

RECENT ADVANCES IN THE TREATMENT OF HIV INFECTION-A REVIEW

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Abstract

HIV is the leading cause for mortality and morbidity across worldwide. HIV infection is considered as medical apocalypse in certain age period, because it caused massive infection spread. However many interpretations and inventions in the treatment of HIV infection, it is still been considered as major disease burden, because it affects directly the immune cells of individuals and make them more vulnerable to common infections. Advances in HIV / AIDS therapy were quick and well-exposed. An improved understanding of HIV pathogenesis has shown the need for aggressive antiretroviral therapy in most HIV-infected people. At least three combinations of drugs are needed to suppress viral replications. In addition, the capacity of pharmaceutical firms to formulate such effective medications into fixed-dose formulations offers innovative new pill stress reduction techniques, thus ensuring adherence and reducing the development of drug-resistance. However, the excitement with which these new drugs were greeted has been tempered by the fact of restricted access in the developing world, further illustrating the gap in the battle against HIV / AIDS between the rich and poor countries. Such therapies would require proper political will and medication access to low and middle income countries. Developing countries' goal continues to increase the scope of ART, but in order to tackle toxicity and drug resistance, both of which threaten the viability of these initiatives, new drugs are also required. Nowadays recent studies focus on obtaining viral sequences found in newly infected individuals to identify and examine the features of all transmitted pathogens which could provide potential targets to develop HIV vaccine. This study focuses on mainly the recent advanced methodologies used in HIV treatment.

Keywords: HIV infection, CCR5 protein, Nucleotide reverse transcriptase inhibitors, Non-nucleotide reverse transcriptase inhibitors, Replication.

INTRODUCTION

India which is one of the largest growing economies has the fastest growing technological advancements. Coronavirus is one of the most-deadly diseases that affect both mammals and birds.[1] This virus initially originated in China due to the ingestion of raw uncooked animal meat. The virus rapidly spreads through droplet infections via touch, saliva and nose discharge.[2] To prevent the spread of this virus, maintenance of cleanliness such as sanitizing of hands, use of mask and glove protection can be considered essential.[3] Another major practice that can limit the spread of corona is the practise of social distancing and isolation. To maintain social distancing, a nation-wide lockdown was initiated from March 23 which was also commonly called as the Janta curfew.[4] The lockdown included the closure of all local shops, malls, theatres, schools and colleges also the selective closure of hospitals.[5]

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The pandemic of Human Immunodeficiency Virus (HIV) infection continues to create the most difficult situation among public health comorbidities. One of the most emotive aspects of HIV is having extremely high levels of genetic variance around 13 subtypes and 51 recombinant forms [1]. Human immunodeficiency virus origination pattern was similar to monkey infecting virus, Simian Immunodeficiency virus (SIV) [2]. HIV belongs to the family Retroviridae genus, lentivirus made based on their morphological and genetic basis [3]. First case of HIV infection was reported in 1981, Centre of disease control initially HIV virus is considered as severe immunodeficiency disease. Later in 1983 it was named as Acquired immunodeficiency syndrome (AIDS). The early identification and characterisation of infection spread about 78 million people infected, in which 39 million individuals died [4, 5]

Till date the infection spread rate has fallen to 38% [6]. In 2018, 37.9 million people were diagnosed with HIV infection. For the first time in 2018, more than half of all new HIV infections globally accounted for individuals from key ethnic groups and their sexual partners in 2018 (an estimated 54 percent). Such populations reported approximately 95% of new HIV infections in Eastern Europe, Central Asia, the Middle East and North [7, 8]. Genome of HIV encodes about 8 viral proteins which are essential for the virus cycle. The life cycle of HIV occurs within the human body. First it binds with virus encounter CD4⁺T cells, after binding fusion occurs, then reverse transcription followed by integration and replication. Final steps are assembling and budding. Human immunodeficiency virus is found in two forms HIV-1 and HIV-2. They both share many similarities like basic genetic arrangement, mode of transmission, replication sequence and both result in AIDS [9, 10]. There are four (M, N, O, P) and eight (HIV -A to H) different lineages coming under HIV -1 and 2. However HIV-2 was found to be less virulent to cause AIDS, compared to HIV-1. HIV-1 virus causes epidemics in central and western Africa [11]. When the clinical trials occur both viruses demonstrate very similar pathological processes, Even though the progression of HIV-2 virus occurs at higher CD4 count cells [12, 13]. HIV-1 was thought to be risen from the cross specific transmission of chimpanzee virus to humans [14]. HIV-2 virus was found to be risen from the cross specific transmission from sooty mangabey virus [15].

Since HIV is a dreadful disease prevailing all over the globe. Transmission occurs by whatever route depends on the infectiousness of index case (first case who transmits the HIV virus) and susceptibility of the host individuals [16]. The infectiousness based on the following category: concentration of HIV and infected cells in the body fluids (blood or genital secretions) [17] and also by virus specific determinants. The mode of transmission is mainly by physical contact or in some cases it is from infected mother to infant (through breast milk) or during delivery due to exposure of body fluids [18, 19]. Approximately 2.4 million people are HIV positive with the current state of HIV infection and death rates in the western and central regions. China, Indonesia and India contributed substantially to around 78 per cent of the total new disease burden in Asia and the Pacific region.

METHODOLOGY

The study setting is a review. The information is obtained by searching the keywords and the data is collected through search engines like Pubmed and google scholar. They were collected with a restriction in time basis from 1989 - 2020. The Inclusion criteria considered review and original research articles based on HIV, Causes, prevention and treatment. Exclusion criteria included retracted articles and articles related to other categories. The article is reviewed from 42 articles collected.

TREATMENT

Patients with this mysterious immune disease known as AIDS arrived at NIH (National Institutes of Health) clinical centre in 1981. At that time there was no effective treatment and medicine. The NIH researchers first focused on viral enzymes (reverse transcriptase) to stop the virus proliferation [20]. Later in 1990 Azidothymidine (AZT) a compound manufactured as an anti-cancer drug was applied into clinical trials. After

randomised critical experiments, it gave a positive hope, by improving the survival rate of AIDS patients [21]. In 1982, several media named the four H clubs as high risk factors for AIDS. In 1984 HIV was recognised as the cause for Acquired immunodeficiency disease. In late 1997 new HAART (Highly active antiretroviral therapy) treatment was invented and it caused a 47 percent decline in overall death rate. Standard ART helps in controlling the multiplication of HIV infection in the infected patient and increases the number of CD4 cells, thus prolonging the asymptomatic phase of infection, slowing the progression of the disease and decreasing the risk of transmission. Later FDA approved combivir, a combined drug therapy was developed. There is no specific treatment for this disease since now. But a variety of drugs has been tried and selected for its effect against infectious viruses. For instance, Zidovudine, Efavirenz, Tenofovir and FTC are used [22- 24]. Out of which antiretroviral drugs showed promising results.

VACCINE EFFICACY

Exact immunity function against HIV has been hidden and is unresolved. Three strong techniques have now attracted scientists and engaged them in the neutralization of antibodies, CD8 T cell mediated immunity and many specific and groundbreaking approaches [25]. Also, traditional ways of inserting live attenuated or inactive form of virus into the host cell became a risk because it contains a permanent integration of proviral DNA into the host chromosome. Recombinant DNA technology later came into the picture as it had previous evidence of vaccine invention for terrible disease hepatitis B. But this approach also became a failure due to extreme mutability of existing strains.

ADVANCE MODALITIES

The main aspect of treating the HIV virus is focusing to interrupt the proliferation and replication process.

SHOCK AND KILL THERAPY

HIV virus infection is incurable, since it creates latent proviral reservoirs that in turn start reproducing virus particles over the lifetime of the host. Shock and kill therapy act as precursors of antiretroviral drugs. By inserting / inducing transcription with latency reversing agents (LRAs) this technique focuses on reverse proviral sequence [26]. But a lot of LRA's are developed to date. None of these resulted in successful practical cure. The doubt about the technique of shock and kill arises when the heterogeneous nature of the proviral reservoirs has been stressed. To date, only clinical trials of in vivo activation of the expression of the viral gene have demonstrated clearance for reactivated cells. To activate the turn over of reactivated cells antibodies, T cell vaccines stimulate the functioning of cells to kill the reactivated cells and continue the latency reversing.

IMMUNOTHERAPY

Viruses remain in the HIV reservoirs throughout the triple therapy. As a rule, HIV virus infects first the CD4 cells and then white blood cells that contain antibodies to the infection. Antiretroviral drugs regulate the functioning of reservoirs but do not eliminate fully [27]. The surface of the cells contains three distinct proteins (PD-1, LAG-3, TIGIT). A number of immunotherapeutic agents used for cancer treatment will stimulate the HIV reservoir by causing latency reversal. Immunotherapy can supercharge the human cells to combat the virus. Approach of functional HIV cure combines with drugs and activate the hidden reservoir to induce vaccines and immune response more stronger than usual

GENE EDITING

Gene mutation means a permanent alteration in the gene-forming DNA sequences. By doing so the genes of infected patients vary from the DNA sequence of ordinary individuals. The gene editing gene used in this case is CCR5, which is present on the immune cell surface. The gene CCR5 facilitates and guides the virus toward the human cell. In the technique of gene editing, genome editing was achieved by generating double strand breaks on the DNA at some locus. In the presence of template DNA, DSBs facilitate non-homologous joining or homologous guided repair. Zinc finger nucleases, a designable zinc finger DNA binding protein or TAL effector derived from *Xanthomonas*, is used for common DSBs in living cells [28].

ANTIRETROVIRAL THERAPY AND DRUGS

Antiretroviral treatment refers to the use of a mixture of two or more drugs to produce mutual beneficial effects. Studying the life cycle of HIV pharmacological targets interferes with the viral replication [29, 30]. Viral entry,

nuclear arrival, reverse transcription, genomic incorporation, and mutation are key molecular events. Currently, there were five classes of antiretroviral drugs under FDA approval. These drugs mainly target four different proteins ie: receptor of host cells, reverse transcriptase, integrase, protease to interfere with the process of viral replication.

FDA APPROVED FIVE CLASS OF DRUG

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

NRTIs were first accepted and are known as the backbone of HIV care. They are favoured as first line medicines. Inhibitors of reverse transcriptase are a group of drugs, which bind to the reverse transcriptase enzyme and interfere with HIV multiplication. NRTIs have a very low genetic defense barrier, the continued use of this medicine causes mutations and cross resistance within the class [31].

FOR ADULT USE- Zidovudine, Stavudine, Lamivudine, Abacavir.

FOR CHILD USE- Zidovudine, Stavudine, Didanosine.

NON-NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS(NNRTIs)

NNRTIs are an integral part of the initial regimen [32]. In developing countries Nevirapine is used for its low cost and convenient dosage schedule. It is also considered safe during pregnancy and efficiently used to prevent vertical transmission [33].

FOR ADULT USE-Nevirapine, Efavirenz, Deiviradine, Rip Irvine

FOR CHILD USE-Nevirapine.

PROTEASE INHIBITOR (PIs)

Protease inhibitors effectively block protease enzyme function in both the acute and chronically infected immune cells. Protease enzyme inhibition allows immature and non-infectious viral particles to be released. PIs have high genetic resistance, use of low-dose ritonavir as a booster for those who do not respond to the initial regimen [34, 35].

FOR ADULT USE-Ritonavir, Indinavir, Saquinavir, Nelfinavir.

FOR CHILD USE-Ritonavir, Nelfinavir, Darunavir

ENTRY INHIBITORS(CCR5 AND FUSION INHIBITORS)

This group of medicines prevents the infection by blocking the CCR5 sites in the cell surface. The presence of vacant CCR5 sites will cause HIV to lose the immune cell entry pathways. The first inhibitor of CCR5 was Aplaviroc, followed by Maraviroc and Virciviroc. The target is the envelope protein subunit GP41 [for Enfuviride] and the Maraviroc small molecule CCR5 receptor antagonist [36]

FOR CHILD USAGE AND POST EXPOSURE PROPHYLAXIS-Enfuviride

INTEGRASE INHIBITOR

Integrase inhibitor inhibits strand transfer of viral DNA to host cell DNA by inhibiting the functioning of integrase enzyme action. The first agent Raltegravir was approved by FDA for both treatment experienced and native patients [37, 38]. The second drug was Elvitegravir on undergoing phase 3 trials.

ADVERSE EFFECTS OF ANTIRETROVIRAL DRUGS

1. Gastrointestinal: Nausea [39], diarrhea, vomiting, taste perversion, constipation, dyspepsia, abdominal pain, hepatotoxicity, and pancreatitis

2.. Central nervous system: Headache, vision problems, dizziness, tinnitus, insomnia [40], paresthesia, pain/numbness/tingling in extremities, peripheral neuropathy, somnolence, excessive sleep at night, memory problems, loss of olfactory function, and hearing impairment . 3. Hematological: Anemia, bilirubinemia, increased urate, and blood in the urine [41]

4. Psychological: Anxiety, confusion, depression, nightmares, elation, and delusions

5. Metabolic : Abnormal fat distribution (lipodystrophy), anorexia, dyspnea, fatigue, lethargy, and weight gain [42]

6. Dermatological : Skin rash, facial discoloration, and pruritus

Socioeconomic status

Socio economic status is directly associated with the ART related death. Because opportunities of lower middle class individuals to perceive ART was less. In a longitudinal study conducted, 80% of individuals who discontinued ART treatment belong to lower class.

ADDED BENEFITS

Compared to other treatments, Antiretroviral therapy (ART) is relatively safest and known to be effective against HIV virus. It's essential because it increases the patient's longevity of lifetime.

CONCLUSION

The emergence of new sequencing and bioinformatics tools are only the beginning to benefit the treatment of HIV and preemptive measures. Despite the complicated genetic variability of HIV virus immunotherapy, genetic editing paves promising future targets for HIV infection studies. Indeed AIDS is contagious, vaccines are still in progress. As a human we are committed to eradicate AIDS. As of now antiretroviral drugs and therapy are visible solutions for HIV infection. Even if the patient undergoes ART, his disability adjusted life year (DALYs) get reduced.

ACKNOWLEDGEMENT

The author extends gratitude to the institution for their support.

CONFLICT OF INTEREST

No conflict of interest declared.

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