage along with compromised protein synthesis are caused by microbial translocation. Collective destruction caused by initial infection results in hypercoagulation in response to the impaired protein synthesis in liver and chronic activation of monocytes and macrophages (Neuhaus et al., 2010). Elevation in protein synthesis and coagulation markers are linked with increased risk of several diseases to be happened at once and even mortality (Kuller et al., 2008; Tien et al., 2010). This progressive infection eventually leads to direct organ-tissue damage, vascular harm, and multimorbidity with aging (Fig. 1). Several events in HIV infection are seen to cause risk factors such as obesity, hypertension, and dysfunction of immune system. Several studies have reported that frequency of activated monocytes is higher in HIV-infected and HIV-treated people that healthy people with no HIV infection. These studies showed that antiretroviral drugs cause drug toxicity and activation of T cells inflammatory monocytes and cytokines, that results in the progression of the infection in even HIV-treated people (Freiberg et al., 2013; French et al., 2009; Hunt et al., 2003; Neuhaus et al., 2010; Sandler et al., 2011).



Fig.1 Development of inflammation-based infection in HIV infected people (Deeks et al., 2013).

Being virus, HIV cannot live without host so live inside a living cell. Structure of HIV is quite simple, lack complex elements unlike bacterial and human cells, this attribute of HIV makes it target specific. This virus uniquely identifies and infect its specific target. Like all other viruses’ genetic material in HIV is also organized into ribonucleic acid (RNA). RNA of the virus is present in a protein coat named as capsid. There are enzymes outside the capsid that are used by the virus for infection and replication inside the host. Overall, this structure is protected by glycoprotein made envelope, which is used by the virus to find its host surface to bind. By using the host’s reverse transcriptase (RT) enzyme HIV synthesize DNA from its RNA by the mechanism of reverse transcription. After completing synthesis of first strand of DNA, RT enzyme uses this DNA as a template and synthesize second strand of DNA. Then this viral DNA moves to the nucleus of the host and enters into the host’s DNA and becomes a provirus. After this infection of the cell becomes permanent. An interesting study performed in 2013 provided a brief history, overview and the causative role of immune system activation in HIV over years (O’Halloran et al., 2019; Paiardini & Müller‐Trutwin, 2013). Transmission of HIV is also specific, this can be transmitted through certain fluids including semen, blood, vaginal fluid, rectal fluid, and breast milk. For virus transmission from one host to other, these fluids must come into contact with mouth, rectum or vagina, open wound of the other host. This virus cannot be transmitted from a person to another through touch, social interaction, saliva, sweat or through mosquitos like dengue (Wilkins, 2020). Possible modes of HIV transmission are anal or vaginal intercourse, blood transfusion, mother to child transmission during pregnancy and breast feeding, and sharing syringes or blades etc. It has been studied that infection within two days of viral attack, infection of CD4+ T lymphocytes can be noticed or diagnosed. Virus promptly localizes at the infection site and then spreads to draining lymph nodes and eventually the distal lymph nodes along with other tissues of the body. This entire process has been reported to occur within timeline of two weeks (Deeks et al., 2015; Spira et al., 1996; Zhang et al., 1999).

Human immune system has several important cells to fight against infections and to demolish abnormal cells, these cells include T-cells/T-lymphocytes. These cells regulate the response of body’s immune system to foreign antigens. HIV specifically targets a certain type of T lymphocytes which is CD4 cells, also called as helper cells. These cells do not provide immunity to the body directly by killing the foreign antigens but direct signals to other immune cells to perform that function. After entering the body of the host HIV finds out those helper cells and cause the infection. These T-lymphocytes along with B-lymphocytes provide defense to the body up to their maximum unless the number of virus replicates increases with a decline in CD4 cells. Virus hijacks the operation of CD4 cells and manipulate them to get multiples copies of the virus. On daily basis 10 million-10 billion virus copies are produced during this phenomenon. Studies showed that infected people have been observed to cross the line to AIDS when cell count of CD4 cells decline to 200 which should be 1000 per microliter in healthy individual (Nowak & McMichael, 1995). After such adverse situations of CD4 cells becoming weakened and their life span being shortened, and their death, immunological failure is caused in host and it open the ways to many other infections (Rodger et al., 2019; Sewell et al., 2017).

HIV affects and targets specific elements of the body’s immune system. Since HIV causes chronic infection in human and some other mammals, if it is left untreated, this can cause progressive destruction to the immune system of the body including multiple opportunistic infections and cancers. On this stage where multimorbidity is reached and immune system of the body is weakened to such extent that different cancers develop and spread. This stage was previously called as AIDS (acquired immune deficiency syndrome) and now commonly called as advanced stage HIV infection. HIV infection is one of the deadliest infections to be emerged in human history. This infection affects millions of people all around the world. The first major infection of HIV emerged in the US in 1980s, when cancers and other infections were more likely to occur in immunocompromised adults (Sharp & Hahn, 2011). HIV infection appeared in healthy homosexual males in California. First, this infection was associated to men/gay community, later research was performed and then it was observed that infection can be in any individual who comes into contact with certain fluids of the infected person irrespective of their gender and health. By 1986, virus was isolated and identified but till then it has destroyed thousands lives across various countries (DiClemente et al., 1986). According to WHO, in 1989 HIV became an endemic with more than 400,000 HIV cases reported (Vaughan et al., 1989). In 2018, 37.8 million people were seen to have HIV infection worldwide and about 770,000 HIV related deaths were reported (Organization, 2018). According to a report in Australia, between 2006-2015, 6741 HIV cases associated to homosexual males interaction, and 2093 were reported linked to heterosexual interaction (Gunaratnam et al., 2019). According to recent reports highest prevalence of HIV infection has been reported in sub-Saharan Africa, which is 68% of the total population (Wilkins, 2020). Worldwide prevalence of HIV infection has been declined, since >56% fall in deaths has been observed by WHO in 2018.

First manifestation of HIV infection is cardiovascular disorders. In 1998, first case of acute myocardial infarction in HIV infected patient was reported. Since then, it was become clear that HIV infected patients tend to have cardiovascular disorders more likely than people without HIV infection. There are controversial researches on this topic, however various studies suggested that cardiovascular infection in HIV infected people is more prevalent due to antiretroviral therapy (Ho & Hsue, 2009). Risk of occurrence of cardiovascular diseases in HIV infected patients is due to initial insults of body metabolism of the patients. Hypercoagulability, chronic inflammation and lymphocyte activation lead to cause vascular dysfunction which eventually results into cardiovascular disorders. Activation of lymphocytes, effect of secretions by HIV protein and secretion of cytokines direct to influence vascular dysfunction. And other biomarkers such as interleukins tend to elevate in HIV infected individuals, due to which chronic endothelial problems occur that may result to cause chronic inflammation and hypercoagulation due to which homeostasis of the body disturbs and eventually cardiovascular disorders manifest in HIV infected people (Dau & Holodniy, 2008).

Another manifestation of HIV is neurological complications in HIV infected people. HIV does not seem to harm neurological cells of the infected person itself. Various studies performed on neurological manifestation in HIV have reported that chronic inflammation occurs in the infected people due to HIV and AIDS. This inflammation disrupts the body homeostasis of the patient by damaging central nervous system (spinal cord and brain) which inhibit glial cells to function normally the way they should. According to John Hopkins Medicine reports, some of the treatments such as drugs used to treat HIV infection also play a role in causing neurological problems along with controlling the viral spread in the body. Some genetic factors also may be the cause of neurological complications in infected people are genetic. It has been proved by research that neurological issues do not occur in HIV infected patient until they reach at the advanced stage of the diseases which is AIDS (Hogan, 2011).

Life-saving intervention/treatment for HIV infection is antiretroviral therapy (ART). HIV infection causes the depletion of CD4+ T cells in the person and due to which various other infections encounter the body and AIDS can be developed. Standard antiretroviral therapy used to have combined nucleoside reverse transcriptase inhibitors with a non-nucleoside reverse transcriptase inhibitor, protease inhibitor, or integrase inhibitor (Maartens et al., 2014). After ART, plasma level of viral load decreased to a certain limit and then further processes of recovery go on. ART protects and restore CD4+ T cells and keep the immune system strong to fight against various other infections and this becomes possible when replication of the virus is stopped. After restoring CD4+ T cells in the patient body, chances of other infections to happen are decreased and AIDS related complications are also controlled (Autran et al., 1997; Palella Jr et al., 1998). Best strategy to control serious HIV infection and to restore balanced CD4 cells in the body, early ART should be mediated which can restore normal body functions and maintain homeostasis of the body by restricting cell imbalance and preserving the normal state of the lymphoid tissues. Success of ART observed so far is that the person diagnosed with HIV in the age of 30 and starts getting treatment can now be expected to live to the age of 75 (Nakagawa et al., 2012; Wilson & Sereti, 2013).

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