Human immunodeficiency virus -1: A brief overview of virology, diagnosis, pathogenesis and treatment

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Abstract

This article intends to present important aspects related to HIV which would serve as an introduction to beginners' of HIV research. A brief overview of the structure, genome organization and the function of viral proteins of HIV-1 required for viral infection and replication are presented. The genetic diversity of HIV-1 along with its diagnosis and pathogenesis, host immune response, transmission routes and prevention methods are also summarized. Finally, the treatments against HIV-1 and drug resistance are briefly discussed. The ratio of different routes of HIV transmission from infected person to a healthy person and the effectiveness of their preventive measures are summarized. The review also describes about HAART, newer therapies like microbicides and vaccines.

Keywords: HIV, AIDS, Structure, Pathogenesis, Infection, Transmission.

1. Introduction

Human Immunodeficiency virus (HIV) is the etiologic agent of AIDS [1]. There are two types of HIV: HIV-1 and HIV-2. HIV-1 type is the predominant virus found worldwide and relatively uncommon HIV-2 type is concentrated in West Africa and is rarely found elsewhere. HIV-1 arouse from a strain of SIV from a Sooty Mangabey monkey (SIV-SM). It is a member of the genus '*Lentivirus*' in the Retroviridae family comprising enveloped RNA viruses [2]. The International committee on Taxonomy has classified the genera of the retroviruses based upon genome organization as simple and complex. The lentiviruses are complex viruses encoding the Gag, Pol, Pro and Env gene products with small regulatory proteins whereas the simple viruses encode only the former [3]. Retroviruses have the characteristic feature of transcribing their genetic material ribonucleic acid (RNA) into linear double stranded DNA by enzyme 'reverse transcriptase (RT), a RNA dependent deoxyribonucleic acid) DNA Polymerase that reverses the classical flow of genetic information. Then the DNA enters the nucleus and integrates as DNA provirus into the host cellular genome. The provirus integrated in to the host cellular genome is either transcriptionally active or remains in a latent state.

The first human retrovirus, human T-cell lymphotropic virus type1 (HTLV-1) discovered by Poise and Gallo in 1979 was reported to cause adult T-cell leukemia, neurological disease and rarely severe immunodeficiency in humans. HTLV-1 is transmitted through sexual contact and through blood transfusion. A closely related virus discovered in the early 1980's was named HTLV-II and it was found to be associated with a few cases of cancer in humans. In 1983, Montagnier and his colleagues discovered a retrovirus in the lymph node of a man with AIDS related complex (ARC) and it was named lympadenopathy associated virus or LAV. Another retrovirus named HTLV-III was identified by Gallo and co-workers from the peripheral blood lymphocytes of AIDS patients. Thus the various forms of single virus resulted in the destruction of lymphocytes and antibody production in AIDS patients and ARC patients. This virus has been named as human immunodeficiency virus type 1(HIV-1) and is accepted as the cause of AIDS [4].

The HIV/AIDS poses to be a destructive pandemic to humans since the first case of AIDS was reported in the United States on December 1, 1981 [5]. As of April 2008, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the WHO has estimated that there are 60 million individuals infected with HIV-1 and 25 million individuals dead [6] and about 30 million people are living with HIV infection in the world. At global level, majority of new HIV-1 infections are resulted due to unprotected sexual intercourse between serodiscordant partners. The United States is the country most heavily affected by the HIV/AIDS pandemic in the industrialized world [7]. The three-quarters of

newly reported cases of HIV-infection constitute US men comprising men having sex with men (MSM) and African MSM [8].

2. Structure and genome

Retroviruses are spherical, enveloped, positive strand RNA viruses with diameter of about 80-120 nm. The infectious virion contains two copies of a single- stranded genomic RNA about 7-11 kb in length. The mature infectious virus particles has an outer lipid bilayer consisting of gp120 and gp41 envelope glycoproteins and a dense cone-shaped core composed of the viral p24 Gag capsid (CA) protein enclosing the two molecules of single stranded RNA. The Gag matrix (MA, p17) protein forms the inner shell below the viral membrane and the nucleocapsid (NC, p7). The genome of HIV is about 10 kb with open reading frames coding for three structural (Gag, Pol and Env) and six accessory proteins (Vif, Vpr, Vpu, Rev, Tat and Nef). The virus has the basic genomic structure of retroviruses: gag-pol-env structural genes symmetrically flanked by two complete viral long-terminal repeats (LTRs) [2].

3. HIV Genetic diversity

The highly genetic variability of HIV-1 is driven by the fact that high mutation rate is caused by the enzyme RT in DNA, resulting about ten base pair changes in the HIV genome per replication cycle; the presence of viral RNA as a dimer and by selective immune pressure [9]. The genetic diversity influences the biological aspects of HIV-1 strains such as infectivity, transmissibility and immunogenicity. Phylogenetic analyses have classified the full length HIV-1 viral genome into three different groups: M (major), O (Outlier) N (non-M/non-O) [1] and P (yet to be predicted) [10]. Group M viruses are the most widespread and responsible for more than 99% of infections worldwide and these have been divided into nine distinct genetic subtypes or clades, designated A to D, F to H, J and K. The reason for the distinction stands as the variation in amino acid composition by at least 20% in the envelope region and 15% in the Gag region. Almost 15 circulating recombinant forms such as B/F, A/F, G/A, B/D, F/B, A/D, D/A and A/E have been identified. The HIV-1 subtypes and CRFs are very unevenly distributed throughout the world, with the most widespread being subtypes A and C.

Subtype A and CRF A/G predominate in West and Central Africa, with subtype A reasonable for the Russian epidemic [11]. Even though, subtype B has been the most common subtype/CRF in Europe, the Americas, Japan and Australia, other subtypes are now becoming more frequent and accounts for at least 25% of new HIV infections in Europe. Subtype C is predominant in Southern and East Africa, India and Nepal. It has caused the world's worst HIV epidemics and is responsible for around half of all infections. 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; J only in Central America; and K only in the Democratic Republic of Congo and Cameroon. The migration, travel and high-risk behavior of HIV-1 infectious people from various parts of the world stand as the reason for the spread of HIV-1.

4. HIV Infection and replication

The infection occurs with the attachment of the virions to the cell surface mediated by an interaction between the extracellular domain of HIV-1 gp120 and cellular receptors. CD4 is the major receptor for HIV-1 and the seven-transmembrane chemokine receptors CCR5 and CXCR4 are the main HIV-1 co-receptors in *vivo* [12, 13]. CXCR4 acts as a co-receptor for the T cell-line-tropic HIV strains whereas CCR5 acts as a co-receptor for macrophage-tropic HIV isolates. Binding of CD4 to gp120 induces conformational changes in gp120 to interact with a chemokine receptor. Binding of gp120 to CD4 and a chemokine receptor triggers further structural changes that allow the fusion of gp41 into the target cell membrane [14].

The viral core is then released into the cytoplasm of the cell. The cellular factors Nef, Vif and viral protein MA uncoats the virus and the viral RNA genome is retrotranscribed into a full-length double stranded DNA by the viral RT [15]. On completion of reverse transcription, the viral DNA is transported to the cell nuclease through nuclear pores by HIV-1 Vpr. In the nuclease, another viral protein, Integrase (IN) catalyses the insertion of viral linear double stranded DNA into a random site in the host chromosome which is referred to as provirus. The integrated proviral

DNA undergoes transcription by RNA Polymerase II through binding of cellular factors to the viral Long Terminal Region (LTR) and translation occur by producing minimal amounts of Tat, Rev and Nef [16]. The transcription of viral RNA from the integrated provirus is similar to transcription of host cell messenger RNA (mRNA). The promoter that is responsible for the regulation of transcription are present in the 5'- or upstream LTR and sequences that signal the termination of RNA synthesis and polyadenylation are present in the 3'- or downstream LTR. The genome of all retroviruses, including HIV can be subdivided into three coding regions: gag, pol and env [2]. The gag-pol gene is primarily translated to produce the Gag and Gag-Pol polyproteins. Gag polyprotein (p55) kDa precursor is proteolytically processed during the maturation of the virus into six structural proteins necessary for a mature virion. There are four HIV gag proteins- p24, p17, p9 and p6 that function as the major capsid protein (CA), the matrix protein (MA), and the two nucleocapsid proteins (NC) respectively. Ultimately, the budding process of the HIV activates the PR that autocatalytically cleaves the Gag and Gag-Pol polyprotein releasing the structural proteins ad enzymes.

5. Pathogenesis

HIV pathogenesis constitutes a series of the course of HIV infection which leads to the development of AIDS or long-term survival. The stages of HIV infection are categorized by utilizing clinical and laboratory parameters. The classification scheme includes the following categories: seronegative infection, seroconversion, asymptomatic seropositive early asymptomatic HIV infection, asymptomatic HIV infection and AIDS. It is noted that patients may or may not advance from one level to another, but they never return from an advanced stage to an earlier stage and patients may skip the symptomatic HIV categories during the advancement of the AIDS However, the pathology of HIV is described by Levy is as follows.

5.1. Primary infection

Primary infection of the sexual mucosa occurs with the local infection of macrophages, dendritic cells and T cells [17]. Dendritic cells which are antigen presenting cells migrate to the lymph nodes and passively deliver HIV to T cells by their immunological synapses. It is also stated that some exposed 'uninfected' humans could experience local mucosal infection without the systematic spread of HIV and seroconversion [18, 19].

At the initial stage of HIV infection itself, the human body's largest lymphoid organ the gut or mucosal-associated lymphoid tissue (MALT) is damaged [20, 21]. The attributes of MALT infection are the depletion of CD4+ T cells and the damage of gut epithelium and the leakage of gut bacteria into the MALT and their lipopolysaccharides (LPS) leading to inflammatory responses [22]. Due to tremendous viral replication of HIV-1 in MALT, viral load detected in the peripheral blood reaches a peak value. A sharp fall in the viral load occurs soon after seroconversion due to the appearance of HIV-specific CD8+ cytotoxic T cells. Two other factors are also considered for the decrease in the viral load: as low viral load occurs, non-neutralizing antibodies appear in conjunction with innate immune response followed by the appearance of neutralizing antibodies appear after several weeks or months. Both these factors lead to the clearance of virus particles [23]. Secondly, the severe depletion of CD4+ CCR5+ T cells in the gut causes insufficiency of new target cells for HIV-1 to maintain a high viral load.

5.2. Chronic infection and progression to AIDS

The viral load in the peripheral blood settles down to a 'set point' after seroconversion and reduction in peak virus production [24]. The 'set point' is considered as a predictive measure of the rate of progression to AIDS. The higher the set point, the speeder the advancement towards immune deficiency. The average of AIDS takes on 9 years and rapid progression on 5 years and those who remain well without a decrease in CD4+ cell counts for 15 years are regarded as long-term non-progressors.

During the clinical asymptomatic period, active HIV replication and destruction of CD4+ T cells in the MALT and in lymph nodes continues but the regenerative power of CD4+ T cells is significant [25]. Initially, most naive and central memory CD4+ T cells are active but their regenerative capacity gets reduced gradually. The decrease in CD4+ T cells count in peripheral blood is an independent marker from viral load of disease progression. When CD4 cell counts fall below 200 cells μl^{-1}, opportunistic infections also occur in the AIDS state.

6. HIV Transmission

HIV is found in varying concentrations or amounts in blood, semen, vaginal fluid, breast milk, saliva, urine and tears. The rate of transmission by saliva, urine and tears are negligible [26]. The transmission of HIV occurs from infected person to a healthy person through three main means where heterosexual transmission accounts the highest rate, secondly mother to child transmission and thirdly the transmission through HIV infected blood and blood products. An effective preventive measure for sexual transmission has proved to be condoms. Male circumcision has shown to decrease transmission in men up to 60%. The treatment of ulcerative genital diseases also reduces HIV infection and transmission. Highly active antiretroviral therapy (HAART) is being evaluated for use in post exposure prophylaxis (PEP). Antiretroviral therapy has also reduced the risk of mother to child transmission. Female condoms, diaphragms, vaginal microbicides or compounds inhibiting HIV adsorption and cell-to-cell contact need further evaluation.

According to a review study carried out by INDEPTH Network of health and demographic surveillance systems (HDSSs) on prevention and treatment of HIV/AIDS in low- and middle-income countries, consistent condom use has been found to be highly protective against HIV infection; women are unable to convince their partners to use it. Populations with high rates of STDs and high-risk sexual behavior are associated with HIV infection; interventions to treat STDs can prevent HIV transmission. Mother-to-child transmission was 2.7 times higher in infants breastfed for less than 6 months and the most promising intervention discovered so far is male circumcision [27].

7. HIV Prevention

The HIV-1 transmission can be prevented by sexual abstinence, delayed sexual debut, reduced number of sexual partners, routine condom use, reduced needle sharing or clean needle use among injection users. The male latex condoms and female condoms, cervical caps, vaginal diaphragm are majorly used by men and women respectively for controlling HIV transmission. The practice of male circumcision reduces female-to-male transmission by approximately 50% to 60% [28]. HAART is used as a preventive measure for mother-to-child transmission during pregnancy, delivery and breast feeding. The treatment of sexually transmitted diseases may also reduce the rate of HIV-1 transmission since these are cofactors of HIV.

8. Diagnosis

The diagnosis of primary HIV-1 infection is made easier by the recognition of high risk population. Unprotected sexual intercourse and needle sharing are the major risk factors for HIV-1 transmission among adolescents and adults and other risk factors include type of exposure, the presence of sexually transmitted infections, captivity, depression, feeling of exclusion from peer groups, drug use, trading sex for drugs or money, and even the use of mediations for erectile dysfunction [29,30]. Transmission can also occur as a result of lower risk exposures such as insertive intercourse and oral sex [31]. The diagnosis of newly infected individuals is a very crucial factor since they put themselves and others at risk for HIV-1 transmission, hence counseling should be provided as early as possible. These individuals with primary infection are likely to have high levels of HIV-1 circulating in blood and genital secretions and substantially contribute to the ongoing epidemic of new infections [32]. It is reported that the diagnosis is often missed in spite of stressing the importance of identifying primary HIV-1 infection and educating health - care providers to recognize this stage of disease.

9. Treatment

9.1. Antiviral drugs

All the steps of viral life cycle can act as targets for antiretroviral therapy. The three major steps in viral life cycle are used as targets for the inhibitory action of drugs. The antiretroviral drugs are categorized in to reverse transcriptors (nucleoside/nucleotide, NRTI and non-nucleoside, NNRTI); protease inhibitors; fusion inhibitors. Another family of HIV antiviral drugs which are being tested in phase I clinical trials are called as integrase inhibitors [33].

The highly active retroviral therapy (HAART) involves the use of agents from at least two distinct classes of aniretrovirals. The standard of care in anti-retroviral therapy includes two NRTI plus a potent third drug, usually a protease inhibitor (PI) [34]. The HAART has resulted in the increase of CD4+ T cell count and decrease in the plasma viral load to undetectable levels and this condition is maintainable for years [35]. However, HAART for long time has certain obstacles like resistance development and emergence of HIV-1 mutation, severe side effects, pharmacokinetic interactions and by patients' personal choice too [36].

Reverse Transcriptase (RT) enzyme uses these NRTI instead of the normal nucleotides and thus interrupt transcription step of HIV replication process. The NNRTI drugs bind specifically to HIV-RT altering the active site, thus reducing the binding of the natural nucleotides. Protease inhibitors prevent the processing of viral capsid proteins resulting in non-infectious virions [37]. HIV fusion inhibitors bind to HR2 (Heptad Repeat) region of gp41 and inhibits HIV entry at the membrane fusion stage [38]. The integrase catalyses the insertion of the viral cDNA (complementary Deoxyribonucleic acid) generated by RT from the viral genome into host chromosomes. Integrase inhibitors prevent virus replication by blocking this process. [33]. The maturation inhibitors are considered as an attractive therapeutic target following HIV-1 protease inhibitors. Non-protease inhibitors acting on maturation inhibits HIV- replication in tissue culture and animal model systems are presently in phase II clinical trials**.** The drug disrupts the processing of Gag at the CA-p2 cleavage site, leading to the accumulation of the CA-p2 processing intermediate [39, 40].

The inhibition of gp120 – CD4 interaction affects the viral attachment and entry process of HIV [41].Binding of HIV-1 gp120 envelope glycoprotein to CD4 induces conformational changes in gp120 thereby exposing a binding site for either co-receptor CCR5 or CXCR4.The phenotypic switch from CCR5 to CXCR4 occurs after several years of infection. The co-receptor antagonists interfere with the gp120-CXCR4/CCR5 complex formation [42]. The various types of inhibitors mentioned above with examples are listed in Table 1.

Table 1. The various types of antiviral drugs used in different stages of HIV lifecycle with examples.

Type of Inhibitors	Examples
Reverse Transcriptase Inhibitors (NRTI's)	Zidoviudine (AZT), lamivudine (3T3), Stavudine (d4T)
Reverse Transcriptase Inhibitors (NNRTI's)	Nevirapine (NVP), Delaviridine (DLV), Efavirenz (EFV)
Protease inhibitors	Amprenavir (APV), Atazanavir (ATV), Indinavir (IDV), Iopinavir (IPV), Nelfinavir (NFV), Ritonavir (RTV) and Saquinavir (SQV)
Fusion inhibitors	Enfuvirtide, T1249
Integrase inhibitors	Raltegravir, Eltegravir
Maturation inhibitors	bevirimat or PA-457
Entry Inhibitors (gp120-CD4)	Zintevir, FP-21399, BMS-378806, PRO 542, BMS 806, PRO 140
CCR5 co-receptor antagonists	TAK-779, TAK-220, SCH-C, SCH-D, E913, AK-602, NSC651016
CXCR4 co-receptor antagonists	AMD 3100, AMD 3465, ALX40-4C, T22, T134, T140

The table represents the various steps of antiretroviral therapy and their respective examples of antiviral drugs under study.

9.1.1. Drug resistance

The emergence of drug resistance is a major limiting factor for drug efficacy. Hence new antiretrovirals acting on alternative targets for avoiding cross resistance with older compounds and improved systematic tolerability profiles are being developed. The occurrence of one or more mutations in the viral RT coding region leads to the development of resistance to RT inhibitors. The resistance mutations are resulted due to the loss of viral fitness in the absence of drugs and sometimes because of the compensatory mutations that improve the viral replication capacity of the virus [43]. Single nucleotide mutations are frequently associated with resistance to non-nucleoside RT

inhibitors. These mutations represent the amino acid substitutions in the viral RT that decrease the enzyme's ability to bind the inhibitor.

Resistance to protease inhibitors is developed due to the acquisition of mutations that result in conformational changes in and around the active site that lead to reduced inhibitor binding. Generally it is reported that the genetic barrier for protease inhibitor resistance is relatively high, requiring two or more amino acid changes to cause significant resistance [44]**.** Resistance to the reported maturation inhibitor confers mutations appearing at the CA-p2 cleavage site [45]. These mutations make HIV-1 less susceptible to inhibitor when introduced in an infectious clone by site-directed mutagenesis [46]. The recent determination of the structure of catalytically active complex of HIV-1 integrase with the viral DNA substrate [47] is found to be good platform for structural analysis and optimization of drug candidates that target HIV integration. The high level resistance to integrase inhibitors occurs due to the accumulation of integrase mutations [48]. Resistance to CXCR4 or CCR5 inhibitors is highly dependent on the HIV-1 envelope backbone, virus heterogeneity and drug efficacy. The patterns of the resistance depends upon the virus and cell culture conditions used [49].

A new study was published in PLOS Medicine involving 50,000 patients in 111 countries in resource – limited settings using the medication non-nucleoside reverse transcriptase inhibitors. The data was collected from 287 studies published between 2000 and 2013. The study stated that a small group of mutations accounted for the major cause of transmission related resistance to HIV drugs. About 93 mutations were found to be present in each virus sequence which indicated HIV drug resistance. The study also found the overall prevalence of transmitted drug resistance ranged from 2.8 percent in Sub-Saharan Africa to 11.5 percent in North America. In South Asia and South-East Asia, the transmission rate remained unchanged for a decade.

Most of the protease and RT positions associated with drug resistance in subtype B viruses are selected by antiretroviral therapy in one or more non-B subtypes. Conversely, no evidence was found that non-B viruses develop resistance by mutations at positions that are not associated with resistance in subtype B viruses [50].

9.2. Microbicides

Clinical research is going on for developing microbicidal compounds targeting the various steps of the life cycle of HIV-1 like membrane disruption, RT inhibitors, entry or fusion inhibitors. Out of these, entry and fusion inhibitors are gaining importance due to its new technology than the earlier generation microbicides [51-54]**.** There are many challenges involved for the flourishment of microbicidal research like ethical issues, lack of a validated animal model and meagre funding by only small companies, institutions and non-profit organizations; not by big pharmaceutical companies. A few RT inhibitors include Tenofovir, TMC-120, UC-781, Carraguard; entry/fusion inhibitors include BMS-378806, BMS-806, PSC-RANTES and its analogues and CMPD167. There are some compounds like praneem polyherbal whose mechanism of action is yet to be determined.

According to FACTS 001, a study testing the efficacy against HIV of a vaginal microbicide gel containing tenofovir, produced a null result. There was no difference found between HIV infection rate in young women given the gel and the rate in young women given a placebo gel [55].

9.3. Vaccines

Even though, most HIV candidate immunogens in clinical trials include subunit vaccines, envelope (Env) glycoprotein–based proteins are the major preferred vaccine target [56]**.** Other proteins that have been targeted are the Pol (polymerase) and Gag proteins. However, the Env proteins are widely targeted because of their expression on the surface of the virions and their significant role in viral–host interactions. In particular, neutralizing antibodies are directed exclusively against the Env proteins. The widely studied recombinant Env proteins are the full-length glycoprotein 160 and the external glycoprotein 120 (gp160 and gp120).

Vaccine development is also encountering formidable challenges due to the high genetic variability of the virus, improper immune correlates, limitations of animal models and various problems associated with the multiple clinical trials [57]. Till today, the efforts to develop an effective vaccine against HIV-1 have failed due to the incomplete understanding of HIV-1 immunity and inability to induce a potent immune response against HIV-1. The two vaccine candidates, gp120 envelope glycoprotein vaccine and adenovirus vector vaccine have failed due to these reasons [58, 59]. Hence, recent vaccine researches are focusing on the induction of cellular immune responses.

In a recent study, the co-evolution of broadly neutralizing antibodies (bnAbs) and the viruses that trigger the production of these antibodies in an HIV-infected individual was reported. The B cells secreted both a "helper" set of

neutralizing antibodies and cross-reactive neutralizing antibodies - found in around 20% of HIV-1 infected individuals. These together guide a vigorous set of bnAbs to HIV strains. The helper antibodies select the viruses that can effectively stimulate bnAbs. One antibody lineage reacted with the virus envelope and selected 'escape mutants' of viruses with virus envelopes unbound to the first lineage. The researchers have developed vaccine immunogens that selectively trigger both the helper neutralizing antibodies and cross-reactive neutralizing antibodies to produce bnAbs during HIV infection [60].

10. Conclusion

The extensive studies on HIV-1 have shed much light on its virology, pathogenesis and molecular mechanisms of viral replication. There is a tremendous advancement in science and technology by various diagnostic and prevention methods as well as in social environments to fight against this disaster by creating mass awareness programmes. The understanding of the molecular biology of the virus has helped us to develop anti-HIV therapy implemented by HAART utilizing both natural and synthetic drugs. Even though the death rate of HIV-infected patients has tremendously decreased by HAART, the emergence of drug resistance and drug toxicity is urging for the development of new antiviral drugs. A proper understanding of the immune response of the body is essential for the development of vaccines. The development of a successful vaccine and newer perspectives like microbicides offer a great hope for reducing the consequences of HIV. A deeper understanding of the molecular biological aspects of the viral life cycle would lead us to design newer therapies against HIV-1.

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