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The Evolution of HIV/AIDS and an Overview of Current Advancement Efforts: Treatments, Cures, Vaccines

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Abstract

Since 1981, HIV/AIDS has existed as a prominent global epidemic. Throughout the years, research on the disease has greatly improved and expanded as technology has advanced. Because a latent reservoir of dormant viruses persists in the T cells of HIV patients, eliminating these infected cells is a primary goal and challenge for research on the virus. Over the past 40 years, there has been significant research on a variety of potential solutions, yet a functional cure remains elusive. Current antiretroviral treatments can effectively ensure the inactivation of the latent reservoir, but patients must take these medications for life. Therefore, researchers are actively searching for a cure that can either eliminate dormant viruses or assist the immune system in eradicating them once treatment is stopped. The most promising methods include the "kick and kill" strategy to reveal the latent reservoir and remove it and gene editing methods to create immunity to the virus in patients. However, both of these techniques require further study to improve their effectiveness. Based on an evaluation of the current research, a combination of approaches may lead to more effective results. This review also covered efforts to create HIV/AIDS vaccines and improve treatment methods. Due to ethical concerns around testing experimental cures in human patients, the scope of HIV/AIDS research has been limited. Many trials contain relatively small sample sizes and primarily include Caucasian men as research subjects. A resurgence in research efforts and greater inclusion of women and people of color in research may provide greater insights in finding effective solutions.

Keywords: HIV/AIDS, Antiretroviral therapy, Treatment, Cure, Vaccine, bnAbs, mRNA

1. Introduction

Human Immunodeficiency Virus, HIV, is an infectious disease that spread from chimpanzees to humans and arrived in Hispaniola from sub-Saharan Africa in the 1960s (Darrow, 2021). From there, the virus spread to North America and has since infected millions worldwide. Its last and most deadly stage, Acquired Immunodeficiency Syndrome (AIDS), became a global epidemic in the 1980s. The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimate that there are currently nearly 40 million people living with HIV (WHO, 2023). HIV is a sexually transmitted disease, spread through bodily fluids like blood, semen, and breast milk. In its early years, it predominantly affected gay men (Darrow, 2021). However, despite misconceptions, HIV can impact people of all sexual orientations.

HIV is a retrovirus with a diameter of 100-130 nm that primarily targets CD4+ T cells (Floderer et al., 2018). CD4+ T cells, also known as helper T cells, are important white blood cells that assist the body in fighting infection by triggering the immune system to attack foreign particles. The HIV retrovirus encodes 3 structural genes: Gag, Pol, and Env. Two important molecules on the HIV envelope that form the spike protein are gp120 (the external glycoprotein) and gp41 (the transmembrane protein). During infection, gp120 binds to the CD4 receptor and a

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coreceptor (either CCR5 or CXCR4) on the T cell and is endocytosed by the T cell (Simon et al., 2006). The virus then releases its viral core into the cell, where the genetic material is incorporated into the cell's own DNA by the virus's reverse transcriptase enzyme. The cell is tricked into using its own protein production mechanisms to produce more of the HIV virus. Since HIV is able to infect and replicate within immune cells, it is very hard to detect and kill the virus. Soon, the population of CD4+ T cells depletes, leading to severe immune dysfunction. HIV is constantly evolving, as it displays the highest-ever recorded biological mutation rate, which poses a challenge to treatment and intervention efforts everywhere (Andrews and Rowland-Jones, 2017).

Additionally, the 1980s AIDS epidemic was heavily characterized by discrimination and homophobia that impacted the public health policies regarding HIV/AIDS. In America, for example, the silence and inaction of President Ronald Reagan in the face of the epidemic resulted in thousands of preventable deaths (Ortiz, 2023). The early discriminatory attitude of governments towards the disease lessened the progress of research during the AIDS epidemic. In the 40 years since the virus first emerged, researchers have worked through countless obstacles to provide treatments for patients and find an effective cure. Many new methods have been proposed, including therapeutic vaccines and antibody techniques. However, despite consistent efforts, there is still no method of eradicating the virus and support for research is waning. This review aimed to contextualize advancements and ethical debates surrounding HIV/AIDS, address gaps in current research and suggest new approaches, and provide a comprehensive source of foundational knowledge as a basis for future HIV/AIDS research.

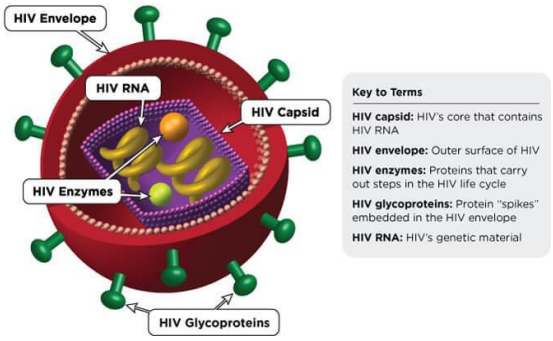

Figure 1. Diagram of the HIV Virus. Adapted from "The HIV Life Cycle," 2021, *National Institutes of Health*. https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-life-cycle

2. Treatments

2.1 Evolution of Treatments

When researchers first developed a treatment for HIV, they tried a monotherapy strategy using just the antiretroviral drug zidovudine (Cohen et al., 1996). Although antiretroviral therapy (ART) showed promise, this 1996 clinical trial proved that implementing only zidovudine was ineffective. Results showed that even if CD4+ T cell counts increased on monotherapy drug treatment, this change was not statistically significant and zidovudine alone showed no clinical benefit. As researchers worked towards finding a viable treatment, they experimented with combining multiple antiretroviral drugs into a treatment cocktail. A four drug ART therapy was found to strongly reduce viral load and replication in people with HIV (Tamalet et al., 1997). This research suggested that this combination could have a clinical benefit related to decreases in HIV RNA levels and increases in CD4+ cells. Because a decrease in the viral load had been found to correlate with a slower progression of disease, this treatment had the potential to greatly extend the lives of HIV patients. This eventually led to the development of ART as it works today.

2.2 How ART Works

Antiretroviral drugs inhibit HIV replication after the virus enters the cell but before its DNA can integrate with the host cell DNA. There are many different cocktails that can be prescribed depending on the patient's condition. Factors include other diseases the patient may have, medications the patient is taking, drug resistance, side effects, convenience, and monetary concerns (National Institutes of Health, 2021). The objective of ART is to bring levels of the HIV virus to an undetectable status within the bloodstream, which generally takes 3 to 6 months, because it is commonly known that a person cannot transmit HIV when their viral load is undetectable. However, HIV/AIDS is a

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chronic disease with no cure, so patients must take ART for the rest of their lives, as although ART halts viral replication, it cannot eliminate the latent viral reservoir (Uldrick et al., 2022). With consistent, daily, implementation of ART, infected cells remain inactive and do not produce the virus. Instead, they maintain the potential to become reactivated and make HIV transmissible again. If ART is not taken as prescribed, the virus reemerges due to the activation of these infected cells. While ART has greatly improved the lifespan of patients with HIV, there are still many requirements and complications imposed on the patient, which is why finding a cure is so necessary.

2.3 Streamlining ART

Due to the effectiveness of ART, many governmental programs have been implemented to help people with HIV gain access to ART. New York City's JumpstART program, for example, studied patients who received access to HIV treatment rapidly following diagnosis (Pathela et al., 2021). JumpstART patients were given ART the day of diagnosis and linkage to care within 30 days. They found that the median time for viral suppression within JumpstART patients was just 31 days, compared to 95 days in non-JumpstART patients. Additionally, achieving viral suppression early disrupts HIV transmission because patients with an undetectable viral load cannot spread the disease. Another similar initiative was the DO ART program in Africa (Gilbert et al., 2021). The UNAIDS target of ending the AIDS epidemic by 2030 has called for viral suppression in 95% of people on ART. In Africa, where AIDS is most prevalent, 65% of patients have achieved this. However, there is difficulty linking people with HIV to the proper care. Many are either unable to access or afford ART. The DO ART program aimed to deliver community-based ART, so people living with HIV did not have to travel to faraway clinics to refill their medication. Fixed, closer clinics greatly improved access to care as patients didn't need to pay for transportation and lose a workday. Globally, access to ART is continuing to become more streamlined so that all patients can be treated.

2.4 Drug Resistant Patients

However, as with any drug treatment, ART is not perfect. It often includes side effects such as nausea, fatigue, and other problems. In addition, some patients are infected with mutated HIV strains that are resistant to many ART drugs. Because HIV is able to replicate and mutate quickly, patients with multidrug-resistant strains need new antiretroviral agents for treatment without resistance or harmful drug-drug interactions. A group of researchers studied ibalizumab, an antibody that blocks the entry of HIV into the cell by binding to the cell's CD4 receptor (Emu et al., 2018). This was successful, as significant antiviral activity was observed in patients where medications had previously failed.

Researchers have also been exploring the concept of capsid inhibitors. Capsid inhibitors are a class of drugs that disrupt the HIV capsid, the protein shell which protects the genetic information and other necessary material of the virus (National Institutes of Health, n.d.). These medications may interfere with multiple processes of the viral life cycle). Capsid inhibitors prevent viral uncoating, interacting directly with the HIV capsid to disrupt proper viral development and in turn, infection.

Another study explored the effect of broadly neutralizing antibodies (bnAbs) on HIV (Julg et al., 2022). bnAbs are antibodies that can recognize and block a variety of HIV strains from infecting healthy T cells. They have been shown to robustly reduce plasma viremia, the detection of residual virus in the plasma of the blood after the cells are removed, in people with HIV who are not on ART. Plasma viremia was found to be a very sensitive marker of HIV infection in the blood of patients (Coombs et al., 1989). Because single or dual bnAb treatments have been relatively unsuccessful, researchers in the 2022 study tested a triple bnAb therapy (Julg et al., 2022). However, they found that even with this, viral rebound, a renewal in infection, occurred quickly. Although the initial decline in viremia was rapid, the response was not as robust as current treatments. They concluded that at least a fourth bnAb would be necessary for this technique to be effective and that further study is needed. Researchers are testing new combinations of treatments to assist as many people as possible. However, the prevalence of drug-resistant HIV strains only further emphasize the need for a functional cure.

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3. Cures

3.1 Challenges in Curing HIV

As some scientists strive for ART-free virologic control in patients, others are working on finding a viable cure for HIV. The challenges of curing HIV lie in the latent reservoir. Because the inactive infected T cells have the potential to become active, lifelong ART must currently be administered. In a patient with undetectable viral load, viral rebound will occur quickly if ART is interrupted. Although researchers have found success with reducing the time it takes for viral rebound to happen, there is still no viable cure. Cells that contain the inactive virus do not identify themselves, so finding a way to selectively kill these cells is difficult. But without eliminating the latent reservoir, there is no way to be completely HIV-free.

3.2 Stem Cell Transplants

So far, only a small group of people have been cured of HIV. In most of these cases, the patients received life-saving transplants to treat cancers that they developed along with HIV. The blood of their donors contained an abnormality in the CCR5 co-receptor of HIV (CCR5Δ32/Δ32). This rare mutation, occurring in about 1% of the population, makes hosts immune to strains of HIV that bind to the CCR5 co-receptor (Gupta, et al. 2019). Some of the cured patients have been off of ART for years with no viral load detected in their blood (Tebas et al., 2021). However, this stem cell treatment is not a viable cure. Due to its high toxicity, it is only used as a last resort for anyone who is already facing a potentially fatal blood cancer or other health condition. This method proved the possibility of an HIV cure, however, it cannot be used in most HIV patients and the hunt for a truly viable solution continues.

3.3 "Kick and Kill"

The primary approach in HIV cure research is the "kick and kill" strategy. The idea is that if scientists can reveal the infected cells that contain HIV and boost the immune system to selectively kill them, patients may be cured. Latency reversing agents (LRAs) have been proposed in order to expose the dormant infected cells (Wei et al., 2014). LRAs can activate the latent reservoir of infected cells and induce transcription of the virus so the immune system can identify cells that contain the virus by the antigens they present. This is the "kick" component of the strategy. In the "kill" step, the immune system is able to find the newly activated HIV cells that formerly made up the latent reservoir, so a strong method to eliminate these cells is necessary. Because histone deacetylase enzymes play a key role in stopping expression of the virus, histone deacetylase inhibitors (HDACi) have been proposed as potential LRAs (Søgaard et al., 2015). HDACi treatment promotes gene transcription and disrupts HIV latency. The most potent of the FDA-approved HDACis is a drug called romidepsin (RMD). RMD has been shown to induce HIV expression in patients on ART, however, is so far unable to reduce the size of the latent reservoir. But in 2016, RMD was used in conjunction with Vacc-4x, a therapeutic HIV vaccine for infected patients meant to boost the "kill" step of this cure approach (Leth et al., 2016). Therapeutic vaccines are given to patients who already have HIV. These vaccines boost the immune system and prime it against HIV viruses, making them especially helpful in eliminating HIV viruses that were previously dormant. Although the amount of HIV DNA decreased overall over the course of this study, the size of the latent reservoir did not.

More recently, researchers combined RMD with the MVA.HIVconsv vaccine (Mothe et al., 2020). This vaccine was meant to boost the immune system and help it attack the infected T cells RMD revealed. It induce bursts of viral replication and increase T cell activation. The study recorded prolonged viremic control in a promising 23% of participants after ART interruption. However, later assessment of this study demonstrated that patients experienced a decrease in both CD4+ and CD8+ T cells after every dose of RMD, suggesting a possible cumulative toxic effect (Moltó et al., 2021). When RMD was combined with the bnAb 3BNC117, none of the experimental groups had significant reductions in the HIV reservoir despite the amount of total HIV DNA declining slightly (Gruell et al., 2022). Unfortunately, HDACi treatments such as romidepsin haven't worked consistently enough to be completely feasible and more research is needed. Perhaps due to the very small, homogenous sample sizes in a majority of these

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studies and the lack of concrete evidence as to the safety of RMD, these methods have still not produced a clinically viable cure. Larger-scale studies which include women and patients of color would help provide more solid evidence on the effectiveness of RMD and the "kick and kill" strategy. Additionally, as shown by the effectiveness of a combination of therapeutic vaccines and RMD compared to just RMD, as seen in Table 1, suggests that a combination of cure approaches may be the most viable solution.

3.4 CRISPR and Gene Editing

Another technique to curing HIV is to use gene editing technology. In a 2018, scientist He Jiankui illegally modified the genes of two twin babies before birth to induce HIV immunity (Cyranoski and Ledford, 2018). He edited the DNA of the embryos to mutate the CCR5 gene, which could lead to HIV resistance. Since this was the first instance of genetically edited babies, the news sparked international outrage. In addition, not all HIV strains rely on the CCR5 receptor for entry, and there is no way to confirm if the children actually became immune. Because gene editing has not been studied enough to determine if there will be negative effects on the children in the future, this experiment was very premature. However, CRISPR/Cas9 gene editing could be a potential HIV cure. In one study, patients were given strong antiretroviral drugs long-acting slow-effective release ART (LASER ART) (Dash et al., 2019). The combination of LASER ART and CRISPR-Cas9 gene editing technology to cut the viral DNA from infected cells eliminated the latent reservoir of HIV from humanized mice. Out of the 7 mice who received the LASER ART and CRISPR combination, 2 mice did not experience viral rebound after LASER ART was stopped. Overall, the CRISPR method shows promise in curing HIV and requires further study before it may be tested in humans. However, the results of the study prove that it is possible to eliminate the latent reservoir, and this approach combined with the therapeutic vaccines in the "kick and kill" strategy may yield more consistent results. Additionally, greater research on prevention of viral genetics from integrating with the T cell genome so the latent reservoir cannot re-establish itself before the immune system eliminates infected cells may benefit future cure- related experiments.

Table1. Comparing the primary experimental methods of curing HIV

Cure Method	Insights	Improvements Needed
Romidepsin: HDACi, "kick and kill"	-Romidepsin can induce viral transcription (HIV RNA in the blood of 5/6 patients increased from undetectable to detectable) -Romidepsin is safe to use -Romidepsin increased T cell activation during the period of administration	-No significant reduction in the viral reservoir, must improve the "kill" component -Small scale study, only included Caucasians
Vacc-4x and romidepsin: Immunization followed by latency reversal, "kick and kill"	-Total HIV DNA in patients declined by 40% -Side effects were mild	-Integrated HIV DNA did not significantly decrease (latent reservoir) -Small sample size
MVA.HIVconsv and romidepsin: Immunization followed by latency reversal, "kick and kill"	-Mostly mild side effects frequently due to MVA.HIVconsv -Induced bursts of viral transcription -Reduced overall HIV DNA levels -Some participants experienced prolonged control of the virus after ART was stopped -Vaccine elicited a strong "kill" response and increased T cell activation	-One serious side effect possibly related to romidepsin -Romidepsin must be administered frequently -Overall effect on latent reservoir was modest -Small sample size
bNAb and romidepsin: neutralizing antibodies followed by latency reversal, "kick and kill"	-Total HIV DNA declined slightly -Romidepsin and bNAb combination was safe overall	-Changes in latent reservoir were not significant -Did not reduce time for virus to reemerge after ART was stopped -Small sample size
LASER ART and CRISPR-Cas9: antiretroviral treatment followed by genetic editing	-Two mice who received both LASER ART and CRISPR-Cas9 did not display viral rebound even after treatment was discontinued -Restoration of CD4+ T cells after LASER ART -Combination treatment was most effective	-Experiment was done in mice which produced human T cells -Requires much more study

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4. Vaccines

4.1 PrEP and PEP

Pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) are drugs used as preventative measures for HIV. They are antiretroviral medications that when taken, stop the replication of HIV within the body by blocking the reverse transcriptase enzyme, which converts RNA into DNA and is essential for replication (Bavinton and Grulich, 2021). PrEP is meant for patients at risk of contracting HIV, such as people whose partners have the disease. It is very effective in stopping HIV, with a 99% success rate. PEP is given to patients who have already been exposed to HIV. However, this treatment is only able to stop a small number of HIV cells from replicating and must be taken shortly after exposure. These two prevention methods are helpful in decreasing HIV cases and transmission, but global access to these drugs is limited. One of the main UNAIDS goals is to increase the number of people on PrEP and PEP. Current PrEP and PEP targets are not being met and these goals must take higher priority to have a substantial effect on HIV cases.

4.2 Antibody Vaccines

Antibody vaccines allow the host immune system to specifically target elements of virus or infected cells. One goal of HIV vaccine research is to induce bnAbs, antibodies capable of neutralizing HIV by targeting the HIV Envelope (Env). Scientists have mapped areas of vulnerability in the HIV Env for bnAbs to target. Some studies have aimed to focus the immune system response on the fusion peptide, a crucial component of the viral entry machinery (Walsh and Seaman, 2021). The fusion peptide is targeted because its N-terminus is poorly immunogenic and usually hidden from the immune system. In mice, the immunogens produced created antibodies that were capable of neutralizing 31% of the 208 HIV strains tested (Xu et al., 2018). If research can induce the production of bnAbs in people with HIV, this could also potentially work as part of a cure. Research has shown that patients who received infusions of bnAb 3BNC117 at the time of ART initiation were able to maintain long-term CD8+ T cell responses (Rosás-Umbert et al., 2022). However, it is difficult to create bnAbs that can neutralize a diverse range of HIV strains and this technique runs into many challenges. Although these vaccines have been improving, they are often difficult to create in labs and vaccinology is moving towards more efficient vaccine techniques. Therefore, this approach may not be the most viable.

4.3 mRNA Vaccines

mRNA vaccines became widely used during the COVID-19 pandemic and could be applied to HIV. Lab-created mRNA coding for a piece of a protein is given to patients (Centers for Disease Control and Prevention, 2023). This allows for the production of antibodies specific to that protein epitope, which prevents future sickness from the virus. In an mRNA vaccine, the RNA does not need to enter the nucleus and can make proteins in the cytoplasm. Although vaccinology hasn't been able to consistently induce bnAbs by vaccines in people with HIV, researchers found that an mRNA vaccine was able to yield a 79% risk reduction per exposure in mice, offering a promising approach to HIV mRNA vaccines (Zhang et al., 2021). It was also able to induce a robust CD4+ T cell response. Although this is a fairly new technique, its early successes, especially in relation to the COVID-19 pandemic, suggest this may be a valuable approach to explore more deeply and could be instrumental in ending the HIV epidemic.

5. Discussion

HIV/AIDS research has been a consistent effort since the 1980s epidemic, and while in America it has now become more chronic illness than death sentence, other countries are less fortunate. Accessibility to lifelong ART, prevention measures such as PrEP, and linkage to medical providers are all issues imposed upon those diagnosed with HIV. Marginalized communities are most impacted by high drug prices, access to transmission prevention methods,

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as well as effective healthcare. In countries in Africa, these issues have dominated HIV transmission, making progress towards UNAIDS goals difficult. Ending the global AIDS epidemic requires continuing to promote accessible treatments with both healthcare and therapeutic access. As with any yet-incurable disease, the objectives remain to develop a cure for HIV. Currently, improving treatment, prevention, and vaccine options remain priorities to ease the burdens of HIV patients. ART is improving so that the drug cocktail needed to control the viral load is less vulnerable and dependent upon the practice of implementation by patients. Therapeutic vaccines demonstrate promise in assisting a patient's immune system to eliminate the virus, aiming to remove the dependence upon ART and keep patients undetectable. Many cure strategies are being promoted to find an effective mechanism for eliminating the latent reservoir. Advances in vaccinology have furthered the options for prevention against HIV. The mRNA vaccine technology, as recently seen and approved for the COVID-19 pandemic, is being actively researched for HIV. Additionally, the bnAb approach could be boosted. An HIV vaccine would greatly slow the number of new infections and is an essential part of ending the epidemic. As a disease with not only epidemiologic but also social history, it has set a precedent for the role of politics in health. HIV/AIDS has impacted our world for decades. Healthcare research has greatly improved since the epidemic first began, and the world has learned a lot from this disease.

6. Conclusion

As the search for an HIV/AIDS cure and functional vaccine continues, the scientific field must come to a consensus on the most viable methods and urge for a renewal of research and discovery. The evidence collected in this review suggests that, through a comparison of the primary cure methods, it may be most beneficial to the future of HIV/AIDS research to approach these techniques from a more collaborative viewpoint, rather than attempting to perfect one single method. The past 40 years of HIV research has yielded much new information and innovation, and combining this knowledge could lead to greater results than the discoveries of current. The main goals of further study should be to test novel, combined approaches on larger sample sizes of participants, including women and people of color, to understand the impact of the virus on all people who are susceptible. It is also suggested that research on the prevention of the latent reservoir from forming may be beneficial to curing HIV, ending the global epidemic, and creating a distributable vaccine. This review should provide a basis for future studies on treating, curing, and immunizing patients with the HIV virus through its comprehensive collection of the current status of HIV/AIDS research.

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