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Investigating the Current and Novel Methods for the Treatment of HIV

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Abstract. Human immunodeficiency virus (HIV), a retrovirus that primarily infects CD4 receptor-bearing cells, can cause significant immune system dysfunction in humans. Although antiretroviral therapy (ART) has extended the life expectancy of individuals with HIV, challenges persist due to drug resistance, adherence issues, and side effects. This review examines both established and emerging HIV treatment strategies, including ART and novel agents like fostemsavir and ibalizumab. It also explores innovative approaches such as therapeutic vaccines, transdermal drug delivery systems (TDDS), hematopoietic stem cell transplantation (HSCT), and chimeric antigen receptor T (CAR-T) cell therapy. The role of artificial intelligence (AI) and machine learning (ML) in optimizing patient care and predicting treatment outcomes is also highlighted. A comprehensive understanding of HIV's life cycle and the challenges of current therapies is crucial for developing more effective treatments and interventions for HIV prevention and management.

Keywords: HIV, antiretroviral therapy, vaccines, artificial intelligence, machine learning.

1. Introduction

Human immunodeficiency virus (HIV), discovered in 1981, attacks the immune system, specifically targeting CD4 T cells, and can lead to acquired immunodeficiency syndrome (AIDS) [1]. HIV is primarily transmitted through the bodily fluids of infected individuals, including blood, breast milk, semen, and vaginal secretions. It can also be passed from mother to child during pregnancy, childbirth, or breastfeeding [2]. As of the end of 2022, the World Health Organization (WHO) estimated that around 39 million people were living with HIV globally [3]. Without appropriate HIV treatment, individuals with AIDS typically survive about three years. However, if a severe opportunistic infection occurs, life expectancy without treatment drops to approximately one year [4]. Therefore, HIV remains a major global public health issue with no effective cure currently available. In addition, HIV also has a negative economic impact on countries. The financial burden on healthcare systems is significant due to expensive medications and patient care costs, thereby overstraining healthcare systems. Understanding the HIV life cycle is crucial for developing effective treatments. Following infecting a host cell, HIV, integrates its viral DNA into the host DNA, followed by replication. Eventually, new viral particles are released to infect other cells (Figure 1). This cycle makes eliminating the virus from the body challenging once it has established viral integration [5].

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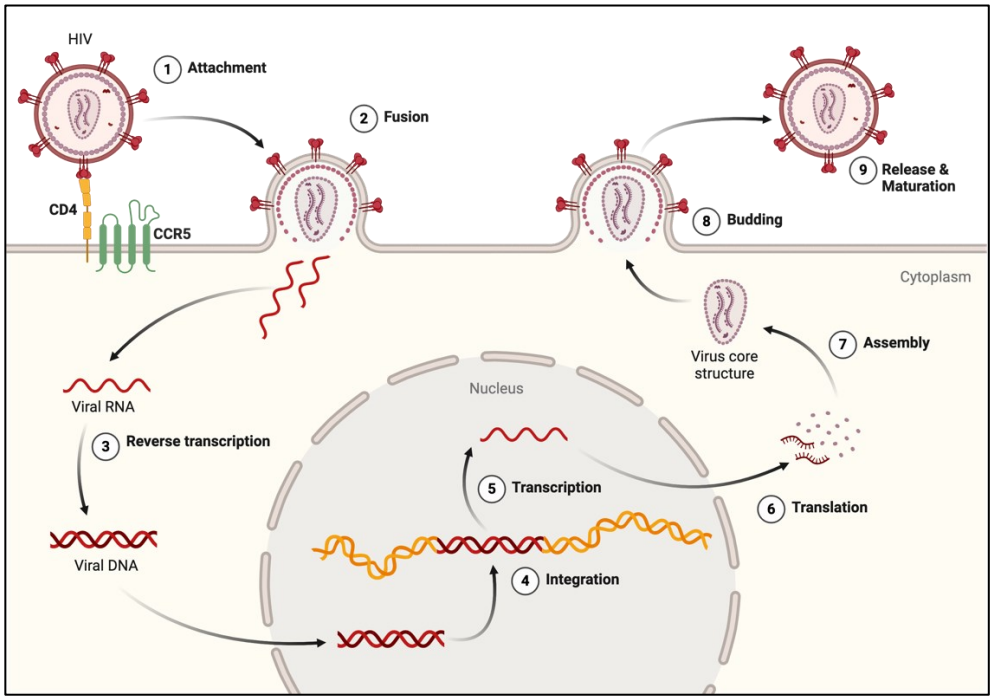


Figure 1. The HIV life cycle. Created with Biorender.com.

Currently, antiretroviral therapy (ART) has been successful in managing HIV infection by suppressing viral replication and improving the quality of life for those infected. With current advancements in HIV medications, the life expectancy of a person living with HIV can be comparable to that of someone without HIV. However, drug-induced and transmitted resistance, side effects, and difficulty in adhering to daily regimens are some of the major challenges of antiretroviral treatment [6]. Additionally, designing a globally effective HIV vaccine also presents numerous challenges, HIV exhibits high genetic variability and subtypes, which complicates the development of a broadly effective vaccine. Its ability of rapid mutation allows it to evade the immune response, making it difficult for a single vaccine to target. HIV envelope glycans which are critical for envelop folding and cleavage during maturation can hide its epitopes and enable HIV to evade the immune system [7].

This paper aims to investigate both current and novel methods for the treatment of HIV including exploring emerging therapies that target different stages of the HIV life cycle, assessing the novel approaches, and evaluating artificial intelligence and machine learning to emphasize the prevention of the disease.

2. Discussion

2.1. Antiretroviral therapy (ART)

Antiretroviral therapy (ART) is a combination of medications to treat HIV which both increase potency and reduce the likelihood of the virus developing resistance [8]. It is by far the most effective HIV treatment; Over 90% of individuals who adhere to ART medications have undetectable HIV levels in their blood within 12 months. Most individuals who initiate ART soon after their diagnosis and adhere to the treatment can achieve the same life expectancy as those who are without HIV [9]. There are generally six major types (Table 1):

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Table 1. Overview of antiretroviral therapies (ARTs) for HIV and their advantages and disadvantages.

Drug category	Target	Advantages	Disadvantages	References
Entry inhibitors	HIV gp120; CCR5, CD4 receptors, etc.	Reduced Resistance Development	fatigue, nausea, and diarrhea, etc. (fostemsavir) diarrhea, dizziness, nausea, and rash, etc. (ibalizumab)	(10,11)
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	HIV reverse transcriptase (active site)	Long-Term Efficacy High oral bioavailability	gastrointestinal disturbances, headaches, fatigue, etc.	(12-14)
Non-nucleotide reverse transcriptase inhibitors (NNRTIs)	HIV reverse transcriptase (allosteric site)	Low cost of production Ease of Administration	Highly susceptible to developing resistance. rash, potential liver toxicity, insomnia, etc.	(15-17)
Integrase strand transfer inhibitors (INSTIs)	HIV integrase enzyme	High Barrier to Resistance well-tolerated	hypersensitivity reactions, headaches, insomnia, fatigue, etc.	(15, 18)
Protease inhibitors (PIs)	HIV protease	Effective against both HIV-1 and HIV-2	arrhythmia, kidney stones, dizziness, etc.	(19)
Capsid inhibitors	HIV Gag polyprotein	Effective against both HIV-1 and HIV-2 Long-Term Efficacy	joint pain, nausea, skin rash, etc.	(20-22)

2.1.1. Entry inhibitors

Entry inhibitors are used to treat HIV because they block the virus from entering and infecting host CD4 cells, which include several subclasses, such as attachment inhibitors, CCR5 antagonists, and anti-CD4 binding antibodies. Attachment inhibitors (e.g. Fostemsavir), block the virus from attaching to gp120 protein on the outer surface of HIV [10]. CCR5, a member of the G protein-coupled receptor family, acts as a co-receptor for HIV entry [11]. Therefore, CCR5 antagonists (e.g. Maraviroc) can prevent HIV from binding to the CCR5 co-receptor, which is crucial for viral entry into the cell. Anti-CD4 binding antibodies (e.g. Ibalizumab), bind to the CD4 receptor on the host cell, thereby preventing the virus from attaching and entering the cell [10].

2.1.2. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

Nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of antiretroviral therapy (ART) approved by the FDA for HIV treatment. NRTIs inhibit reverse transcriptase, the enzyme responsible for converting HIV RNA into DNA. Administered as prodrugs, NRTIs are activated by cellular kinases within host cells. Structurally similar to viral nucleosides but lacking a hydroxyl group at the 3' position of their deoxyribose sugar, NRTIs prevent the formation of phosphodiester bonds with the next 5'

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nucleoside, thereby halting the viral nucleoside chain. As a result, NRTIs act as competitive inhibitors of reverse transcriptase [12, 13]. In 1987, Zidovudine was approved in the US, marking the first antiretroviral medication [14]. However, the side effects of Zidovudine were noticed, such as nausea, vomiting, and hepatotoxicity.

2.1.3. Non-nucleotide reverse transcriptase inhibitors (NNRTIs)

The NNRTIs block reverse transcriptase, by binding to an allosteric hydrophobic pocket away from the active site where NRTIs bind to. They act as non-competitive inhibitors to induce a conformational change, thereby inhibiting enzyme activity. The advantages of NNRTIs compared to NRTIs include cost-effectiveness to produce and it is Single-tablet regimens [15]. However, one limitation of this type of drug is that their efficacies are likely to be affected by different conditions upon oral absorption such as diet and pH, among other factors [16]. The approval of NNRTIs is later than NRTIs - Nevirapine (NVP) was approved in 1996 by the FDA [17]. Nevirapine can also cause severe side effects including liver problems and severe skin rash.

2.1.4. Integrase strand transfer inhibitors (INSTIs)

INSTIs target the HIV integrase enzyme, which facilitates the integration of viral DNA into the host cell genome (Figure 1). By blocking this enzyme, INSTIs prevent the virus permanently infecting the host cells. Although INSTIs were first discovered over a decade ago, they are generally well-tolerated and have fewer serious side effects compared to older classes of antiretroviral drugs [18]. The initial integrase inhibitor approved by the FDA in 2007 was raltegravir, with the most recent approval being elvitegravir in 2014. While INSTIs are known for their tolerability, potential side effects include hypersensitivity reactions, headaches, insomnia, and fatigue [15].

2.1.5. Protease inhibitors (PIs)

HIV protease is a critical enzyme in the HIV life cycle, responsible for cleaving newly synthesized polyproteins into mature, functional proteins that HIV needs for replication (Figure 1). PIs competitively bind to this enzyme, mimicking its natural substrate. By inhibiting protease activity, PIs lead to the production of immature viral particles, reducing viral replication and spread. The first PI, ritonavir, was approved for use in the United States in 1996. However, a major limitation of PIs is that the HIV protease gene is highly prone to mutations, which can rapidly lead to drug resistance. This challenge can be circumvented by using PIs in combination with other antiretroviral agents to prevent resistance. Additionally, PIs are associated with side effects such as arrhythmia, kidney stones, and dizziness [19].

2.1.6. Capsid inhibitors

The HIV capsid is essential in both the early and late phases of the viral life cycle. In the early phase, after fusing with the host cell, the capsid is released into the cytoplasm, where it uncoats, a process closely associated with the reverse transcription of the viral genome. Later, the Gag polyprotein, which serves as a precursor to the capsid protein, assembles at the plasma membrane to produce immature, non-infectious viral particles. Capsid inhibitors work by interfering with the capsid's formation, stability, or disassembly [20]. Lenacapavir, a novel first-in-class, long-acting HIV-1 capsid inhibitor, was approved by the FDA in 2022 [21]. It interferes with capsid function at multiple stages of the HIV life cycle and is a potent antiviral with a low risk of metabolic interactions, allowing for infrequent dosing. However, it is associated with side effects such as joint pain, nausea, skin rash, and sudden numbness or weakness in the arms and legs [22].

2.2. Novel antiretroviral therapy drugs

2.2.1. Post-Attachment Inhibitors Ibalizumab

Ibalizumab is a recombinant humanized immunoglobulin (Ig) G4 monoclonal antibody that acts as a CD4-directed post-attachment inhibitor by inhibiting HIV entry into the CD4 T cell. It binds to domain

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2 of the CD4 receptor on host immune cells, preventing the binding of HIV to the co-receptors (CCR5 or CXCR4) of CD4+ T cells while maintaining their normal immune functions. This drug was approved by the U.S. FDA in 2018, and it was the first drug to target the CD4 receptor [23], paving the way for a novel class of medications available in the market. This innovative drug is generally well-tolerated with some adverse effects such as rash, headaches, dizziness, and nausea. In addition, it does not exhibit cross-resistance with other HIV drugs, and it has a low risk of eliminating CD4+ cells via antibody-dependent cellular cytotoxicity (ADCC) [24].

2.2.2. Integration Inhibitors LEDGINs

Lens Epithelium-Derived Growth Factor (LEDGF/p75) is a host protein that plays a crucial role in viral integration, interfering with integrase and guiding it to chromatin regions in the host cell's nucleus. LEDGFIN refers to Lens Epithelium-Derived Growth Factor Inhibitor; it blocks the interaction between LEDGF/p75 and the HIV integrase enzyme [25]. The advantage of LEDGINs is that they target a host factor (LEDGF/p75) rather than the virus itself, which can reduce the likelihood of viral resistance compared to drugs that directly target viral proteins [26]. Whilst, LEDGFINs are still in preclinical trials, and there is currently insufficient data to fully evaluate their long-term efficacy, safety, and potential side effects in humans [25].

2.2.3. Attachment Inhibitor Fostemsavir

Fostemsavir was recently approved by the FDA in 2020 and was administered as part of combination therapy. It is a prodrug of temsavir that acts as an attachment inhibitor. Fostemsavir works by binding to HIV-1 gp120, which is an essential protein for the virus to attach to the CD4 receptor on host immune cells, thereby preventing viral attachment to CD4 receptors. This innovative mechanism of action makes fostemsavir particularly useful for individuals who have developed resistance to multiple drug classes. However, Fostemsavir may be expensive and requires twice-daily dosing, which may be less convenient than other long-acting options [27]. Fostemsavir is typically well-tolerated, whereas the immune reconstitution inflammatory syndrome is a notable side effect [28].

2.3. Novel approaches

2.3.1. Transdermal Drug Delivery Systems (TDDS)

TDDS is a novel, non-invasive, and patient-friendly drug delivery system that allows drugs to penetrate the skin and enter the body's circulation to provide therapeutic effects. This approach can reduce issues associated with antiretroviral (ARV) drugs, such as the pharmacokinetic variations of oral administration, including limited bioavailability, prolonged administration, and hepatic first-pass metabolism [29]. TDDS enables medication to be administered without requiring specialized skills and bypasses first-pass metabolism in the liver. However, various biological factors (e.g., skin condition, age, and metabolism), physicochemical properties (e.g., skin moisture, pH, and molecular size), and environmental factors (e.g., sunlight, seasons, and air pollution) can influence TDDS. Small size and low molecular weight of most ARV enable them to pass through skin barriers and enter the bloodstream via passive diffusion. TDDS also provides various approaches for HIV treatment including transdermal patches, chemical penetration enhancers, lipid-based nano-delivery systems, microneedles, and iontophoresis [30]. These innovative approaches can greatly quality of life, given that ARV needs long-term adherence. Its non-invasive, self-administered nature allows for long-term drug release (up to one week), reducing the need for frequent dosing. Bypassing the gastrointestinal side effects typically associated with oral antiretroviral drugs further enhances compliance. Moreover, TDDS is generally cost-effective, making it a practical option for long-term treatment [31].

2.3.2. Therapeutic Vaccines

Although ART has been highly effective, there is still no complete cure for HIV, and treatment remains lifelong. One promising alternative strategy is the therapeutic vaccines for HIV, which aim to treat

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individuals already infected with HIV rather than preventing infection like traditional vaccines. These vaccines can enhance the immune system's ability to control HIV within the body [32]. Currently, therapeutic vaccines are more advanced in the cancer field. For example, Sipuleucel-T has been approved by the FDA for the treatment of prostate cancer by collecting T cells to eradicate tumor cells after reinfusion [33]. Similarly, therapeutic HIV vaccines aim to amplify the T-cell responses to eliminate infected cells. However, significant challenges exist primarily due to the virus's enormous genetic diversity, multiple transmission routes, its capacity to establish hidden reservoirs within the body, and its ability to evade the immune system [34].

Despite these challenges, there have been some promising developments. The RV144 Thai trial, for example, demonstrated 60% efficacy at 12 months post-immunization, though this efficacy decreased to 31% at 3.5 years. This remains the only study to show a positive signal for an HIV vaccine, and future large-scale studies are required to extend and validate these findings. Additionally, novel approaches, such as the Ad26 mosaic trials, focus on generating robust T-lymphocyte responses and neutralizing antibodies, and they are safe and well-tolerated in early clinical trials [35].

2.3.3. Hematopoietic Stem Cell Transplantation (HSCT)

HSCT in HIV patients has become a standard treatment option for individuals with HIV who also have hematologic malignancies with a poor prognosis. The two most well-known cases of functional cures for HIV are known as the "Berlin patient" and the "London patient" both received allogeneic CCR5Δ32/Δ32 HSCT, which created an HIV-resistant immune system using HSCT with non-functional *CCR5* [36]. It was suggested that homozygosity for the CCR5Δ32 mutation does not provide complete resistance to HIV-1. Therefore, targeting other receptors beyond *CCR5*, such as *CXCR4*—which encodes another co-receptor for HIV entry—holds significant potential for HIV treatment [37]. Although it has a remarkable curative potential, there are apparent limitations. The chance of finding an appropriate donor with the CCR5-Δ32 mutation is extremely low, as the mutation is found in less than 1% of the population [38]. In addition, HSCT is a complex and high-risk procedure, and graft-versus-host disease (GVHD) is also a major concern in HCT [37].

2.3.4. Chimeric antigen receptor T (CAR-T) cell therapy

Over the past decades, CAR-T cell therapy has achieved great success in hematological malignancies and is further applied to infectious diseases and non-hematopoietic cancers. Now, it is being explored as a potential treatment for HIV and has gradually shown its advantages in the field of HIV infection [39]. CAR-T cells are T cells with engineered synthetic receptors that can directly bind to specific proteins on the surface of cancer cells and are independent of the major histocompatibility complex (MHC) receptor to recognize and eliminate cells expressing a specific target antigen [40].

During the final stages of HIV infection into CD4+ cells, new viruses will bud off from their host cells. One of the HIV envelope proteins, gp120, will remain on the cell membrane of the host cells due to its anchoring role in the membrane of the virus. Hence, the CAR can be genetically engineered to specifically target the gp120, facilitating the elimination of the infected CD4+ cells [41].

2.4. Artificial Intelligence and Machine Learning

HIV treatment faces significant challenges in identifying patients at risk of losing follow-up and uncontrolled viremia. To address this, a model has been developed to accurately identify patients at risk of disengagement from treatment and intervene while they are still receiving care, allowing for more efficient and effective use of resources. This approach alleviates the burden on healthcare workers and addresses issues in high-risk groups, which are major drivers of healthcare costs [42].

The goal of creating this model is to evaluate whether applying machine learning algorithms to routinely collect longitudinal AIDS phenotype and clinical outcome data in a South African program can reliably predict patients at risk of adverse outcomes. The predictions focus on two key outcomes: attending the next scheduled outpatient visit and suppressing the next HIV viral load (VL) [43]. The initial process of recursive feature selection helps identify the most predictive factors, such as

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demographic characteristics, medication regimen data, visit history, and antiretroviral therapy monitoring laboratory results. Three classification algorithms were tested to develop these predictive models: logistic regression, random forest, and AdaBoost [44].

Despite their complexity and initially broad classification scope for subgroups, the machine learning models demonstrated the ability to distinguish between high-risk and low-risk patients effectively. Whilst these models cannot identify the underlying causes of disengagement from healthcare services, they do help in accurately identifying low-risk patients. This capability is invaluable for healthcare providers, allowing them to focus resources and interventions on patients at greater risk of disengagement, thus optimizing time and resources and implementing targeted interventions based on specific situations [44].

This analysis highlights the critical need to understand individual risk profiles and aligns with recent efforts to advance data science for more accurate public health modeling. By pinpointing high-risk groups with poor treatment outcomes, healthcare providers can improve patient triage, optimizing efficiency and resource allocation. This approach allows clinics to achieve better health outcomes without requiring additional resources for data collection or staffing. The algorithmic results can also be aggregated at the institutional level to create risk-scoring subgroups, helping identify which programs should target specific populations for intervention [45].

Although these predictive factors help us understand risk differences, they currently do not fully explain how or why they affect individual patient outcomes. The next step is to explore how specific values or combinations of certain levels of predictive variables may be associated with specific outcomes. This shift focuses on the work of retaining patients from merely tracking those who disengage and re-enter medical facilities to intervening with high-risk patients while they are still in care, predicting potential issues such as unsuppressed viral loads before clinical manifestations, thus enabling proactive and targeted interventions [44].

3. Conclusion

Despite significant advancements in antiretroviral therapy (ART) for AIDS, a complete cure remains elusive. Ongoing challenges, such as drug resistance, adherence difficulties, and side effects, underscore the need for continued innovation in treatment. Emerging ART drugs like ibalizumab, fostemsavir, and LEDGINs offer hope by targeting different stages of the HIV life cycle, while novel delivery systems, such as transdermal drug delivery systems (TDDS), aim to enhance patient adherence and convenience. Additionally, cutting-edge approaches, including CAR-T cell therapy and hematopoietic stem cell transplantation (HSCT), show potential for more advanced interventions, though they come with limitations. The integration of artificial intelligence (AI) and machine learning (ML) presents promising opportunities for predicting treatment outcomes, optimizing resource allocation, and enhancing patient engagement. Future research should focus on addressing these obstacles to develop more effective therapies and ultimately achieve a functional cure for HIV.

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