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Review Article

Insight to Epidemiology, Pathophysiology and Prevention of Human Immunodeficiency Virus Type-1

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ABSTRACT

Human immunodeficiency virus type 1(HIV-1) is a global pandemic with a prevalence of 35 million people living with it in 2013 compared to 29.8 million in 2001, but the people living with HIV are living longer owing to broader access to antiretroviral therapy. There has been a decline in new infections being reported by 38.23% from 2001 to 2013 which is appreciable. There has been a substantial increase in the understanding of the pathogenesis mechanism of HIV-1 at cellular level with role of host molecules like intra cellular adhesion molecule 1 (ICAM1) being investigated which increases the viral infectivity and viral micro RNA's such asvmiR98 and vmiR99 playing a role in latent HIV-1 infection. RV144 trial of HIV-1 vaccine conducted in Thailand showed 31% reduction in HIV-1 acquisition. Major developments in prevention of HIV-1 include antiretroviral therapy for preventing vertical transmission from mother to child, medical male circumcision, and antiretroviral therapy to prevent sexual transmission. Research towards broader understanding in key targets of HIV-1 infectivity and vaccine development are in progress.

Keywords: Human immunodeficiency virus 1, pathophysiology, prevention, vaccine.

INTRODUCTION

HIV (Human Immunodeficiency Virus) is a Retrovirus which contains RNA (Ribonucleic acid) as its genetic material. Within the retrovirus family it belongs to the sub group "Lentivirus" or "Slow" virus. Lentiviruses are known to have a long time gap between initial infection and appearance of serious symptoms. This is the reason why the most people are unaware of its infection and can spread the virus to the others. HIV is the causative agent of AIDS (Acquired Immuno Deficiency Syndrome) characterized by progressive deterioration of the immune system due to the destruction of CD4+T helper cells leading to compromised immune defense mechanisms of body exposing it to opportunistic infections and ultimately death.

There are two types of HIV found i.e. HIV- 1 and HIV-2, each with its subtypes and genetic diversities, HIV 1 is the major cause of AIDS pandemic and has a diverse genetic heterogeneity which is governed by various factors like deficit in proof reading ability of reverse transcriptase enzyme, immune factors of host, rapid multiplicity of HIV-1 in vivo, the variability thus accounts for variants among HIV-1 which are divided over three major phylogenic groups i.e. Group M (Main), Group O (Outlier) and Group N (which is Non M/Non O). [1] Group M is subdivided into 10 phylogenetic recognized clades (A to K). Group M is responsible for majority of the infections with HIV 1 worldwide. [2]

EPIDEMOLOGICAL HISTORY OF HIV/AIDS

HIV is considered as a global pandemic, UNAIDS-2014 gap report estimates that there were 35 million [33.2 to 37.2 million] people living with HIV at the end of the year 2013, as compared to that of 29.8 million [28.1 to 31.9 million] in 2001. [3]

AIDS was initially known as "slim disease" as it was associated with diarrhea and weight loss. The first cases of AIDS/HIV in Africa were described in the early 1980's where it affected the heterosexual populations in Sub Saharan African countries including Zaire (now Democratic Republic of Congo), Rwanda, and Uganda. [4]

The epidemic in Africa has always been majorly driven by the heterosexual transmission; in other regions such as Caribbean and Latin America, epidemic of HIV was also associated with injection drug use (IDU) and men who have sex with men (MSM). In these regions, the HIV epidemic was started in the late 1970s and early 1980s. By the year 2000, the Caribbean ranked second in the prevalence of HIV-1-infected adult population outside sub-Saharan Africa (PAHO, WHO, UNAIDS 2001). [5] In Asia, HIV/AIDS was first reported in Thailand, India - in the state of Tamil Nadu, and China around the mid to late 1980s. [4]

AIDS related deaths accounted for 1.5million [1.4 to1.7 million] globally in 2013 in which 1.1 million [1.0 to 1.3 million] aids related deaths are accounted from Sub Saharan Africa region alone, [6] There were 1.7 million aids related deaths in adults and children in the year 2001 compared to 1.2 million aids related deaths in adults and children's in 2013. [7] There were 3.2 million children living with HIV in 2013 globally with new infections of about 240 000 being reported in the same year globally, there is an overall decline of 58% in the new infections being reported in children. [6]

Whilst the rate of people living with HIV have gone up from 29.8 million in 2001 to 35.0 million in 2013, the rate of new HIV infections have be cut off by 38.23% from 3.4 million in 2001 to 2.1 million in 2013. [6]

PATHOGENESIS OF HUMAN IMMUNODEFECIENCY VIRUS

Understanding the life cycle of HIV is necessary because the current strategies used for treatment of HIV target various points in this cycle. Once HIV enters the human body, the outer glycoprotein (gp160) on its surface, which is composed of two subunits (gp120 and gp41) has affinity for CD4 receptors, proteins present on the surface of T-helper lymphocytes, monocytes, macrophages, dendritic cells, and brain microglia. The gp120 subunit is responsible for CD4 binding.

Once initial binding occurs, the intimate association of HIV with the cell is enhanced by further binding to chemokine co receptors. The two major chemokine receptors used by HIV to enter CD4+ cells are CCR5 and CXCR4. [8] HIV isolates may contain a mixture of viruses that target one or the other of these co receptors, and some viral strains may be dual-tropic (i.e., can use both co receptors). The HIV strain that preferentially uses CCR5, R5 viruses, are macrophage-tropic and nonsyncytium-inducing (syncytium is cell clumping). The R5 virus typically is implicated in most cases of sexually transmitted HIV. The HIV strain that targets CXCR4, designated X4 virus, is T-cell–tropic and often is predominant in the later stage of disease. X4 virus is syncytium-inducing. CD4 and co receptor attachment of HIV to the cell promotes membrane fusion, which is mediated by gp41, and finally internalization of the viral genetic material and enzymes necessary for replication.

After internalization, the viral protein shell surrounding the nucleic acid (capsid) is uncoated in preparation for replication. The genetic material of HIV is positive-sense (5′ to 3′) single stranded RNA; the virus must transcribe this RNA

into DNA (transcription normally occurs from DNA to RNA; HIV works backward, hence the name *retrovirus*). To do so, HIV is equipped with the unique enzyme RNA-dependent DNA polymerase (reverse transcriptase). Reverse transcriptase first synthesizes a complementary strand of DNA using the viral RNA as a template. The RNA portion of this DNA-RNA hybrid is then partially removed by ribonuclease H (R Nase H), allowing reverse transcriptase to complete the synthesis of a double-stranded DNA molecule. Unfortunately, the fidelity of reverse transcriptase is poor, and many mistakes are made during the process. These errors in the final DNA product contribute to the rapid mutation of the virus, which enables the virus to evade the immune response (which complicates vaccine development), and promotes drug resistance to evolve. Following reverse transcription, the final double-stranded DNA product migrates into the nucleus and is integrated into the host cell chromosome by integrase, another enzyme unique to HIV.

The integration of HIV into the host chromosome is troublesome. Most notably, HIV can establish a persistent, latent infection, particularly in long-lived cells of the immune system such as memory T lymphocytes. [9] The virus is effectively hidden in these cells, and this characteristic has greatly inhibited the ability to cure HIV infection. Second, random integration of HIV may cause cellular abnormalities and induce apoptosis.

After integration, HIV preferentially replicates in activated cells. Activation by antigens, cytokines, or other factors stimulate the cell to produce nuclear factor kappa B (NF-κB), an enhancer-binding protein. NF-κB normally regulates the expression of T-lymphocyte genes involved in growth but also can inadvertently activate replication of HIV. HIV-1 encodes 9 genes of which (Gag, Pol and Env) are structural genes and six regulatory and accessory proteins genes: Tat, Nef, Rev, Vpu, Vif, and Vpr, which enhance replication and inhibit innate immunity. [10] For example, the Tat protein is a potent amplifier of HIV gene expression; it binds to a specific RNA sequence of HIV that initiates and stabilizes transcription elongation. Vif is viral protein that binds human ABOBEC3, a cytosine deaminase that converts viral RNA cytosine to uracil and thereby provides innate cellular immunity. [11] Assembly of new virion particles occurs in a stepwise manner beginning with the coalescence of HIV proteins beneath the host cell lipid bilayer. The nucleocapsid subsequently is formed with viral single-stranded RNA and other components packaged inside. Once packaged, the virion then buds through the plasma membrane, acquiring the characteristics of the host lipid bilayer. After the virus buds, the maturation process begins. Within the virion, protease, another enzyme unique to HIV, begins cleaving a large precursor polypeptide (gag-pol) int into functional proteins that are necessary to produce a complete virus. Without this enzyme, the virion is immature and unable to infect other cells.

HIV-1 exhibits a very high turnover rate, with an estimated 10 billion new viruses produced each day. More than 99% of these viruses are produced in newly infected activated cells. Ultimately, most infected cells and some uninfected bystander cells will be destroyed from a number of mechanisms, including cell lysis by newly budding virions, cytotoxic T-lymphocyte–induced cell killing, syncytia formation, and apoptosis. Syncytia formation occurs when viral proteins expressed on the surface of the infected cell act as ligands for receptors expressed on uninfected cells. Uninfected cells clump onto the infected cell and fuse into a giant multinucleated cell. The syncytium-inducing X4 virus phenotype may develop later in disease and is associated with more rapid disease progression. [12] Destruction of the CD4 cells leads to profoundly compromised immune function and consequently AIDS.

CELLULAR FACTORS THAT PROMOTES VIRAL REPLICATION

The working mechanism of HIV-1 became clearer through the identification of cellular ligands that are earmarked by the virus for its replication. Of these, CD4 functions as a receptor for HIV-1. [13,14] Important studies proving that the infection of macrophages and lymphocytes by HIV-1 could be inhibited by specific chemokines hinted that chemokine receptors have a role in HIV-1 replication. A year later, the chemokine receptor CXCR4 and, shortly after, the chemokine receptor CCR5 was identified as coreceptors for HIV-1. [15] There have been significant advances in the identification of various cellular cofactors that affect events in replication after entry of the virus. The cellular transcription factor, nuclear factor of activated T cells (NFAT) - a rate limiting in quiescent T cells, has been implicated as a cofactor for reverse transcription. [16] Several cellular proteins are suspected to function as cofactors in establishing the provirus. Such factors might help HIV-1 to select an integration site that is optimal for gene expression of the virus in order to support an active, rather than a latent state of transcription. Significant advances have been made in identifying various cellular cofactors that are essential for the activities of the chief regulatory proteins of the virus, namely Rev and Tat. It was observed that Tat simply serve to recruit a cellular protein called cyclin-T1, which distinctly increases the efficiency of viral transcription, Rev, which has a crucial central role in moving viral RNA from nucleus to the sites of translation, requires a cellular nuclear export protein known as CRM-1 for its function. [17,18] Cellular factors that participate in terminal events of the viral replication cycle are being steadily identified. Setting the stage in this area the finding of cyclophilin A, which is involved in protein folding, associates with the viral Gag protein vital for viral infectivity. More recently, a human ATP-binding protein known as HP-68 has been shown to bind HIV-1 Gag and to involve in the conformation of the viral core. [19] Tumor suppressor gene 101 (TSG-101) is a third cellular protein that interacts with Gag to promote budding of the virus from the plasma membrane. [20,21]

Despite these important advances, we have barely scratched the surface to identify the cellular ligands for HIV-1. This is not due to lack of identifiable candidates, but difficulty in validating which factors are functionally valuable for HIV-1 replication. RNA-mediated interference (RNAi) demonstrates a prime opportunity to modulate the expression of cellular genes in order to gauge their impact on viral replication.

Studies have demonstrated that Intracellular adhesion molecule 1 (ICAM-1) which is a component of host cell surface molecule act as a strong attachment factor and increases the infectivity of HIV-1 substantially, the exact mechanism through which such constituents gets inserted and enhance the infectivity remain(s) uncertain. [22]

There are many micro RNAs (mi RNAs) which are derived from viral genome are identified which play important role in viral replication and its interaction with host are identified. Among these mi RNAs, a recently identified HIV1 encoded mi RNA, denoted as miR-H3 is found to specifically enhance the production of virus and its mutation resulted in significant impairment in replication of HIV1. [23] New research on the micro RNA's have found that there are Novel HIV micro RNA's like vmiR88 and vmiR99 in the systemic circulation of HIV positive patients which serves as ligands for TLR8 signalling that facilitates macrophage TNFα release which may contribute towards chronic activation of immune system. [24] Of late Duverger et al proved that proto onco gens PIM-1 plays important role in reactivation of latent HIV-1 infection. [25]

PREVENTION OF HIV-1 INFECTION

Sexual transmission:

Antiretroviral therapy

Prevention of sexual transmission of HIV has been a major priority since the beginning of the epidemic, but no single intervention is effective enough to curtain the spread and multi level interventions are necessary to control the spread of epidemic.Several major advancements took place in recent years in regards to prevention interventions. [26] The most powerful intervention in limiting the spread of HIV through sexual transmission is use of antiretroviral therapy, as evident by the findings of the HPTN 052 study. In this study the HIV infected partner from a serodiscordant couple with CD4+ T cells count of 350-550 cells per µL were randomized to receive immediate antiretroviral therapy (early ART arm), or delayed ART arm when their CD4+ T cells count droped 200-250 cells per µL. From this study it was observed that there was a relative reduction of 96% in HIV-1 linked transmission resulted from early initiation of ART compared to delayed ART therapy. [27]

Male Circumcision (MC)

Benefits of MC in reducing heterosexual HIV transmission were demonstrated with three consecutive randomized trials from Africa with reduction of 53-60% in heterosexual HIV transmission. [28] Three large randomized control trials enrolling >10,000 men were conducted in Kenya, South Africa and Uganda, which showed a reduction of 50-60% heterosexual HIV acquisition. [29-31] The results from these trials offer an insight into the acquisition of HIV-1 in men, pointing that the inner mucosa of the foreskin is a key target for HIV-1. [32]

Behavioural Interventions

These intervention methods were foremost utilized in prevention of HIV-1 spread. These interventions focused on routine condom use, reducing number of sexual partners, delayed sexual debut, reducing needle sharing among injection drug users. [33] Reductions in prevalence of HIV-1 in many countries, including the United States, Australia, Brazil, Thailand, Uganda and Kenya, have been possible as a result of combinations of behavioral intervention methods. [34]

Mother to child transmission (Vertical Transmission)

In recent past there has been a remarkable progress towards reduction of HIV-1 vertical transmission. Implementation of recommendations for prevention of HIV-1 vertical transmission have resulted in ten times reduction in the risk of transmission and complete elimination of HIV -1 vertical transmission is now feasible. Antiretrovial therapy is the mainstay in preventing vertical HIV-1 transmission. Combinational antiretroviral therapy is effective in preventing vertical transmission, reducing sexual HIV transmission and reducing morbidity and mortality. [29] Access to HIV testing in antenatal care in combination with vertical transmission interventions is important in preventing the spread in high HIV-1 prevalence countries.

Treating STDs

Sexually transmitted diseases are described as cofactor for HIV-1 transmission, rendering HIV-1 negative subject more susceptible for infection. [35] Symptomatic and asymptomatic herpes simplex type 2 (HSV-2) infections are believed to contribute towards HIV-1 spread. [36] However use of HSV suppressive therapy failed to prove a significant benefit in two clinical trials. [37] More research is needed in the area of other interventions in treating co infections of HIV-1.

Vaccines

The challenges faced in development of an effective vaccine for HIV include the genetic diversity of the HIV, poor understanding of the HIV-1 immunity and difficulty in development of antigens that are highly immunogenic in nature. RV144 trial [38] performed in Thailand is the only trial showing 31% reduction in the HIV acquisition with vaccine. More research in identifying the targets for neutralizing antibodies is needed in development of more efficacious and safe vaccine. [39]

CONCLUSION

The pathogenesis mechanism of HIV-1 is complex and still not fully understood with major targets of host to viral infectivity like ICAM-1 and viral proteins like micro RNA's for latent activation of infection being investigated recently. As the major targets for vial activation and infectivity will be identified more novel approaches in the antiretroviral therapy can be expected which can offer a greater coverage to limit viral activity. Combinational anti retroviral therapy is key for preventing sexual and latent transmission of HIV-1 and much focus is being given in this aspect which can be evident from UNAIDS data showing reduction of new infections. Research towards development and improvement of vaccine is needed to limit the acquisition of virus, which if resulted to be safe and effective can be a major breakthrough in HIV-1 research.

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