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So Near, Yet So Far- HIV Cure

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ABSTRACT

HIV/AIDS is a chronic well manageable disease. HAART improves the quality of life of people living with HIV/AIDS, but the treatment has to be continued life long, as the total cure has not been established. Cost of treatment, drug toxicities, interaction with other drugs and persistence of inflammation and acceleration of ageing process, all put together, warrant an urgent need for a total cure. Even though two cases had been proved to be cured, still a practical cure is far beyond the reach. Numerous approaches and strategies had been put forth to achieve a cure; still they are to be proved with human studies. This article reviews the major approaches, recent advances in the venture of HIV cure and the safety concerns involved.

Keywords: HAART Improve, Interaction with other drugs, Venture of HIV cure, Safety concerns

INTRODUCTION

HAART revolutionized the management of HIV disease into a well manageable one. The longevity of the people living with HIV/AIDS is in no way inferior to that of those without HIV, their quality of life also improved a lot and the incidence of AIDS defining diseases have declined considerably. Newer molecules are introduced regularly which can suit individual's needs and newer FDC (Fixed dose combination) are made it easy to adhere to treatment. The dose of Efavirenz was reduced and found equally effective with lesser side effects. Many newer molecules are on the pipeline. But in spite of all these, the long awaiting sterilized cure is getting delayed. The sterilized cure would no doubt be beneficial as it will certainly reduce morbidity, mortality, new infections, economic burden of the individuals and their countries, adverse effects due to the lifelong exposure to drugs, acceleration of ageing etc. The main barrier to a sterilizing cure is the presence of a 'latent reservoir'; a population of HIV infected cells that persist for the lifetime of the individual despite ART and the HIV specific immune response [1,2]. So, the identification of various sources of viral reservoirs like Latent CD4 cells, CNS-microglial cells, macrophages, monocytes- (Peripheral Blood Mononuclear cells), reproductive system, lymph nodes, spleen and gut tissues get the prime importance in the research [3].

The Types of "Cure"

The FDA defines HIV cure research as "any investigation that evaluates [1] a therapeutic intervention or approach that controls or eliminates HIV infection to the point where no further medical interventions are needed to maintain health and [2] preliminary scientific concepts that might ultimately lead to such a therapeutic intervention" [4].

To be considered cured; an infected person would need to meet three criteria

1. Be able to live a normal, healthy lifespan
2. Be off antiretroviral therapy or any other HIV-related medications
3. Be incapable of transmitting the virus to others

STRATEGIES AVAILABLE

Genetic approach

- Hit early Hit hard: Early starting the treatment before the establishment of latent reservoir.
- Kick and kill or Shock and Kill: Flushing the reservoir cells into the blood stream and made the virus susceptible for ART or immune mechanism.
- Keep the reservoir to be inactive and remain dormant for ever.

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CURE SUCCESS

Despite these challenges, 2 and possibly 3 eradicative cures exist. In addition to the CD4 receptor, HIV requires a second co-receptor to infect a cell. One such receptor, the CCR5, is congenitally absent in 0% to 2.3% of individuals.

The "Berlin Patient" (Timothy Ray Brown), as part of treatment for acute myeloid leukemia (AML), received full-intensity conditioning chemotherapy, whole body radiation and 2 transplants from an HLA antigen-matched donor with CCR5 coreceptor Δ32 deletion. The "London Patient" (Adam Castillejo), as part of treatment for Hodgkin lymphoma, also received a stem cell transplant from a donor with the CCR5Δ coreceptor Δ32 deletion. However, he did not receive radiation but instead received *reduced* intensity conditioning chemotherapy. Both Brown and Castillejo have been deemed cured (no HIV viremia, off ART). A third patient, known as the Düsseldorf patient, remains under evaluation; the 49 years old man received a bone marrow transplant from a CCR5 coreceptor Δ32 deletion donor in February 2013 for AML. Physicians discontinued ART in November 2018 and the patient's HIV remained undetectable as of March 2020 [4].

(However, the two "Boston patients"-nicknamed for the Massachusetts city where they were treated-received bone-marrow transplants with cells that were not resistant to HIV. Researchers reported that the virus has rebounded in both of the Boston patients) [5].

To compare different reservoir-clearing strategies, Diaz and colleagues in 2015 recruited the São Paulo Patient and other individuals who had controlled their HIV infections with ARVs. The most aggressive approach, used in this man and four others, added two ARVs to the three they were already taking, in the hope this would rout out any HIV that might have dodged the standard treatment. On top of this "intensification," the study group received nicotinamide, which can, in theory, prod infected cells to "wake up" the latent virus. When those cells make new HIV, they either self-destruct or are vulnerable to immune attack [4].

"Hit Early and Hit and Hard"

That is, treatment should be started as early as possible during PHI. That is to hit hard with ART before the latent reservoir formed inside the body.

Mississippi baby

Mother was not identified as HIV positive till labor started. She was not on ART. Confirmed the presence of HIV DNA particles with the baby and ART started within 30 hrs after birth. After 18 months baby missed from follow up. After 2 years, ART stopped for more than a year and once again the baby came to follow up. Surprisingly viral load was undetectable with the baby. ART withheld and the baby was under continuous vigilance. But viral relapse happened after 3 years [6].

Genetic modifications by drugs

With the help of zinc finger nucleases, DNA editing enzymes, eliminating the CCR5 expression over CD4 cells seems to be safe and have a modified cell have the half-life of 48 weeks, but was expensive and difficult to scale upwards [7].

Using the CRISPR/Cas gene-editing technology, the Cowan and Rossi teams knocked the CCR5 receptor out of blood stem cells that they showed could give rise to differentiated blood cells that did not have CCR5. In theory, such gene-edited stem cells could be introduced into HIV patients via bone marrow transplantation, the procedure used to transplant blood stem cells into leukemia patients, to give rise to HIV-resistant immune systems [8].

Researchers engineered a molecule known as a Chimeric Antigen Receptor (CAR) and inserted a gene for that molecule into blood-forming stem cells, which they transplanted into mice genetically engineered to have human immune systems. It significantly reduced HIV levels in mice with a genetic therapy that induces immune cells to fight better against the virus. The CAR is a two-part receptor that recognizes an antigen (such as HIV) and in this case instructs immune cells to locate and kill HIV-infected cells. The transplant of the CAR-carrying blood stem cells gave rise to functional immune cells that could kill HIV in the mice. Consequently, the mice experienced an 80 to 95% drop in viral load. The researchers concluded that such a genetic therapy may be feasible in HIV-positive humans [9].

KICK and KILL (Shock and Kill) method

Presently the reason for which we are not able to achieve a complete cure with the help of ART in spite our achievement of undetectable viral load is said to be the presence of dormant virus or HIV latency. In shock and kill, immune stimulants shock the latent virus from hidden reservoirs and then attempt to kill reactivated HIV.

Now they identified an enzyme called as Histone Deacetylase (HDAC) which is responsible to keep up latency. Several companies are looking into HDAC-Inhibitors. Some in vitro HDAC studies seemed to be promising but yet to be confirmed by clinical studies. Flush these latent CD4 HIV infected cells with drugs like Vorinostat and Panobinostat (HDAC inhibitors) into the circulation. Make susceptible for ART after expressed out of these reservoirs [10].

Histone Deacetylase Inhibitors (HDI) have a broad spectrum of epigenetic activities. Vorinostat is marketed under the name Zolinza for the treatment of cutaneous T cell lymphoma (CTCL) when the disease persists, gets worse, or comes back during or after treatment with other medicines [11].

Another approach is keeping the latent and dormant HIV to remain inactive for ever

A natural compound called as Cortistatin A has been found to significantly reduce the rate of reactivation of immune cells latently infected with HIV. Cortistatin A was isolated from a marine sponge known as Corticium simplex. It has been shown to inhibit Tat, a viral protein that is instrumental in prompting the virus to replicate. This study showed that the compound reduced viral reactivation by an average of 92.3% [12].

Infected animals given an anti-integrin antibody achieved control of SIV without antiretroviral therapy; the mechanism is unknown. Most CD4 cells in the body reside in gastrointestinal tissues. A cell surface integrin called α4β7 helps guide $CD4^+$ cells to the gut mucosa, where they are susceptible to infection and depletion by HIV or Simian Immunodeficiency Virus (SIV). Now, in a study of monkeys infected with SIV, investigators have assessed whether an antibody against α4β7 can tip the balance toward immune control of the virus.

The researchers infected 18 rhesus macaques with SIV and 5 weeks later, started the monkeys on Anti-Retroviral Therapy (ART). After the animals achieved an undetectable viral load, they received either a α4β7 antibody or a nonspecific, placebo antibody every 3 weeks, for eight infusions total. All treatment was then stopped. As expected, the animals that received the placebo antibody had rapid viral rebound when ART was stopped. By contrast, eight animals that received the anti-integrin antibody maintained low-to-undetectable viral loads for more than 9 months after ART withdrawal. The animals that received the active antibody had restoration of $CD4^+$ cells in the circulation and gastrointestinal tissues, perhaps because the virus was not depleting these cells. These animals also had an increase in the proportion of cytokine-synthesizing natural killer cells, indicating innate immune responses were being bolstered by the treatment [13].

The combination of injectable antiviral therapy soon after the infection and vesatolimod (a novel immune-activating drug) quickly suppressed viral load and delayed antibody responses to the virus in a monkey study, suggesting a possible role for vesatolimod in a cure strategy.

Scientists working towards cure are trying to better describe the 'latent reservoir' of HIV DNA in elite controllers-individuals living with HIV who control HIV replication without taking antiretroviral therapy-in order to understand these individuals' natural control of the virus. They reported that elite controllers have low levels of intact provirus (virus able to replicate) and these are associated with having receptor molecules on the surface of their immune cells that are less responsive to HIV infection [13].

An intravenous post-attachment inhibitor is approved for treatment of multidrug-resistant HIV infection

Ibalizumab is a humanized monoclonal antibody that binds to CD4 on human cells and thereby prevents HIV entry (a CD4-directed post attachment inhibitor). The medication was approved on March 6, 2018, for treatment of multidrug-resistant HIV in adults failing Anti-Retroviral Therapy (ART).

In a phase 3 trial, 40 heavily treatment experienced patients with resistance to three antiretroviral drug classes, but with at least one active remaining drug, were enrolled in a single-arm trial. Following a loading dose of ibalizumab, 83% of participants had a ≥0.5 log drop in HIV RNA level. After receiving the loading dose, participants had optimization of their regimen with addition of other antiretroviral agents, including at least one active drug and ibalizumab was continued every 2 weeks. At week 25, 50% of participants had HIV RNA levels <200 copies/mL.

Ibalizumab is given as a single 2000 mg loading dose (infused over at least 30 min) followed by a maintenance dose of 800 mg every 2 weeks (infused over at least 15 min). Patients should be observed for infusion-related adverse events for at least 1h after the loading dose and if there are no ill effects, for 15min after maintenance doses. The most common side effects are diarrhea, dizziness, nausea and rash.

There are no anticipated drug interactions. Renal insufficiency is not expected to affect ibalizumab's pharmacokinetics. Resistance to other antiretroviral agents does not seem to affect ibalizumab's activity [14].

Safety data are insufficient for this drug to be used in pregnancy or in pediatric patients. The anticipated annual wholesale acquisition cost of ibalizumab is $118,000).

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