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VARIOUS STRATEGIES TO PRODUCE VACCINES AGAINST AIDS

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ABSTRACT

There has been a high demand for vaccine against HIV (Human Immunodeficiency Virus) as it is one of the most potent mass killers in our world. Many clinical trials have been done to produce vaccine but most of them become ineffective after a certain period of time. Various strategies like the incorporation of viral gene in an organism which produces viral protein, activates the immune system against it, use of live attenuated virus, use of viral derived peptides, use of recombinant disarmed virus to evoke immune systems are be utilized but in one way or another HIV escapes the immune response. The main reason for this is the high mutation rate in envelope proteins of the virus that helps virus to escape immune surveillance. Most of the above strategies have been proved useless by the HIV virus but one strategy that can promise to produce a safe vaccine against HIV virus is gene therapy. It has provided many successful results but still it is in trial period and not been used in humans. At present, the only way to cope with HIV infection is HAART (highly active anti-retroviral therapy) that uses combinations of two or more drugs which generally include two nucleoside reverse transcriptase inhibitor (NRTIs) and either non-nucleoside reverse transcriptase inhibitor (NNRTIs) or integrase inhibitor or protease inhibitor. This strategy can not cure but can reduce the rate of increase of viral load on patient to let him live few more years. This all show nature of HIV which keeps on continuously changing.

Keywords: AIDS, HIV, HAART, NRTIs, NNRTIs, $CD4^{+}T$.

INTRODUCTION

As we all know, HIV is one of the most potent killer of the present world. Hence, various approaches have been utilized to produce vaccine against HIV virus. This review is highlighting the unique problems faced in the vaccine development, recent advances in vaccine development against HIV, clinical trials and failure of traditional vaccine strategies. Different vaccine approaches for HIV infection include DNA vaccine, recombinant viral vector vaccine, subunit vaccine, epitope based vaccine etc. Vaccines have been developed to induce innate, adaptive, mucosal, cellular immunities. Most vaccines work by stimulating antibody response against the disease of interest by exposing the person to dead or live attenuated pathogen which produces memory in immune system against that pathogen and in future, when person gets exposed to that pathogen, its immune system protects the person efficiently. HAART is the best practice present at current against HIV. It includes use of cocktail of two or more drugs which generally include two NRTI's and either NNRTI's or integrase inhibitor or protease inhibitor. But still HAART is not a cure as it just slows down the infection and just let the person live few more years only. The c-DNA synthesised from HIV RNA by reverse transcriptase inserted into the host DNA as a provirus and remains in latent hidden form for years before it is triggered into an active form. No known drug till date has got any effect on this provirus. Hence, the threat of HIV persists in the infected person.

TAXONOMICAL STATUS

ORDER: virales

FAMILY: retroviridae

SUBFAMILY: orthoretrovirinae

GENUS: lentivirus

SPECIES: Human Immunodeficiency Virus

HIV STRUCTURE AND GENETIC ORGANIZATION

HIV STRUCTURE

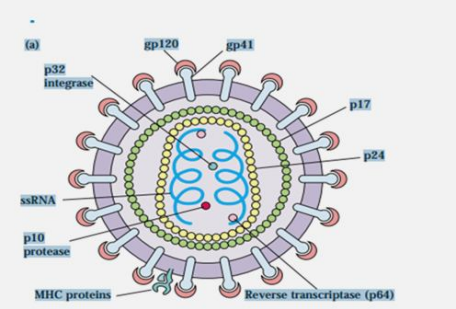


FIGURE 1: STRUCTURE OF HIV

1. Viral Envelop HIV virus is roughly spherical and approx 120 nm in diameter i.e. 1/10,000 of mm . Outermost coat of virus is known as viral envelop that generally consists of phospholipid bilayer which is derived from host cell membrane during the process of budding out from the host. Envelop consists throughout the proteins of host in addition to 72 copies at average of Env protein embedded. Env protein appears as knob and consists of two types of glycoproteins:

1) gp120: forms cap of ENV with homo trimer [1].
2) gp41: forms stem of Env with homo trimer .These are transmembrane proteins and act as anchor for Env protein [2].

gp120 and gp41 are bound non-covalently enable HIV to enter $CD4^{+}T$ helper cells using CD4, a cell surface molecule on T_H cell as viral receptor. These proteins are targeted by researchers to develop the HIV vaccine [3].

2. Viral Core The genome is surrounded by a nucleo-capsid consisting of an inner layer of protein called p24 and an outer layer of matrix protein called p17. Core is in shape of bullet consist of approx 2,000 copies of viral protein p24.

Inside the core, 2 HIV-RNA are present that are single stranded , identical and have associated enzymes: reverse transcriptase, integrase and protease packed inside the core [4].

GENETIC ORGANISATION

Core consists of two identical single stranded RNA. Both RNA terminals possess RNA sequence called Long Terminal Repeats (LTR) that act as switches to control production of new viruses and can be triggered by proteins either from HIV or the host cell. HIV genome consists of 9 genes out of which 3 genes are common to whole retroviral family, these are env, gag and pol. Besides these 6 regulatory genes that are unique to HIV that guides the whole life cycle of HIV in various ways are tat ,rev, nef, vpr, vif [5,6].

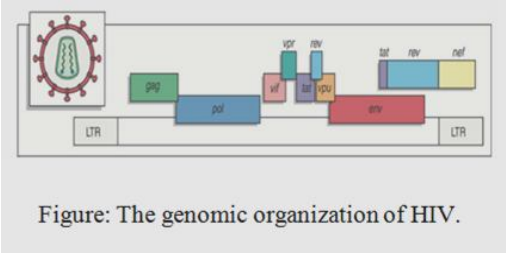


Figure: The genomic organization of HIV.

GENE	GENE PRODUCT	GENE FUNCTION
gag	Group-specific antigen	Core proteins and matrix proteins
pol	Polymerase	Reverse transcriptase, protease, and integrase enzymes
env	Envelope	Transmembrane glycoproteins. gp120 binds CD4 and CCR5; gp41 is required for virus fusion and internalization
tat	Transactivator	positive regulator of transcription
rev	Regulator of viral expression	Allows export of unspliced and partially spliced transcripts from nucleus
vif	Viral infectivity	Affects particle infectivity
vpr	Viral protein R	Transport of DNA to nucleus . Augments virion production. Cell-cycle arrest
vpu	Viral protein U	Promotes intracellular degradation of CD4 and enhances release of virus from cell membrane
nef	Negative_regulation factor	Augments viral replication *in vivo* and *in vitro*. Decreases CD4, MHC class I and II expression

TABLE: The genomic organization of HIV [7]

*Env gene produces protein called gp160 that is broken down by a viral enzyme to form gp120 and gp41 the component of env protein.

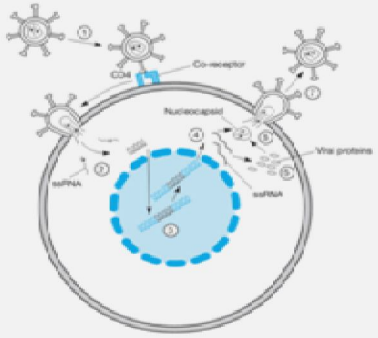


Figure: Life cycle of HIV [8]

1). The virus binds to CD4 +ve cells through binding of gp120 to CD4 and interactions between the virus and chemokine co-receptors. 2) The nucleocapsid enters the cell, where it unfolds, releasing viral RNA, which is reverse-transcribed to double-stranded DNA. 3) The viral DNA integrates in the host genome, where it lies dormant as a provirus. 4) Following cell activation, viral DNA directs the transcription of viral RNA. 5) Viral proteins are translated from the RNA. 6) The viral proteins and single-stranded viral RNA assemble to form new viral particles. 7) The virus buds from the cell, picking up some of the cell membrane, and the complete viral particles can infect other cells.

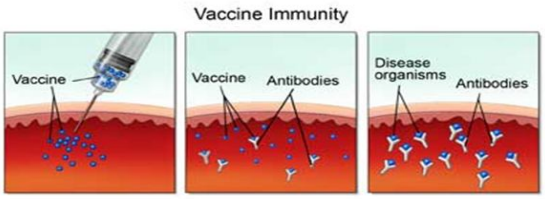
HIV VACCINES

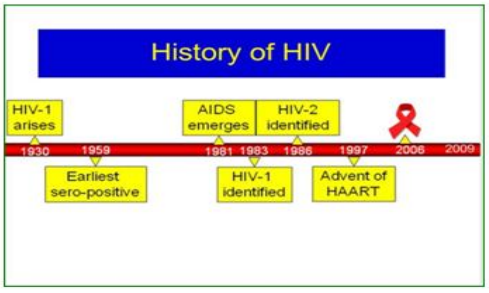
Definition of Vaccine- Vaccines are harmless agents, perceived as enemies. They are molecules, usually but not necessarily proteins, that elicit an immune response. They provide protective immunity against a potential pathogen by stimulating immune system to produce antibodies against the viral proteins, so that any exposure following the vaccination will be met with infection-specific resistance.

History-AIDS was first reported in June 5, 1981, when the U.S. Center for disease control (CDC) at Atlanta recorded a cluster of *Pneumocytis carnii pneumonia*, in five homosexual men in Los Angles [9]. The CDC did not have an official name for this disease that were associated with it, for example, lymphadenopathy, the disease after which the discovery of HIV originally named the virus [10].

AIDS is now become pandemic [11]. The causative agent HIV, a retrovirus identified in 1984 by Francoise Barre-Sinoussi and Luck Montangnier for which they were awarded the Noble prize in 2008. In 2009, not only did scientists discover that some HIV-negative people in long-term relationships with HIV-positive people have antibodies that seem to protect them during oral sex, there appears to be some success seen in an HIV vaccine trial in Thailand.

HIV vaccines were produced against their envelope proteins but after certain period all of them become useless because of high mutation rates in those proteins, this proves to be most effective barrier in way of producing vaccine against HIV [12].





CLINICAL TRIALS TO DATE

Phase I

Canarypox was the first candidate HIV vaccine that has induced cross-clade functional CTL responses. At least, 13 different gp120 and gp160 envelope candidates were evaluated, in AIDS Vaccine Evaluation Group. They induced neutralizing antibody but rarely induced $CD8^+$ cytotoxic T lymphocytes (CTL) by increasing the complexity of the canarypox vectors by inclusion of more genes/epitopes has CTL induction level in patients increased to a greater extent than increasing the dose of the viral vector. CTLs from patient were able to kill peripheral blood mononuclear cells infected with primary isolates of HIV. In 2011, researchers in National Biotech Centre in Madrid unveiled data from the Phase I clinical trial of their new vaccine. The first phase I trial of the candidate vaccine in Africa was launched early in 1999 with Ugandan volunteers.

Phase II

On December 13, 2004, the HIV Vaccine Trials Network (HVTN) began recruiting for the STEP. The trial was co-funded by the National Institute of Allergy and Infectious Diseases (NIAID). Merck developed the experimental vaccine called V520 to stimulate HIV-specific cellular immunity, which produces T cells that kill HIV-infected cells.V520 contains a weakened adenovirus that serves as a carrier for three subtypes B HIV genes (gag / pol / nef). MARKAD5 HIV-1, gag /pol/nef or trivalent vaccine, is based on adenovirus. Adenovirus

is used as a vector, or a delivery vehicle to transport three synthetically produced HIV genes into cell. These genes stimulate the body to generate a potent cellular immune response to HIV, producing killer T cells to recognize and kill HIV infected cell. The failure of the STEP trial brought into scrutiny both the use of viral vectors and cellular responses as a correlate of protection.

Phase III

After the failure of the STEP vaccine trial, the results of the next phase III vaccine trial was of great interest. Inducing both humoral and cellular responses to HIV antigens had been investigated as early as 1986 when recombinant vaccinia virus was used to delivery envelope gp41 and gp120 induced both humoral and cellular responses in macaques [13]. In February 2003, VaxGen announced that their AIDSVAX vaccine was a failure in North America as there was not a significant reduction of HIV infection within the patient [14]. This same vaccine was retested

in Thailand within a vaccine regimen called RV 144 in 2003, with positive results. In both cases the vaccines targeted gp120 and were specific for the geographical regions [15]. In October 2009, the results of the RV 144 trial were published. The patient was tested for HIV every six months for three years. After three years, the vaccine group saw HIV infection rates reduced by more than 30% .In 2011, AIDS conference in Bangkok revealed that participants receiving vaccines in the RV 144 trial, who produced IgG antibodies against the V2 loop of the HIV outer envelope were 43% less likely to become infected than those who did not, while IgA production was associated with a 54% greater risk of infection than those who did not produce the antibodies (but not worse than placebo). Viruses collected from vaccinated participants possessed mutations in the V2 region. For these reasons further vaccine development was focused on vaccines designed to provoke an IgG reaction against the V2 loop.

ALVAC and AIDSVAX Clinical Trial

The ALVAC vaccine contains a clade E envelope and a gag/pol from clade B Vaccine groups received four injections of the canarypox virus vector vaccine ALVAC, followed by two booster injections with the AIDSVAX B/E recombinant gp120. Greater cytokine responses were measured in the $CD4^{+}$T cells of vaccinated individuals. When it came to trial end points there was no significant difference in viral loads of individuals who got infected whether or not they got the vaccine. The two main strategies being used to overcome virus variability are using centralized sequence usually based on envelopes of one or multiple clades, mosaic antigens and polyvalent vaccines consisting of multiple genes of HIV from one or multiple clades [16, 17].

OBSTACLES TO MAKING THE HIV VACCINES

1. **Reverse Transcriptase: Error prone-** The property of all retrovirus, including HIV and simian immuno deficiency virus(SIV), is conversion of the viral RNA genome into a double standard DNA molecule [18].This process is mediated by the viral reverse transcriptase (RT), an enzyme that is incorporated into the virion during viral assembly. Because RTs have no proof reading activity, their error rates of several orders of magnitude are higher than those of cellular DNA polymerases [19]. HIV mediated reverse transcription generates on average one mutation out of 2000-5000 polymerized nucleotides it transcribed and in this way it may evade

detection by antibodies or T cell generated in response to viral proteins [20].

2. Viral Recombination-When two HIV-1 virions with different genetic sequences enter the same cell, homologous recombination or packaging of RNA from different parent viruses leads to entirely new HIV-1 genomes. When individuals infected with HIV become infected with a second strain of the virus i.e. super infection, the two viral strains can exchange genetic information, creating a third, recombinant strain of the virus, which leads to a loss of immune control of viral levels [21, 22].

3. Gut as a Viral Reservoir- The gut associated lymphoid tissue (GALT) is the viral reservoir and is the largest lymphoid organ infected by HIV-1. Simian immunodeficiency virus (SIV) has indicated that the gut is an important site for $CD4^+$T-cell depletion and this appears to be similar in humans. The inflammatory reaction in the gut plays a key role in $CD4^+$T cell loss, as a lack of $CD4^+$T cell replenishment in the gut of HAART treated HIV-1 infected individuals was associated with increased inflammatory gene expression and immune activation [23, 24].

4. Genetic Diversity of HIV-1 Isolates

HIV clades are distinct subgroups of HIV, by geographical region. It may not be possible to develop a vaccine to protect people from all HIV clades, or it may not be possible to vaccinate against certain clades. HIV clades were an important step in the research needed to identify the origins of the HIV epidemic [25].

5. Envelope Proteins

Envelope glycoprotein gp41 (or gp120) is a glycoprotein exposed on the surface of the HIV envelope. gp120 is essential for entry of virus into cells. First it binds to the CD4 receptor and then goes inside the cell. gp120 was the first targets of HIV vaccine research. HIV vaccine target to gp120 development was difficult because of chemical and structural properties of gp120, which make it difficult for antibodies to bind to it. gp120 can also be captured by T cells due to its loose binding with gp41 [5].

6. Vaccine-elicited Neutralizing Antibody

Neutralizing antibodies induced by the replicating viruses. These antibodies bind to viral particles and block the ability of the particles to attach and infect cells. The neutralizing antibodies protect against HIV infection. Several broadly neutralizing antibodies completely prevented virus acquisition in nonhuman primate models of AIDS. Some of the subunit envelope immunogens evaluated so for generate antibodies that block infection by HIV-1 isolates that have envelope proteins similar in sequence to those used in vaccine [26].

INNATE IMMUNITY AND HIV VACCINE

Innate immunity can limit and induce HIV replication. Continuous activation of innate immune system for prolonged period can result in dysregulation of T and B cell response contributing to immune deficiency chronic HIV infection. The innate immune system plays a key role with the adaptive arm, in clearing HIV infected cell. Innate immunity can contribute to HIV vaccinology by the use of toll like receptors (TLR) adjuvants. Therapeutic vaccine, during the early stage of infection, transfers autologous DC with inactivated HIV-1. The failure of previous HIV-1 vaccine trials to induce B and T cell immunity, need to look beyond adaptive immunity in order to gain control of HIV infection. It is becoming evident that both innate and adaptive arms of the immune system need to be harnessed in order to develop a successful HIV vaccine.

Different cells of the innate immune system, such as dendritic cells (DCs) and macrophages, are positioned at pathogen entry and detect invading microbes by recognizing their pathogen associated molecular pattern (PAMPs). Innate immune cells contain numerous receptors known as pattern recognition receptors (PRRs), which allow them to bind to and recognize PAMPs [27].

1. Dendritic Cell-based Vaccines- HIV infection normally hijacks immune system responses and uses the DCs to cross the mucosa and get the CD4 cells. The vaccines targeting antigens to DCs offer a potent and novel means of improving vaccine delivery that allows dose sparing and control of the type of immune response. HIV vaccines based on DC-targeting using recombinant anti-DC antibodies fused to antigens [28, 29].

MUCOSAL IMMUNITY IN HIV VACCINE

Mucosal immune response blocks the transmission of the virus at a mucosal surface. Vaccine-induced systemic immune responses can confer effective protection against mucosal transmitted viruses. HIV can use one of 2 co-receptors (CCR5 or CXCR4) after CD4 binding for viral entry; mucosal transmission is almost exclusively restricted to viruses that use CCR5. The heterogeneity of transmitted HIV-1 strains that traverse the mucosal barrier is quite diverse, and this viral heterogeneity poses problems for HIV-1 vaccine development. Anti-HIV-1 antibody responses could potentially help control HIV-1 if they were present at the time of transmission. Antibodies aggregate virions, thus preventing virion movement across mucosa lepithelia, inhibit transcytosis; fix

complement and lyse virions; inactivate virus through macrophage Fc-mediated uptake; and mediate antibody-dependent cell mediated cytotoxicity (ADCC) [30].

TYPES OF HIV VACCINE

Main approaches of HIV vaccines are-

1. Recombinant Sub-unit Vaccines

Subunit vaccines, constructed from the viral envelope protein, could be rapidly and efficiently developed using the modern techniques available through genetic engineering. Immunization with the viral envelope glycoprotein, gp120, should generate neutralizing antibodies that would prevent infection, yielding protective immunity [31].

2. Whole Inactivated Vaccines

Creating vaccines based on inactivated or 'killed' viruses is another classic technique, which was used in creating the first successful polio vaccine. However, this technique is considered risky, as vaccine recipients could easily be infected with HIV if the inactivation process should fail [31].

3. Peptide Vaccines

Vaccinating with a whole protein is a use of fragment of a protein, called a peptide, which consists of a few amino acids. A vaccine containing the V3 sequences from several strains of HIV has been used in animals and produced antibodies which are able to neutralize several laboratory-adapted virus strains. Peptide vaccines have been tested in HIV-positive patients, with some antibody and cellular immune responses against HIV [32].

4. Live Attenuated Vaccines

An attenuated vaccine is created by reducing the virulence of a pathogen, but still keeping it viable (or "live"). Attenuation takes an infectious agent and alters it so that it becomes harmless or less virulent. Attenuation occurs by the deletion of several accessory functions from the viral genome, either individually or in combination. Live attenuated HIV vaccines are unsafe. Research in monkeys indicated that a live-attenuated vaccine, made by deleting the *nef* gene, protected monkeys against SIV, but caused AIDS so this approach has got inherent risks [31].

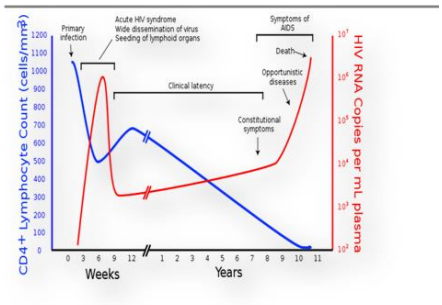
5. Recombinant Vector Vaccines

In this vaccination strategy, the gene encoding a major antigen of a virulent pathogen is introduced into an attenuated organism which serves as vector. Recombinant live vaccines are not without limitation, they have an advantage over subunit vaccine as they induce both cell mediated and humoral antibody response (as do live attenuated vaccines). The body's immune response to the viral vector, mutations of the virus in the body and toxicity issue could limit effectiveness [33].

VIRAL VECTORS AS DELIVERY SYSTEMS

A vector is another virus that is not harmful and acts as the delivery system to carry HIV antigens to the immune system. Scientists design a vector to carry only a small part of the HIV genetic material so that there is no way it can cause HIV infection. Once inside the body's cells, this genetic material is converted to protein. The small piece of HIV protein is called an "immunogen" because it causes an immune response.

Ad5 viral vector- It is the most promising live recombinant vector in HIV vaccine. It is gene-deleted adenovirus that was developed as a vector for gene therapy. Genes of HIV can be inserted by molecular approaches into live, replication-competent microorganisms. The resulting recombinant microorganisms then can serve to carry these genes. Upon infection with these recombinant microorganisms, immunity is elicited to the vector and to the product of the HIV gene carried by that vector. 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 [34].



CD4⁺ T CELLS: HALLMARKS FOR AIDS

DNA VACCINES

DNA vaccination is technique for protecting the body against disease by injecting it with genetically engineered DNA to produce an immune response. Single-dose HIV DNA vaccine can induce a long-lasting HIV-specific immune response in nonhuman primates. DNA *vaccines* are made up of a small, circular piece of bacterial DNA (called a plasmid) that has been genetically engineered to produce one or two specific proteins (antigens) from a pathogen. The vaccine DNA is injected into the cells of the body, where the "inner machinery" of the host cells "reads" the DNA and uses it to synthesize the pathogen's proteins. Because these proteins are recognized as foreign, when they are processed by the host cells and displayed on their surface, the immune system is alerted, which then triggers a range of immune response [35, 36].

The reason of loss of mucosal $CD4^+$T cells is that the majority of the mucosal $CD4^+$T cells express the CCR5 co- receptor, whereas a small fraction of $CD4^+$T cells in the bloodstream do so. When $CD4^+$T cells numbers decline below a critical level of 200 cells per micro L, cell mediated immunity is

lost. Acute HIV infection usually progresses over time to clinical latent HIV infection and then to early symptomatic HIV infection and latter to AIDS, which is identified either on the basis of the amount of $CD4^+$T cells remaining in the blood, and/or the presence of certain opportunistic pathogen induced infections [37]. Several explanations have been advanced for the depletion of these cells in patient. In early studies, direct viral infection and destruction of $CD4^+$T cells were discounted as the primary cause, because the large number of circulating HIV infected T cells predicted by the model were not found. Most recent studies indicate that the reason for the difficulty in finding the indicated cells is that they are so rapidly killed by HIV; the half-life of an actively infected $CD4^+$T cells is less than 1.5 days. Smaller number of $CD4^+$T cells become infected but do not actively replicate virus. These latently infected cells persist for long periods, and the integrated pro viral DNA replicates in the cell division along with cell DNA. Studies in which viral load is decreased by antiretroviral therapy show a concurrent increase in $CD4^+$T cell numbers in the peripheral blood. These data support model of dynamic interaction between virus and T cells, with simultaneous high level viral production and rapid depletion of infected $CD4^+$T cells. Although other mechanism for depletion of $CD4^+$T cells may be envisioned, infection which HIV remains the prime respects [38, 39]. Not only depletion of $CD4^+$T cells but other immunologic consequences can be measured in HIV infected individual during the progression to AIDS, including a decrease or absence of delayed hypersensitivity to antigens to which the individual normally reacts. Serum levels of immunoglobulin, especially IgG and IgA, show sharp increase in the AIDS patients. This increase may be due to increased level in HIV infected individuals of a B cell subpopulation with low CD21 expression and enhanced immunoglobulin secretion. This population proliferates poorly in response to B cell mitogens. Cellular parameters of immunologic responses in a predictable sequences: responses to specific antigens (eg influenza virus) are first lost, then response to mitogens such as concanavalin A or phytohemagglutinin can no longer be detected [38].

HIV THERAPY FROM HIGHLY ACTIVE ANTIVIRAL THERAPY (HAART)

A combination therapy, HAART is the latest procedure to cope with HIV infection. In HAART, patient is treated with two nucleoside analogues and one protease inhibitor. This strategy helps to overcome the

ability of the virus to rapidly drug resistant mutants. HAART decreases the viral load to undetectable level and the health of patient improves. Though, it is a bit successful in improving life of HIV infected people but it also have drawbacks like it includes strict time schedule and large number of pills have to be taken every day. Additionally, it may lead to various side effects and some serious patients may not be benefitted by this treatment. Although, HAART was a great success but some AIDS experts are not convinced as there is possibility of presence of latent $CD4^{+}T$ cells and macrophages may act as reservoir of infectious virus, if provirus is activated by some means. In addition, viruses present in brain may not be detected by anti-retroviral drugs as these cannot penetrate these sites and these remain undetectable[40].

DRUG THERAPIES FOR HIV AND AIDS

1. Drug Resistance

During treatment drug resistant mutations occur in viral genes within some weeks. If patients do not adhere perfectly to their drug regimen, the virus rapidly eliminates its vulnerability. Viral resistance to antiviral drug occur in two forms; primary and acquired. In both, primary and acquired resistance genotype mutation can compromise the effectiveness of antiretroviral drug and result in ineffective suppression of viral replication. Antiretroviral therapy, that only partially suppresses viral replication ,will result in the accumulation of additional mutations [41].

2. Protease Inhibitors (PIs)

PIs are lipophilic compounds and function by inhibiting the HIV protease that cleaves the gag-pol protein into its functional subunits, and so prevent final assemble of HIV virions. It thus interferes with HIV maturation and replication [41].

3. Integrase Inhibitor

The integration of the pro viral DNA into the host cell DNA involves multiple steps that are catalyzed by HIV-1 enzyme integrase. This involves a series of DNA cutting and joining reaction in which pro viral and host DNA are prepared for strand transfer, the process by which the processed ends of the two DNA strand are joined together [41].

4. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs /NtRTIs)

At the first time, agents approved by FDA for treatment of HIV-1 infection are nucleotide /nucleoside analogues that interfere with the viral replication by this enzyme. These drugs are known as chain terminators. To be active, NRTIs and NtRTIs require phosphorylation. NRTIs require three phosphorylation and this process is influenced by a number of cellular factors including cell type, cell cycle, and activation and infection of the cell in which

they occur. NtRTIs undergo only 2 phosphorylation and it is the initial rate limiting step of NRTIs activation process that is not required. NtRTIs are more suitable for development as microbicides than NRTIs [41].

5. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

They do not require metabolic activation and are extremely effective in halting virus replication, especially when used in combination with NRTIs. Most commonly used NNRTIs are- Nevirapine and Efavirenz. The NNRTIs bind near the catalytic site of RT and alter the enzyme ability to change conformation. The increased enzyme rigidity prevents its normal polymerization function [42].

CONCLUSION

Infection of human by the HIV causes a progressive, multi-factorial impairment of the immune system leading to AIDS. The failure of vaccine candidate to protect against HIV infection and progression to AIDS has led to a renewed focus on the biological mechanism responsible for HIV latency. Hopefully, a greater understanding of precisely how the immune system is weakened and why the use of limited period of the therapy combining with antiretroviral drugs targeting the latent reservoir may one day allow for total eradication of HIV infection. The unique biology of HIV replication and high rate of mutations have made it harder than initially believed to come up with a preventive measure against AIDS. In view of the importance of CTLs in containing HIV spread in an infected individual, a number of vaccine strategies are being pursued for elicitation of these immune effector cells. These strategies include the use of plasmid DNA, live recombinant viral vectors, and combined modality or prime/boost approaches. Effective vaccination may ultimately requires two or more vaccines used in conjunction, an approach to vaccine development that differs from traditional vaccine designs. Early phase testing of these novel vaccine strategies is on going in human volunteer populations. HIV vaccine that at least slows disease progression, if not one that prevents infection, is now possible. In future, studies are required on DNA vaccines improving the immunogenicity in larger animals and in humans. The DNA vaccine platform has driven significantly weaker immune responses in non-human primates and in humans compared with mice. It seems to be less immunogenic compared with recombinant viral vectors such as adenoviral vectors or recombinant protein for induction of antibody responses. However, DNA vaccine technology efforts optimize the platform to increase antigen expression and

vaccine immunogenicity and lots of efforts are under way globally in this context.

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