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Treatment of AIDS: Development of Medicine by Innovation with Special Emphasis on Protease Inhibitors

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ABSTRACT: In the light of the recent events in the world concerning COVID-19 virus, it is important to review the challenges faced by the world by another pandemic, AIDS. The painstaking research by the scientists, the pharmaceutical companies, the medical professionals have led to this day when AIDS patients are living their whole life span. Though we do not have any vaccine for AIDS but by intelligent use of medication, we have been able to combat the disease to a large extent. HIV is a RNA virus, whose treatment is mainly done by finding the structure and function of the proteins that are vital to its life cycle. Designing a drug/inhibitor to make those proteins ineffective constitutes the next step. WHO has recognized AIDS as a pandemic almost 40 years back but the world is yet to find a cure or a vaccine. The current treatment method is called HAART, Highly Active Anti Retroviral Therapy, where different types of inhibitors,eg. Reverse Transcriptase inhibitors, Protease inhibitors; each arresting a different important protein are given in combination. The virus replicates very fast and forms mutations which render it ineffective to the inhibitors thus resistance to the inhibitors develop. Hence development of new types of inhibitors is crucial to the problem. There are certain similarities between AIDS and COVID-19, both in terms of the attacking virus and effective medication, which make it more important than ever that the research on HIV is revisited and knowledge we gain from it is used to battle the new pandemic. © 2020 iGlobal Research and Publishing Foundation. All rights reserved.

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INTRODUCTION

AIDS or Acute Immuno Deficiency Syndrom was first reported in humans in the year 1920. The disease was due to the proliferation of the Human Immunodeficiency virus (HIV) in our body. Chimpanzees carry a virus, SIV or Simian Immunodeficiency Virus, which is very similar to HIV and apparently which crossed over from the chimpanzees to humans due to the fact that the people living in that area hunted and ate those chimpanzees or was exposed to an open wound[1].Eerily similar to the recent theories of how CORONA virus spread from the wet markets in China. Another similarity between AIDS and CORONA is that both are caused by RNA virus. In light of recent events, hence it has become very important to revisit the research and medicines of AIDS and to link how research and its application has led to different treatment modules in AIDS.

The most recent data (last data update on 2nd August, 2019) from the World Health Organization (WHO) shows that there are 37.9 million people living with AIDS worldwide and in the South East Asian countries the number is 38 lakhs[2]. In India the number of HIV patients were 21.40 lakhs in 2017 showing a steady decline in new HIV infection [3]. In 1983 WHO recognized AIDS as a worldwide pandemic, by definition which means that that it is spread over a large are and is actively spreading. WHO launched the global program on AIDS in 1987 and 1st December was declared as World AIDS Day in 1988[4]. The Human Immunodeficiency Virus is a retrovirus which means that it replicates from its RNA and not from its DNA. It works by destroying the CD4+ T cells in out body which is responsible for our immunity, thus making us susceptible to opportunistic infections [5]. The trials for vaccine are still ongoing for AIDS and currently there is no cure for AIDS. The treatment for AIDS is known as **H**ighly

Active **A**nti **R**etroviral **T**herapy (HAART) [6], which does not cure the disease but slows down its progression. The time between initial HIV infection and development of AIDS can be as long as 9-11 years. If the infected person does not receive any treatment at this point then life expectancy is around 1 year after AIDS is detected. If treatment is started immediately after the onset of infection then patient can have life expectancy of 20 to 50 years. Most of the AIDS patients die of other infections or cancer. Children are especially vulnerable, most of the infected infants die between the age of 2-5 years [7]. The economic implication of AIDS is also severe. As the therapy is expensive hence it puts a pressure on the household, also because the patients themselves almost always are not properly employed due to social stigma, mental depression it causes a loss in human capital. The problem is compounded by the fact that it is mostly prevalent in the poor countries of the Africa and South-East Asia[8]. HIV infection primarily passes through exchange of body fluids, e,g blood, semen, etc. Hence unprotected sexual intercourse, faulty blood transfusion procedure, use of contaminated syringes (while using drugs) are the main causes for HIV transmission. Another major reason is transmission from an infected mother to unborn child in pregnancy. As it has no known cure, cost of treatment is huge, and other implications in patients personal life is manifold hence, preventive methods, i.e use of condoms, single partner relationships, saying no to drug abuse, and use of new syringes should be practiced.

Pathogenesis

It is a type of lentivirus which are characterized by long incubation period leading to chronic illness of longer durations in humans and other mammals [9]. It enters the human cell as a single stranded RNA and then gets converted to a double stranded DNA, a process called reverse transcription. Beyond that the DNA gets integrated into the cell [10]. After this the virus may become latent and survive in the host cell for years or it can replicate by a process called transcription whereby the viral DNA gets converted to RNA and viral proteins and gets releases from the cell starting off the cycle of replication. **Table 1** represents the stages of the interaction of HIV with the human CD4 cell.

Table 1: Different stages in the interaction of Human Immunodeficiency Virus with the Human CD4 cells

Stages of HIV -CD4 cell interaction	Action (enzyme required)	Type of Medicine
Attachment	HIV attaches itself to the co-receptors (CCR5/CXCR4) on the CD4 cell surface	CCR5 Antagonist
Fusion	HIV envelope and CD4 cell membrane fuse together so that the virus can pass into the cell	Fusion Inhibitors
Reverse Transciption	Viral enzymes (Reverse Transcriptase)change viral RNA to DNA so that it can combine with the cell DNA in the nucleus	Reverse Transcriptase Inhibitors
Integration	Viral enzyme(Integrase) help HIV integrate its DNA onto the cell DNA.	Integrase Inhibitors
Replication	Uses cell machinery (Transcriptase) to replicate viral proteins.	Transcriptase Inhibitors
Assembly	Viral proteins and RNA assemble near the surface to form non infectious immature virus	Caspid Assembly Inhibitors
Budding	The new virus buds out of the surface and viral enzyme (Protease) cuts the long proteins of the non infectious forms to give the infectious variety.	Protease Inhibitors

Strategy to fight AIDS and HAART

As HIV drastically compromises the human immune system, patients after being diagnosed with HIV in the initial days hardly lived for more than a year. But with the advent in medical science and with retro viral therapy an AIDS patient though compromised can expect to complete his/her normal life span [11]. There have been 2 cases in the world where the person has been cured of HIV completely. There are some enzymes in the virus that are essential to the life cycle of the virus, Reverse Transcriptase, Transcriptase, Integrase, HIV-Protease etc. The retro viral therapy is a targeted approach to specifically destroy or inactivate the enzymes or receptors that the virus needs to replicate [12]. HAART is essentially a combination of different drugs, targeted at the different part of the HIV life cycle. The drugs that inhibit the action of the enzymes are called inhibitors. The first inhibitor introduced was a reverse transciptase inhibitor. These again can be of two types, nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI). Later another drug to inhibit HIV-Protease, the Protease Inhibitor (PI) was introduced. Apart from this Chloroquin/Hydroxychloroquin is also used for its antiviral activity [13]. A typical HAART cocktail will have 2 NRTI, 1NNRTI, 1PI.

Discovery of Inhibitors

Lot of research is required to lead the way. The concerned enzyme need to be isolated and studied in terms of it structure, functionality etc. After that its interaction with the cell organelles are studied and then important structure function relationships are established. Then inhibitors or drugs are designed to break or prevent that structure/function and then again studied to see the efficiency, toxicity etc, of the inhibitors. After a series of inhibitors are studied, then with the prospective candidates clinical trials are started. Hence it is a long and tedious process.

Early Days of Treatment and its limitations

Initially a single drug was given to HIV-patients. But, there are several limitations to the single drug therapy regime. As the virus replicates the viral proteins mutate under the pressure of the inhibitors and hence the inhibitors need to be constantly reinvented and revisited as the protein becomes resistant to the treatment [14]. The drugs are very toxic, hence the side effects need to be considered and the medicines need to be constantly improved and updated. This lead to the retroviral therapy where a combination of drugs was more effective than the single drug therapy [15].The clinical trial became easier and faster with the understanding that the HIV viral load can be measured by the CD4 cell count and it was more effective and precise than clinically studying a patients well being[16]. The first inhibitor to be used in a single drug therapy was a Nucleoside Reverse Transcriptase Inhibitor Azidothymidine (AZT), it was approved by FDA in 1987. Thereafter it was given in combination with other NRTIs. Prolong use of AZT results in mutation in the viral reverse transcriptase and consequence resistance to AZT. In 1995 a major breakthrough happened when another class of inhibitors the Protease Inhibitor (PI) Saquinavir was introduced[17]. As the different type of inhibitors acted on different viral proteins hence a combination therapy called HAART was started which resulted in less resistance and was efficient for a longer period of time [18].

Current Method of Treatment (HAART)

Currently there are more than 30 medicines included in HAART and constant research is underway. The newest entrant in this is the Non- nucleoside Reverse Transcriptase Inhibitors [19], Nevirapine, Delavirdine etc. They are easier to produce and cheaper hence they are good candidates for HAART therapy in poorer countries. Scientists and Pharmaceutical companies are in constant effort to invent and market drugs that inhibit other important enzymes of the virus. The receptor on CD4 cell that attaches itself to the HIV is CCR5. The drug blocking the co receptor CCR5 on the CD4 cell Maraviroc, which got FDA approval in 2007 is currently in use [20]. The Integrase inhibitor drugs Raltegravir, Elvitegravir which also came out in 2007 are providing a lot of opportunities for the medical professional in the HAART[21]. Raltegravir works by competing with the metal binding sites of the viral integrase.

Future of Retroviral Drugs

The future direction of this research does not only look at different kinds of inhibitor drugs but also its ease of use. As these drugs need to be taken by patients throughout his/her life hence this aspect is relevant and important. Scientists are working on drugs and means of providing them so that instead of daily dose they can be taken weekly or monthly. Also instead of oral drugs, paches or implants are being researched. Long acting drugs like Rilpivirine LA and Cabotegravir are in trial [19]. The toxicity of the retroviral drugs is another of its challenges. Hence search is on for less toxic alternatives. This has led to the works on broadly neutralizing antibodies, which are less toxic, longer lasting inside human body and can fight with multiple strains of HIV infections. Many other types of retroviral inhibitors are in various stages of clinical trial eg. Islatravir, which is a nucleoside reverse transcriptase translocation inhibitor[22], Fostemsavir that blocks the gp120 receptor on the viral surface, the Caspid Assembly inhibitor that inhibits the viral assembly in its protein shell or capsid.[23]. Another direction is the creation of a therapeutic vaccine, which will be given to people with HIV i.e not to prevent but to stimulate the immune system to prevent further attacks of HIV[24].

Role of HIV-Protease and the development of Protease Inhibitor

The development of a protease inhibitor was one of the successes of structure based drug design. After the discovery of HIV-protease it took almost 10 years for the first inhibitors to go for trial [25]. The first protease inhibitor to be marketed was Saquinavir. In different research labs the structure and function of the protein HIV-1 protease was studied. HIV-1 protease is a protein that is an aspartic protease, essential in cleaving the Gag and Gag-Pol polyproteins in the immature, inactive virus in nine cleavage site to create the proteins necessary for maturation of the virus to its active form. The protein is a 22kDa homidimer each subunit consisting of 99 amino acids [26]. The active site of the protein has a Asp(25)-Thr(26)-Gly(27) triad, typical of aspartic protease. The protein is functional only as a dimer, each monomer contributing one Asp (25) to the active site. Additionally when it attaches to a substrate it has two molecular flaps that comes at a distance of 7 A^o of each other [27]. The integral role of HIV- Protease in viral life cycle makes it a popular target for drug design. The inhibitors essentially mimic the substrate, a structure resembling (-NH-CO) by a hydroxyl ethylene group CH_2-CO (OH)- and prevent it from interacting with the substrate. The inhibitors fit the active site and the first inhibitor thus designed was Saquinavir[28]. It was marketed in 1995, Apart from the hydroxyl ethylene group a decahydroisoquinoline was added in the design, to improve the solubility and potency of the drug by arresting its conformational freedom. Ritonavir, Indinovir two other protease inhibitors were marketed in 1996. From 1997-2006, seven more PI came to the market by different pharmaceutical companies. Darunavir, marketed in 2018 is the latest Protease inhibitor.

Resistance development in Protease Inhibitors and current research to address it

The resistance formed by the virus to the PI is a major obstacle in the treatment regime of the virus. The substrate envelope theory states that the protease recognize its substrate based not on the amino acid sequence but on the spatial structure. Hence, mutated viruses can undergo successful maturation but becomes resistant to the inhibitors. Hence, the inhibitors become inactive after a certain period of treatment. The mutations happen at places where the inhibitor contact protease residues beyond the substrate envelope [29]. There are 26 mutations found that have developed in response to protease inhibitors. Out of which 15 are major enough to change the drug efficacy [30]. Mutation at Leu (90) affect Saquinavir and Nelfinavir but Indinavir is affected by mutations at Met46, Val82, Ile 84. As most protease inhibitor

shares the same basic structure hence some mutations can cause simultaneous resistance to many PI together. Hence, fight for inhibitors is a continuous process. The HIV Drug Resistance Database at Stanford University was formed in 1998 with sequences of HIV reverse transcriptase and protease from patients under antiretroviral therapy to aid in research.

New paths of research are undertaken now for the HIV-1 Protease to find inhibitors not only based on the active site but to locate other vulnerable positions in the protein, so that newer kind of inhibitors can be designed. This is essential to limit the mutations to influence the efficacy of the drugs. Many studies have focused on the kinetics of the fording pathway of HIV-1 protease [31,32] either singly or with inhibitors. It has been observed that HIV protease fold in a two step mechanism where the monomers come together in a slow first step followed by a rapid folding to the dimer. As the protein is active only as a dimer hence if by any means the dimerisation process can be affected then HIV protease will not be able to function. Another path of research is to study the different mutations that the HIV protease is showing a studying its effect on the structure and function of the mutated proteins [33].

AIDS and COVID- A lesson to learn

There are some similarities between the two viruses, HIV and CIVID-19. Both of them are RNA virus and attack the T-Cells. The areas in the world ravaged by AIDS, Africa has reported fewer deaths by COVID-19. In the present scenario there are many studies to relate the medicines of AIDS to COVID -19, the most discussed and controversial being Hydroxychloroquin and Remdisivir[34]. However, Protease inhibitors like Lopinavir, Ritonavir combinations have not shown expected results [35]. Emtricitabine , a nucleoside reverse transcriptase inhibitor is currently under clinical trial[36] in combination with other drugs. Though there have not yet been any vaccine for AIDS, but the mutational ability of COVID-19 is much less than HIV also it does not integrate itself in our body as HIV hence the body puts up a fight against it. May be due to this a vaccine for COVID-19 may be viable rather than for HIV. Hence, the future of HIV research looks promising, due to this added impetus.

CONCLUSION

A global pandemic like AIDS tests the scientific minds to come up with solutions and use their ingenuity for the benefits of mankind. It took the world more than 50 years to learn about the virus, investigate medicines to fight it and find a viable treatment regime, HAART. HIV-Protease inhibitors have proved to be very effective and 11 protease drugs have been approved so far. However, as the virus mutates very rapidly hence continuous ongoing research is required to develop new inhibitors. The insight gained from AIDS research has proved to be useful in our fight against COVID-19. But the AIDS story in itself is an inspiring testimony to the fight of humankind to beat any adversaries.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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DATA AVAILABILITY

Not declared.

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