

Human Immunodeficiency Virus (HIV)- Still a Challenge to Combat!

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Abstract

Human Immunodeficiency virus (HIV) and its associated disease, Acquired Immunodeficiency syndrome (AIDS) are one of the biggest challenge faced by researchers as to develop efficient antiretroviral therapy as well as vaccine. It poses a major health problem globally and considered a big social stigma for sufferers. HIV-1 pathogenesis is very complex, multi-factorial, which involves the interaction of host and viral proteins besides other factors. HIV-1 infection is found to cause severe apoptosis in T-cells and the reasons are only partially understood. HIV-1 envelope interacts with CD4 glycoprotein receptor and one of the several chemokine receptors to gain entry into a susceptible cell, like T-helper and macrophages. This review in short, covers the general aspects of HIV morphology, genome; and structural and auxillary genes and their combitorial effect in HIV-1 pathogenecity and infection.

Keywords

HIV, AIDS, Genome, Auxiliary Proteins, Co-infections

Introduction

Retroviruses are the viruses that contain RNA as the core genome and replicate with the help of an enzyme, namely reverse transcriptase (RT), a RNA-dependent DNA polymerase coded from viral genome. Types HIV-1 and HIV-2 come under subfamily *Lentivirinae* of the family *Retroviridae* on the basis of genetic, morphological and pathological criteria (Gonda *et al*, 1986; Haase, 1986). HIV-1 and HIV-2, both cause immune deficiency, but it appeared that infection caused by HIV-1 is more virulent (Marlink *et al*, 1994). HIV primarily infects vital human immunity cells such as helper T cells, more precisely CD4 cells, macrophages Macrophage and dendritic cells (DCs). This infection in turn resulted in loss of cell mediated immune response and thus, body eventually become more susceptible to several opportunistic pathogens causing severe co-infections; developing AIDS. Estimated number of people living with the infection is 35.3 million, out of this a big proportion is of adolescents (10-19 years), about 2.1 million (WHO 10 facts on HIV/AIDS, 2014). Since its discovery in 1981, approximately 36 million people have died so far. In the year 2012, 1.6 million HIV/AIDS infected people have died (Table 1, Fig. 1).

Table 1. Statistics by UNAIDS/WHO in 2014

	Estimate
People living with HIV/ AIDS in 2013	35.3 million
Adolescnstns with HIV/ AIDS in 2012	2.1 million
People newly infected with HIV in 2012	2.3 million
AIDS deaths in 2012	1.6 million
Children living with HIV in 2012	3.34 million
Total deaths so far	36 million

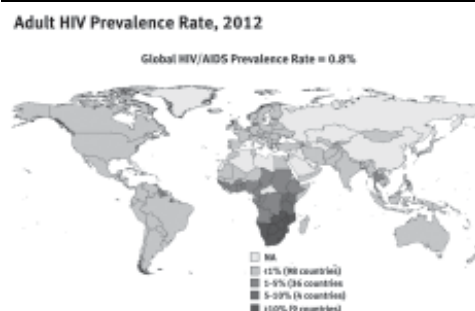


Fig. 1. Prevalence of HIV around the world (adapted from Kaiser Family Foundation, www.globalhealthfacts.org)

Various ways for HIV transmission:

- unprotected sexual intercourse with an infected person
- contaminated blood transfusions
- transmission via contaminated needles, syringes or other sharp instruments
- transmission from mother to infant during pregnancy, childbirth and breastfeeding.

But there are several precautions to prevent transmission of HIV:

- practicing safe sexual behaviors
- periodical testing and if required, treatment for sexually transmitted diseases
- avoidance of injecting drugs
- be ensured that blood or blood products are tested for HIV prior to usage.

Classification of HIV

High genetic variability in HIV, make it different from many other viruses. HIV generates 10^9 to 10^{10} virions per day, resulting in huge diversity as a result of its fast replication cycle. Also high mutation rate of $\sim 3 \times 10^{-5}$ /nucleotide base/cycle of replication and recombinogenic properties of RT are responsible for HIV diversity (Robertson *et al*, 1995). It is broadly classified into two major subtypes; HIV-1 and HIV-2. The most common strains of virus are include in subtype HIV-1 that is further subdivided into M, N, and O groups.

Group M

It is the most common type of HIV, with more than 90% of HIV cases being that of HIV-1 group M. It is subdivided further into various clades, designated by a letter again. Classification can be further complicated due to mutational changes in virus during the course of infection, and can give rise to "circulating recombinant form" or CRF, for example, CRF A/C is a combination of subtypes A and C in which the former is common in West Africa (Bobkov *et al*, 2004) and the later in Europe, America, Japan, Thailand, and Australia. In Southern and Eastern Africa, India and Nepal, it is the subtype C that is more prevalent and subtype D is usually found in Eastern and Central Africa. Subtype E has never been purified, and is always seen in combination with subtype A as CRF A/E (Goudsmit, 1997). Subtypes F, G and H are mainly restricted to various regions of Africa and Subtype J is limited to Central America. Subtype K is restricted to the Democratic Republic of Congo and Cameroon.

Group N

This group, discovered in 1998, is very rare and found only in Cameroon.

Group O

This strain is also very rare and not usually seen outside of West-central Africa. Like Group N and Group O, HIV-2 has not been widely seen outside of Africa.

Role of co-pathogenesis in supporting HIV infections

Co-infections of HIV and other viral or bacterial origins represent a major health crisis around the world. Some of the most common and usually fatal co-infections that occur and help in progression of HIV/ AIDS in patients are caused by *Mycobacterium tuberculosis*, *Hepatitis C virus* and *Hepatitis B virus*.

Mycobacterium tuberculosis

It is the most common opportunistic co-infection occurring in HIV-infected, especially inpatients in developing and under-developed countries. Tuberculosis not only, accelerates HIV-associated morbidity and mortality but also propogates viral replication at much faster pace (Toossi *et al*, 2001). The interaction between this deadly combination is bi-directional.

The progressive decline and dysfunction of CD4 cells is the benchmark for HIV-1 infection progression (Fauci, 1996), and these cells are critical in preventing the onset of *M. tuberculosis* infection. HIV-1 infection confers one of the most known risk for the development of active tuberculosis. Several studies have been done both at the cellular and clinical levels to observe the effects of tuberculosis on HIV-1 infection. Tuberculosis enhances viral replication via mechanisms that involve activation of the cell-mediated immune system. In both the chronic infections, expression of activation markers by natural killer cells (iNKT) are up-regulated, suggesting their important role in the immune response and infection (Montoya *et al*, 2008). Polyfunctional *M. Tb*-specific CD4 and CD8 T cell responses are maintained in the blood of HIV-1+ve individuals. The disease status of HIV-1 affects the functional capacity of the immune responses (Day *et al*, 2008). The active tuberculosis enhances the progression of HIV infection. It exerts effect on its survival in the early stages of HIV infection as there is a reserve capacity of the host immune response (Pawlowski *et al*, 2012).

Viral hepatitis

HIV-1 compromises human immunity mainly by destroying CD4+ T cells, and that paves way for opportunistic infections and reactivation of latent pathogens. Among the infectious pathogens, many

viruses, including hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis G virus (HGV), transfusion-transmitted virus (TTV) and human T-cell lymphotropic virus type 1 (HTLV-1), share a similar route of transmission and risk factors with HIV. HBV and HCV are the major causes of acute hepatitis, and large number of infected patients' further progress to the chronic diseases such as liver necrosis, cirrhosis and hepatocellular carcinoma. Viral hepatitis has become an alarming cause of morbidity and mortality among HIV infected patients. HIV accelerates HBV and HCV liver disease, especially when HIV-associated immunodeficiency progresses (<http://aidsinfo.nih.gov>).

HIV Structure and Genome

It consists of two copies of positive single-stranded RNA, responsible for coding virus's nine genes that are enclosed in a conical capsid which is composed of the viral protein p24, and virus particles being surrounded by an envelope. Spikes consisting glycoproteins gp120 and gp41, around 72 in number are projected from the envelope.

The RNA genome of HIV consists of nine genes (*gag*, *pol*, *env*, *tat*, *rev*, *nef*, *vif*, *vpr*, *vpu*) encoding 19 proteins. Out of these nine genes; *gag*, *pol* and *env* genes encode for the structural proteins while the rest encode for viral regulatory proteins. These viral proteins regulate the ability of virus to infect cells, onset its replication and cause disease (Suzuki and Craigie 2007).

TAT is transactivator of HIV promoters as it binds with TAR RNA element and transactivates LTR promoter. Rev protein binds to RRE and promotes shuttling of RNAs from the nucleus and the cytoplasm. It helps in nuclear export of late, unspliced RNA.

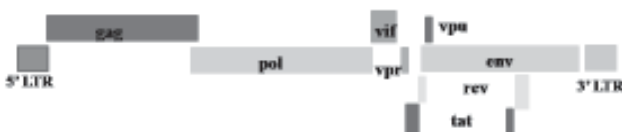


Fig. 2. HIV Genome

Virion infectivity factor or *vif* protein mediates ubiquitinated degradation of APOBEC3G (a protein of cytidine deaminases that cause G to A hypermutations in viral strand and thus renders viral inactive or susceptible to action of uracil glycosylases). *Vpr* causes G2 cell cycle arrest and nuclear import of preinitiation complex. *Nef* protein is involved in down regulation of CD4 and MHC class I. The *Vpu* protein enhances virion release from infected cells and CD4 degradation (Lin *et al*, 2005). The ends of each strand of HIV RNA contain the long terminal repeat (LTR) that are RNA sequences and act as switches to control formation of new virus progenies. Triggering

the activity of LTR could be due to proteins from either HIV or the host cells (Fig. 2).

Life cycle of HIV-1

Like other viruses, HIV can replicate only inside its host cells. Interaction of the trimeric complex with viral envelope (gp 160 spikes) and CD4 and a chemokine receptor namely, CXCR4 or CCR5 is required for the entry of virus in the CD4+veT cells or macrophages. gp120 of viral envelop is involved in high affinity attachment with CD4. A lot of structural changes occur in the envelop as gp120 binds with the CD4 protein, exposing the chemokine binding domains of gp120. This conformational change allow them to interact with the target chemokine receptor. This change is responsible for a more stable two-pronged attachment, thus permitting gp41 to penetrate the cell membrane (Chan and Kim, 1998; Wyatt and Sodroski, 1998). The contents of HIV that include viral RNA and various enzymes like RT, integrase, ribonuclease and protease are then released into the cell leaving behind the envelope. During transport to the nucleus, the viral single strand RNA genome is transcribed into double strand DNA by the viral RT, then integrated into a host chromosome with the help of viral integrase enzyme. This process of reverse transcription is highly error prone and during this process various mutations occur in the virus. When the cell becomes activated, it treats HIV genes in much the same way as human genes and converts them into mRNA (using human enzymes). Then the mRNA is transported outside the nucleus, and is used as a blueprint for producing new HIV proteins and enzymes. In this replication process, smaller fragments of RNA are produced by splicing and also, the regulatory proteins TAT (which encourages new virus production) and Rev are synthesized. Increasing concentrations of Rev blocks further splicing of viral mRNA. The structural proteins Gag and Env are also produced from the full-length mRNA and viral genome is packaged into new virus particles.

Assembling of new virions is the final step of the viral cycle. It begins in the host cells at the plasma membrane where Env protein (gp160) is transported from endoplasmic reticulum to the golgi complex where proteolytic cleavage generates two glycoproteins; gp41 and gp120. These are then transported to the plasma membrane of the host cell before the new virions bud from the host cell. The various structural components assemble to produce a mature HIV virion and are ready to infect another cell.

HIV consists of several auxiliary proteins that play crucial supportive role in viral propagation and infection. The various such HIV proteins with their potential functions are summarized in table 2 (Swanson and Malim, 2008).

Table 2. Various HIV-1 auxiliary proteins and their functions

Virus protein	Function	Host factor	Results of interactions
Vif	Suppresses host antiviral factors, APOBEC3G/F	APOBEC3G/F ElonginC, Cullin5	causes ubiquitinated degradation of APOBEC3G/F
Vpr	G2/M cell cycle arrest	Nucleoporins CDC25C	Post entry nuclear import Cell cycle arrest
Tat	Potent activator of viral transcription elongation	Cyclin T1 Importin-?]Promotes viral transcription Nuclear import receptor Induction of apoptosis
Rev	Induces nuclear export of viral RNAs	CRM1/Exportin- ? 1 Importin-?	Nuclear export receptor, Nuclear import receptor
Vpu	CD4/MHC down regulation; induces virions release	CD4 CD137	Recruits ubiquitin ligase to CD4 resulting in CD4 degradation Blocks virion release
Nef	CD4/MHC down regulation; T-cell activation; blocks apoptosis; pathogenicity determinant	CD4, CD28, MHC-I, MHC-II, TCR-CD3? Several kinases Dynamin-2	Connects host surface proteins to clathrin - dependent/independent sorting pathways to regulate trafficking, Roles in signal transduction, blocking apoptosis Enhances viral infectivity

The accessory proteins are essential not only in imparting pathogenesis *in vivo* but also for viral replication. One such important auxiliary gene is Tat which is essential for efficient transcription of viral genes and for viral replication. Tat differentially modulates pathogenic properties of the viral subtypes and plays a very important role in viral infectivity and pathogenesis. It has been earlier studied that subtype-C Tat might have a relatively higher ordered and less flexible structure than subtype-B Tat. It has also been demonstrated that subtype-C Tat as a protein was consistently inferior to subtype-B Tat in a variety of biological assays (Siddappa *et al*, 2006). This study emphasised the need for clade based studies of various HIV-1 auxiliary proteins. There have been reports where clade specific differences in Tat and Vpr activities had been demonstrated (Bano *et al*, 2007; Mishra *et al*, 2008).

Another unique HIV-1 accessory protein is Vif. Human immune cells-T lymphocytes, monocytes or macrophages are the main reservoirs for HIV-1 *in vivo*. *In vitro* studies in these specified cell lines with HIV-1 strains carrying mutant Vif, have shown that these strains produced non-infectious viral progenies. By contrast, research carried out by using other HIV-1 mutated accessory proteins, such as Nef, Vpr and Vpu, leads to reduced but replication competent viruses. This tells about the requirement of Vif by HIV-1 for production of infectious progenies so as to continue with the infection.

Conclusion

A common scenario among HIV infected patients is the evolution of virus as resistant to anti-retroviral drugs, besides toxicity and pharmacokinetic differences between individuals. Although cytotoxic responses against key viral genes can be generated, broadly neutralizing antibodies are very poorly generated. One of the main reasons being heavy glycosylation of HIV-1 envelope protein which buries the epitopes (cryptic) important for mounting an effective immune response. These are the two major hurdles for generating a vaccine against HIV. Besides, the correlates of immune protection are not known and scientists now believe that the answer may come from the elite controllers in humans or from monkeys who harbor a similar virus in large numbers throughout their life time and do not come down with disease. HIV-1 infection results in massive apoptosis in T-cells and the roles played by individual viral genes have not been explored in details. It is important for successful virus replication to overcome initially the host restriction but for the dissemination of virus it is in the interest of the virus to cause lysis of the susceptible cells and case subsequent spread.

References

- Bano, A.S., Gupta N., Sood, V., Banerjea, A.C. (2007) Vpr from HIV-1 subtypes B and C exhibit significant differences in their ability to transactivate LTR-mediated gene expression and also in their ability to promote apoptotic DNA ladder formation. *AIDS* **21** (13): 1832.
- Bobkov, A.F., Kazennova E.V., Selimova, L.M. (2004) Temporal trends in the HIV-1 epidemic in Russia: predominance of subtype A. *J Med Virol* **74** (2): 191.
- Chan, D.C., Kim, P.S. (1998) HIV entry and its inhibition. *Cell* **93** (5): 681.
- Day, C.L., Mkhwanazi, N., Reddy, S., Mncube, Z., van der Stok, M., Klenerman, P., Walker, B.D. (2008) Detection of polyfunctional Mycobacterium tuberculosis-specific T cells and association with viral load in HIV-1-infected persons. *J Infect Dis* **197** (7): 990.
- Fauci, A.S., Pantaleo, G., Stanley, S., Weissman, D. (1996) Immunopathogenic mechanisms of HIV infection. *Ann Intern Med* **124**(7): 654-63.
- Gonda, M.A., Braun, M.J., Clements, J.E., Pyper, J.M., Wong-staal, F. (1986) Human T-cell lymphotropic virus type III shares sequence homology with a family of pathogenic lentiviruses. *Proc Natl Acad Sci USA* **83**: 4007.
- Goudsmit, J. (1997) *Viral Sex; The Nature of AIDS: Oxford University Press, New York* pp. 51.
- Haase A. T. (1986). Pathogenesis of lentivirus infections. *Nature* **322**: 131.
- Lin, S.H., Pauzai, C.D., Burkrinsky, M., Zhao, R.Y. (2005) Roles of HIV-1 proteins in viral pathogenesis and host-pathogen interactions. *Cell Research* **15** (11-12): 923.
- Marlink, R., Kanki, P., Thior, I. (1994) Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science* **265**: 1587.
- Mishra, M., Vetrivel, S., Siddappa, N.B., Ranga, U., Seth, P. (2008) Clade-specific differences in neurotoxicity of human immunodeficiency virus-1 B and C Tat of human neurons: significance of dicysteine C30C31 motif. *Ann Neurol* **63** (3): 366.
- Montoya, C.J., Cataño, J.C., Ramirez, Z., Rugeles, M.T., Wilson, S.B., Landay, A.L. (2008) Invariant NKT cells from HIV-1 or Mycobacterium tuberculosis-infected patients express an activated phenotype. *Clin Immunol* **127**(1).
- Pawlowski, A., Jansson, M., Sköld, M., Rottenberg, M.E., Källenius, G., (2012) Tuberculosis and HIV Co-Infection. *PLoS Pathog* **8** (2): e1002464.
- Robertson, D.L., Hahn, B.H., Sharp, P.M. (1995) Recombination in AIDS viruses. *J Mol Evol* **40** (3): 249.
- Toossi, Z., Johnson, J.L., Kanost, R.A., Mianda, W., Luzze, H., Peters, P., Okwera, A., Joloba, M., Mugenyi, P., Mugerwa, R.D., Aung, H., Ellner, J.J., Hirsch, C.S. (2001) Increased replication of HIV-1 at sites of Mycobacterium tuberculosis infection: potential mechanisms of viral activation. *J Acquir Immune Deficiency Syndromes* **28**: 1-8.
- Siddappa, N.B., Venkatramanan, M., Venkatesh, P., Janki, M.V., Jayasuryan, N., Desai, A., Ravi V., Ranga, U. (2006) Transactivation and signaling functions of Tat are not correlated: biological and immunological characterization of HIV-1 subtype-C Tat protein. *Retrovirology* **3**: 53.
- Suzuki, Y., Craigie, R. (2007) The road to chromatin - nuclear entry of retroviruses. *Nat Rev Microbiol* **5** (3): 187.
- Swanson, C.M., Malim, M.H. (2008) Snapshot-HIV proteins. *Cell* **133**: 742.
- Wyatt, R., Sodroski, J. (1998) The HIV-1 envelope glycoproteins: fusogens, antigens, and immunogens. *Science* **280** (5371): 1884.