The research progress of the functional cure of AIDS
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ABSTRACT
  Acquired Immune Deficiency Syndrome remains incurable even though it has been more than thirty years since first discovered in 1981. Highly Active Anti-retroviral Therapy provides effective treatment to AIDS patients. However, Human Immunodeficiency Virus will rebound due to the existence of the latent viral reservoir if Active Anti-retroviral Therapy (ART) interrupted. Functional cure refers to keep viral load at low or undetectable level (at least for a certain period of time) after interrupting antiretroviral treatment. This brief review focuses on the achievement in functional cure of AIDS.

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Article @ Virology

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Abbreviations: AIDs, Acquired Immunodeficiency Syndrome; HAART, Highly Active Anti-retroviral Therapy; HSCT, Hematopoietic stem cell transplantation; HIV, Human Immunodeficiency Virus

Introduction
Although AIDS has been more than thirty years since fist discovered in 1981, it remains incurable. HAART, so-called cocktail therapy, provides effective treatment to AIDS patients, which has been proved can improve the survival time and quality of life of patients with HIV²¹.  
²¹ AIDS has been changed from a deadly infection into a chronic, treatable infection disease. However, despite these achievements, HAART is not curative. HAART cannot completely remove the HIV due to the presence of a long-lived infection cell
population that harbors replication-competent virus known as the latent viral reservoir\cite{3,4}, and the HIV-infected individuals need long-term and even lifelong medication, once withdrawal of therapy, the virus will be reactivated and rapidly rebound\cite{5,6}. In order to achieve the purpose of curing AIDS, scientists have explored new methods of treatment for AIDS. Researchers turn to think about how to control the plasma virus at the same time to reduce the virus in the latent viral reservoir, and stopping therapy without recurrence, that is, to achieve a functional cure for AIDS. These studies of "Berlin patients", "Boston" and "the children of the Mississippi" have brought inspiration and hope for the functional cure of AIDS. Therefore, we urgently need to know the latest research progress of functional cure.

1. The treatment strategy for AIDS

The life cycle of HIV includes: adsorption, fusion, implantation of RNA, synthesis of DNA by reverse transcription, integration into the host chromosome, replication, synthesis of protein, assembly. The enzymes involved are: reverse transcriptase, integrated enzyme, and protease. The main treatment strategy is to develop the corresponding drugs to intervene of the key enzymes in the HIV life cycle, as well as the invasion process, such as: chemokine receptor antagonist, fusion inhibitors, reverse transcriptase inhibitors, integrated enzyme inhibitors, protease inhibitors, etc. now, we try to use one or several drugs to control the virus in the latent viral reservoir and to reestablish the immune system.

These drugs in the treatment of AIDS has played an important role, greatly extended the life of the HIV-infected individuals, improved the quality of life, but cannot cure patients, once interruption of therapy, HIV virus will again appear.

2. Curable case of AIDS

There is only one case of AIDS patients was considered to be cured in the world - the "Berlin patient" - \cite{7}. In 2007, the AIDS patient Timothy brown, suffering from leukemia had to receive CCR5Δ32 mutational homozygous donor hematopoietic stem cell transplantation (HSCT) twice. Then it is surprise that the patient has not been detected HIV virus in the blood and tissue samples after discontinued antiretroviral therapy (ART) before the first transplant, and did not receive ART for the next 7 years, which suggesting that the patient has been cured. why was he cured? What is the mechanism? Scholars believe that patients received the CCR5Δ32 mutant homozygous stem cells, is unable to express the chemokine receptor CCR5, Just because it is lack of auxiliary receptor mediated in the process of HIV invasion so that it is unable to infect the body \cite{7}. In addition, the viral replication via the chemokine receptor CXCR4 may be
dependent on CCR5 \cite{8,9}. Moreover, there are some other hypotheses: the transplantation preconditioning scheme may reduce the HIV infection of the cells, transplantation of donor genes prevent infection, transplant resisting host response (GVHR) may have cleared the latent viral reservoir \cite{10}, and however, follow-up studies are needed to confirm the mechanism.

3. The functional cure of AIDS

However, the miracle of the "Berlin patient" did not reproduce. Two patients are known as the "Boston patients" \cite{11, 12} of AIDS receiving the same stem cell transplantation therapy, while taking antiviral drugs, controlling the virus level under the test line. Then to interrupt therapy of ART. Unfortunately the both were detected HIV virus in their blood after 12 weeks and 32 weeks Respectively \cite{13}. Other related studies have also appeared similar results. On the premise that the cure of AIDS cannot be realized, the scholars put forward the functional cure of AIDS \cite{10}, namely: keep viral load at low or undetectable level (at least for a certain period of time) after interrupting antiretroviral treatment.

Although Functional cure still cannot cure AIDS, compared to the HAART, it is a great progress. The patient does not have to continue to take medicine that also can be a good control of the disease. According to the present research progress, the method of functional cure may have the following types: HAART at Early stage, stem cell transplantation and gene therapy, CCR5 antagonist, clearing the latent viral reservoir and so on.

3.1 The early stage of infection by HAART

In 2013, The American Johns Hopkins Children's medical center and the University of Mississippi reported 1 case of functional cure for HIV infected persons -" Mississippi children "\cite{12} in the conference of reverse transcription virus and opportunistic infection that be held in Atlanta. After the baby has been born for 30 h, a combination of antiretroviral therapy (cART) was performed. After a period of time of treatment, the test showed that the number of HIV virus in the baby's blood was significantly decreased, in the twenty-ninth days of routine examination of the body, there has been detected no virus. After eighteen months of treatment, we Interrupt therapy .then we found that the HIV antibody in the body was still negative after 10 months of Interruption of treatment, and the routine blood test Show no HIV virus , suggesting that ART can effectively control the infection. But Unluckily, We still detected the virus when the child is full of 4 years of age, the gene sequence analysis of virus strains are the same as that from the mother \cite{14}. It indicates that the disease has a relapse,
and the therapy has failed to cure AIDS on function.

In other treatments, M. Butler Karina et al. [15] reported that a baby who received antiretroviral therapy until 4 years old, RNA HIV was detected in the blood in seventh days after stopping treatment, and twenty-second days later the DNA of virus was detected then the HIV antibody was detected in twenty-ninth days.

Although ART failed to successfully cure or functional cure AIDS in the early stage, the therapy still showed that the virus was able to remove and inhibit, and it indicate that the HIV virus appeared in treated patients to be latter than that of the nontreated patients after interruption of therapy [16]. Bitnun Ari et al. study [17] found that early combined ART can reduce the infection of CD4+T in peripheral blood, and it can inhibit the virus. For why there are such results, some scholars believe that may be infected at early, ART can prevent the formation of HIV storage pool or limit the size of it [18], so that patients can get longer controlling virus after stopping the drug. Therefore, as soon as possible and effective ART therapy to treat HIV-infected patients early still has important value [19].

But these cases also reflects some problems, after the interruption of antiretroviral treatment, HIV virus can be in the body after a long time to reemerge, and the time of reproduce is not what we can predict. Therefore, the early treatment of HIV needs to be further studied.

3.2 Blocking the immune cells of CD4 focal apoptosis reaction

A Research shows that the CD4 cells were reduced in HIV-infection individuals. the main reason for the decrease of immune cells in HIV patients was that the majority of CD4 cells were resting CD4 cells, and these resting cells could be reduced because of the HIV virus invasion [20]. Therefore, to study the occurrence of apoptosis, it is helpful to maintain the number of CD4 cells and cellular immune function, and help to eliminate the latent virus after stopping the drug, thus it is possible to find a new way of the function cure of AIDS in future.

3.3 Stem cell transplantation therapy and gene therapy

In the process of HIV invasion, HIV virus main use the chemokine receptor CCR5 as the auxiliary receptor into patients’ body [21]. the thirty-second nucleotide in the sequence of the CCR5 gene missed will lead to the change of the reading frame, and change the function of CCR5. As a result, the populations who are lack of CCR5 allele homozygote will not be infected [22]. "The Berlin patient" due to transplant stem cells CCR5Δ32 homozygote cures AIDS. So stem cell transplantation has become a potential way for function cure in AIDS.

We found that HIV cannot attack the T
cells based on the CCR5Δ32 homozygote, therefore, we explore molecular techniques to modify stem cells, make it become the CCR5 Δ 32 cells homozygote, and inject it into the patients’ body[23, 24]. We have known that HIV only infect the CD4+ cells in the immune system, these cells are derived from hematopoietic stem cells (HSC), so it can be used to insert the Anti HIV gene into the HSC gene to maintain the immune system and clear HIV virus[23, 25]. This is a feasible method in theory.

Recently, the study found that a marked increase in the expression of CCR5Δ32 and the expression of CCR5 and CXCR4 decreased significantly when we integrated the target gene CCR5Δ32, CCR5siRNA, HIV-1 poli and HIV-1inti into the adenovirus vector and induce peripheral blood mononuclear cells (PBMC) into dendritic cells. HIV-1 cells infected PBMC, the expression level of p24 HIV antigen was found to be lower than that of unmodified cells in the modified cells, which indicates that viral replication is inhibited, and the resistance to HIV-1 is significantly increased after modification[26]. But the results of in vitro experiments can have the same effect in the human body is unknown. In addition to the study of modified genes, the researchers also studied the zinc finger nucleic acid enzyme technology, such as knocking out CCR5 gene [27], thereby blocking CCR5 expression, indirect blocking HIV virus replication. The way is also one of the research directions of the functional cure of AIDS.

3.4 CCR5 antagonist of chemokine receptor

In the process of HIV invasion, in addition to the necessary CD4 receptor, it also needs to be an important accessory receptor, CCR5 and CXCR4, which plays an important role in the conformation changes that derived from the HIVgp120 glycoprotein Distinguishing surface cell CD4 glycoprotein. In the early stage of infection, CCR5 was the main auxiliary receptor [21]. CCR5 is an ideal target for HIV receptor antagonist, and its combination with CCR5 makes the CCR5 conformation change, which is not conducive to the identification of HIVgp120 or CCR5 HIV, blocking the combination of HIV and CCR5 cells, resulting in the reduction of the number of cell binding or unable to complete the invasion process, which plays a role in prevention and control of infection. Studies have indicated that the CCRT antagonist combined with HAART treatment can shrink the latent virus [28], but whether will it apply to the large sample. that needs further study

3.5 Clear the HIV repository

Taking into account that most of the HIV-infected individuals are not at the early stage, and the very low success rate of the stem cell transplantation, these indicate that may not apply to most of the
AIDS patients.

In most patients, the virus will soon be back because of the presence of the latent viral reservoir. HIV integrated into the human genome sequence, the active viral gene can cause the cell to die and immune response. But HIV can be latent in the resting memory T cells and long-term existence, so the drug and immune system cannot clear it [29, 30].

The latent viral reservoir refers to an HIV-infected cell population that harbors integrated, replication-competent HIV virus [31]. HIV latent infection not only can be establish in resting T CD4+ cells, but also can be established in the monocytes / macrophages [32], which are more resistant to cells apoptosis. The existence of the latent viral reservoir is a barrier to cure AIDS, it indicates that we can remove The latent viral reservoir, activate latent HIV virus and other methods to achieve the purpose of cure. There are more Researchs in this area. Such as:

Xiying Qu et al [33] reported a study that zinc-finger nucleases was designed to remove the fragment of HIV virus in HIV infected cells, obtained good results, and provided a possible way to cure HIV infection.

At the same time, studies have demonstrated that protein kinase C pathway activator can induce cells treated by HAART to produce RNA HIV [34]. It has a great research prospects for functional cure AIDS.

It is found that the inhibitor of histone (HDAC) can activate the HIV of latent infection, and enhance the level of gene transcription [1, 35]. But so far, we Compare some studies of HDACS in the activation of the virus, as well as the test of drug safety ,it shows that the effectiveness of HDACS is not clear [36], so the study of HDAC should have more in-depth clinical trials.

4. Summary
In summary, scholars have proposed many methods in functional cure of AIDS. In addition to the above methods, there are the immune intervention [37], directly killing virus [38], development of vaccine [39] and so on .but How to effectively remove The latent viral reservoir, and to establish the immune system is the main question to cure AIDS. At present, there is no effective method to cure the disease, so do a good job in the prevention and antiretroviral therapy of infection at the early stage is still an effective method of treatment.

References
[2]. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative


[14]. McCarthy M. HIV is detected in child thought to have been cured[J]. BMJ, 2014, 349: g4614.


