A literature based on entry and development of human immunodeficiency virus into the human host

Arif Billah, Mosharaf Hossain*

ABSTRACT

HIV is a global threat cause of millions of lives and evolved as one of the most dangerous epidemics in the recent era. Among all other viruses infect human, the nature, evolution and development of HIV have fluctuated. This paper is constructed by focusing on a brief of entry and development of HIV into the human being based on the literature. Summary of the paper clarifies that, HIV spillover from chimpanzees, mangabey and western gorilla to the human being and mutated from SIV into HIV long before discovery in several possible human-animal contacts in Africa. Genetic mutations also found significant into the human host and several subgroups of HIV was identified. Possible ways of entry to the human host are distinguished as the exposure of horizontal and vertical transmission of HIV where the relative risks of these exposures were also quantified. The development process after exposure by HIV is found similar regarding the ways of transmission. Untreated subjects have shown different immunological dysfunction, even death, depending on the severity of the HIV and consequences of the acquired immune deficiency syndrome.

Keywords: Development, HIV, Human host, Transmission

INTRODUCTION

Significance in public health

History of human-virus cohabitation has variations in case of acquiring from nature, development in the body as a host and transmits later as an epidemic. HIV is a global threat to millions of lives and has developed into one of the most dangerous epidemics of recent times. This paper is constructed by relying on a literature-based brief of HIV’s entry and introduction into the human being.

After the first discovered tobacco mosaic virus in 1892 and filterable fever virus in 1901, there are more than 1/3 zoonotic human viruses emerged and infect humans spontaneously. HIV is one of the virus species discovered retrovirus in our modern curse. Five intermediate stages have been identified through which animal pathogen altered into a human affecting pathogen.1 These zoonotic infections and spillover of the viruses create great concern in the field of phylogenetic study and a global surveillance system is required.2

HIV and advance level of HIV resulted in AIDS is a global concern. According to the latest statistics of HIV/AIDS, estimated 37.9 million people were living with HIV including 36.2 million adult (age≥15), around 7.7 million people died from HIV/AIDS-related illness and 1.7 million are newly affected by HIV at the end of 2018.3 After 1999, the rate of new infection was the highest and declines thereafter and the HIV/AIDS pattern
have been changed. Before initiating any study on HIV, it is necessary to gather a baseline history and evolution of HIV.

HUMAN IMMUNODEFICIENCY VIRUS

Infection of HIV and the syndromes of opportunistic illness characterized late-stage of HIV is acquired immunodeficiency syndrome (AIDS). HIV pathogen generically belongs to the lentivirus, subgroup of the retrovirus and subfamily of orthoretrovirinae. HIV is a viral cross-species transmission that originated from zoonotic and adapted in the human host in the association of required adapted factors such as viral, cellular and environmental factors.

Table 1: HIV taxonomy.

<table>
<thead>
<tr>
<th>Classification of HIV taxonomy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Realm</td>
<td>Riboviria</td>
</tr>
<tr>
<td>Phylum</td>
<td>Negamaviricota</td>
</tr>
<tr>
<td>Subphylum</td>
<td>Polyploviricota</td>
</tr>
<tr>
<td>Order</td>
<td>Ortevirales</td>
</tr>
<tr>
<td>Family</td>
<td>Retroviridae</td>
</tr>
<tr>
<td>Subfamily</td>
<td>Orthoretrovirinae</td>
</tr>
<tr>
<td>Genus</td>
<td>Lentivirus</td>
</tr>
<tr>
<td>Species</td>
<td>Human immunodeficiency virus 1 and 2</td>
</tr>
</tbody>
</table>


Figure 1: Relative risks of different types of HIV epidemics in human species.

There are two types of HIV viruses regarding with the genetic combination of these viruses that affect the human i.e., HIV-1 and HIV-2. Type 1 HIV is the most common epidemic all over the world whereas later one causes less than one per cent of the total HIV epidemics mostly found in West Africa, Europe and India. The relative risk of HIV-2 compared to HIV-1 is very low and differs between the mode of transmission. A prospective clinical study determined 33% lower probability of HIV related disease and reduced development of abnormal CD4 count in HIV-2 compared to HIV-1 indicates that HIV-2 have a slower and longer asymptomatic phase than HIV-1. Again, HIV-1 have different sub-groups i.e., M, N, O and P whereas the sub-group M discovered first causes almost 90% of the HIV epidemics. Rest of them have lower rate of prevalence summarized in the following figure based on several studies.

For the descriptive simplicity, this paper tried to divide the whole process of HIV entry to the human host (species and body) and development into the host.

THE ENTRY OF THE HIV VIRUS INTO THE HUMAN HOST

The myth of evolving HIV from African green monkeys at lake Victoria in eastern Africa (more specifically, Rakai district in Uganda and the Kagera region in Tanzania) has been verified. Studies confirmed that HIV infection into human species is the result of multiple complex evolutionary of cross-species transmissions of simian immunodeficiency viruses (SIVs). Phylogenetic and statistical analysis of HIV indicates the entry of the HIV virus to the human species had occurred during 1915 to 1941, before its official recognition as the AIDS epidemic/pandemic in 5th of June 1981. However, one transmission event involving SIVcpz from chimpanzees in southern Cameroon, gave rise to the principal cause of AIDS pandemic HIV-1 group M and the genetic changes provide spill over of HIV from other animals (specifically, monkeys to apes) to the humans.

Figure 2: Origin of human AIDS viruses source: from the paper of Sharp and Hahn.

Among the several possibilities of how it transfused into the human being, human-ape encounter in west-central Africa have been identified most significant for initiation of HIV/AIDS epidemic. A study revealed 11 cross-species transmission events are known and four of these have resulted in significant human to human transmission that generating both types of HIV through hunting down agricultural pets. HIV-1 virus was transmitted to the human population from chimpanzees of Eastern (P. t. schweinfurthii) and central Africa (P. t. troglodytes) with SIVcpz infection. On the other hand, sooty mangabey (Cercocebus atys) infected by SIVsmm, found...
responsible for HIV-2 transmission.\textsuperscript{17} Phylogenetic relationships of the SIVcpz with HIV-1 and SIVsmm with HIV-2 confirmed these transmission, adaptation and epidemic hypothesis of the HIV/AIDS.\textsuperscript{19}

The official appearance comes with five young men in Los Angeles who practices heterosexual lifestyles died by rare pneumonia (\textit{Pneumocystis carinii}) in May 1981. Before the end of the year, a group of intravenous drug users (mutually non-homosexual) manifests the same condition and later on the infants of these group joined in the list that suggests the mother to child transmission of the rare disease condition.\textsuperscript{14} Professor Luc Montagnier and his team identified a retrovirus affecting in the T-lymphocytes of the blood of the rare disease patients in late 1983 and Robert Gallo isolated HIV-1 from a larger group of patients including diverse types of patients in 1984.\textsuperscript{20} In less than two years from the segregation of the HIV by Gallo and his teams, Jay Levy and his team in San Francisco confirmed it as the virus-derived immune deficiency defects of the epidemic renamed AIDS (Acquired Immunodeficiency Syndrome) and the virus is called HIV (Human Immunodeficiency Virus).\textsuperscript{21} After four years of the epidemic, American and French researcher found another uncommon and rare virus (HIV-2) that manifests the similar condition of the HIV/AIDS from West Africa.\textsuperscript{22}

\textbf{THE ENTRY OF THE HIV VIRUS TO A HUMAN HOST}

It is well established that, HIV virus is able to enter in the human body through the vagina and anal during sexual intercourse, mouth for children during breastfeeding and oral sex and blood mixing intravenous injections and injured affected skin.\textsuperscript{23} A systematic review about the risk estimates of HIV acquisition found that risk of HIV transmission is greatest for blood transfusion (0.9250) followed by mother to child transmission (0.2260), anal intercourse (0.0149), needle-sharing injection drug use (0.0063), percutaneous needle sticks injuries (0.0023), vaginal intercourse (0.0012) and oral sex is the lowest.\textsuperscript{24} The direct route of HIV exposure is supposed via injections and a blood transfusion from any undetected affected subject is larger than for other modes of HIV transmission.

The most possible via of HIV transmission are mucous membranes, mucosa, blood and breastmilk. During sexual transmission, once the virus reaches the submucosa, dendrite cells and fibroblasts have been shown in vitro of being capable of facilitating the transfer of the viral particles to susceptible cells, where the genital fluids and hormones play a positive role in the transmission of HIV.\textsuperscript{23} Several studies reported the HIV-infections that is more likely happened through oral exposure with the direct contact of female and male genital fluids, anal to oral and oral to oral contact.\textsuperscript{25,26}

In the case of mother to child, which is another form of oral transmission (also known as the vertical transmission) HIV transmission could occur before, during and after birth.\textsuperscript{27} Besides, uninfected babies from HIV infected mothers have the risk of acquiring HIV through breastfeeding because breastmilk of HIV positive mother has contained HIV DNA. High maternal viral load in the breastmilk, duration of breastfeeding and rate of feeding non-breastmilk are possible influential factors of breastmilk HIV transmission (20\% to 40\%).\textsuperscript{28} After entering the submucosal region, the procedure of affecting the CD4 cell is the same.

\textbf{DEVELOPMENT OF THE HIV VIRUS IN A HUMAN HOST}

Viruses need a perfect host to replicate themselves into millions. Like other viruses, HIV also depends on proteins and other genetic components of the host cells to multiply itself. HIV attack the CD4+T cells; a part of white blood cells which is one of the main defence mechanisms of the immune system; in order to replicate new copies. As a defence mechanism, the human immune system creates more CD4 cells to fight against the viruses and HIV virus attacked those cells for their replication. CD4+ is a thymus-derived lymphocyte (T-lymphocytes) cellular immunity are the primary targets of HIV infection and activated HIV-specific CD4+T cells are preferentially infected. From the early stage of the HIV infection, the declining rate of CD4+ cells is associated with rapid disease progression.\textsuperscript{29} This cycle of immune activation or inflammation continued until the treatment started. Following 7 consecutive stages are followed to multiply in the body starting from HIV encounters in a CD4 cell.\textsuperscript{30}

Binding - during HIV attacks to the host cell (CD4, CD8, macrophage and lymphocytes), the virus binds to host receptor and co-receptors. A conformational change occurred in host cells and envelop protein of HIV after attachment with the host cell that aid to open a route and permits binding to the coreceptor, on the cell surface.\textsuperscript{31,32}

Fusion - the HIV viral envelope fuses with the CD4 cell membrane and inserts HIV RNA and enzymes into the cell cytoplasm. The binding process allows another conformational change in viral protein on the viral membrane that creates a channel to injects the viral RNA into the plasma membrane of the target cell.\textsuperscript{33}

Reverse transcription - in this stage, HIV viral RNA converted into HIV DNA using the reverse transcriptase enzyme secreted from the virus. Now the whole process occurs in the cytoplasm of the host cell, where the single-strand HIV RNA genome destroys itself and copies into complementary DNA. Complementary DNA of HIV can enter into the host cell nucleus with the help of rev protein of the HIV genome and combine with the cell’s genetic materials.\textsuperscript{31}
Integration - new viral DNA is transported into the cell nucleus. Inside the host nucleus, HIV releases integrase enzyme to insert the viral DNA into the host DNA. Integration of the viral DNA finalises the HIV infection of the cell and initiate the establishment of continual infection.14

Replication - the virus begins to use the mechanism of the host cell to create long chains of HIV proteins which are the building blocks for more HIV. Different novel genes enable viral endurance and regulation of HIV replication using the cellular machinery the replication.15

Assembly - new HIV RNA and HIV proteins made by the host cell move to the surface of the cell and assemble into immature HIV. The newly assembled material (virion) initially formed as a non-infectious, immature virion which turns into the infectious one after processing the viral protein and using the host cell membrane.

Budding - immature HIV pushes itself out of the host cell. Once outside the cell, the new HIV releases protease enzyme that breaks up the long protein chains in the immature virus, creating the infectious virus. It takes approximately a day after infection the first progeny viruses are released from the infected cell.16

Two main genetic material (TAT) enhances the transcription process of complementary DNA and (env) facilitates the binding process with the susceptible cells. During the replication cycle, auxiliary proteins of viral DNA (VIF and VPR) provide a mechanism that continues the synthesis whereas the rest of two extra auxiliary genetic materials (VPU and NEF) promote virus budding and remove the surface proteins.17

These newly released viruses (virions) go on to infect new CD4 cells and recycle the process millions of times each day until treatment started. Infected cells are eliminated from the blood by cellular toxic HIV components.18 Developing of the HIV of at various stage manifests different symptoms and an untreated PLWHA can get affected with some immune infectious diseases. During the chronic phase of the infection, blood CD4+T cell count declines slowly; this loss can be partially reversed by successful antiretroviral treatment, but it is accelerated during AIDS.19

DISCUSSION

This paper tried to review the transmission of human immunodeficiency virus from nature to human host, genetic mutations and development of the virus into the human immune system and develop a disease called AIDS. Published works of literature are the base of this paper.

There is a debate on the acquisition of the HIV into the human host, but it is confirmed by the phylogenetic study that, African mammals are commonly affected by the leading lentivirus simian immunodeficiency virus (SIV) which later on transmitted to the human in any of the human-animal encounter events. Several studies searching for the source of infection that leads to the pandemic confirms that both HIV’s are the result of multiple complex evolutionary cross-species transmissions of simian immunodeficiency viruses (SIVs) that naturally affect the African primates and cross-invade during human-animal encounters. Studies confirmed that the HIV-1 virus was transmitted to the human population from the infected chimpanzees of eastern and central Africa whereas infected sooty mangabey found responsible for HIV-2 transmission. Possible events were confiscated into animal hunting, animal attack on the hunters, animal trafficking etc. One of the possible encounters was recorded by the Peeters, that, haunting wild animals especially rainforest monkeys for bushmeat and pet can lead to the exposure of human blood or mucous with the affected animal. Nevertheless, capturing, butchering and handling bushmeat that is one of the important sources of protein among the African people, provide a huge opportunity to enacted with the animal viruses (SIV) into the human host.18 The virus mutated from the protein construction and RNA level to the human cell for survival and transformed into HIV. Phylogenetic relationships of the SIVcpz and HIV-1 and SIVsmm with HIV-2 confirmed these transmission, adaptation and epidemic hypothesis of the HIV/AIDS.19 This process was developed far behind than the virus emerged as the epidemics. Worobey team compared the sample of viral sequence that collected from the patient’s tissue in 1959-60. Calculating the genetic changes over time and observing the pattern of spread in the Kinshasa city the team extrapolate that, pandemic HIV evolved from the sample population at the early of the nineteenth century.20 The potentiality and incubation of this HIV

were not published since the first case of the rare immunological dysfunction emerged in the United States of America. Distinctive types of HIV are also seen as the epidemic marched on and derived type one and type two with subgroups based on the genetic formation and variation of attachment in case of modifications of protein activities. Though, most dangerous one is group M virus from type 1 category.

Primarily, this was surfaced as the disease of sexually disoriented people like homosexuals and transformed sexual orientations such as gay, transgenders and lesbians. Later, it is also uncovered among the heterosexuals. Pregnant women were also encountered with the virus and able to spread the infection to their newborn babies. The global epidemic then ongoing by affecting and killing thousands of people regardless of age, sex and socio-economic status. Preliminary reason for such an epidemic is the unidentified ways of transmission. Differential attributes of HIV transmission to progression, such as longer incubation period, diverse clinical manifestations compared with the other sexually transmitted diseases, and sensitive issue on the mode of diffusion were primarily aiding to spread the disease spontaneously. People with stigma, beliefs on a curse from God (because the disease started with the sexually disoriented people who are seemed curse of god in many cultures), technological limitations and conspiracies are geared up HIV to spread on all over the world. All those diverse cases help researchers to identify how the disease transmits to one person to another, possible risk factors/behaviours were open with a set of possible solutions to halt the HIV epidemics.

HIV is responsible for the immunological dysfunction by destroying the main defence mechanism (CD4 T lymphocytes) of the human body. This disease was transmitted by horizontally- unprotected sexual activities, intravenous drug use or unsterile injecting tools sharing and vertically- mother to child transmission. HIV/AIDS was also categorized in one of the sexually transmitted diseases as it first appeared with the sexual transmission process with the sexually disoriented people. The comparison of the HIV infects process and other sexually transmitted diseases imply a variety of disease causation process. HIV directly does not cause any disease; it has only weakened the immune system and initiate a susceptible situation of the human body to gear up for other diseases. Unlike other retroviruses, the HIV has a distinct receptor that attaches to the susceptible cells (CD4 and other immunologic cells) as well as it possesses several counterattacks to defeat the human defence mechanism and inactivates those host cells to multiply themselves. A recent study found a rapid decrease of CD4 and CD8 T helper cells at the initial stage and rapidly progress to the disease as the viral loads' increases.29 This process done in the seven continuous steps that is, binding with the target cell (CD4), inserting the viral RNA (fusion), converting the viral RNA into the viral DNA (reverse transcription), integrate with the host cell DNA (Integration), destroying the host cell DNA and converting into multiple new uninfected virions (replication), assemble those virions with the protein-coated cells and create a complete look of newly infected HIV (Assembly) and leave the destroyed host cell (budding). Bodily, more CD4 cells are created to halt the invasion but help the invaders (HIV virus) to grow more- a process of self-defense destroying own defence system. This cycle leads to destroy the immune system of the human body and become very susceptible to other disease related to the immune system. Illustratively, thousands of newly produced HIV from a single host cell (CD4) spread to different sites of the body through blood flows.

The immediate response of the bodily immune system collapsed and initial flu-like symptoms manifest in affected people. Without intervention, it spread over the body that harbour susceptible cells. Mostly, dysfunction of the immune system of a human host acquires pneumonia, tuberculosis, hepatitis, typhoid, toxoplasmosis, meningitis and others that are associated with the damaged immune system. These are called opportunistic infections. An HIV affected person then advanced his/her infectious level to the acquired diseases that are associated with the damaged immune system is called acquired immunodeficiency syndrome (AIDS) and died by those severe level of acquired diseases.

CONCLUSION

This study is only based on the published literature on HIV viruses from a different discipline to describe the HIV infection in the human host from nature. The root of HIV existed in the animal and transferred to human host during early of the nineteenth century but there is still controversy of the zoonotic nature of this virus because it derived from SIV existed in wild Africa and transformed into HIV after transmitting in the human host. Evidence suggests several virions from a different genetic combination of HIV existed in and relative prevalence of HIV more dependent on the genetic structure.

Recent progression of the HIV epidemic can be seen with different policies and programmes of global organizations in diverse perspectives. The process of progression of HIV is almost same after infecting the core (CD4 T lymphocytes) cells whether the entry may vary by either self- induced transmission (during sex and injections) or vertical transmission (mother to child). Though treatment strategy has been developed and all possible risk factors are identified but the entry of the HIV into the human either from nature or development as a life-threatening condition are always important to assess in health-related epidemiological studies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required
REFERENCES


