An Overview of HIV and AIDS; Current and Future Treatment Options

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Introduction

Acquired Immunodeficiency Virus (AIDS) occurs as a result of infection by the human immunodeficiency virus, or HIV. HIV and AIDS have a long history in the United States of America, mainly becoming infamous during the outbreak that began in 1981 (1). From 1981 to 1995 the annual death toll in individuals with AIDS rose from just 451 to 50,628 (2). CDC scientists found that HIV could be transmitted through sexual activity as well causing widespread panic throughout the nation (3). There was an effort to educate the nation on safe sex practices, such as education in schools, or organizations like Planned Parenthood, who offered treatment/testing (4). There quickly arose a stigma, perpetuating that AIDS was most commonly a problem within the LGBTQ+ community, and primarily gay men (5). This was because it seemed to affect the homosexual population the most. However, by the end of 1981, cases were arising in heterosexual individuals who were drug users (6). Further research since then has indicated that HIV can be transmitted regardless of sexual orientation through means of unprotected sex, sharing needles, and mother-to-child transmission, the main methods being through bodily fluids such as blood and fluids exchanged during sexual activity (7).

Researchers found that HIV attacks the body's CD4 cells, cells that protect and are vital to the human immune system (8). HIV is classified as a retrovirus, or a virus that utilizes RNA as its genetic material instead of DNA (9). Retroviruses contain an enzyme called reverse transcriptase, which is able to create a complementary DNA copy of the viral RNA. This DNA can then integrate into the host genome, from which it can be further replicated (10). Since the virus integrates into the host DNA, HIV becomes difficult to treat, leaving it with no cure. This has exacerbated the fear and stigma around AIDS, however there are a variety of different treatment options that show promising results. This paper will evaluate the efficacy of currently available HIV/AIDS treatment options and will explore potential future treatment options, comparing and contrasting the benefits and drawbacks of each to illustrate the best treatment options to move forward with.

Current Treatments

Most current treatments for HIV and AIDS involve the use of antiretroviral therapies (ARTs/ARVs). These therapies work by interfering with the replication of HIV within the CD4 cells and utilize different methods to do so. Drug classes in the context of ARTs are differentiated by the way they interfere with HIV. Depending on which part of the cell or step of the replication process they inhibit, ARTs are classified under different categories referred to as drug classes (11). The FDA lists 10 different drug classes, each of which contain several different drugs that can be used to treat HIV (12). Some examples of these treatments include the drugs Doravirine, Ritonavir, and Maraviroc, which are part of the drug classes of Non-nucleoside Reverse Transcriptase Inhibitor, Protease Inhibitor, and CCR5 Antagonist (13, 14, 15). When someone is positive for HIV, they are generally recommended to take three different HIV medicines from at least

two different drug classes, to prevent antibiotic resistance to the virus over time (15). The first ART to work against HIV was a nucleoside reverse transcriptase inhibitor, Zidovudine, which first entered clinical trials in 1964 (16) and was approved in 1987 (17). Zidovudine is a synthetic analogue to thymidine, meaning it is an altered form of thymidine (18) Zidovudine is phosphorylated, which means a phosphate group is added in the cell. Then it competes against the natural substrate, thymidine triphosphate, to replace it in the HIV DNA chain, inhibiting the reverse transcriptase that aids in turning RNA into DNA (19).This then stops the formation of the HIV DNA chain (20). Since the approval of Zidovudine, there have been over 30 different drugs approved by the FDA for HIV treatment (21).

Along with these already approved treatments, there are treatments that have very recently gotten approved, one of them being lenacapvir, which was approved by the FDA in 2022 (22). A clinical trial was conducted that showed that lenacapvir helped patients generate a substantial increase in CD4 compared to controls. Further, in cohort 1, 30 of 36 participants had less than 50 HIV-1 RNA copies per mL, and 31 of 36 participants had less than 200 HIV RNA copies per mL, at week 52 (23). This demonstrated that lenacapvir could successfully reduce the HIV-1 RNA copy present in patients' bodies. Lencapavir is officially marketed under the brand name Sunlenca. It falls under the capsid inhibitor drug class and works by interfering with nuclear transport, virus assembly, and capsid core formation (HIV-1) (24). Lenacapvir is administered twice a year as an injection (25), making it more convenient in comparison to other readily-available HIV medicines like *Biktarvy,* a daily pill combining three ARVs in one (26). Lenacapvir costs around $42,250 per patient each year, proving to be expensive. This can deter people from considering ART's as viable treatment options. However, the efficacy of lenacapvir provides hope going forward for more long-lasting options. While these treatments show promise, they do have some downsides, including cost and permanence.

Future Treatments

ART treatments do not provide an actual cure, and more permanent options like gene editing could be promising avenues to explore. Several gene editing tools exist, including one that has dominated the gene therapy landscape called CRISPR-Cas9. CRISPR-Cas9 works by utilizing a guide RNA and a Cas-9 protein which binds to the gRNA and uses it to identify the complementary DNA sequence (27). When the Cas9 protein reaches its target site, it can create a double stranded DNA break. Then the genome can be repaired if template is provided, however the gene can also be disrupted if insertions/deletions are introduced at the break sites (28). Gene editing is an exciting new avenue for researchers to explore as it could be used to cure diseases in the human genome, and could even be used for new treatment paths outside of direct human genome mutation repair, like through providing immunity to viruses like HIV. Some researchers have already started to explore these avenues.

In one study, researchers ran a trial on monkeys, which were infected with Simian immunodeficiency Virus (SIV). Researchers used software to identify specific sequences in the SIV genome that should be targeted for DNA editing, which is similar to the techniques used for HIV-1 in humans. The Cas9 enzyme, guided by the gRNAs, cut the viral DNA within the host cells. This cut led to the complete removal of the virus's genetic material from the host cell. This demonstrated that gene editing could be used to get rid of viral DNA within the genes (29). Although this study demonstrates that gene editing is a promising technique to treat disease by cutting up viral DNA, it does not actually provide immunity to the virus, which means that it is not an effective long term treatment option

When HIV enters the body, it attaches to the CD4 cells by bonding to the CCR5 receptors located on the cell. Once the virus attaches, it will enter the cell at the beginning of the replication cycle (30). In some rare cases there are people who naturally lack CCR5 receptors in their CD4 cells, making them immune to HIV/AIDS. Although rare, about 13% of people have this mutation, called the Delta-32 mutation, in which 32 base pairs within the genetic code for CCR5 receptors are deleted (31). And in some cases, this mutation can be “transferred” from one person to another. This can occur through allogeneic or haematopoietic stem-cell transplantation , in which a patient receives a bone marrow transplant from someone with the mutation (32,33). The first known example of this involved the Berlin patient, who received a stem-cell transplant from a donor who was homozygous for the Delta-32 mutation, in order to treat his leukemia (34). This incident led to researchers experimenting with gene editing and the Delta-32 mutation.

Since researchers know that the Delta-32 mutation is what produces immunity to HIV, gene editing could potentially be used to target that section of the genome and engineer HIV immunity within people. Some studies have already explored the efficacy of gene editing on HIV immunity. One trial showed that CCR5 gene-edited human $CD4^+$ T cells (helper cells) were found to be resistant to HIV-1 infection (35). In another study, researchers designed two gRNAs that targeted the Delta 32 region. The editing resulted in a lack of CCR5 expression, which resulted in cells that were protected from infection by HIV-1. These results were replicated in another cell line showing similar resistance to HIV-1, while resistance to other strains of HIV (CXCR4) was not observed. This treatment was also tested in humanized mice that showed a significant reduction in CCR5 levels, indicating that CRISPR-Cas9 editing can successfully reduce the expression of the CCR5 gene, limiting the spread and replication of HIV-1 (36).

Discussion

Although ARTs are currently available to those living with AIDS, gene editing may provide a better treatment option in the future. ARTs are treatments that patients have to take for life, and often patients have to take multiple ARTs at once. Even recently approved ARTs like lenacapvir have to be taken every 6 months in the form of an

injection. This can eventually add up over time and end up being financially draining. The lifetime treatment cost for HIV treatments can be up to $400,000 per HIV infected persons (37). Another aspect is the side effects that ARTs pose. Recently approved ARTs like lenacapvir do demonstrate reduced HIV RNA count, but there are side effects that affect mental and physical health. Some of the side effects for Lenacapvir include pain, swelling, nausea, and nodule formation (38). Genetic editing is theoretically a permanent treatment intervention, in contrast to ARTs, meaning that HIV infected persons would only receive one treatment and would ideally not need ARTs or other medication going forward. In the case of HIV treatment, and the Delta-32 mutation, once the 32 base pairs within the genome are deleted, the body will stop producing the receptors necessary for HIV to attach and spread, which will slow and eventually stop the infection. However, there are significant risks to gene editing such as off-target effects in the genome, which is when the Cas-9 acts on segments of the DNA that it is not intended to fix (39). Another risk is an immune reaction as a response to the editing, which can happen if a virus is used to deliver the genetic treatment (40). Further, many places in the world do not have access to the technology and information required in order to perform a gene editing procedure, or may not permit gene editing, in the case of human treatment.

Conclusion

In conclusion, traditional treatment methods of HIV such as ART's and ARVs are effective but not ideal, as they are costly, and not permanent. This has made gene editing a new and exciting option for researchers to look into, and to try and provide immunity to HIV. Although gene editing is not as accessible as other options, in countries such as America where gene editing has been recently approved by the FDA, for example to treat sickle disease, gene editing could be an effective and viable option to treat HIV, and could be more promising than ARTs (41). In order to get these gene therapies developed, they would have to be researched thoroughly, to make sure that it was safe for use, and to have made sure there were reduced chances for any off-target effects. These new therapies will hopefully provide an easier and more permanent solution to treating and curing HIV.

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