The Progress of AIDS Treatment Methods And Interventions

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Abstract. The immune system, the body's built-in system of disease prevention, is targeted by the human immunodeficiency virus (HIV). If left untreated, HIV can severely weaken the immune system, making it unable to resist infection. This article introduces the existing treatment methods, such as taking drugs to prevent HIV, taking blocking drugs to prevent virus invasion, antiviral treatment, and the methods being studied and expected to cure AIDS: "activation and eradication" and gene editing. This article focuses on the treatment mechanism of HIV patients in recent years and various HIV drugs and their mechanisms of action. This paper briefly introduces the mechanism of action of HIV virus pairs, and classifies and summarizes the existing mechanisms of HIV drug treatment at the molecular level with time as the axis.

Keywords: HIV, AIDS, mechanism, treatment

1. Introduction
The HIV is a long-lasting retrovirus that affects human T-cells and targets the human immune system. If patients with the virus are not treated with aggressive medical therapy or a full course of medication, they will develop acquired immune deficiency syndrome (AIDS), also known as AIDS. And in terms of the current global situation and trends, approximately 84.2 million [64 million-113 million] people living with HIV have been identified globally since the beginning of the epidemic, while at the same time, nearly 40.1 million [33.6-48.6 million] patients have died from various major diseases caused by HIV. Meanwhile, throughout the world, by early 2022, there will already be approximately 38.4 million [range:33.9 to 43.8 million] HIV-positive individuals who are HIV-positive. And worldwide it is estimated that about 26.88 million [2304-30.72 million] patients are between the ages of 15 and 49 years. According to the WHO survey, the region most severely affected by HIV remains Africa, where 3.4% of individuals (almost 1 in 25) have HIV/AIDS, representing a majority of two-thirds of the world's living humans infected with HIV (source from WHO). The progression of humans from initial HIV infection to the development of AIDS involves a very subtle and gradual progression. The onset of HIV generally exists in 3 periods, namely the acute phase, the asymptomatic phase and the AIDS phase. The typical time of survival after virus infection is estimated to be 10 years or so if no active treatment is given, (source from wiki) and patients with HIV frequently experience this time when their risk of receiving infections and getting malignancies is noticeably higher, which can lead to a variety of diseases, and eventually losing their lives to pathogens due to the lack of an immune system in the body. However, HIV can be controlled to a certain extent in patients who are known to be infected with the virus if they proactively undergo appropriate medical intervention and treatment. At this stage, patients with HIV who receive effective HIV treatment can achieve a degree of health and

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longevity, while protecting their partners. For people with CD4 counts between 200 and 350 one year after starting medical treatment for HIV and interventions, and with no detectable viral load through testing methods, the life expectancy of this segment of the human population will be comparable to the length of life of an average human [1].

Therefore, proactive and effective medical interventions for HIV-infected patients and interventions are important and critical for HIV patients themselves who are known to be infected with HIV. So far, taking HIV drugs on a daily basis is the most successful way to curb the excessive proliferation of HIV in the body. Protease inhibitors; Integrase inhibitor; Nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors are among them. The mainstay HIV treatment is antiretroviral therapy (ART), however there is currently no treatment, making daily medicine essential.

This paper introduce the existing treatments that exist of AIDS and the progress of various interventions. The discussion included the mechanism of action of HIV treatment at the molecular level, which was classified and summarized.

1.1. The mechanism of action of AIDS virus
Since the beginning of the 20th century, 2DRS treatment schemes with higher safety and less side effects have been popularized. In the treatment schemes of 2DRS, one or all NRTIs are often removed to reduce the toxicity to the body caused by Art treatment, At the same time, the effectiveness of the treatment can be maintained by increasing the role of PI in the treatment plan [38].

The mechanism of action of AIDS virus is to invade and attack and destroy CD4 T lymphocytes in the human immune system, thus the human body lacks some important immune functions [2]. The HIV-1 replication cycle in human cells includes four links: attachment and entry, transcription and translation, maturation and budding, as well as reverse transcription and integration. Retroviruses have the ability to convert their RNA genomes into DNA forms, which then undergo a process of integration into host cell chromosomes [3], and then express the viral genome and translate viral proteins in infected cells [4]. The gp120/gp41 protein on The CD4 T cell receptor and HIV-1 envelope have an affinity for one another, (gp120 Envelope Glycoprotein Structures from Primary Isolates and Laboratory Adaptations) HIV-1 virus can easily pass through the cell membrane to guide its own genetic material into CD4+ T immune cells [5]. Until this point, the process of virus recognition of host cells is over, and the next step is to uncoat the virus and perform RNA reverse transcription into DNA in the host cell, with the host cell then a series of transcription copy translation to achieve their own virus genome in the host for the purpose of breeding (source from wiki). During replication, there are four different viral enzymes: integrase, protease, RT and RNaseH embedded in RT need to be used by HIV-1, and Pol gene coding will encode them.

1.2. The mechanism of AIDS’ treatment
Therefore, AIDS drugs reduce the HIV viral load in human body to a certain extent by inhibiting a series of value-added behaviors such as self replication and reverse transcription of AIDS virus in cells[source from wiki]. Through the external intervention of drugs, the immune system that is less attacked by HIV will have the opportunity to recover and then re proliferate and differentiate new CD4 cells. Therefore, even if a lifelong patient will carry HIV virus, the viral load in the body can be controlled within a certain range [6], so as to ensure the integrity of the immune system function, and to a certain extent, resist internal and external infections and reduce the probability of HIV related cancer.

So far, there are 6 types of drugs approved by the Drug Administration (FDA) as agents with specific targeted inhibition, and a total of 24 drugs can be used to treat HIV-1 infection. These drugs can be divided into the following six categories according to their unique molecular mechanisms and the distribution of different drug resistance: (1) NNRTIs: non–nucleoside reverse transcriptase inhibitors (2) NRTI: nucleoside-analog reverse transcriptase inhibitors (3) PIs: protease inhibitors (4) integrase inhibitors (5) fusion inhibitors and (6) coreceptor antagonists[7]. NRTIs and NNRTIs are
two kinds of antiretroviral drugs, which adhere to reverse transcriptase inhibitors, a broad group. The targets of antiretroviral drugs include protease, RT and integrase required for HIV replication.

1.2.1. Tat-mediated transcription of HIV-1
The Tat is a small nuclear viral protein that extends by facilitating transcription of RNA polymerase II from a LTR promoter, which Plays a major role in viral transcriptional regulation [8]. Following integration of the HIV-1 DNA into the host cell's DNA, the step of transcription requires HIV regulatory protein Tat and HIV-RNA element interaction (TAR) [9], which is a unique mechanism of virus itself. Therefore, it is regarded as an important therapeutic target with research value.

Once the transcriptional activator takes the dominant position, it means that the process from transcription to extension begins. Before it begins, the transcriptional repressor has been acting. Tat protein is also bound by the secondary structure of nascent TAR RNA to reach the next step. During the extension process, some newly generated transcripts successfully spliced can also be found on tat. The results show that the HIV transcription and subsequent replication cause a positive feedback loop of Tat-dependent [10].

1.2.2. NNRTIs. The manner in which NNRTIs work is to use its own characteristics to bind, encourage the growth of hydrophobic vesicles nearby but not overlapping active sites [11]. Through this change, the space conformation change of the enzyme is induced in the interaction between NNRTIs and HIV-1 reverse transcriptase, then the reverse transcriptase's action in the catalysis is changed. The target of several kinds of drugs belonging to antiretroviral drugs lies in the process of virus invading T cells. RT is used as the target of two different types of antiretroviral drugs, NATLS and NNRTISIS, because it can be compatible with the non-catalytic allosteric pocket on the enzyme [12]. It is also the NNRTIs point binding that decreases the activity of the polymerase by altering the spatial conformation of the substrate binding site.

Only when NNRTIs are present, a pocket that binds NNRTIs will manifest and the components of the NNRTIs binding pocket are divided into hydrophobic residues and hydrophilic residues. Recently, benzimidazole derivatives are also being developed as such drugs [13].

1.2.3. Nucleoside / nucleotide reverse transcriptase inhibitor (NRTI). Among these classes of drugs, the earliest FDA-approved drugs are NRTIs [source form FDA]. Only after the host cells enter and phosphorylate by cell kinases can NRTIs exert its antiviral effect as a leading drug. When the sugar (2'- deoxyribosyl) part of NRTIs lacks 3' - hydroxyl group, the 5' - nucleoside triphosphate entering from the outside will be prevented from forming a 3' - 5' - phosphate diester bond with NRTIs. In this scenario, the viral DNA strand's proliferation will be stopped. One of two conditions will result in strand termination growth: DNA synthesis that is RNA- or DNA-dependent, using either the (-) or (+) Production of the proviral DNA strand for HIV-1 was reduced [14]. Now, NRTI examples include zidovudine, abacavir, ntrutabine, and lamivudine, and examples of nrttis include tenofovir and adefovir [source form new.qq.com]. The use of either treatment usually leads to resistance to HIV.

Therefore, two mechanisms mediate the resistance to NRTIs: pyrophosphorylation with ATP and prevention of NRTI incorporation into nascent chains. The first mechanism is based on the principle that NRTIs are removed from the third end of the newly formed chain, thereby terminating the reversal of the chain. Mutations in NRTI arise in RT and are connected to thymidine analog mutations (TAMs) or nucleoside / nucleotide related mutations (NAMS)[15]. The M184V/I and the K65R are two mutations connected to the second mechanism. It should be noted that in the case of patients receiving long-term treatment, additional mutations will also be accumulated due to continuous treatment, leading to higher drug resistance[16].

1.2.4. Protease inhibitors (PIs). Beacuse the correct assembly and HIV production are highly comparable to the regulation of HIV protease, and HIV protease plays a crucial role between them, so
PI is widely used in various HAART treatments and plays a major role [17]. PI is a competitive enzyme in pharmacology, and HIV-1 protease will be replaced by PI in a competitive manner [18].

1.2.5. Integrase inhibitors. It is called integrase inhibitor (inis) because it can inhibit and block the action of integrase. As a newly discovered targeted integrase inhibitor, it is suitable for the clinical market because of its low toxicity and high efficiency [19]. Compared with PI, it has better tolerance and less negative effects on drug-drug interactions [20]. INI is also known as an integrase strand transfer inhibitor because it particularly inhibits the strand transfer procedure, which prevents HIV-1 DNA from integrating into host cell DNA [21]. Since integration is a crucial step in retroviral replication, blocking integration can prevent further transmission of the virus.

1.2.6. Fusion inhibitors. An HIV fusion inhibitor based on proteins will be available in 2022 was designed and constructed, called FLT (fn3-l35-t144). Human serum albumin (HSA) is reversibly bound by it through its FN3 component, as a result, t144 is more successful than the strains of HIV-1 IIIB (x4) and BAL (R5) [22].

1.2.7. Coreceptor antagonists. In the CCR5 transmembrane helix, hydrophobic pockets are where small-molecule CCR5 antagonists bind [23]. These molecules are essentially allosteric inhibitors. HIV-1 envelope binding would be blocked by small-molecule inhibitors of CCR5, but not bound to natural chemokines, allowing signal transduction under the Ideal case [24].

1.3. A Newly developed method
Even though in the clinical aspect ART is very effective in the treatment of AIDS, and the existing treatment method ART has successfully made AIDS into a chronic disease, [Anti-HIV antibodies in combination offer long-lasting virological suppression] But at the molecular level, it does not completely cure AIDS patients because in most resting memory CD4+ T cells, they are still present as host cells with HIV-1 provirus integrated in the genome [25]. When ART is interrupted, the HIV virus parasitized in the patient will still be active again, resulting in the patient facing a significant risk of getting diseases. This virus reservoir, which under the ART treatment has been stabilized by therapeutic intervention, can also develop reseed full-blown infection upon treatment interruption within a few weeks in the case of ART treatment is interrupted, re-initiating rebound viremia [10]. Therefore, a brand-new idea was proposed: (1)“Lock and Block” (2)“Shoc-K and B-Lock”

1. By means of gene recombination of the host cell group to permanently destroy or cut off the reverse-transcribed HIV DNA fragment onto the host DNA, and then suppress the transcription, translation and expression of the virus gene fragment in the patient [26]. Alternative approaches might include "Lock and Block" intervention, which inhibits provirus transcription to stop viral propagation, or alteration of the HIV provirus genome by genome editing. These approaches aim to prohibit the reemergence of the virus from latently infected cells.
2. Or by reactivating the virus in the cell bank and using the autoimmune system or cytopathic effect to achieve the goal of virus elimination and metabolism by itself. Also known as “shock and kill strategy”. The proposed strategy of "shock and killing" is to expose these harmful cells to the process of cellular immunity or apoptosis, in which the mechanism of using latent reversal agents (LRA) to induce the expression of HIV provirus is applied [27].

1.4. Mechanism of indole alkaloids
Indole derivatives are a class of substances that inhibit HIV enzymes, including enzymes like reverse transcriptase, integrase, and protease. N-arylsulfonyl indole derivatives exhibit selective affinity for human serotonin 5-HT6 receptors, thereby achieving effective anti-HIV-1 activity [28][29].
2. Treatments

In the 1990s, the first treatment as an HIV-1-specific antiviral drug was announced to the world, and the emergence of HAART was pioneering in lowering AIDS-related morbidity and death as well as HIV-1 infection. The standard treatment regimen for HIV has been the three drug regimen (3DR) since 1996. These three drugs include two NNRTI or PI and NRTI with two types. Since the beginning of the 20th century, 2DRS treatment schemes with higher safety and less side effects have been popularized. In the treatment schemes of 2DRS, one or all NRTIs are often removed to reduce the toxicity to the body caused by Art treatment. At the same time, the effectiveness of the treatment can be maintained by increasing the role of PI in the treatment plan [20].

Next is the specific treatment method based on the time line of human being infected with HIV and specific treatment prospect planning for specific regions.

2.1. Pre-exposure prophylaxis (PrEP)

PrEP is the most effective preventive measure before exposure to HIV. It is appropriate for those who have a very high risk of infection but have never had HIV: PrEP, which is a biological preventive monitoring.

Suspected HIV-infected individuals with high-risk exposures due to sexual contact can take daily oral emtricitabine (FTC)-tenofovir disoproxil fumarate (TDF) to prevent virus from multiplying in the body and becoming HIV-infected[30]. Daily PrEP of tenofovir-emtricitabine fumarate has proved to aid in preventing new HIV infections in high-risk groups [31]. The probability of primary HIV infection and seroconversion in the body after taking such drugs is extremely low [30]. So far, FTC-TDF offers a high level of security, little impact on bone density, kidney function, or the outcome of a pregnancy, and medication resistance is uncommon [32]. In the males who have intercourse with males, including gay men, the PrEP study conducted in Peru, discovered that: subjects taking FTC-TDF were less likely to take the drug daily if they persisted. The risk of contracting HIV is reduced by 99% (source from zhihu). Therefore, it is an effective method to popularize PrEP drugs in areas with a major risk of HIV infection, and methods such as taking the drugs as prescribed by doctors can be extremely successful in somewhat lowering the likelihood of HIV transmission.

2.2. Post-exposure prophylaxis [PEP]

PEP contains two drugs (lamivudine [3TC] and zidovudine [ZDV]; stavudine [d4T] and 3TC; or didanosine [DDI] and d4T). In cases where one is known to have had high-risk exposures: high-risk sex, high-risk blood transfusions, shared syringe drug use, etc., the replication of HIV can be inhibited by blocking the fusion of HIV virus with CD4+T, CD8+T cell and entry into cells through uninterrupted administration of HIV-blocking drugs. In most cases, PEP drugs can block HIV infected T cells in the very early stage of known infection, i.e. within 72 hours. PEP blocks HIV infection of T cells through antiviral drugs. Therefore, the earlier the PEP drug is taken, the better it is within 24 hours and not more than 72 hours. And after 72 hours, the HIV reservoirs will be established early in this period. As early as around 1990, Pep began to be used by workers with HIV for occupational reasons. Only 8 of the 1,535 MSM who were taking PEP, who are male sexual partners, were identified as potentially failing the PEP therapy, according to the inquiry and research report, rate of 5,000 per 1,000 [source form zhihu].

2.3. Highly active antiretroviral combination therapy (HAART) and antiretroviral therapy (ART)

The main core of HAART, also known as high-efficiency combined antiretroviral therapy, is that at least three different types of drugs are mixed with each other, and finally a combined mixture is obtained to exert its effect. The remarkable therapeutic effect of combined antiretroviral therapy can inhibit viral replication to a certain extent, so that the plasma HIV-1 viral load (vLoad) can be decreased to the minimum detectable level in the most sensitive clinical studies at this stage to < 50 RNA copies/mL should prevail, thereby maintaining the patient's own immune system in a condition where it can achieve self-reconstruction to some extent. Once the patient's own immune system
recover to a certain degree of function, it implies that CD4 cells can be generated autologously, and the rise in the amount of CD4 T cells overall can attest to the exceptional effectiveness of HART therapy[1][33]. In addition, if the patient takes drugs according to the doctor's instructions and actively cooperates with the treatment, HIV viral load can be kept under detection levels, which means that the patient does not have the possibility of infecting the virus, that is, U=U (undetectable equals untransmitteable)[source for sohu.com].

2.4. Some treatment options in specific regions
Due to different regions and different medical conditions, it is also an effective measure to reduce the incidence of AIDS from a different perspective in some areas with backward medical conditions and high incidence of AIDS. For example, in some African countries, because the number of patients receiving correct and long-term medical treatment is small (only 20% of the patients are receiving treatment), and the number of patients who know that they are suffering from diseases is even small (14%). Therefore, in addition to the routine daily medication, For example, implants or injectable drugs may be a better treatment option [34].

2.5. Cabotegravir/rilpivirine
Cabenuva (Cabotegravir /Rilpivirine), composed of Cabotegravir (CAB) and Rilpivirine (RPV), is the first LA injectable antiretroviral drug Prepared from the nanoscale. According to the ATLAS and FLAIR trials, the only regimen with the same efficacy as oral antiretroviral combination therapy (cART) was monthly Cabotegravir/Rilpivirine, which was particularly effective in suppressing HIV-1 viral load in patients. Therefore, the regimen proven to be an effective substitute for managing HIV infection [35].

2.6. Indole derivatives
Newly, it was discovered as an anti-HIV drug due to its anti-HIV potential. Indole drugs such as delavirdine have been used in clinical practice, and some indole drugs are still in the process of being researched and developed or undergoing clinical evaluation. It is not difficult to see that indole drugs will be Potential Contestants in Future Anti-HIV-1 Drugs [36]. Among all indole analogues, the compounds that showed the strongest anti-HIV-1 activity were 2c, 2j-l and 2n-o. The evidence suggests the indole derivatives can often result in more useful analogs.

3. Conclusion
The global spread of AIDS and the high mortality rate of the disease have troubled mankind for a long time. Currently, the drugs targeted mainly include: NRTIs, NNRTI, PI, Fusion inhibitors, CCR5 antagonists, post-attachment inhibitors. By inhibiting reverse transcriptase, NRTIs work. NNRTI is famous for first binding and then changing the conformation of reverse transcriptase. Blocking an enzyme called integrase is the efficacy of integrase inhibitor. Protease inhibitors (PIs) block enzymes called proteases to inhibit the proliferation of HIV. Fusion inhibitors, CCR5 antagonists and post-attachment inhibitors belong to HIV / AIDS drugs that protect CD4 immune system cells from HIV infection. Fusion inhibitors work by stopping HIV from entering cells to hinder fusion. Different molecules on CD4 cells are inhibited from binding to HIV by CCR5 antagonists and post attachment inhibitors. These inhibitors can inhibit the process of HIV entering cells. Although there is currently no treatment for AIDS, with the progress of medicine, the treatment of HIV is gradually developing. We should be optimistic about AIDS.

References


