

# THERAPEUTIC APPROACHES WITH STEM CELLS TO CURE HIV

*Data de aceite: 02/05/2024*

### **Gabrielly Rodrigues Borges dos Santos**

Centro Universitário de Goiânia -  
UNICEUG  
<https://lattes.cnpq.br/7472430596917086>

### **Larissa de Oliveira Rosa Marques**

Specializing in Medical Genetics and  
Molecular Biology at IESE Especializações  
<http://lattes.cnpq.br/8093665238893969>

### **Igor Mendes Moreira de Oliveira**

Centro Universitário de Goiânia -  
UNICEUG  
<https://lattes.cnpq.br/8641359440292849>

### **Benedito Rodrigues da Silva Neto**

Instituto de Patologia Tropical e Saúde  
Pública – IPTSP/UFG  
<http://lattes.cnpq.br/5082780010357040>

**ABSTRACT:** The Human Immunodeficiency Virus (HIV) is responsible for the development of Acquired Immunodeficiency Syndrome (AIDS), a disease which, despite treatment, there is currently no cure for. However, some tests have been carried out on patients with hematological diseases such as leukemia. Stem cell transplantation is a treatment that allows the virus to go into remission and then be eliminated. The treatment involves transplanting stem cells

from donors who are homozygous for the mutation in the CCR5 gene in delta 32, because CCR5 $\Delta$ 32 is naturally resistant to the virus, as it causes a deletion of the CCR5 receptors in the cells, making it possible for the virus not to enter the body's cells, leaving the individual HIV-free. Based on this information, the aim of this work is to demonstrate new possibilities for treatment and possible exhumation of the HIV/AIDS virus through stem cell transplantation.

**KEYWORDS:** CCR5-32. Patient from Berlin. HIV + Leukemia. HIV cure. Stem cells. HIV.

## INTRODUCTION

Acquired Immunodeficiency Syndrome, also known as AIDS, is the last stage of HIV infection when left untreated. It was first described in 1981 in a report presented by the US Centers for Disease Control (MMWR, 1981). In the years that followed, the virus was identified and named human immunodeficiency virus (HIV) (BARRE- SINOUSI et al., 1983). A large number of people around the world have died from AIDS-related causes, however there has been a decline since the peak in

2005, partly due to the fact that HIV-infected people are having more access to antiretroviral drugs. Currently, around 40 million people live with HIV/AIDS in the world (UNAIDS, 2012). In recent years, the total number of HIV infections in the world has continued to fall, but in some countries the drop has exceeded 50%, while in others it has not exceeded 20% (UNAIDS, 2012). HIV is a virus of the Retroviridae family, genus Lentivirinae. This group of retroviruses can cause long-term occult infection, short-term cytopathic effects, as well as slow- or fast-developing lethal diseases.

The progression of HIV infection can be divided into three phases, the first being the acute phase, which takes place between the third and sixth week after infection, when the virus reaches high levels of replication, with a drop in CD4 cell rates and the appearance of the first clinical manifestations. Then there is the asymptomatic or clinical latency phase, which can be characterized by an active immune response to the virus and a consequent drop in plasma viral levels, which remains at stable levels and can last for months or even years. The last phase is the symptomatic period, with the appearance of opportunistic infections that characterize the clinical picture of AIDS (COFFIN, 1995; ROBINSON, 2002).

HIV infection of host cells occurs through the binding of the gp120 glycoprotein to the CD4 cell surface glycoprotein. The two receptors that are most relevant to HIV replication are CCR5 and CXCR4. More than a dozen G protein-coupled receptors can mediate the entry of some HIV strains when they are expressed in transfected cells in vitro (LUSSO, 2006). CCR5 and CXCR4 are structurally related to the chymosins that belong to the G protein-coupled receptor superfamily (GPRS) (ALKHATIB, 2009).

With the introduction of antiretroviral therapy (ART), AIDS began to be seen as a chronic disease. If treated correctly, it reduces the likelihood of death for these people. The early introduction of ART reduces the rates of sexual transmission of HIV, bringing benefits not only for the individual, who has a better quality of life, but also for public health. Despite all the improvements and advances that ART has brought to the treatment of HIV/AIDS, it still cannot be considered widely effective, as it does not reduce chronic inflammation and is not capable of eliminating immune dysfunction. It is essential that we find a definitive and widely effective form of treatment and possible cure, and the use of stem cells is a door of hope as well as a promising method for this case.

## **BACKGROUND**

The Human Immunodeficiency Virus, known as HIV, is a virus that affects the immune system and destroys CD4 T lymphocytes (CD4 cells), leaving the body vulnerable to infections known as opportunistic diseases. The search for a treatment or even a possible cure has been a challenge, as the virus has the ability to camouflage itself inside human cells.

In recent years, millions of people around the world have died from HIV-related causes. Although HIV-positive people are now living a normal life with the use of retroviral drugs, science is still studying different approaches, such as stem cell transplants with the CCR5-32 genetic mutation.

In view of these developments in the study of HIV, this study aims to demonstrate new therapeutic possibilities against the virus, whether by transplanting stem cells from donors with the CCR5 $\Delta$ 32 mutation, or even the possibility of new approaches to treatment and protection against HIV infection.

## LITERATURE REVIEW

### Emergence of HIV

The human immunodeficiency virus (HIV) became known in the 1980s where it became part of the world stage, every country in the world recognized it and reported HIV infection in their population (De Lay P, UNAIDS; personal communication). The pandemic was first recognized on June 5, 1981, when the US Centers for Disease Control and Prevention (CDC) reported five cases of pneumonia caused by *Pneumocystis jirovecii* (then called *Pneumocystis carinii*) in gay men living in Los Angeles. The new disease was thought to be limited to homosexual men only, however a few months later cases were reported in injecting drug addicts and non-homosexuals outside the US (in the UK).

Other immunodeficiency diseases were soon reported in different populations in many countries, including Haiti and some African countries. In May 1983, a retrovirus (which was later named human immunodeficiency virus, or HIV) was isolated from an AIDS patient in France; months later, the US Food and Drug Administration approved a commercial test to detect the virus. By 1985, several cases of AIDS had been reported to the WHO in Geneva.

### Epidemiology

HIV affects the whole world, data shows that in 2020 the total number of people living with HIV was 38 million where 70% of these people live in Africa, it was also reported that 690,000 people died from AIDS-related illnesses by the end of 2019. Around 75.7 million people have been infected since the beginning of the epidemic and more than 32.7 million have died. AIDS-related mortality has fallen by 39% since 2010 (UNAIDS, 2020). Of the 38 million, around 20.6 million live in Eastern and Southern Africa. Latin America ranks fourth in number of infected people in the world. Brazil is the country with the highest number of HIV cases in the region (UNAIDS, 2018).

In 2012, 11,896 deaths from AIDS were reported in Brazil, which corresponds to an AIDS mortality coefficient of 5.5 per 100,000 inhabitants (standardized coefficient). The coefficients by region were: 7.7 in the South, 5.6 in the North and Southeast, 4.7 in the Midwest and 4.0 in the Northeast. Over the last 10 years, there has been a 14% reduction

in the mortality rate in Brazil. As with detection rates, the trend over the last 10 years in the mortality coefficient shows a discrepancy between the regions: an increase in the North (60.0%), Northeast (33.3%) and Midwest (4.4%) and a reduction in the Southeast (31.7%) and South (7.2%) (BRASIL, 2013).

Currently, the main treatment for HIV/AIDS is antiretroviral therapy (ART), which is responsible for improving the quality of life and increasing the survival rate of these patients. However, ART has various side effects, depending on the type of medication, the daily use of various medications, and it is unable to reduce chronic inflammation and immune dysfunction. Its interruption leads to a rapid increase in viremia within a few weeks, thus limiting its effectiveness (ZHEN, 2014; HÜTTER et al., 2009). Thus, many researchers are currently looking for stable, more effective and safer methods of treatment for HIV/AIDS. The research involved in stem cell treatment can therefore include halogenated or autologous stem cells.

## **Etiology and Pathogenesis of HIV**

### *Structure of the HIV virus*

The Human Immunodeficiency Virus (HIV) belongs to the genus Lentivirus and is a member of the Retroviridae family. Its structure is made up of glycoproteins and proteins. Its viral envelope is located on the outside and is made up of a set of proteins consisting of glycoprotein120 and glycoprotein41, together with a bilipid layer (Figure 1) (SILVA et. al. 2020). Just below the viral envelope, the layer composed of the p17 protein can be seen. Just below the The capsid is composed of the p24 protein and below it isthe viral genome, composed of ribonucleic acid (RNA), together with the presence of proteins such as the nucleocapsid (p7) and the enzymes reverse transcriptase (p51), protease (p11) and integrase (p31) (SILVA et. al. 2020).

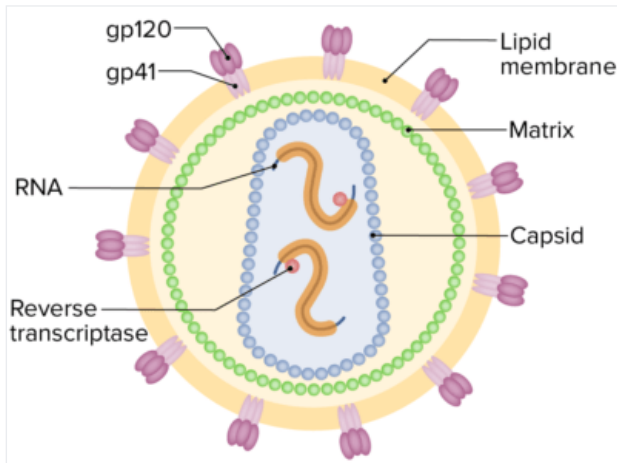


Figure 1: HIV viral structure

Source: (<https://www.lecturio.de/artikel/medizin/retroviren-hiv/>)

Only two viral types have been discovered to date, the first being the most virulent and most common in causing AIDS worldwide (HIV-1) and the second being structurally differentiated and responsible for generating a slower progression of AIDS (HIV-2) (NETO, et. al. 2020).

## HIV INFECTION

Once in the bloodstream, HIV attacks cells and, if left untreated, can progress to AIDS. HIV infection occurs in macrophages and CD4+ T lymphocytes, and over time it infects memory CD4+ T cells. It is through alterations in this cell's DNA that HIV makes copies of itself and, after multiplying, breaks through the lymphocytes in search of others to infect.

Continue the infection, following an endless cycle (Figure 2) (RODRIGUES et al., 2018).

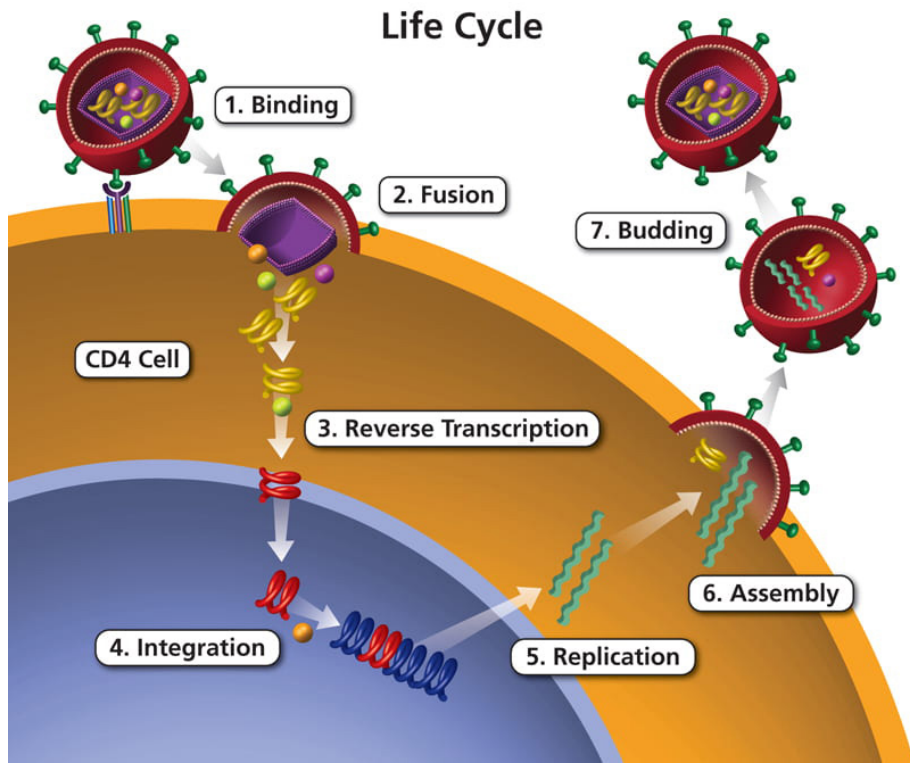


Figure 2: The life cycle of the HIV virus

Source: U. S. Department of Health and Human Services, 2018.

The virus has two main coreceptors for HIV entry into cells, CXCR4 and CCR5. CXCR4 is used by the virus in T-cell lineages, and CCR5 in macrophage lineages. However, other coreceptors have already been identified, such as CCR3, which is a chymosin expressed in eosinophils and microglia cells, and is used by some strains of HIV to infect microglia (BITANTE; FILHO, 2017).

### Transmission of the HIV virus

The HIV virus can be transmitted through contact with blood, which includes blood transfusion, vertical transmission (childbirth), sharps transmission, transmission by sexually transmitted infection, or transmission by breast milk. The HIV virus is present in body fluids in free form (virus particles spread throughout the body) or inside infected host cells. Among the means of transmission of the virus are unprotected sexual intercourse, the use of contaminated syringes and the transmission of HIV.

Congenitally (from mother to baby) during pregnancy or breastfeeding (NETO, et. al. 2020). Soon after transmission, the patient develops some signs and symptoms such as: fever, headache, weakness, pharyngitis, rash and myalgia (muscle pain). Digestive problems such as nausea, vomiting, weight loss, diarrhea and oral ulcers can also occur (LOPES, et. al. 2019). Because they are common symptoms, the manifestations can be associated with signs of usual diseases such as viruses, especially because they are symptoms that disappear in 3 or even 4 weeks, which makes it difficult to diagnose HIV early. As the infection develops, symptoms such as low-grade fever, weight loss (when more calories are expended than gained), fatigue, chronic diarrhea, among others, become nonspecific, but neurological changes and bacterial infections may appear (LOPES, et. al. 2019).

## HIV prevention

Among the prevention methods that can be used are HIV testing, which is provided free of charge by the Unified Health System (SUS), the use of condoms, which can be obtained free of charge from the government, and pre-exposure prophylaxis (PrEP), which has become popular in recent years, especially among sex workers and homosexuals, PrEP is a new method of preventing HIV infection, aimed at those who don't have HIV in their system, which consists of taking a combination of pills a day. It's important to note that PrEP doesn't protect against other STIs such as syphilis, chlamydia and gonorrhea and therefore must be combined with other forms of prevention.

Post-exposure prophylaxis (PEP), which consists of the use of medication to reduce the risk of acquiring these infections, should be used after any situation in which there is a risk of contagion, be it: sexual violence; unprotected sexual intercourse ( without the use of a condom or with the condom breaking); occupational accidents (with sharp instruments or direct contact with biological material), for HIV-positive mothers there is a whole treatment so that vertical transmission does not occur (through pregnancy or breastfeeding) and we also have the treatment of people with HIV.

Who are already living with HIV using antiretroviral drugs (ARVs). All these methods can be used on their own or in combination. With the knowledge of different HIV prevention methods with proven efficacy, it is possible to think up new forms and prevention schemes for health users around the country.

### *Clinical Diagnosis*

One of the objectives of the initial assessment of a person with a possible diagnosis of HIV infection is to establish a solid doctor-patient relationship, and using language that is accessible to the patient is important in order to explain essential aspects of HIV infection. The first step is to identify any condition that requires immediate intervention, such as signs and symptoms suggestive of opportunistic manifestations like fever, prolonged malaise,

swollen lymph nodes on the body, red spots on the skin, sore throat and joint pain. Some people don't show any symptoms for many years while the virus slowly replicates itself, then assess the need for laboratory tests, carry out a full physical examination if the tests are reactive for HIV, assess the patient's level of knowledge about the virus and put an end to any doubts. Explain the meaning of HIV infection and how it evolves. Once doubts about the pathogen have been resolved, the subject of transmission and prevention must be addressed.

### *Laboratory Diagnosis*

For a good laboratory diagnosis, there are four generations of immunoassays, with each generation improving on its predecessor in terms of test performance and reducing the detection period. The nomenclature of the tests can vary, as can the first and second generation tests, which can be called "IgG sensitive", as they are tests that only identify IgG (HURT, et. al. 2017). The diagnosis of HIV infection in Brazil in individuals over the age of two is based on the detection of antibodies, according to Ordinance No. 59/GM/MS, of January 29, 2003 ([www.aids.gov.br](http://www.aids.gov.br)), from which screening tests have a high degree of sensitivity, while confirmatory tests have a high degree of specificity, tests with high sensitivity have a few false-positive results.

In Brazil, only tests registered with the Ministry of Health's National Health Surveillance Agency (ANVISA) can be used for the laboratory diagnosis of HIV infection. One of the criteria for registering these tests is that they have 100% sensitivity and at least 99.5% specificity in a laboratory evaluation carried out by sensitivity, which is the ability to detect antigens or antibodies in the sample, even when present in small quantities, and specificity, which is the ability of a test to characterize non-Reagent samples, in which antigens or antibodies are not present. In serological screening for anti-HIV-1 and anti-HIV-2, viral antibodies and antigens are sought, and tests such as ELISA can be used.

Which is highly sensitive to the presence of anti-HIV antibodies and was the first to be developed to detect the presence of these antibodies in blood donations, it is now routinely used in diagnoses developed for HIV infection (GINESTE et al., 2002; apud BENJAMINI et al., 1996), 1996) rapid tests, also known as immunoassays, in which, if the result is reactive or indeterminate, a new sample is taken to confirm the result and, if the result persists, the diagnosis must be confirmed. To do this, indirect immunofluorescence (IFI) and Western Blot tests are carried out, which detect the presence of antibodies to various HIV proteins, mainly to p24 or p31, gp41 and gp120/gp160. The presence of antibodies to these viral proteins is considered proof of infection (GINESTE et al., 2002).



## *Treatment*

Some treatment methods are used to prevent the virus from multiplying, thus increasing the immunity of the infected person. These drugs are called antiretroviral therapy (ART). Different drugs can be used to target specific stages of the HIV life cycle, such as HIV drugs that block the virus from binding to CD4 receptors are called entry inhibitors.

The reverse transcription stage can be blocked by two different reverse transcriptase inhibitors: nucleoside/maré and non-nucleoside (Rai, Pannek, & Fichtenbaum, 2018). Drugs that prevent the viral integration process are called integrase inhibitors, while the production of new viruses by assembling different components is blocked by protease inhibitors. Budding inhibitors block the exit of the new HIV virus from old CD4 cells, while maturation inhibitors prevent the last assembly process.

HIV treatment should begin at the time of diagnosis to reduce the likelihood of illness and death by up to 57% (Poorolajal, Hooshmand, Mahjub, Esmailnasab, & Jenabi, 2016). Starting treatment when the CD4 cell count has dropped to 350 cells per milliliter increases adverse effects and reduces the survival period. Favorable treatment maintains immunity, preserving thus increasing CD4 cells and reducing the likelihood of transmission of infection through low viral loads (CZŁONKOWSKA A.; et al, 2018).

## **Stem Cell Transplantation**

### *Hematopoietic stem cells*

Stem cells are undifferentiated cells or cells with a low degree of differentiation, found in embryonic and extraembryonic tissues. They can remain quiescent until adulthood, through self-replication, or differentiate into various tissues, based on the expression of certain genes, and carry out specific functions.

Hematopoietic cells are produced in the bone marrow (BM). Hematopoietic stem cells (HSC) contain a long-term capacity for self-renewal, as well as the ability to transform into any other blood cell (TSUKAMOTO, 2020). This more “restricted” differentiation potential allows their use to be controlled and applied more directly in regenerative therapies, with the main biological sources being bone marrow, umbilical cord and placental blood and peripheral blood (LUNA, 2013; SILVA JUNIOR; ODONGO; DULLEY, 2009).

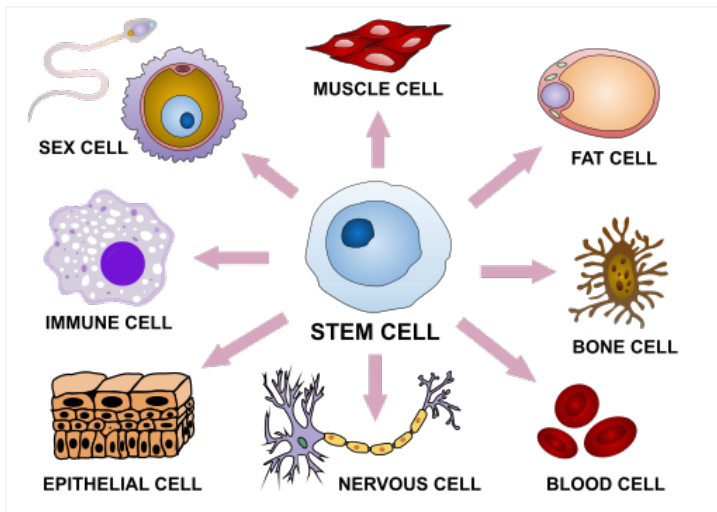


Figure 3: Cells created from stem cell

Source: (<https://alevelbiology.co.uk/gcse/cell-differentiation/>)

The first hematopoietic stem cell transplants in HIV patients were carried out in the early 1980s, even before there was a broad understanding of the requirements of the virus in the human body and the development of highly effective antiretroviral therapy. Already at that time, there was an expectation that stem cells could, to some extent, restore the immune system of people living with HIV who had manifestations of cancer and serious infections associated with AIDS (HÜTTER; ZAIA, 2011).

These hematopoietic stem cell transplants led to the first HIV/AIDS cure, known as “The Berlin Patient”, through an experimental therapeutic process (ALLERS 15660 n. 60 | 2022 | p. 154-176 et al., 2011; HÜTTER et al., 2009).

### The Berlin patient and the CCR5 $\Delta$ 32 mutation

In May 2006, Timothy Ray Brown, an American living in Berlin, arrived at the office of hematologist Dr. Gero Hütter at the Berlin Hospital.

Charité University. He was thin, weak and had severely compromised organs due to a recent diagnosis of acute myeloid leukemia (AML). According to the patient himself, this would be the “second death sentence”, in his words. The first “death sentence” was announced in 1995, at the age of 29, when he was diagnosed positive for HIV.

With no response to the AML treatment, the doctors believed that Timothy would only live a few months. Conventional treatment based on chemotherapy and drugs had a 10 to 15% chance of remission for a short period, until the leukemia returned. Timothy’s lifeline was a bone marrow transplant. Because he was still young, energetic and optimistic, Hütter concluded that he would be the ideal patient for a bone marrow transplant. Although he had experience and training in oncology, Hütter was not an HIV specialist.

Despite this, like many doctors who graduated in the 1980s and 1990s, he was affected by the epidemic. The fear instilled by the emergence of the hitherto unknown acquired immunodeficiency syndrome (AIDS) in 1981 coincided with the beginning of his sexual and clinical activity. When he started medical school in 1992, there was still no effective treatment for the disease.

In that context, he saw many people die. For the treatment of AML, four rounds of chemotherapy would be required, each lasting a week and with intervals of several weeks between sessions. In each session, tubes stretching from his neck to his heart were inserted into Timothy. During the first round, the procedure went well. In the second round, he came down with fungal pneumonia and underwent antifungal treatment. During the third round, sepsis occurred, a set of severe manifestations throughout the body produced by an infection.

The three rounds of chemotherapy caused a high fever, liver and kidney failure. Timothy became so weak that he was admitted to an intensive care unit and induced into a coma. During the 16 hours he was in a coma, the doctors thought he wouldn't survive and warned his partner. However, he made a full recovery and the leukemia went into remission in 2006. Hütter then suggested that he take a vacation. During the remission of the leukemia, Timothy was offered an experimental treatment that could cure him of the leukemia.

Of HIV: the transplantation of stem cells from a donor with a genetic mutation. At medical school, Hütter had read an article describing a rare genetic mutation called "CCR5 delta-32", but relatively common in northern Europe, capable of conferring natural resistance to HIV.

The mutation occurs because the chymosin receptor CCR5 serves as a corrector for HIV, allowing the virus to enter human CD4 T cells and macrophages. In the absence of CCR5, the virus cannot successfully initiate infection. The CCR5 Delta 32 mutation causes a frameshift with a premature stop codon and generates an incomplete form of CCR5, the incomplete protein is not expressed on the cell surface and therefore viral binding to the receptor is prevented. Therefore, individuals homozygous for CCR5 Delta 32 were protected against HIV (Figure 2) (XU CELL BIOSCI, 2020).

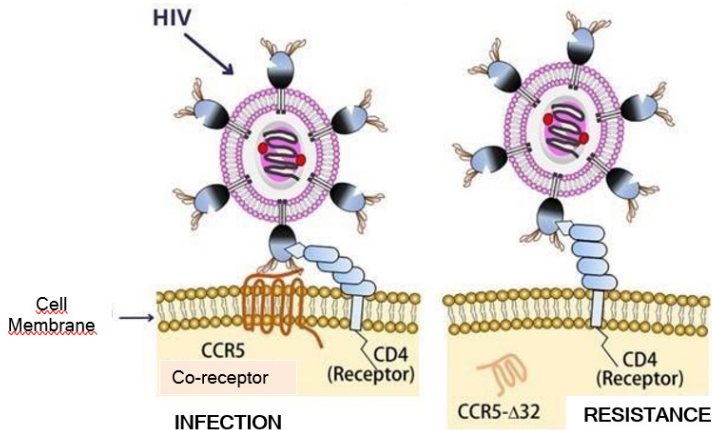


Figure 4: Molecular mechanism of CCR5 in HIV infection and the protective effect of cytoplasmic CCR5- $\Delta$ 32 against HIV-1 infection

Source: Xu Cell Biosci, 2020.

After talking to friends, family and a doctor specializing in transplants, Timothy turned down the offer. He refused because he didn't think it was necessary to become a "guinea pig" and be subjected to a highly risky experiment. But at the end of 2006, the leukemia returned, and it became clear that the stem cell transplant was necessary for Timothy's survival. Before the third chemotherapy treatment, Hütter had taken a sample of Timothy's blood to send to the German Red Cross stem cell donor bank. Germany proved to be the ideal place to locate the donor with the CCR5 delta-32 mutation. Hütter convinced the people in the registry to test the donors for the mutation. Donor number 61 had both copies of the mutation. When he was contacted, he agreed to donate his bone marrow if necessary.

The procedures Timothy would undergo entailed a series of risks, the first of which would occur even before the transplant. As is standard procedure for a stem cell transplant, he underwent a "conditioning regimen" (ALLERS et al., 2011; HÜTTER et al., 2009), an intense process of chemotherapy and radiation that destroys the immune system in order to make room for the development of the transplanted stem cells, during which numerous errors could occur, such as the so-called "graft-versus-host disease", i.e. when the cells of the new immune system don't recognize the organism and start attacking the patient's cells, causing infection.

Timothy received the transplant on February 6, 2007, at the Charité Hospital in Berlin. In agreement with the doctors, antiretroviral therapy for HIV treatment was stopped at this time. This was considered an important action so that the drugs would not damage the transplanted cells' ability to survive in the new body and so that a possible cure could be announced. At any sign of the virus in the blood, the drugs would be resumed, as would the rounds of chemotherapy carried out before the transplant, and immunosuppressant drugs were also used to prevent post-transplant rejection of the stem cells. Timothy survived the operation and the "graft" was achieved 13 days after the procedure.

The recovery process went well and Timothy was able to return to work and physical activity. In the months that followed, HIV was not found in his blood, but more precise tests still needed to be carried out, and so it continued until the beginning of 2008, when the leukemia returned, and with this return the doctors opted for a second transplant, this one from the same donor as the previous one.

First, because now Timothy's system would be used to the same immune system.

Timothy's second transplant cured his leukemia, but it was much more difficult for him than the first because neurological problems occurred as a side effect of the chemotherapy and irradiation used in the ablation. In his case, the doctors suspected that the leukemia might have spread to his brain and ordered a biopsy. The result was negative, but it brought new problems. As a result of the intervention, he temporarily lost the ability to walk and speak, as well as having his sight affected, but Timothy continued to receive immunosuppressive treatment to prevent rejection of the transplanted cells for 38 months.

During the 38-month follow-up period, the donor cells repopulated the immune system of the intestinal mucosa to such an extent that the frequency of CD4+ cells became almost twice as high as in healthy HIV-negative controls, and this phenomenon was also observed in a control group of ten HIV-negative individuals who received stem cell transfers. The repopulation of CD4+ cells was accompanied by the complete disappearance of the host's CD4+ cells, and after two years, Timothy had the CD4+ count of a healthy adult of the same age. CCR5-carrying macrophages could not be detected after 38 months, suggesting that chemotherapy had destroyed these longer-lived cells and that they had also been replaced by donor cells with the CCR5 $\Delta$ 32 mutation (ALLERS et al., 2011; HÜTTER et al., 2009).

HIV remained undetectable in viral load (RNA) tests and viral DNA tests inside cells, and HIV antibody levels decreased to the point where there was no reactivity to the essential HIV antibodies, this was the first sign that he was HIV-free after 11 years of living together. Timothy started going to the gym and his muscles began to develop again, in contrast to the debilitating syndrome he had experienced as a result of his HIV infection (BROWN, 2015).

## The London patient

In 2003, Venezuelan Adam Castillejo was diagnosed with HIV-1 and in 2012, he developed stage IV-B Hodgkin's lymphoma (nodular sclerosis). He became known as the second HIV case to be cured. (MAZUR; SCHAUREN, 2020) It was indicated that a halogen transplant, from a non-parental donor for the treatment of lymphoma, this donor would present the CCR5 $\Delta$ 32 mutation that could be a way to provide a cure for HIV according to doctors. (MAZUR; SCHAUREN, 2020). In May 2016, Adam received a bone marrow transplant to treat Hodgkin's Lymphoma. After the transplant, he had an HIV remission thanks to the donor who was homozygous for CCR5 $\Delta$ 32 (a mutation that prevents the HIV virus from entering the cells) and thirty days later he was discharged. There was a

complication due to an Epstein-Barr virus infection and grade I graft-versus-host disease, but they were treated. Post-transplantation, the return of lymphoid tissues to normal levels was assessed, as well as complete chimerism in his leukocyte cells and TCD3+ fractions, and also the loss of CCR5 expression on the surface of TCD4 and TCD8 cells. ART was only discontinued 16 months after the transplant (MAZUR; SCHAUREN, 2020). It was not possible to locate functional HIV in his semen, cerebrospinal fluid, blood, lymph nodes or intestinal tissue. The patient was thus the second person to be cured of the Human Immunodeficiency Virus (HIV) (DURAND, et. al. 2020).

## **METHODOLOGY**

To develop this work, a literature review was carried out, obtaining information from articles in Portuguese and English selected from 2012 to 2023 on the subject, using Google Scholar, Pubmed and Scielo as data sources. Descriptors such as “CCR5-32”, “Berlin Patient”, “HIV+Leukemia”, “HIV Cure”, “Stem Cells”, “HIV” and others were used to search for articles.

## **RESULTS AND DISCUSSION**

In order to carry out a bone marrow transplant for the purpose of treating HIV, it would be extremely necessary to identify a compatible donor and administer antiretroviral drugs. However, the treatment has been shown to be effective due to its curative potential (DURAND, et. al. 2020), due to the lack of bone marrow transplantation for more urgent hematological diseases, it creates a challenge for treatment with transplantation. For this reason, treatment can only be carried out on patients who have a hematological disease together with HIV. Transplantation also causes concern due to possible complications with infectious diseases and interactions between suppressive agents (DURAND, et. al. 2020).

Although transplantation can offer gene therapy, there is great difficulty in finding donors who are homozygous for CCR5 $\Delta$ 32 and compatible for Human Leukocyte Antigen (HLA) along with the presence of the X4 strain of HIV that use the alternative cell receptor CXCR4 (DURAND, et. al. 2020). Although ART has made enormous progress in the treatment of HIV/AIDS, it is not fully effective because it cannot reduce chronic inflammation or prevent immune system dysfunction. In addition, cytopenia contributes significantly to reducing the effectiveness of antiretroviral therapies, as it helps to develop opportunistic infections and AIDS neoplasms. It would therefore be important to look for a definitive treatment, where the use of stem cells is an effective treatment. Thus, HIV treatment through hematopoietic stem cell transplantation is the best way to obtain a cure for HIV infection in a healthy and effective way (YUAN, et. al. 2019).

## CONCLUSION

Although there is treatment with antiretroviral therapy (ART) for the HIV virus, these drugs do not provide a cure for HIV-positive patients, causing them to remain with the virus in its latent form in their bodies throughout their lives, which ends up harming the patient in several ways, the main one being in terms of immunity, as they will always be subject to new infections, cases where the patient does not take the treatment correctly, and the infection ends up evolving into AIDS, which can lead to the patient's death. With this in mind, the cure for HIV/AIDS has become a possible alternative through the transplantation of stem cells from donors who are homozygous for the CCR5 $\Delta$ 32 mutation, making the cells immune to the entry of the virus, since they don't have the CCR5 receptor. This type of treatment has made it possible to combine the exhumation of the virus from host cells with the immune response established thanks to donor cells that are resistant to the virus. Therefore, once the transplant has been carried out on HIV-infected patients, it eliminates the virus from their host cells, thus enabling a life without the virus in the body and consequently without AIDS.

## REFERENCES

ALKHATIB G. The biology of CCR5 and CXCR4. *Curr Opin HIV AIDS* 2009;4:96- 103.

ALLERS, Kristina et al. 2011. "Evidence for the cure of HIV infection by CCR5 $\Delta$ 32/ $\Delta$ 32 stem cell transplantation". *Blood*, 117(10): 2791-2799.

Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983;220:868-871.

BENJAMIN, Ruha. 2013. *People's science: Bodies and rights on the stem cell frontier*. Stanford, California: Stanford University Press.

BITANTE, J. O.; FILHO, O. R. Gene therapy: New perspective in the advance to cure HIV infection. 2017. Available at Accessed on September 8, 2019.

BRAZIL. Ordinance No. 204, of February 17, 2016. National List of Compulsory Notification of diseases, illnesses and public health events in public and private health services throughout the country, under the terms of the annex, and makes other provisions. *Diário Oficial da União, Brasília, DF, n. 32, revoking Ordinance No. 1,271 of 06 February 2014*, p. 01-05, 2016b. [https://bvsmms.saude.gov.br/bvs/saudelegis/gm/2016/prt0204\\_17\\_02\\_2016.html](https://bvsmms.saude.gov.br/bvs/saudelegis/gm/2016/prt0204_17_02_2016.html).

BROWN, Timothy Ray. 2015. "I Am the Berlin Patient: A Personal Reflection". *AIDS Research and Human Retroviruses*, 31(1): 2-3.

COFFIN JM. HIV Population Dynamics in Vivo: Implications for Genetic Variation, Pathogenesis and Therapy. *Science* 1995;267:483-489.

DALEY, G. Q. Stem cells and the evolving notion of cellular identity. The Royal Society Publishing, RSTB, 370: 20140376, 2015. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4634003/pdf/rstb20140376.pdf>. Accessed on: October 17, 2022.

DURAND, C. M. et. al. . Allogeneic bone marrow transplantation with post-transplant cyclophosphamide for patients with HIV and haematological malignancies: a feasibility study. *The Lancet HIV*, (), S2352301820300734, 2020. Doi:10.1016/S2352-3018(20)30073-4. Disponível em :[https://sci-hub-hkvisa.net/10.1016/S2352-3018\(20\)30073-4](https://sci-hub-hkvisa.net/10.1016/S2352-3018(20)30073-4). Accessed on: October 21, 2022.

GINESTE, Débora Cristina, 2002. <https://hdl.handle.net/1884/32952>

HURT, C. B. et. al. Selecting an HIV Test: A Narrative Review for Clinicians and Researchers. *Sex Transm Dis*. 44(12): 739-746. December 2017. Doi: 10.1097/OLQ.0000000000000719. Disponível em: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5718364/#ffn\\_sectitle](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5718364/#ffn_sectitle). Accessed on 02 Nov. 2022

HÜTTER, G.; NOWAK, D.; MOSSNER, M.; GANEPOLA, S.; MÜSSIG, A.; ALLERS, K.; SCHNEIDER, T.; HOFMANN, J.; KÜCHERER, C.; BLAU, O. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N. Engl. J. Med.*, v. 360, n. 7, p.692- 698, 2009.

HÜTTER, Gero; ZAIA, J. A. Allogeneic haematopoietic stem cell transplantation in patients with human immunodeficiency virus: the experiences of more than 25 years. *Clinical and Experimental Immunology*, [s.l.], v. 163, n. 3, p. 284-295, 2011.

LOPES, A. O. L. et. al.. Epidemiological and clinical aspects of HIV-infected patients. *RBAC*. RBAC 51(4):296-9, 2019. DOI: 10.21877/2448-3877.201900721. Available at: <http://www.rbac.org.br/wp-content/uploads/2020/04/RBAC-vol-51-4-2019-ref-721.pdf>. Accessed on: October 20, 2022.

LUNA, Naara. The construction of scientific fact: representations of stem cells. *Revista de Antropologia*, [s.l.], v. 56, n. 1, p. 322-358, 2013.

Lusso P. HIV and the chemokine system: 10 years later. *EMBO J*25 2006;447.

MAZUR, B. F.; SCHAUREN, J. Hematopoietic Stem Cell Transplantation in HIV-1 Infected Patients. *Biosciences, Biotechnology and Health*, Curitiba, v. 13 n. n. 27: 68-74, maiode2020. Disponível at: <https://interin.utp.br/index.php/GR1/article/view/2634/2147>;. Accessed on October 28, 2022.

MELLO, L. Beyond the tooth fairy: Stem cells obtained from milk tooth pulp. *Profissão Biotec*. ISSN 2675-6013. v. 8, 2021. Available at: <https://profissaobiotec.com.br/celulas-tronco-obtidas-a-partir-da-polpa-do-dente-de-le-ite/>. Accessed on October 27, 2022.

MMWR. Morbidity and mortality weekly report: Pneumocystis pneumonia. *Los Angeles* 1981;30:250-252. NAIDS. Available on January 1, 2020.

NETO, L. F. S. P. et. al. Brazilian Protocol for Sexually Transmitted Infections 2020: HIV infection in adolescents and adults. *Consenso*. Brasília, 30(Esp.1):e2020588, 2021. Doi: 10.1590/S1679-4974202100013.esp1. Available at: <http://scielo.iec.gov.br/pdf/>

RODRIGUES, J. S.; FONSECA, L. C.; ALMEIDA, T. A. N. C. Evaluation of immunity CD4 cells in the fight against the HIV virus, *Revista Saúde em Foco*, v. 10, P. 718- 724, 2018.

SILVA, D. F. et. al. The CCR5Δ32 genotype in HIV-infected patients who are candidates for bone marrow transplantation. *Brazilian Journal Of Development*. Curitiba, v. 3, n. 3, p. 5082-5106 may/jun. 2020. Available at: .Accessed on October 28, 2022.



SILVA, M.J.S., et. al. Development of Diseases and Complications after Bone Marrow Transplantation. Brazilian Journal Of Development. v. 6. n. 12. p.98279-98294. 2020. Disponível at: <https://www.brazilianjournals.com/ojs/index.php/BRJD/article/view/21622/17245>. Accessed on Sep. 13, 2022

TELELAB. AIDS. GOV. Rapid test for investigation of HIV infection using the TR DPP® HIV 1/2 Bio-Manguinhos with blood sample. Available at: [https://telelab.aids.gov.br/moodle/pluginfile.php/22171/mod\\_resource/content/2/HIV%20-%20Manual%20Aula%209.pdf](https://telelab.aids.gov.br/moodle/pluginfile.php/22171/mod_resource/content/2/HIV%20-%20Manual%20Aula%209.pdf)

THE LONDON PATIENT - a message of hope on World AIDS Day. UK-CAB channel, November 30, 2020. 1 video (49:05 min). Available at: <https://www.youtube.com/watch?v=wmjmPV9Gz8I>. Accessed on: 15/11/2021.

TIMOTHY BROWN, the “Berlin Patient”, the only person in the world cured of HIV AIDS. MrBayareanews” channel, August 29, 2011. 1 video (26:35 min). Available at: <https://www.youtube.com/watch?v=4m2O4-7MWac>. Accessed on: 15/11/2021

TSUKAMOTO, T. Hematopoietic Stem/Progenitor Cells and the Pathogenesis of HIV/AIDS. *Frontiers in Cellular and Infection Microbiology*, 10(), 60, 2020. Doi:10.3389/fcimb.2020.00060. Disponível em :<https://sci-hub.hkvisa.net/10.3389/fcimb.2020.00060>. Accessed on October 14, 2022.

UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2012. Available [unaids.org.br/wp-content/uploads/2019/08/RetrospectivaUNAIDS\\_2018\\_](https://www.unaids.org.br/wp-content/uploads/2019/08/RetrospectivaUNAIDS_2018_)

XU, L.; YANG, H.; GAO, Y.; CHEN, Z.; XIE, L., LIU, Y.; LIU, Y.; WANG, X.; LI, H.; LAI, W.; HE, Y.; YAO, A.; MA, L.; SHAO, Y.; ZHANG, B.; WANG, C.; CHEN, H.; DENG, H. CRISPR/Cas9-Mediated CCR5 Ablation in Human Hematopoietic Stem/Progenitor Cells Confers HIV-1 Resistance In Vivo. *Molecular Therapy*. v. 25, n. 8, p. 1782-1789, 2017. GAO, Z.; FAN, M.; DAS A. T.; HERRERA-CARRILLO, E.; BERKHOUT, B. Extinction of all infectious HIV in cell culture by the CRISPR-Cas12a system with only a single crRNA. *Nucleic Acids Research*. v. 48, n. 10, p. 5527- 5539, 2020

YUAN, Y. HIV-1 Tat protein inhibits the hematopoietic support function of human bone marrow mesenchymal stem cells. *Elsevier*, 273-197756, 2019. Doi:10.1016/j.virusres.2019.197756. Disponível em :<https://sci-hub.hkvisa.net/10.1016/j.virusres.2019.197756>. Accessed on: 20 Oct. 2022

Zhen A, Kitchen S. Stem-cell-based gene therapy for HIV infection. *Viruses* 2013 Dec 24;6(1):1-12.