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NOVEL DRUG THERAPIES FOR THE TREATMENT OF HIV/AIDS

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ABSTRACT

As HIV/AIDS remains a significant concern, effective drug treatments are essential for managing the disease across large populations. Highly Active Antiretroviral Therapy (HAART) offers effective control over viral replication but comes with potential side effects, particularly with long-term use. Current treatments face challenges such as multidrug resistance, the spread of drug-resistant HIV strains, and the need for lifelong therapy. To enhance patient adherence and simplify treatment regimens, there is a need for effective fixed-dose combinations (FDCs). In this review, novel drug therapies for the treatment of HIV/AIDS will be here discussed. Several new drugs, delivery systems, and vaccines have undergone testing in pre-clinical and clinical trials. In terms of drug delivery, modifying the administration route for some traditional antiretrovirals has been successful, addressing various patient compliance issues. Nanotechnology has introduced innovative solutions for formulation challenges, such as drug solubility and distribution in the body. Encapsulating antiretroviral drugs in nanosystems has led to better drug release and improved pharmacokinetic profiles.

Keywords: Acquired immunodeficiency syndrome, Combination anti-retroviral therapy, Ibalizumab, Cabotegravir, Rilpivirine, Leronlimab, Fostemsavir, Nanosystem.

INTRODUCTION

AIDS (acquired immunodeficiency syndrome) is a severe and life-threatening disease caused by HIV infection. [1]. Over the years, numerous therapeutic targets and antiretroviral drugs have been developed based on the HIV replication cycle. Nowadays, initial treatment regimens typically consist of at least three different medications. Generally, antiretroviral drugs are categorized into seven main types based on their mechanisms of action. [2,3]

TABLE 1

classification of antiretroviral therapy.

CLASS	DRUGS
Nucleoside reverse transcriptase inhibitors (NRTIs)	Zidovudine(AZT), Didanosine(ddl), Stavudine(d4T), Lamivudine(3TC), Abacavir(ABC), Tenofovir(TDF)
Non- nucleoside reverse transcriptase inhibitors(NNRTIs)	Nevirapine(NVP), Efavirenz(EFV), Delavirdine(DLV)
Protease inhibitors(PIs)	Ritonavir(RTV), Atazanavir(ATV), Indinavir (INV), Saquinavir(SQV), Lopinavir(LPV)
Integrase inhibitor	Raltegravir, Dolutegravir(DTG)
CCR-5 receptor inhibitor	Maraviroc
Fusion inhibitor	Enfuvirtide(T-20)
Pharmacokinetic enhancers	Cobicistat

Combination antiretroviral therapy (c-ART) is considered an effective approach by utilizing a regimen of drugs with different targets. Fixed-dose combinations of ARVs, administered as a single tablet, have been approved and were first introduced in 1996. However, since then, some issues have emerged, such as the interference of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) with the metabolism of other common medications. [4] Ritonavir, initially used with first-generation PIs like lopinavir or saquinavir, and later with second-generation PIs such as atazanavir and darunavir, has been found to affect the metabolism process. This interference allows for higher concentrations of other antiretroviral and enables longer intervals between their administrations.

TABLE 2

Fixed-dose combination of ARVs administered as a single tablet approved until date according to literature and EMA information. [5-10]

APPROVED DRUGS	ACTIVE SUBSTANCES
Genvoya® Biktarvy®	150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir 50 mg bictegravir/200 mg emtricitabine/25 mg tenofovir alafenamide
Atripla®	600 mg efavirenz/200 mg emtricitabine/245 mg tenofovir-DF
Rezolsta®	800 mg darunavir/150 mg cobicistat
Triumeq®	50 mg dolutegravir/600 mg abacavir/300 mg lamivudine
Evotaz®	300 mg atazanavir/150 mg cobicistat
Descovy®	200 mg emtricitabine/10 mg tenofovir alafenamide 200 mg emtricitabine/25 mg tenofovir alafenamide

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Nowadays, the diverse therapeutic options and c-ART regimens have transformed AIDS into a manageable chronic condition with reduced mortality. [11] While c-ART remains the most effective treatment available, it is not without its drawbacks. Patients must adhere to lifelong medication, which carries a significant risk of developing drug resistance and experiencing viral rebound. Additionally, these individuals often face a range of side effects. [12,13].

There are currently several new drugs and vaccines being tested in pre-clinical and clinical trials for HIV treatment or prophylaxis. Hereby, the most recent clinical studies on phase III will be further discussed.

A. POST-ATTACHMENT INHIBITORS: IBALIZUMAB

Ibalizumab is the first drug designed to target the CD4 receptor, classifying it as a post attachment inhibitor [14,15]. The FDA recommends an initial subcutaneous dose of 2000 mg, followed by a maintenance dose of 800 mg every two weeks. [14] The drug's half-life is estimated to be between 3 and 3.5 days. [16,17] Ibalizumab is generally well tolerated, though it can cause side effects such as rash, headaches, dizziness, nausea, and diarrhea. [17,18]

In conclusion, ibalizumab represents a promising and relatively safe treatment option for patients who experience resistance to standard ARV regimens. Its dosing schedule may enhance patient adherence and autonomy by reducing the frequency of administration. [16]

B. LONG-ACTING INJECTABLE CABOTEGRAVIR/RILPIVIRINE FORMULATION

Cabotegravir (CR) (Vocabria®) is an integrase strand transfer inhibitor (NSTI) structurally like dolutegravir.[19,20] Cabotegravir is available as a once-daily oral tablet and as injectable forms, both intramuscular (IM) and subcutaneous (SC). The injectable version is formulated as a longacting (LA) suspension, with dosing intervals ranging from monthly to quarterly. Before starting the injections, patients take oral tablets of cabotegravir (Vocabria®) and rilpivirine (Edurant®) for about a month to evaluate tolerance. Following this, cabotegravir IM injection (Vocabria) is administered alongside rilpivirine IM injection (Rekambys®) as a comprehensive long-acting regimen, with doses given either monthly or every two months.[20,21] Cabotegravir has a notably long half-life of 20 to 40 days and is heavily bound to albumin, with elimination through the liver. No dose adjustments are necessary for patients with liver impairment.[20] Rilpivirine, an NNRTI, also has a long half-life, ranging from 30 to 90 days, and may affect liver and pancreatic enzymes, potentially causing side effects such as headaches, nausea, dizziness, and fatigue.[20].

In 2021, the FDA approved the combination of cabotegravir and rilpivirine under the brand name Cabenuva®. This was the first HIV-1 treatment regimen that required administration only once a month. Cabenuva® consists of two separate long-acting injectable suspensions of cabotegravir and rilpivirine. The regimen also involves taking Vocabria® 30 mg tablets and rilpivirine 25 mg tablets (Edurant®) before starting the injections to ensure that the long-acting formulations are well tolerated.[22-24].

C. LERONLIMAB (PRO 140)

Leronlimab (PRO 140) is a humanized IgG4 monoclonal antibody, and it shares several similarities with Maraviroc. However, their distinct binding sites imply that these medications might work together synergistically.[25] Given its high tolerance and strong resistance to developing resistance, this new drug could potentially be effective for both pre- and postexposure prophylaxis.[26]

D. FOSTEMSAVIR

Fostemsavir (Rukobia®) is a prodrug of temsavir, which functions as an attachment inhibitor. It does not show significant interactions with other classes of antiretroviral drugs.[27] Approved by the EMA in February 2021, Rukobia® is intended for use in patients with multi-drug resistant HIV-1. One of its most serious side effects is immune reconstitution inflammatory syndrome. Additionally, it has been found to interact with certain medications, including rifampicin, antiseizure drugs like carbamazepine and phenytoin, as well as certain anticancer drugs.[28]

E. UB-421

The safety and effectiveness of UB-421 have been evaluated in multiple clinical trials. One such study, a phase II/III trial that began in September 2019, first tested UB-421 in conjunction with a failing ART regimen for one

week. Subsequently, UB-421 was assessed with an optimized background regimen for 24 weeks. The primary measure of outcomes was the change in viral load from baseline.[29] Additionally, a phase III trial commenced in January 2020 to primarily assess the drug's efficacy, safety, and tolerability as a monotherapy.[30]

F. GENE BASED THERAPIES

At the 12th International AIDS Society (IAS) Conference in Brisbane in 2023, it was highlighted that CCR5-targeted gene editing could potentially offer a cure for people living with HIV/AIDS (PLWHA). Mutations that block the CCR5 receptor can prevent HIV from infecting CD4 Tcells.[31] For instance, individuals who are heterozygous for the CCR5 delta 32 mutation experience slower disease progression. Research into CCR5 inhibitors, such as Maraviroc, might lead to the development of a new class of HIV/AIDS drugs. Advances in gene-based technologies and therapies are creating new methods for effectively targeting and inhibiting HIV within the body. The CRISPR/Cas9 genome editing tool, for example, has emerged as a powerful means to completely inhibit viral replication without requiring ongoing treatment. CRISPR/Cas9 approaches can effectively eliminate HIV-1 by targeting and removing the integrated provirus and its reservoirs, potentially making a cure for HIV a reality and allowing for a healthier life free from reemergent infections. [32]

G. NANOTECHNOLOGY BASED DRUGS

A major challenge with current HIV medications is their short duration in the bloodstream and limited access to targeted tissues. However, nanotechnology offers a potential solution by enhancing the delivery of antiretroviral (ARV) drugs. Nanosystems, which are engineered nanodrug carriers, include five main types for HIV drug delivery: liposomes, dendrimers, polymeric nanoparticles, solid lipid nanoparticles, and inorganic nanoparticle systems. These Nano biotechnologies can significantly improve the performance of ART drugs and transform delivery methods.

Nanocarriers help overcome therapeutic limitations of existing drugs by enhancing drug delivery, bioavailability, and physicochemical stability. For example, when zidovudine, an amphiphilic drug, is encapsulated in liposomes, it shows significantly improved distribution in the reticuloendothelial system and brain, as well as a longer half-life compared to standard zidovudine. This method reduces toxicity and boosts efficacy. Research has shown that incorporating ARV drugs like acyclovir, indinavir, zidovudine, and lamivudine into liposomal structures results in a 12-fold increase in drug concentration in blood plasma compared to traditional formulations. [33].

CONCLUSION

HIV infection remains one of the major global pandemics. In the 1990s, the advent of the first antiretroviral drugs and combination antiretroviral therapy (c-ART) transformed HIV from a fatal illness into a manageable chronic condition, allowing those infected to live as long as those who are not. However, c-ART has its drawbacks, including side effects, the need for frequent drug administration, and the risk of viral resistance, and it still does not offer a definitive cure.

New ART options are emerging that aim for a more permanent solution for people living with HIV/AIDS (PLWHA). Future research should focus on understanding the sources and characteristics of viral replication, the relationship between cellular reservoirs, residual plasma viremia, and resistant viruses, and developing methods to reverse latency. Advances in gene therapy, new vaccine strategies, and long-acting injectable formulations hold the greatest promise for eradicating HIV infection. Nanotechnology has demonstrated potential in providing targeted and controlled release of antiretrovirals, addressing formulation challenges such as cytotoxicity.

Despite ongoing efforts, an effective HIV vaccine remains elusive. To date, there have been limited successful vaccine trials. Continued research is critical, particularly in the areas of prophylactic vaccines, pharmacokinetics, and pharmacodynamics, along with well-defined in vivo studies of new antiretroviral drugs.

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