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# Two kinds of drugs for treating AIDS

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**Abstract:**

This research provides an in-depth analysis of Efavirenz and Maraviroc, two key antiretroviral drugs used in HIV/AIDS treatment. It examines their mechanisms of action, chemical structures, pharmacological properties, and safety profiles. The study aims to identify the clinical advantages of these drugs and their potential in future HIV therapeutic strategies, considering the limitations of current antiretroviral therapies.

**Keywords:** HIV, Reverse Transcriptase Inhibitors, CCR5 inhibitor, Efavirenz, Maraviroc

## 1 Introduction

By the end of 2023, the total number of people living with HIV/AIDS and HIV virus carriers in China had already reached 1.29 million. A survey showed that between 2011 and 2018, the number of AIDS-related deaths had already reached 205,582 [1]. However, the number of people with AIDS and the number of deaths are still on an upward trend. Given the incidence rate in the population and the mortality rate of patients, it is very necessary to study the drugs related to the treatment of AIDS.

Common medications for treating AIDS on the market can be broadly categorized into reverse transcriptase inhibitors and CCR-5 inhibitors, also known as viral fusion inhibitors [2].

In this work, we will focus on analyzing the differences in mechanism of action, chemical structure, pharmacological properties, and medication risks between the Reverse Transcriptase Inhibitors efavirenz and the first approved CCR-5 inhibitor, maraviroc, by searching relevant literature and collecting data. The purpose of this paper is to provide effective and innovative suggestions for future drug development and rational drug use.

## 2 Content

In this part, this article will discuss the etiology of AIDS in-depth and explore the mechanism of HIV damage to the body. It will also explore the range of antiretroviral drugs currently available to treat the disease, providing a comprehensive assessment of their efficacy and safety. In addition, this article will present the analysis of clinical data related to these drugs, providing insights into their performance in reality and their economic benefits in the healthcare system.

### 2.1 The introduction of AIDS

AIDS (Acquired immune deficiency syndrome) is a serious disease caused by damage to the immune system, which is triggered by the human immunodeficiency virus (HIV). HIV is an RNA virus that attacks the immune system, specifically targeting and damaging CD4+ t cells, which are key in the body's defense against pathogens, leading to poor or even dysfunction of the immune system in patients. The report of five patients in the United States, published on June 5, 1981, was the world's first documented case of AIDS. AIDS is primarily transmitted through blood, sexual contact, and from mother to child. The symptoms and complications of AIDS are diverse.

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Patients typically go through an acute phase, an asymptomatic phase, and the AIDS phase. In the early stages, individuals may experience symptoms such as fever, nausea, colds, diarrhea, rash, and swollen lymph nodes. In the advanced stages, patients often become susceptible to infections and tumors, which are often the main causes of death in AIDS patients.

### 2.2 The pathogenesis of AIDS

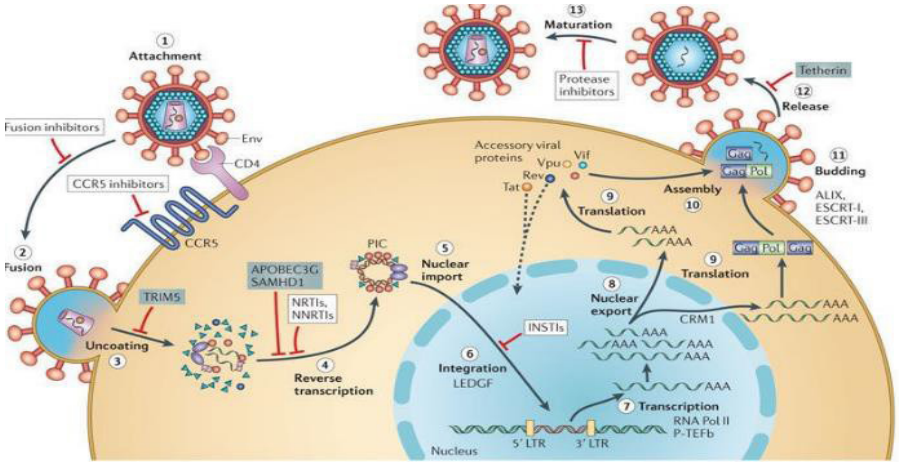



**Figure 1. The course of life of HIV[3]**

The pathogenesis of AIDS, caused by the Human Immunodeficiency Virus (HIV) [3], is a multi-step process that begins with Attachment[1] HIV initially attaches to the host's CD4+ T cells through its surface glycoprotein gp120, engaging with the CD4 receptor and a coreceptor such as CCR5 or CXCR4. This is swiftly followed by Fusion[2] where the virus and cell membranes fuse, allowing the virus to enter the cell. Once inside, the virus undergoes Uncoating[3]: the viral capsid is removed, releasing viral RNA and enzymes into the host cell. The viral RNA is then converted into DNA (cDNA) by HIV's Reverse Transcription[4] using its reverse transcriptase enzyme. The viral DNA is then Nuclear Import[5] transported into the nucleus, where it is integrated into the host's chromosomal DNA with the aid of viral integrase, forming a provirus[6]. This DNA is transcribed by the host's RNA polymerase during Transcription[7] to produce viral RNA, which is then Translated[8] into viral proteins. The components of the virus, including RNA, structural proteins (Gag), and enzymes (Pol), gather at the cell membrane for Assembly[9]. New virus particles Bud[10]: from the cell membrane, acquiring a lipid envelope. During Maturation[11], the virus particles mature as the viral protease cleaves the Gag and Gag-Pol polyproteins into individual proteins. Finally, the Release[12] of mature virions from the host cell is the last step, which can be inhibited by Tetherin inhibitors or fusion inhibitors. The continuous cycle of these steps leads to the depletion of CD4+ T cells, weakening the immune system and creating an environment conducive to opportunistic infections and tumors that are characteristic of AIDS.

### 2.3 Common anti-drugs for treating AIDS

Treating AIDS often involves a combination therapy strategy, which primarily consists of antiretroviral drugs and common antiviral medications that enhance the body's immune system [4]. Treating AIDS often involves a combination therapy strategy, which primarily consists of antiretroviral drugs and common antiviral medications that enhance the body's immune system.

### 2.4 Efavirenz, a Reverse Transcriptase Inhibitor.

Since the first case of AIDS was discovered, related research has already revealed the pathogenic mechanism of the Human Immunodeficiency Virus (HIV). Based on the aforementioned mechanism, scientists have studied many drugs that specifically target AIDS. Since the introduction of zidovudine (AZT) in 1987 as the first FDA-approved antiretroviral drug, a plethora of anti-AIDS medications have emerged on the market. Among them, reverse transcriptase inhibitors hold a significant share of the market. Zidovudine(AZT) , shown in structure and nomenclature in figure 2, is a nucleoside reverse transcriptase inhibitor. After being metabolized by the infected viral cells, it generates active substances that selectively inhibit the HIV reverse transcriptase, thereby causing the synthesis of the HIV chain to be obstructed and thus suppressing the proliferation of HIV.

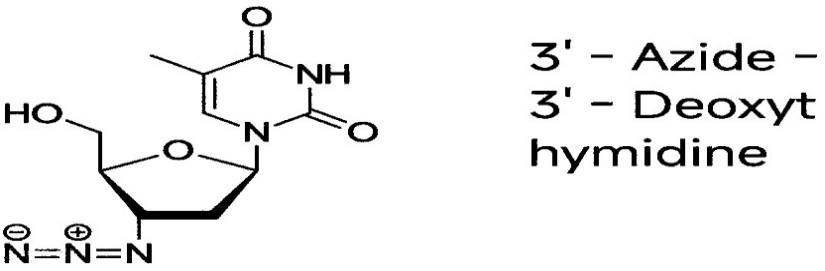
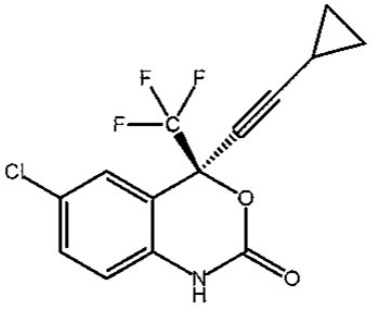



**Figure 2. The structure of AZT**

Despite research and experimental data indicating that antiretroviral drugs have significant therapeutic effects on AIDS patients, it cannot be ignored that the side effects and adverse reactions brought by zidovudine often cause suffering for the patients. In clinical use, zidovudine has been found to cause side effects such as anemia, neutropenia, leukopenia, nausea and vomiting, diarrhea, gastrointestinal bloating, as well as liver metabolism issues and psychiatric disorders in patients [5]. What's even more frightening is that, in addition to the aforementioned adverse reactions, a study conducted in 2000 indicated that the use of AZT could lead to heart dysfunction in mice. Similarly, some patients have developed cardiomyopathy and other cardiovascular diseases after using AZT. Considering the toxic side effects of AZT and the emergence of drug-resistant HIV mutations in clinical practice, AZT is now rarely used in large quantities in clinical settings. Instead, non-nucleoside reverse transcriptase inhibitors (NNRTIs) with relatively fewer side effects have taken their place, with Efavirenz being one of them.

Efavirenz, as a non-nucleoside reverse transcriptase inhibitor (NNRTI), is currently a first-line medication in clinical use in China. Its structure is shown in Figure 3.



(4S)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro-1H-3,1-benzoxazin-2-one

**Figure 3. The structure of Efavirenz**

Unlike the first approved nucleoside reverse transcriptase inhibitor, zidovudine, efavirenz is a non-competitive inhibitor of the HIV reverse transcriptase enzyme during the viral replication process, thereby limiting the proliferation of the virus [6]. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) effectively inhibit the polymerization activity of HIV reverse transcriptase (RT), which is a key enzyme for producing double-stranded viral DNA genomes [7]. This enzyme is crucial for the subsequent ability of the AIDS virus to evade the immune system in the human body, as it is produced by reverse transcription from a single-stranded viral RNA sequence. HIV reverse transcriptase is an asymmetric heterodimer composed of two subunits: the p66 subunit that performs the enzymatic functions of the reverse transcriptase; and the p55 subunit that provides structural and conformational support. The p66 subunit, when conceptualized in three dimensions, resembles the shape of a right hand and includes four subunits: the fingers, palm, thumb, and connection subdomains. The drug target of NRTIs, that is, the catalytic site of HIV-1 polymerase, is located in the palm subdomain. It is shown in the figure 4.

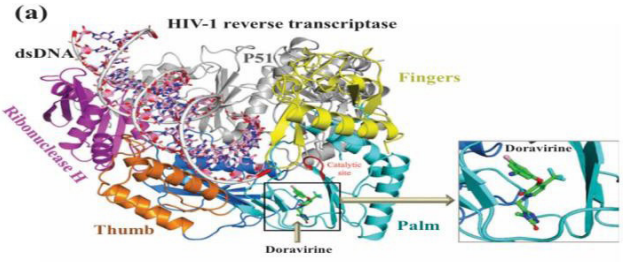



**Figure 4. The structure of reverse transcriptase [6]**

Non-competitive NNRTIs alter the spatial structure to specifically form a hydrophobic pocket (Figure 5), which many believe may be the mechanism of action of non-nu-

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cleoside reverse transcript.

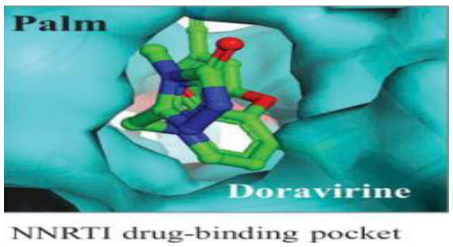



**Figure 5. The NNRTIs react with reverse transcriptase [6]**

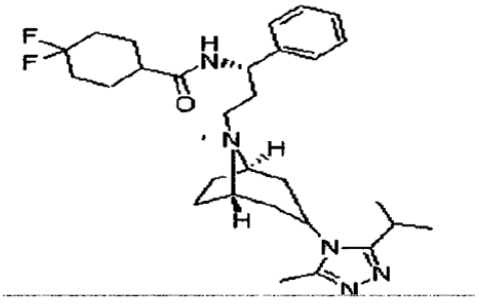
Despite being proven effective [8] in principle and in clinical practice, the toxic side effects of efavirenz remain an important consideration in clinical medication use. Compared to zidovudine, efavirenz has fewer side effects. However, relevant research indicates that due to physiological changes during pregnancy, such as slowed intestinal motility, increased liver enzyme activity, and increased glomerular filtration rate, there may be some differences in the pharmacokinetics of pregnant women compared to the general population [9]. Due to the lack of related data, the toxic side effects of efavirenz on pregnant women [10] still require further study.

In addition to this, in 2019, researchers used mass spectrometry imaging technology to observe the distribution of six antiretroviral drugs (including efavirenz) in intestinal tissue sections of three different species [11]. They found that the distribution was not uniform, with some areas of the intestinal tissue having insufficient concentrations of certain drugs, while a large amount of HIV RNA was expressed in those areas where there was no drug or where the drug concentration was too low. This indicates that even if patients take efavirenz, it may still lead to low-level replication of HIV, making it difficult to eradicate the virus completely.

Given the above situation, to prevent the serious adverse reactions and drug resistance that may result from the use of a single drug, a so-called "cocktail therapy" is commonly adopted in clinical practice [12]. This involves the rational and effective combination of drugs that act on the stages of viral replication to achieve a better antiviral effect [13].

## 2.5 Maraviroc, a CCR5 inhibitor

Maraviroc, as a medication that has only been approved and marketed in recent years, operates through a mechanism that is distinctly different from common antiretroviral drugs. Most conventional antiretroviral medications act on the process of reverse transcriptase, converting RNA into DNA. In contrast, Maraviroc is the first approved CCR-5 inhibitor; it impedes the proliferation of the virus within the body by preventing the virus from entering the receptor cells. Its structure is shown in Figure 6.



4,4-Difluoro-N-[(1S)-3-[(1R,5S)-3-(3-methyl-5-propan-2-yl-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octan-8-yl]-1-phenylpropyl]cyclohexane-1-carboxamide

**Figure 6 The structure of Maraviroc**

The CCR5 is a G protein-coupled receptor that plays a crucial role in the activation and coordination of both innate and adaptive immune responses by regulating the migration and effector functions of memory and cytotoxic T cells, macrophages, and dendritic cells. In addition to being related to HIV infection, CCR5 is also associated with a variety of immune-related diseases, cancers, and pathogen infections [14]. The specific process of CCR5 action is illustrated in Figure 7.

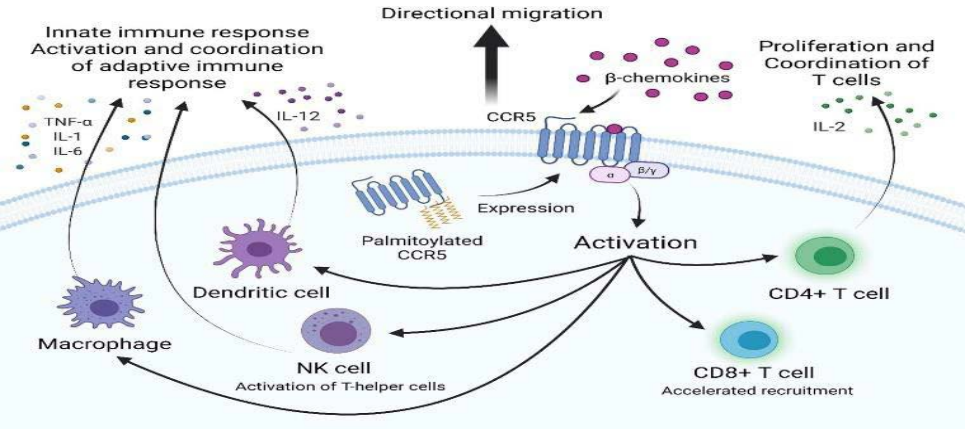



**Figure 7. CCR5 action [14]**

Maraviroc, as an oral CCR5 antagonist, possesses high affinity and can bind [15] to the allosteric site of CCR5, inhibiting the interaction between the virus and the receptor. This interaction is crucial for HIV to enter host cells and helper T cells, and by blocking it, Maraviroc achieves an antiviral effect.

Selective for HIV-1 strains that use CCR5 as a coreceptor, Maraviroc targets these specific strains, meaning its action is focused on viruses that rely on CCR5 to infect cells [16]. Furthermore, Maraviroc can induce immunological changes that are beneficial for the control of HIV-1 disease.

It may increase the number of immune cells, such as CD4+ and CD8+ lymphocytes, potentially through the activation of the NF-κB signaling pathway. This may help prevent excessive T-cell activation, which is a common problem in HIV-1 infection. By modulating the immune response in this way, Maraviroc helps control the progression of HIV-1 disease.

Compared with conventional nucleoside and non-nucleoside reverse transcriptase inhibitors, Maraviroc is more promising for clinical treatment. A study conducted in 2020 showed that Maraviroc can activate HIV during incubation and intervene to suppress it. However, traditional antiretroviral therapy (ART), which is mainly characterized by the inhibition of reverse transcriptase, has been faced with the problem of being unable to effectively inhibit latent virus. The emergence of Maraviroc offers great potential for eradicating HIV and curing AIDS.

Maraviroc's ability to target the CCR5 co-receptor provides a different mechanism of action compared to traditional antiretroviral drugs. The CCR5 co-receptor is essential for HIV to enter cells. By blocking this co-receptor [17], Maraviroc can prevent the virus from entering cells, thereby inhibiting viral replication. In addition, it has the potential to activate latent HIV, which in turn could destroy the viral reservoir, a major obstacle to treating HIV. This dual role of preventing new infections and targeting existing latent viruses makes Maraviroc a promising candidate for an HIV eradication strategy.

In addition to its therapeutic potential, Maraviroc also appears to have clinical advantages over traditional antiretroviral drugs such as Efavirenz in terms of side effects. A 2024 study showed that high concentrations of Maraviroc(MVC) did not increase the levels of activation markers in CD4 T cells, nor did they increase the glycolytic or oxidative metabolic rate [18]. In addition, MVC did not cause significant changes in the frequency and activation levels of memory cell subpopulations [19]. This suggests that maraviroc has a higher clinical safety profile.

Unlike drugs such as AZT(Zidovudine) and Efavirenz, which have harmful effects on the cardiovascular system, Maraviroc not only avoids this harm but also has a protective effect against the burden of atherosclerosis [20]. This dual benefit of Maraviroc—safety in terms of side effects and a protective role in cardiovascular health—makes it an even more compelling option for clinical use in the treatment of HIV-1.

## 3 Conclusion

### 3.1 Limitation of this research

The article focuses solely on two major classes of AIDS treatments — reverse transcriptase inhibitors and CCR5 inhibitors—without covering all anti-HIV drugs and emerging frontiers in therapeutic strategies. Due to the lack of extensive clinical data, the paper does not delve deeply into the impact of drug resistance and individual patient variability on the efficacy of these medications, drawing conclusions based only on existing literature and related research. Additionally, the paper does not discuss the cost of treatment with these drugs, the quality of life for patients taking them, or the issue of drug resistance.

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### 3.2 Envisions of future research on HIV

From the first reported case of AIDS to the present day, from the first drug approved for the treatment of AIDS, AZT, to the current variety of therapeutic agents, and from the earliest reverse transcriptase inhibitors to the latest HIV-1 capsid inhibitor Lenacapavir, the journey has seen the efforts of numerous scientists over the years, all hoping to one day achieve a complete cure for AIDS. Future research on antiretroviral drugs for AIDS could be approached from several angles:

1) By conducting physiological and biochemical tests on the few known cases of individuals who have been cured of AIDS worldwide, extracting some of their body fluids to prepare anti-HIV antibodies, and testing their clinical feasibility.

2) Studying the life cycle of HIV to explore how individual variability affects HIV replication, which could lead to customized therapies for different patients.

3) Searching for new drug targets by conducting biological and virological experiments to screen for promising drug targets and design new drugs based on these findings.

4) Trying alternative medication strategies to cocktail therapy, such as using CCR5 inhibitors in conjunction with reverse transcriptase inhibitors to enhance therapeutic efficacy.

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