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Antiretroviral Strategies for Treatment of HIV

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Abstract

Since 1981 when first AIDS cases were identified in United States followed by Africa there has been growing understanding in the trajectory of HIV/AIDS across the world. The disease has caused unpredicted suffering, loss of life and disruption of family, social and economic abilities. Many therapies were introduced to treat AIDS. Those therapies have provided many insights in development of vaccine to decrease the pathogenecity and virulence of HIV. Here I will be discussing the strategies involved in the development of therapies for HIV. The treatments include Traditional vaccine designs, Novel Vaccine Designs and Antiretrovirals such as Protease inhibitors, Nucleotide Inhibitors, GP120 Inhibitors and modes of their action.

Keywords: HIV/AIDS, Antiretroviral therapy (ART), Antivirals, Antiretrovirals, CD4+ Cells, Cytotoxic T lymphocytes (CTLs), Reverse Transcriptase, Protease Inhibitors.

Introduction

HIV (Human Immuno deficiency Virus) is a *Lenti* virus a member of Retro viral family which causes Acquired Immuno Deficiency Syndrome (AIDS) – which particularly affects Immune system. HIV remains the greatest public health crises in the world today [1]. HIV infection is characterized by a prolonged asymptomatic period of years to decades, which is followed by the fatal illness. Various complications characterize AIDS, including wasting, neurological impairment, and opportunistic infections and malignancies. Human immunodeficiency virus (HIV) infection has been associated with rhabdomyolysis [2]. The asymptomatic period was often considered as relatively quiescent with regard to viral replication with the frequent usage of the misnomer 'clinical latency' [3]. Disseminated histoplasmosis is associated with Acquired Immunodeficiency Syndrome (AIDS), involves different organ systems and may be fatal if untreated [4]. PAfrican histoplasmosis is related with HIV [5]. HIV offers a difficult target for vaccine development. The HIV isolates that infect humans and cause AIDS include a genetically diverse population of viruses [6]. Genetic diversity is also continuously generated in the course of an HIV infection in a single infected individual, as the inaccurate enzymatic machinery of this virus's replication results in ongoing production of mutant virions.

Replication of HIV-1 is a complex process that is accomplished by various structural and non-structural viral proteins. Integrase (IN) is a key enzymatic molecule of HIV-1 that is not only essential for the viral cDNA integration but is also a contributor to various events at early stage of HIV-1 replication, such as the reverse transcription, nuclear import and chromatin targeting of the viral cDNA [7]. Chronic human immunodeficiency virus (HIV) infection is characterized by defects in the immune system including depletion of CD4+ T-cells and impaired T-cell function. Successful Antiretroviral Therapy (ART) suppresses viral replication [8]. Research suggests that Physical Activity (PA) is inversely related to numerous metabolic disorders in people who are living with HIV [9]. Lower Respiratory Tract Infections (LRTI) continues to be a major cause of morbidity and mortality in people living with HIV [10].

Hiv and pandemic potential

HIV is among the leading causes of death worldwide and it causes more deaths than any other infectious diseases. Sub-Saharan Africa is disproportionally affected by HIV, comprising over two thirds (22.5 million) of the people living with HIV/AIDS worldwide and 76% of the AIDS deaths [11]. The official start of the pandemic occurred in the summer of 1981 when the US Centers for Disease Control and Prevention reported on a cluster of *Pneumocystis carinii pneumonia* (PCP) in five homosexual men [12,13]. In 2007 worldwide, the number of adults and children living with HIV was estimated at 33.2 million, including 2.5 million children, with 2.5 million new cases that year, and 2.1 million AIDS deaths [14]. By 2010, it is estimated that 18 million children will be orphaned due to losing parents in the epidemic in Sub-Saharan Africa, the region that has most of the world's AIDS orphans [15]. The estimated number of children under the age of 15 years living with this virus globally is 2.3 million as of 2005. Asia and Africa continue to carry the greatest burden of this disease with over 1.9 million (82.6%) children infected with HIV [16]. In tropical areas, one of the most prominent features of HIV infection is its frequent association with opportunistic or not often parasitical infectious diseases [17]. Some studies indicated that AIDS can be transmitted through rapid use of Injection drugs [18]. Liver disease caused by HIV-1/HCV co-infection is characterized by the inflammation and cell-death [19,20].

Strategies in development of HIV vaccine

The introduction of Antiretrovirals has changed the course of HIV disease from invariably fatal illness to chronic but manageable one. Preferred viral suppression treatment includes Protease inhibitor-Integrase inhibitor, nucleoside reverse transcript inhibitor, gp protein inhibitors, etc., which were proven to suppress antiretroviral activity [21]. Antiretroviral therapy refers to the use of pharmacologic agents that have specific inhibitory effects on HIV replication. Antiretroviral agents belongs to six distinct classes of drugs, the nucleoside and nucleotide reverse transcriptase Inhibitors, The non nucleoside reverse transcriptase Inhibitors, The protease Inhibitors, The fusion inhibitors,

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The CRR 5 Co receptor antagonistic and The Integrase Inhibitors [22]. Antiretroviral therapy for the treatment of human immunodeficiency virus infection has improved steadily since the advent of potent combination therapy in 1996 [23]. New drugs have been approved that offer new mechanisms of action, improvements in potency and activity even against multidrug-resistant viruses, dosing convenience, and tolerability [24]. Accurate quantification of HIV-1 Viral Load (VL) in plasma compartment is crucial for disease monitoring and management in HIV [25]. After active anti retroviral therapy have become standard a few issues of such therapy have been clarified; still many points remained incompletely understood [26]. Highly active antiretroviral therapy (HAART) has significantly changed the morbidity and mortality associated with HIV-1 infection. A non-nucleoside reverse transcriptase inhibitor (NNRTI) combined with two or three nucleoside reverse transcriptase inhibitors have shown better results [27,28].

Traditional vaccine designs

The studies done to date to elucidate the replication of HIV and the immunopathogenesis of AIDS suggest that HIV is unique in its biology and may therefore not be amenable to control by immune responses elicited through traditional vaccine modalities [29]. The traditional design vaccines include live/ attenuated virus, inactivated virus with adjuvents, recombinant envelope proteins. The development of traditional vaccines has proven to be efficient against diseases like Polio, small pox and measles. This avenue of HIV vaccine development is somewhat controversial as this type of vaccines does not elicit antibody responses that neutralize HIV isolates and these immunogens do not elicit CTL. These studies showed that prior infection with such attenuated vaccines prevent infection with wild type virus [30]. While reports of these findings raised hopes that a live attenuated HIV vaccine might be feasible, subsequent studies have shown that this approach to HIV vaccine design is flawed. Metal ion complexes have the potential to form novel types of antiviral compounds, due to their ability to form octahedral and square-planar molecular geometries and their intrinsic charge density it is shown that it has anti viral properties against two isolates of HIV [31].

Further work in the SIV/macaque model showed that newborn monkeys or adult monkeys infected for a long period of time with such vaccine strains of virus eventually develop AIDS and die [32,33]. However, this vaccine protection proved neither broad nor robust [34]. Several features of HIV envelope contribute to its ability to evade effective surveillance by the humoral immune system. The HIV envelope is a trimer of heterodimers. Each heterodimer consists of a surface subunit (gp120) and a transmembrane subunit (gp41) that is noncovalently bound to each other. Maintenance of this native trimeric structure appears necessary to elicit the production of neutralizing antibodies. Conversely, the native structure of the HIV envelope shields it from many potentially neutralizing epitopes, such as the co-receptor binding site, which is made accessible only after CD4+ T cell binding [35]. Similarly, mutational substitution studies of glycosylation sites demonstrated that changes at these sites affected neutralization of distant epitopes [36]. Thus, the traditional approaches have proved disappointing in the effort to create an effective HIV vaccine.

Barriers of traditional vaccines:

- Vaccine developed through live attenuated virus will rose to pathogenecity.
- Inactivated virus with adjuvants restricts specificity of neutralizing antibodies and do not generate CTLs.
- Recombinant envelop proteins have not neutralized antibodies and not generated CTLs.

Novel vaccine designs

Recognizing the limitations of the traditional vaccines strategies for development of novel vaccine designs explored. The most promising of these are the use of plasmid DNA or recombinant vaccines. Live recombinant vectors are also being explored as tools for eliciting immune responses against HIV. Genes of HIV can be inserted by molecular approaches into live, replication-competent microorganisms [37]. The resulting recombinant microorganisms then can serve to carry these genes. Such immunogens have proven particularly useful for eliciting CTLs, since the HIV proteins are produced intracellularly by the replicating vector and therefore enter the MHC class I processing pathway. The most promising of the live recombinant vectors assessed to date as a potential HIV vaccine is the gene-deleted adenovirus that was developed as a vector for gene therapy. These vectors have elicited both high-titer antibody and high-frequency CTL responses in these animal models. In fact, early-phase HIV immunogenicity trials with this vector are ongoing in humans [38].

Barriers to AIDS vaccine development: Obstacles to the development of an effective AIDS vaccine include factors related to the biology of HIV-1 infection and practical realities of developing and testing an AIDS vaccine.

- ✓ The extensive sequence variation of HIV isolates poses a considerable barrier to vaccine development.
- ✓ The lack of information regarding what types of immune responses may protect against HIV infection.
- ✓ Like other retroviruses, HIV integrates into the host genome where it can remain in a latent form that does not express HIV structural proteins and is thus less likely to be eliminated by host cellular and humoral immune responses.
- ✓ HIV-1 is predominantly transmitted by mucosal routes, yet our knowledge of the events occurring during mucosal infection and the immune responses responsible for defending against mucosal infection are quite limited.
- ✓ In addition, HIV transmission may occur by both cell-free and cell-associated viral particles. Cell-associated virus is thought to be resistant to neutralizing antibodies and will not be recognized by host CTL responses, unless there is a fortuitous match between the HLA molecules between the host and donor.

Anti retroviral therapy

The introduction of the highly active antiretroviral therapy (HAART) in 1996 has drastically reduced the morbidity and mortality associated with the HIV infection. Although short term toxicities of the antiretroviral drugs are being reported, there's dearth of data on their long term complications [39]. There are currently 20 antiretroviral drugs that have been approved for treatment of HIV. They were divided into six classes of ART which inhibit HIV replication. Each of these classes of drugs inhibits HIV replication at different stages in HIV life cycle [40,41]. The decision of ART depends upon the CD4+ count of each individual [42,43]. The principles of therapy of HIV infection

are based on understanding of the immunologic damage caused by ongoing viral mutation from early in the infection process through late stages of the disease. Because the virus is highly mutable, every effort should be made to shut down viral replication completely [44]. The goals of treatment are to suppress plasma viremia for as long as possible, to delay the selection of drug resistance mutations, and to preserve immune function [45]. HIV-positive individuals with tuberculosis are particularly vulnerable since standard anti-TB (ATT) and anti-HIV drugs (ART) are not very effective in this category of patients and prognosis is worse than for two infections separately. Sometimes ART may worsen the disease condition [46]. Depending upon their inhibition ART drugs are of following types [47]. When salvage therapy is considered, better outcome is expected if antiretroviral regimen includes a class to which the patient has not been exposed previously. Therefore classes of antiretroviral drugs directed at targets other than reverse transcriptase or protease are of potential great interest [48].

Protease inhibitors: HIV-1 protease activity is critical for the terminal maturation of infectious virions. Protease inhibitors specific for HIV-1 competitively inhibit this enzyme, thereby preventing the maturation of virions capable of infecting other cells. All four available drugs are potent inhibitors of HIV-1 protease in vitro. It is this class of drugs that has created the greatest optimism since the beginning of the AIDS epidemic [49]. To achieve long-term viral suppression, protease inhibitor therapy must be managed carefully [50,51]. The protease inhibitor drugs currently available for HIV are Indinavir, Nelfinavir, Ritonavir, Saquinavir, and Amprenavir. Other drugs are under investigation [52]. Patients receiving amprenavir (APV)-based highly active antiretroviral therapy (HAART) for 1.3-4.2 years (mean, 3.1 years) were switched to equimolar fosamprenavir (FPV) doses with no other changes in their treatment regimens. After switching, clinical status generally remained stable or improved [53,54]. Enfuvirtide is currently being produced by solid- and solution-phase hybrid synthesis and is used as the drug of last resort for treatment of drug resistant HIV [55].

Nucleoside reverse transcriptase inhibitors: Nucleoside reverse transcriptase inhibitors are found to be crucial drugs in therapeutic strategies aiming at controlling of HIV. These drugs were proven to be safe, well tolerated and effective in prolonging life particularly when used in combinations with other therapies. The primary mechanism of this is inhibiting RNA dependent DNA polymerase reverse transcriptase enzyme. Studies of the NRTIs in enzyme assays and cell cultures demonstrate the following hierarchy of mitochondrial DNA polymerase γ inhibition: zalcitabine ≥ didanosine ≥ stavudine > lamivudine > zidovudine > abacavir [56]. In vitro investigations have also documented impairment of the mitochondrial enzymes adenylate kinase and the adenosine diphosphate/adenosine triphosphate translocator. Inhibition of DNA polymerase γ and other mitochondrial enzymes can gradually lead to mitochondrial dysfunction and cellular toxicity [57]. The clinical manifestations of NRTI-induced mitochondrial toxicity resemble those of inherited mitochondrial diseases (i.e., hepatic steatosis, lactic acidosis, myopathy, nephrotoxicity, peripheral neuropathy, and pancreatitis). Fat redistribution syndrome, or HIV-associated lipodystrophy, is another side effect attributed in part to NRTI therapy [58]. The morphologic and metabolic complications of this syndrome are similar to those of the mitochondrial disorder known as multiple symmetric lipomatosis, suggesting that this too may be related to mitochondrial toxicity [59,60]. The patho-physiology of less common adverse effects of nucleoside analogue therapy, such as diabetes, ototoxicity, and retinal lesions, may be related to mitochondrial dysfunction but have not been adequately studied [51]. Intrapartum and neonatal single-dose nevirapine (NVP) reduces the risk of mother-to-child HIV transmission but also induces viral resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs. This drug resistance largely fades over time [61,62]. Although nucleoside reverse-transcriptase inhibitors (NRTIs) remain a critical component of current HIV-1 treatment regimens, they have been associated with functional and structural mitochondrial abnormalities, leading to several adverse events, such as pancreatitis, peripheral neuropathy, and lactic acidosis [63].

Inhibition of gp120 protein: The infection with HIV-1 begins with the interaction of its envelope glycoprotein gp120 with a host cell receptor [64]. This binding creates a conformational change in gp120, which then opens the co-receptor binding sites for the attachment of the chemokine receptors CCR5 and CXCR4. Increasing conformational changes in gp120 activate the fusion peptide on the N-terminus of another viral envelope protein, gp41 [65]. This activation leads to the creation of a six-helix bundle complex that fuses the virus to cell membranes and eventually internalizes HIV-1 via a pH-dependent mechanism [64,65]. These factors along with other studies have indicated that the functionality of gp120 is crucial for the uptake of HIV-1 [66]. The dendritic cells present in the mucosal tissue, together with CD4+ T lymphocytes and macrophages, are among the first cells to encounter HIV-1 [67]. The dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) molecule plays a crucial role in binding HIV-1 through high affinity interaction with viral envelope glycoprotein gp120 [68]. DC-SIGN, a mannose-binding C-type lectin expressed on cells in the mucosal tissue of the rectum, uterus and cervix, facilitates early HIV-1 infection after sexual transmission. Attempts were being made to inhibit activity of GP120 by using DC-SIGN which inhibit binding of HIV1 complex to dendritic cells and prevent viral transmission [69]. Furthermore RNA interference and carbohydrate binding agents have been shown as potential means while blocking this process [70,71].

Other antiretroviral drugs

Apart from Protease Inhibitors, Nucleoside inhibitors and gp 120 Inhibitors other antiretroviral drugs include:

- Nucleotide Reverse Transcriptase Inhibitors
- Zinc Finger Inhibitors
- Fusion Inhibitors [72]
- Antisense Antivirals
- Cellular Inhibitors
- Sulfated polysaccharides [73]

Conclusion

There have been outstanding advantages in our knowledge of immunopathogenesis of HIV since the discovery. The traditional vaccine developed against AIDS has got some barriers in provoking CTLs and decreasing its pathogenecity. To overcome this, Novel Vaccines were developed which have elicited high titer antibody and generated high frequency of CTLs. It has got some limits such as sequence variation; lack of information regarding immune responses, etc., Antiretrovirals has proven to provoke good immune responses during treatment. The described drug targets represent some of the most noted examples of recent scientific breakthroughs that are opening unexplored avenues

to novel anti- HIV target discovery and validation, and should feed the antiretroviral drug development pipeline in the near future.

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