

# The Clinic trials of Human Immunodeficiency Virus

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**Abstract.** This review paper looks for future improvement for HIV. It is obvious that HIV has become a pandemic disease and causes serious problems to human life quality, social stability and public health. However, there are still a lot people get infected by HIV and the mortality of HIV patients has decreased compared with the time that the disease was discovered. By understanding the virus structure and the mechanisms when the pathogen enters the body, humans can find ways to solve AIDS infection in these ways, from the source of the pathogen, the transmission path, and patients infected by HIV. Second, by analyzing two successful cases of HIV cured patients and the failure cases, humans find out that not everybody is suitable for the same treatments as the two successful cases did. Although, nowadays, scientists are working on HIV vaccines, the process is very slow as there are still a lot of mysteries in human immunodeficiency virus and HIV vaccines. Few types of vaccines were undergoing clinical trials. Humans still have a long way to go to overcome HIV, but as more and more attention are paid to HIV patients and the projects which are trying to overcome it, HIV patients' life quality had improved a lot and their life cycles are prolonged.

**Keywords:** HIV, Clinical, Diagnosis, Treatment.

## 1. Introduction

Human immunodeficiency virus, HIV, was reported by CDC in 1981. The report stated that “five young, gay men across Los Angeles had been diagnosed with an unusual lung infection known as pneumocystis pneumonia (PCP) -- and two of them had died.” This was the first time people were exposed to AIDS [1]. HIV has a very long incubation period, from 0.5 years to 20 years, to get the advanced AIDS stage. Human immunodeficiency virus is highly contagious. The disease can transmit through sexual activity, drug injection, blood transmission and from mother to her baby during pregnancy, birth and breastfeeding. HIV viruses will attack the human immune system, especially the amount of CD4 protein will decrease, where CD4 proteins act as the receptor for immune recognition. HIV virus are sensitive to UV light and when the temperature is above 60°C, virus becomes denatured. Two types of HIV had been found around the world, HIV-1 and HIV-2, which are the etiologic agent for human. Both human immunodeficiency viruses can lead to AIDS, and they have a lot of similarities, including the way of gene replication, the pathway of transmission and clinic sequence. [2] HIV-1 patients are found around the world, while most HIV-2 patients are found in West Africa. And for HIV-1, there are three groups, M, N and O. The group M for HIV causes the majority of infections around the world.

Symptoms of HIV can be variable, as it was flu ill-like symptoms for the first 1-2 weeks after people are infected. And soon enter the stage where there are no obvious symptoms from clinic view. After few years, a lot of symptoms will occur. HIV infection results in HIV diseases and opportunistic infections caused by other pathogens. At the advanced stage of HIV, number of CD4+ cells decreases. Also at the advanced stage of HIV, the most common symptom is rapid weight loss of patients. Also, at the advanced AIDS stage, patients might appear some nervous symptoms, like deterioration in memory, apathy and epilepsy. As a long period with HIV gradually destroys human immunity, the inner environment is much more suitable for pathogens to carry out a series of metabolisms as no antibodies are produced and they will not be affected. Normally, HIV patients with opportunistic infections have higher motility. Lung conditions in patients with advanced AIDS mainly include fungal infections, pulmonary Kapos sarcoma (KS), lymphoma, and non-tuberculous divergent bacteria infections.

Some problems occur during medical cures to unknown HIV patients. In emergency department of hospital, commonly, for patients who are in a state of syncope, it is not possible to determine whether a patient has AIDS by asking or visualizing the patient's clinical presentation, which increases the risk of AIDS infection among healthcare workers. For some places with lower quality of medication, hospitals do not have enough medical appliances, such as needle syringes, surgical equipment, etc. To ensure that the hospital can function well, medical equipment will be reused in places with bad medical conditions. If equipments are not good for disinfection, it will increase the risk of other patients getting an infectious disease, like HIV and Ebola.

A lot of discoveries had been done for the mechanism of the disease and useful treatments for HIV patients. This essay would discuss the disease from its mechanisms, diagnosis for HIV patients, treatment for the disease in this essay, and pay more attention to analyzing successful cases of HIV patients who had been cured.

## 2. The discovery of HIV

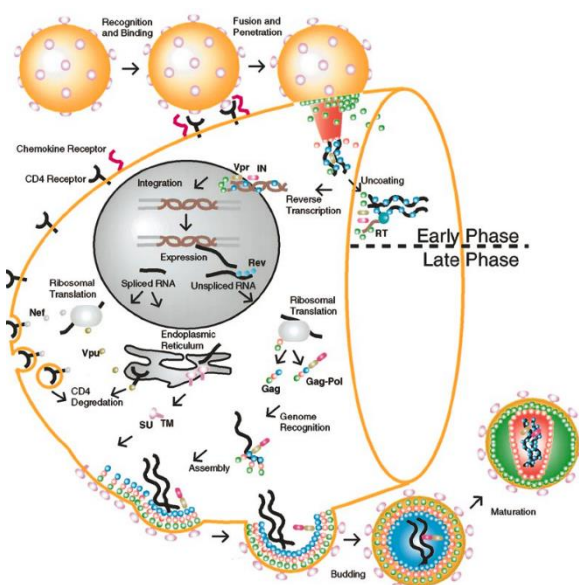
Based on data given by WHO, 79.3 million people are infected by HIV and 36.3 million patients died from HIV or opportunistic infections or tumors as HIV starts infecting humans [3]. During the acute HIV stage, patients always come out the symptoms similar to flu, like sore throat, fever and rash. When the disease spectrum enters the clinic latency stage, there are no symptoms and patients might not feel that they are ill. However, at this stage, virus still replicates and for patients who have detectable viral load and do not take any treatment, the patients can transmit the disease. This period might last for 10 to 15 years, but the exact incubation period depends on different patients. For the last stage of HIV, patients will get symptoms of HIV, like rapid weight loss, pneumonia and diarrhea that lasts for more than 1 week. Also, at this stage, patients may get the opportunistic infection, including CMV retinitis which leads patients to become blind, HSV infection (causing fever blisters around mouth, genitals and anus) [4]. At the latency stage of HIV (the last stage), it can also cause damage to essential organs. Damages toward essential organs including PCP, Mycobacterium tuberculosis (particularly in drug takers and prisoners), cardiac complications (may involves pericardial effusion, cardiomyopathy, right or left ventricular hypertrophy). [5] myocarditis, endocarditis, malignancy, coronary artery disease, and cardiotoxicity of medications.

The transmission for HIV have variable routes. Human can be infected through unsafe sexual behaviors, blood or a series of blood products, injection drugs and maternal-fetal transmission. However, patients at the window stage of HIV will increase the risk of transmission HIV to others by donating their blood. At the window stage, patients have not developed detectable antibodies. For most drug users, the risk of transmitting HIV increases by sharing needles, the duration of injecting drugs and the number of partners. The main risk of infecting HIV among healthcare workers is through medical devices stained with the blood of AIDS patients, like needle sticking.

## 3. The mechanism for HIV disease and structures of virus

The life cycle of HIV virus can be divided into 6 stages, viral attachment, viral fusion (penetration), un-coating, reverse transcription, integration, viral latency and protein synthesis. When pathogen of HIV enters the human body, it will bind with the immune cell with CD4 receptor and then enter the human cell. The replication cycle for HIV-1 can be divided into 2 phases, early phase and late phase. For the early phase, human immune cells will recognize HIV-1 cells using the CD4 cells and  $\beta$ -chemokine receptor. The receptors on the virus are found as gp120 and gp41. As the virus enters human cell, it will release its genetic material, viral RNA. Viral RNA is reverse-transcribed by enzyme called reverse transcriptase, forming the complementary strand of DNA. Integrase found in HIV will inject the viral DNA into human cell genomes. Now, human cells are completely infected by the HIV virus and the human cell now are regarded as pro-virus. The graph below shows the replication cycle for HIV-1 type.

For the structure of HIV, like all types of viruses, the central genetic material (viral RNA) is surrounded by protein coat. Protein coat works as a protection toward central genetic material. Protein coat contains specific glycoproteins, gp 41 and gp 120. These glycoproteins can be used to identify the virus. Inside protein coat, the genome of HIV is found in folded RNA. Many enzymes that used for reverse transcription are found in the area close to the central genetic materials. One of the main characteristics of lentiviruses is that their gene materials have strong variability, which means that their genes have high risk error rate. This is one of the problems that scientists have problems with developing HIV vaccines.



**Figure 1.** The mechanisms when the HIV combines with CD4 cells [6]

#### 4. Identification and treatment of HIV

At present, the detection of AIDS mainly consists of HIV-RNA detection and HIV-Ab detection. In particular, the asymptomatic patients of HIV who are serologic HIV-Ab test are significant source for HIV transmission. For some patients, patients who test positive for HIV-RNA but negative for HIV-Ab are still highly contagious. The detection method of HIV-Ab has two advantages. The first one is that HIV-Ab has specificity, low fault tolerance rate and high sensitivity. Second, when a patient is infected with HIV, antibodies produced by the immune system against the virus remain in the blood for life (except for a brief early window). There are two main methods for testing HIV-Ab, enzyme linked immunosorbent assay (ELISA) and particle agglutination. The specificity and sensitivity of precise result using ELISA test and rapid test can reach to 100%. When diagnosing HIV, the final result must be distinguished from Epstein-Barr virus infection and enterovirus meningitis. And to get final diagnosis, healthcarers should organize the local situation (whether the local community have high percentage of people infected by HIV) and the detail symptoms, like typhoid fever or infection caused by Rickettsia.

To treat HIV, ART/HAART (Antiretroviral Therapy/Highly Active Antiretroviral Therapy) is used to treat the disease. ART/HAART involves multiple antiretroviral drugs. The initial purpose of ART is to reduce mortality of patients and improve their life quality. ART/HAART can also reduce the virus load in blood. The treatment involves a series of types of antiviral drugs, including NRTIs (Nucleoside Reverse Transcriptase Inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors), PIs (protease inhibitor), Raltegravir and CCR5 inhibitors. These drugs have different target on the HIV virus. Drawbacks are found towards ART/HAART, patients need to take lifelong treatment and the toxins in antiviral drugs may be accumulating in patients. As a review written by Margolis A. M. and teammates, "Overdose with ARVs is not commonly reported. The most serious overdose outcomes have been reported in neonates who were inadvertently administered

supratherapeutic doses of HIV prophylaxis medications.” [7] Therefore, scientists are working on gene therapy for HIV. In 2014, a report from Didigu and colleagues promised the result that the host gene modification in HIV-positive mice was successful as mice did not appear functional immune defects [8]. For pregnant women, based on the study called “ACTG 076”, it stated that the risk of transmitting disease to the next generation through mothers had been reduced to 1 in 12 babies would be infected by HIV as their mother took AZT (zidovudine, a type of antiviral drug) before they gave birth to their babies [9].

## 5. Successfully cured cases of HIV patients

A HIV patient, Timothy Ray Brown (also known as “Berlin patient”) was reported as he had been cured of HIV. Like most HIV patients, he received the ART after he had been diagnosed as HIV positive. A hematopoietic stem cell transplant saved him from HIV when he was diagnosed with acute leukemia.

At the end of 2006, patient agreed with the surgery about stem-cell transplantation. Dr. Hütter was aware that the  $\Delta 32$  variants on the CCR5 genes conferred would protect the patients from HIV. After finding a large number of donors for the stem-cell, he finally found one donor with which stem cells are matched. After Mr. Brown stopped the HIV treatment, the team did the stem cell transplantation. The surgery eliminated the acute leukemia and also, as the patient stopped taking HIV treatment, the viral load for HIV disappeared [10].

Another HIV patient in London received the HSCT (Hematopoietic Stem Cell Transplantation) to treat Hodgkin’s lymphoma. ART/HAART was disturbed for 16 months after the HSCT. HIV remission had been kept for him after 18 months and there are undetectable HIV RNA and undetectable DNA with CD4+ cells which were lower than one copy per milliliter [11].

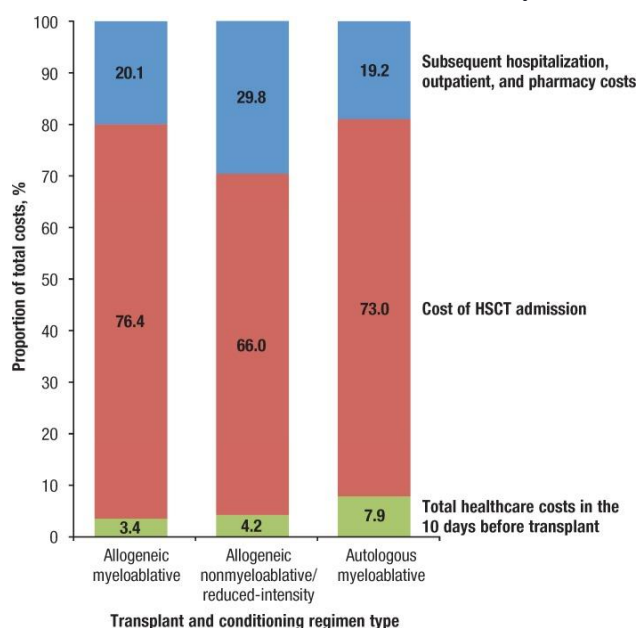
These two successful cases of HIV-cured patients gave scientists a new idea to treat HIV-1. However, a treatment like HSCT has some drawbacks. Firstly, this treatment is not suitable for every HIV-1 patient. The problem is that it is difficult to find correct donor for the stem cells. Secondly, based on the two cases mentioned above, it can be very easy to find out that the “Berlin patient” and “London patient” had severe diseases related to blood system, the purpose for them to take HSCT was to try to cure their disease related to the blood system.

## 6. Limitations

There were 2 cases reported in Boston as HIV was re-found in patients’ bodies. Both of them were diagnosed with HIV infections and hematologic malignancies. And both of them received the HSCT as treatment. However, some differences were found between Boston cases and “Berlin patients”. As mentioned before, “Berlin patients” received HSCT where the CCR5 genes have mutated. For cases in Boston, one case received HSCT without the CCR5  $\Delta 32$  mutation and another case received HSCT where the donor cells contains wide-type CCR5 genes and rebounded for 9 months [8]. The problem for these two cases might be that they do not receive same treatment as the treatment on “Berlin patient” as the donor cells have different types of CCR5 genes.

These two cases stated that not all HIV patients are suitable for HSCT to eliminate HIV in body even they are diagnosed with HIV infection. Also, the cost for HSCT is usually huge, not only time taken for the process of finding the proper donor for the cell with CCR5 genes, but also for the financial support. Usually, the cost for HSCT is between \$87000 and \$300000. HSCT has great damage to main organs. Research done by Deirdre Sawinski reported that patients who got HSCT increased the risk of acute kidney diseases and chronic kidney disease (CDK) [12]. According to Deirdre Sawinski, the risk of getting chronic kidney disease (CKD) after HSCT increases twice among population. And for recipients of HSCT, the risk of CKD can be affected by different factors, for instance, older age and hypertension. In the early stage when patients got treatment of HSCT, HC (hemorrhagic cystiti) was found and was regarded as a serious complication after HSCT. The results

for HC can involve prolongation of hospitalization, death. Nowadays, scientists are working on developing vaccines toward HIV. Normally, vaccines are used to prevent and cure people by containing either the un-live antigen or antibodies and injecting into human bodies since it was discovered. There were only four types of HIV vaccines were tested. There are two approaches for HIV vaccines, the empirical approach and the theoretical approach, to develop the HIV vaccines. For theoretical approach, the basement of this approach is the understanding toward human immunity, how the antigen affects the immune system. Two types of vaccines are designed for this approach, the cell-based vaccine and the antibody-based vaccine. The target for the cell-based vaccine is waking the human-self immune response instead just injecting the antibody. For the antibody-based vaccine, scientists have found out that some people living with HIV may develop bNAbs (broadly neutralization antibodies) naturally after few weeks to few years. And for bNAbs, it will not affect the people living with HIV, but it can eradicate the cell infected by HIV.



**Figure 2.** The cost of the HSCT during the hospitalization [13]

## 7. Conclusion

To overcome and eliminate HIV, as human treat smallpox, human still have long way to go. Although there are two cases reported as they were cured, they were just exceptions. Their target to accept HSCT were not cure HIV but for more serious diseases which were not related to HIV. HIV are now widely spreading, government, social, non-profit organizations should put effort to stop HIV. Children nowadays are educated and they know some basic knowledge about HIV, including the transmission of HIV and the results of people infected by HIV. Scientists are working on developing HIV vaccines. The AMP studies were set up in 2016, trying to determine the hypothesis that bNAbs can prevent HIV effectively [14]. According to VRC (Vaccine Research Center) scientists, “a vaccine based on the fusion peptide—a vulnerable site on HIV that helps the virus fuse with a cell to infect it—elicited neutralizing antibodies in mice, guinea pigs and monkeys [14].” In the future, the efforts of the whole society and the development of vaccines will be of great help to the lives of AIDS patients.

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