IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# Stem Cell Therapy: A New Approach For HIV Treatment

Juili Santosh Bharankar, Dr. Shivani Kakkar Khanna

Department of Biotechnology, B. K. Birla College of Arts, Science and Commerce (Autonomous), Kalyan

**Abstract:**

Acquired Immunodeficiency Syndrome (AIDS) is caused due to the Human Immunodeficiency Virus (HIV). HIV infection is one of the world's most lethal infectious diseases. For more than 30 years, it has been a pandemic. Even though the antiretroviral therapy can control the HIV infection, it cannot cure it forever. Hence, the human stem cell-based therapy has emerged as an approach for the HIV treatment. Genetically modified Hematopoietic Stem Cells can be used for the HIV treatment. This topic is currently under research. The main purpose of this review is to study a new approach for treating HIV infection by the use of genetically modified stem cell-based therapy.

**Keywords:** Hematopoietic Stem Cells, CCR5Δ32 mutation, CCR5 gene, Stem Cell Transplantation.

## 1. Introduction:

Acquired Immunodeficiency Syndrome (AIDS) is a medical condition which is caused due to the Human Immunodeficiency Virus (HIV). HIV infection is a current threat and it can be simply termed as a curse on the human race [1]. HIV causes the continuous weakening of the immune system in humans. Progression of AIDS was foreseen by the generalized immune activation that is related to the HIV infection [2]. The HIV-1 pandemic is an intricate mixture of diversified epidemics in and between countries and regions of the world. Approximately about 38·6 (33·4–46·0) million people live with HIV-1 worldwide. About 25 million of people have died already. In 2005 alone, there have been approximately 4·1 million new HIV-1 infections and 2·8 million deaths due to AIDS [3]. Anti-Retroviral Therapy (ART) is general treatment given for HIV infection [4]. For almost more than a decade, Highly Active Anti-Retroviral Therapy (HAART) has drastically changed HIV related mortality and morbidity. It has also improved the quality of life of the HIV infected patients. HAART therapy includes incorporation of three or more anti-retroviral therapy medications [5]. The antiretroviral therapy (ART) is effective in controlling viral replication, but ART drugs can have some side effects [4].

A mark of HIV infection is its enormous genetic diversity and very fast evolution in and among the infected individuals. HIV diversity is because of the lack of proof-reading mechanism by its Reverse Transcriptase

Enzyme that transcribe its RNA genome into DNA before its incorporation into the host genome where it either remains latent or is expressed using the host cell machinery [7]. HIV diversity is also affected by an oversized population size and the high recombination rate [6]. HIV genetic diversity has given rise to big challenges for the prevention, control, and cure of the infection [7].

Stem Cell Therapy is considered as a possible cure for the HIV-1 infection [8]. Stem Cell Therapy is basically the use of Stem Cells to cure or prevent the disease [9]. Previously Stem Cell Therapy was used for the treatment of GvHD (graft vs host diseases), also was used for the treatment of other virus-related diseases like chronic hepatitis in Hepatitis B Virus (HBV), and acute lung injury (ALI) in influenza virus. Recent Studies have indicated that the Stem Cell Therapy may be an option for the treatment of Covid-19 patients [10]. Remarkable progress has been made recently to make use of Stem Cell Therapy based approaches to treat the HIV infection [11]. The Primary purpose for this review is to study a new approach for treating HIV infection by the use of the Stem Cell Therapy.

## 2. Review of Literature:

### 2.1. Human Immunodeficiency Virus (HIV) Infection:

The Human Immunodeficiency Virus (HIV) is the member of the genus Lentivirus and is the member of the family of Retroviridae and subfamily Orthoretrovirinae. Based on the genetic characteristics and variations in the viral antigens, the HIV virus is classified into two types – HIV-1 and HIV-2 [12]. The Human Immunodeficiency Virus (HIV) encodes in all for the three structural proteins, two enveloped proteins, six accessory proteins and three enzymes. The studies from the past ten years have contributed the high resolution and the three-dimensional structural data for all the viral enzymes, structural and envelope proteins and also for three of the accessory proteins [13]. HIV virus includes of an outer envelope containing the lipid bilayer with spikes of glycoproteins (gp), gp41 and gp120 which are encoded by the env gene. These glycoproteins (gp) are arranged in such a fashion that gp120 project from the surface of the HIV virus. The envelope is within membrane made up of nucleocapsid i.e., p17 which is matrix protein, that surrounds a central core of protein p24 which is capsid protein. It is encoded by the gag gene. Inside this core there are two copies of single stranded RNA. P7 and p9 proteins are bounded to the RNA and are said to be involved in the regulation of the gene expression. Various molecules of the enzymes such as reverse transcriptase, protease and integrase are present in the centre and are encoded by the pol gene. This enzyme is responsible for the conversion of the viral RNA into the pro-viral DNA [14].

HIV is transmitted by the sexual transmission followed by the exposure to cell-free or cell-associated infectious virus in semen or mucosal surfaces which is the most common route of HIV transmission worldwide. The other routes for the HIV transmission include the transmission through injection drug, blood transfusions, and from HIV infected mother to foetus [15]. HIV infection has been the pandemic for over 30 years. HIV infection epidemiology gradually changes with the time [16].

The pathogenic mechanism and virology of the HIV virus infection are being investigated constantly [17]. The pathogenic cycle of the HIV virus starts with the binding or attachment of the virus to the cell membrane proteins of the host and it ends with the release of the viral proteins from the host cell [18]. The HIV replication cycle can be summarized in seven steps they are: 1) Binding / Attachment, 2) Fusion, 3) Reverse Transcription,

4) Integration, 5) Replication, 6) Assembly, 7) Budding [17]. HIV-1 Env is the type I membrane protein present in the viral membrane [19]. To carry the viral load into the cell, HIV Env which is consisted of gp120 and gp41 subunits, initially attaches to the host cell, binding CD4 cells. This leads to the confirmational changes Env. This allows the co-receptor binding, that is mediated partly by the V3 loop of the Env. This leads to the initiation of membrane fusion procedure as the fusion peptide of gp41 gets inserted into the target membrane, which is followed by six-helix bundle formation and total membrane fusion [20]. Following the interactions of the receptor and co-receptor and following the fusion between viral and cellular membranes, the viral core enters into the cytoplasm of the cell. Once it gets inside the cell, the viral associated Reverse Transcriptase enzyme conducts the synthesis of a linear double-stranded DNA copy of the single-stranded viral genome. This complex process is known as reverse transcription [21]. Next step in HIV replication cycle is integration. HIV integration into the host genome is an essential step in the HIV life cycle. Linear retroviral cDNA is the substrate for Integrase mediated DNA recombination. Integration is progressed in three steps: 1) 3' processing, 2) DNA strand transfer and 3) Gap repair. 3' Processing and DNA strand transfer are definite endonucleolytic reactions catalysed by the Integrase. On the contrary, gap repair is likely catalysed by host cell enzymes [22]. The genes of the integrated HIV virus are only expressed in the cells in which the cellular transcription factors were induced. The expression of the HIV genes is controlled by the complex regulatory systems that includes cis-acting viral components and both the viral and cellular proteins [21]. The viral genetic material integration into the genetic material of the host cell makes eradication of the virus without any injury or damage to the host cell. Hence the virus seizes the host cells replication system. Hence when the cellular DNA is transcribed, the viral DNA form an RNA transcript. Further the conversion of this RNA into messenger RNA (mRNA) and genomic viral RNA occurs. Further this viral mRNA is translated into the viral proteins. These viral proteins along with the genomic RNA are congregated into the new viral particles. This is the last stage in HIV cycle which requires the viral enzyme, protease. Eventually, the new viral particles are liberated or released from the infected cell and proceed to infect the other healthy cells in the host body [23].

HIV infection begins without showing any signs, symptoms or any indications of ill feeling. It is joined by the slight changes in the immune system. This stage ranges up to the period of three months after the infection is caused until seroconversion where HIV-specific antibodies can be identified in the people following the recent exposure to the HIV virus. The result of the infection and the time span for the disease development with the clinical symptoms may differ significantly within the individuals, but it often progresses slowly. It requires some years to develop the symptoms of the advanced HIV diseases and immunosuppression from the primary infection [24].

### 2.2. The Stem Cell Therapy:

The Stem Cell Transplant (SCT) have become an accepted treatment for the leukaemia and lymphomas and also in some of the non-malignant diseases like aplastic anaemia or thalassemia. There are two significant concepts which are eminent in Stem Cell Therapy they are: the autologous SCT and the allogeneic SCT. In the autologous SCT settings, patients generally donate their own stem cells, to get reinfused after the high dose of chemotherapy to treat their cancer disease. While for allogenic SCT, an identical or matching donor is required.

The matching is done on the basis of the human leukocyte antigen (HLA) system and 5 gene loci (A, B, C, DRB, DRQ) with 2 allelic variants each [29].

The stem cells have the capacity to construct each tissue in the human body, thus have great capability in future therapeutic uses in regeneration and repair of tissues. To call them the "stem cell", they must exhibit the two significant features. First is that, the stem cell must show the unlimited cell division or self-regeneration to produce the progeny which is precisely equivalent to the original cell. Second is that, the stem cell must be efficient enough to give rise to a specialized cell type that can becomes part of the healthy animal species [25]. The Stem cells can be classified into five classes they are: 1) Totipotent Stem Cells which includes Embryonic Stem cells such as zygotes, they can differentiate into any cell types. 2) Pluripotent Stem Cells which again includes Embryonic Stem cells and induced pluripotent stem cells (iPSCs), they can differentiate into the cells from any of the three germ layers. 3) Multipotent Stem Cells which includes Adult Stem Cells such as mesenchymal and hematopoietic stem cells, they can differentiate into a limited range of cell types. 4) Oligopotent Stem Cells which include Adult Stem Cells such as lymphoid and myeloid stem cells, they can also differentiate into a limited number of cell types. 5) Unipotent Stem Cells which includes Adult Stem Cells such as satellite and epidermal stem cells, these types of cells can differentiate into single cell types [26].

Stem Cell Therapy are characterized as any treatment for a disease or a medical condition that essentially includes the utilization of any type of live human stem cells including the embryonic stem cells, adult stem cells and iPSCs. The Stem cells provide the best solution when there is a requirement for tissue and organ transplantation through their capacity to differentiate into the particular cell types that are essential for repairing the diseased tissues [27].

The Stem Cells are being investigated for types of chronic weakening diseases, that have till now got away with remedial measures or treatments from conventional allopathic methodologies, with an expectation that cell therapy would repair, multiply, replace and reconnect the tissues and organs. This revives the expectations and hope and ignite the confidence in such therapies [28]. Various animal studies and clinical trials shows that the stem cell therapy can be used for the treatment for Parkinson's disease, spinal cord injury, heart failure, cancer, arthritis, haematological disease, diabetes, peripheral vascular disease, acute and steroid refractory graft versus host disease, Crohn's disease, in dental issues etc. [28]. The Stem Cell Therapy is also used in the treatment of virus-related diseases like chronic hepatitis in Hepatitis B Virus (HBV), and acute lung injury (ALI) in influenza virus. Recent Studies have indicated that the Stem Cell Therapy may be an option for the treatment of Covid-19 patients [10]. Stem Cell Therapy is also considered as a possible cure for the HIV infection [8].

### 2.3. The Stem Cell Therapy for HIV infection Treatment:

Immune system destruction by the HIV is due to the loss of CD4+ T cells within the peripheral blood and lymphoid tissues. The entry of the virus into the CD4+ cells is interceded by the interaction with a cellular chemokine receptor, of which, CCR5 and CXCR4 are the most common. Since the ensuing viral replication needs cellular gene expression processes, activated CD4+ cells are the essential targets of effective HIV infection. Thus, the HIV infection mostly leads to the decrease in activated memory CD4+ T cells, the greater part of which live in the gastrointestinal (GI) mucosa. Even though the therapeutic control of HIV replication

enables the immune system to restore partly and slow down the development of the disease, the cure for the HIV infection still remains unattainable in spite of the use of the presently available antiretroviral drugs [30].

The utilization of Hematopoietic Stem Cells (HSCs) depicts a possible powerful therapeutic approach that has the capacity to reinstate entire functional immunity to the affected individual. An effective stem cell-based antiretroviral therapeutic approach would need to fulfil two significant demands. One is that the approach would need to permit the reconstitution of immune responses that would conquer the hurdles which are important to clear the viral infection (virus) from the body. Second is that the lately developed would themselves must be secured from direct infection caused due to HIV virus. This subsequently prevents them from turning into another repository of infected cells [11].

There are people who are more than once exposed to HIV infection yet remained sero-negative. They are likewise called to be as exceptionally exposed sero-negative people [32]. A huge number of populations in the world wide are highly sensitive towards the HIV-1 infections. Currently there are approximately 38 million infected people in all the continents. Among the overall global population which is sensitive towards HIV-1 infection, there are a small number of HIV-1 infected individuals which were noticed that in spite of the high-risk sexual exposure to HIV-1, they showed the resistance towards the infection [31]. Various studies by the scientists have found that there is a homozygous defect in a HIV-1 co-receptor, that results in the resistance to HIV-1 infection in the exposed individuals. Researchers studied the arrangement of the CCR5Δ32 mutation in the CCR5 gene that is situated in p21.3 sequence of Chromosome 3 in the Caucasian population in the Northern Europe. It was concluded that the people homozygous for a mutant CCR5 allele that carries a 32 bp deletion are extremely resistant towards the HIV infections. Out of the Europe the CCR5Δ32 mutation is seen at exceptionally low frequencies in the people from the Asia, India, Saudi Arabia, and Pakistan and is missing from Oceania, Sub-Saharan Africa, and the Americas. It was put forward that the resistance towards HIV-1 infection was originated from a single mutation that occurred two or three thousand years prior, in the human population of the Northern Europe [31].

The first patient in the world to get cured of HIV infection, by using the Stem Cell Therapy was referred as the "Berlin Patient". This patient went through the two rounds of complete body irradiation and the allogenic haematopoietic stem cell transplantation from the donor cells that didn't express the CCR5 i.e., CCR5Δ 32/Δ32 gene. This patient underwent the stem cell therapy originally for the treatment of the acute myeloid leukaemia [33]. The Berlin patient was detected HIV positive in 1995. Then he was diagnosed with the acute myeloid leukaemia. The patient received the first stem cell transplant in 2007 from the donor who had a mutation called CCR5Δ32 on the CD4 cells. Patient stopped taking HIV medication after SCT. After 3 months the HIV was no longer found in the blood. The patient then again was diagnosed with leukaemia and underwent the second stem cell transplant from the same donor in 2008. "Berlin Patient" was the first patient in the world to get cured from HIV infection [34].

The second patient to get cured of HIV infection is referred as the "London Patient". "London Patient" also received the allogenic Stem Cell Transplant with CCR5Δ32/Δ32 donor cells for Hodgkin's Lymphoma. The London patient has been not on the ART therapy for at least 30 months, and keeps on having no detectable plasma HIV RNA. Even though the London case is comparatively similar in various perspectives to the Berlin

patient's case. The difference was that the Berlin patient received a completely myeloablative SCT, including complete body irradiation and required a second SCT following tumour repeat. It was an interesting fact that the Berlin patient was already heterozygous for the CCR5Δ32 mutation. While the London patient received a less intensive transplant conditioning regimen and didn't have a previous CCR5Δ32 heterozygous mutation [35].

## 3. Methods of Stem Cell Transplantation for HIV Treatment:

The long-term control of the HIV infection can be made possible by the CCR5Δ 32 Stem Cell Transplantation [38]. There can be two ways by which stem cell therapy can be used for the treatment of HIV infection one is the direct stem cell transplantation from the donor cells that do not express the CCR5 i.e., CCR5Δ 32 gene [33], and another way can be disrupting the CCR5 by genetically modifying the stem cells and transplanting them into the HIV positive patient [37].

The direct allogenic haematopoietic Stem Cell Transplantation from the donor cells that do not express CCR5 gene was done in two patients one is "Berlin Patient" and another one is "London Patient" [33]. CCR5 is a G Protein coupled chemokine receptor that likewise functions as an important co-receptor during the entry of the HIV virus [36]. CCR5 is a protein that is located on the surface of the CD4 cells, that acts as the entrance for the HIV virus to invade into the cell. If this entrance is removed then the CD4 cells won't be infected and the individual will not get the HIV infection [34]. There are certain healthy individuals who have mutation in the CCR5 gene that stops the expression of a functional protein. This CCR5Δ32 mutation is available only in 5% - 14% of people of European population and very rare in African and Asian population [36]. Hence disrupting the CCR5 by genetically modifying the stem cells can be used for the HIV cure [37].

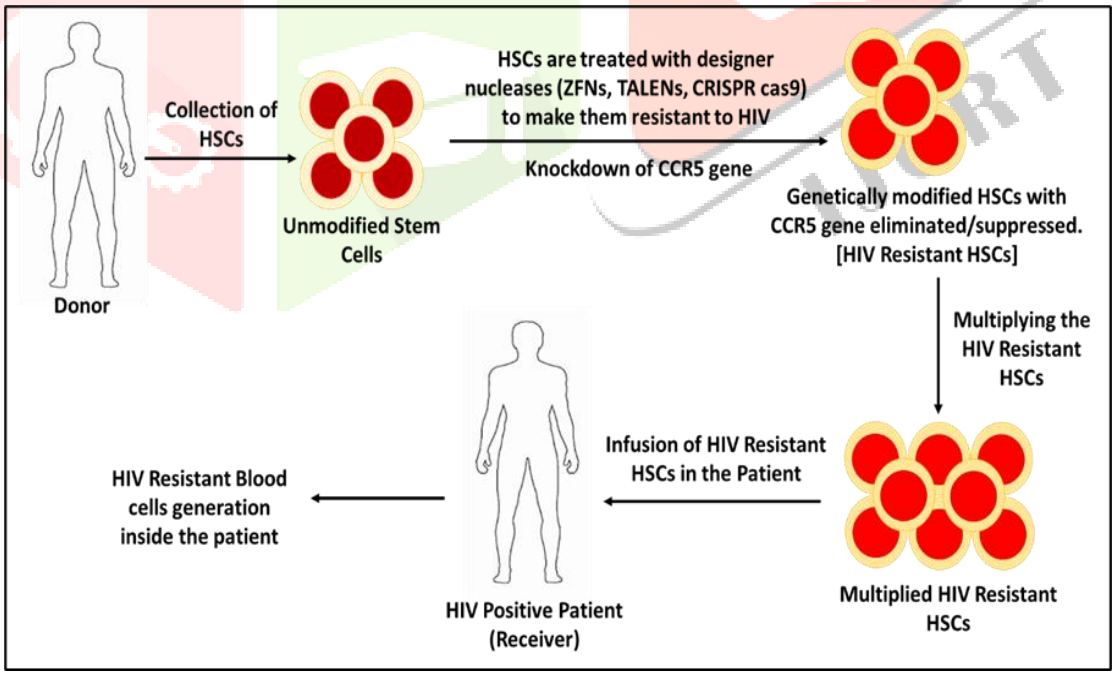


**Fig 1:** Stem Cell Transplantation by Genetically Modifying the Stem Cells for HIV Resistance

The current advances in gene editing includes transcription activator–like effectors nucleases (TALENs), engineered clustered regularly interspaced palindromic repeats (CRISPR) coupled to a CRISPR-associated (Cas) nuclease and Zinc finger nuclease [37]. Rather than allogeneic transplantation, the current approaches in the field of gene therapy have introduced a technique for producing a functional knock-out of CCR5 expression from a patient's own cells i.e., autologous transplantation. By precisely modifying a hematopoietic stem and

progenitor (HSPC) cells population to copy a CCR5Δ32 phenotype, it would be feasible not only to utilize a patient's own cells, but also to pick any HLA-matched individual in the allogeneic transplantation setting [39]. The disruption of the CCR5 co-receptor gene can be done by designer nucleases mentioned above. This technique has significant advantage over conventional knockdown utilizing RNA interference since it allows the generation of HIV-resistant cells in a single treatment [40].

## 4. Discussions:

Acquired Immunodeficiency Syndrome (AIDS) is a medical condition which is caused due to the Human Immunodeficiency Virus (HIV). HIV infection is a current threat and it can be simply termed as a curse on the human race [1]. The pathogenic cycle of the HIV virus starts with the binding or attachment of the virus to the cell membrane proteins of the host and it ends with the release of the viral proteins from the host cell [18]. CD4 cells has CCR5 protein located on its surface, this acts as the entrance for the HIV virus into the cell [34]. Since the HIV/AIDS has been identified, there has been the dire need for developing the new therapeutic methods for the treatment of the HIV infection. Since the current antiretroviral treatments (ART) are not being able to cure the disease, human stem cell-based therapy has emerged as an approach for the HIV treatment [41]. Until now there have been two cases which have been cured from HIV infection by using the Stem Cell Transplant. The first patient in the world to get cured of HIV infection, by using the Stem Cell Therapy was referred as the "Berlin Patient" and the second patient to get cured of HIV infection is referred as the "London Patient". In the case of "Berlin Patient", he went through the two allogenic haematopoietic stem cell transplantation, from the donor cells that have homozygous mutation in the HIV co-receptor CCR5 i.e., CCR5Δ32/Δ32. This therapy was actually done for treating the acute myeloid leukaemia of the patient. Similarly, in the "London Patient" who was infected with HIV-1 also went through the allogenic haematopoietic stem cell transplantation to treat Hodgkin's lymphoma by using the cells from a CCR5Δ35/Δ32 donor [42]. "London Patient" case is comparatively similar to Berlin Patient's case. The difference was that the Berlin patient received fully myeloablative stem cell transplant including the total body irradiation, and received the second stem cell transplant when the tumour returned. While the London Patient received the less intensive stem cell transplant [35]. But in both the cases the patients were lucky enough to found the appropriate matches. Hence the Genetically modified hematopoietic stem cells can also be used for the HIV treatment.

CCR5 gene is located on the surface of the CD4 cells. This gene acts as a gateway for HIV virus to enter into the cell. If this gene is suppressed or eliminated then person will not get infected by HIV [34]. Haematopoietic Stem Cells can be genetically modified in such a way that the CCR5 receptor on the CD4 cells will suppressed or eliminated. The research is still going on for this topic. There is need to understand if this CCR5 receptor could be knock out in HIV patients, and this may be possible by the gene therapy.

## 5. Conclusion:

Acquired Immunodeficiency Syndrome (AIDS) is a medical condition which is caused due to the Human Immunodeficiency Virus (HIV). HIV infection is one of the world's deadliest infectious diseases and also a curse on the human race. Antiretroviral drugs are generally given for the treatment of HIV. It is called Antiretroviral Therapy (ART). Antiretroviral Therapy can control the HIV infection and also the transmission. Since HIV infection is persistent, the antiretroviral therapy had to be continued for the entire life in HIV

patients. Even though the antiretroviral therapy can control the HIV infection, it cannot cure it forever. Hence, the human stem cell-based therapy has emerged as an approach for the HIV treatment. The allogenic haematopoietic Stem Cell Transplantation from the donor cells that do not express CCR5 gene was done in two patients. Genetically modified Haematopoietic Stem Cells for the treatment of HIV has become a topic of research interest. Since it is not possible that every HIV positive patient will get a matching stem cell from the donor cells that do not express the CCR5 gene. Hence the haematopoietic stem cells can be genetically modified in such a way that they will not expresses the CCR5 gene or this gene will get eliminated or suppressed. So that these genetically modified stem cells can be used as a treatment for the HIV infection. But this topic of using genetically modified haematopoietic stem cells for HIV cure is still under the research.

## 6. Future Prospectus:

It is evident that the Hematopoietic Stem Cell Transplant can contribute in treatment of HIV infection. The hematopoietic stem cell transplant from the donor cell that do not express CCR5 gene have successfully treated the two patients and this treatment approach can be further used in the treatment of HIV infections. Besides this method, genetically modified hematopoietic stem cells, that are modified in such a way, so that the CCR5 gene is eliminated, can also be used for the HIV cure. Hence the CCR5-guided methodologies can lead to long-term remission of HIV. If the more research is done in this area, then the Genetically Modified Hematopoietic Stem Cell Therapy or Stem Cell Transplantation can be used in future as the better approach for the HIV treatment.

## 7. References:


1. Bhatti A.B., Usman M., Kandi V., (2016), Current Scenario of HIV/AIDS, Treatment options, and Major Challenges with compliance to Antiretroviral Therapy. J. Currens. 8(3): e515.
2. Lingan K., (2018), A Review on Various Aspects of HIV Infection. J. HIV Curr. Res. 3: 128.
3. Simon V., Ho D.D., Karim Q.A., (2006), HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. J. Lancet. 368(9534): 489-504.
4. Pace M., Frater J., (2014), A Cure for HIV: Is it in sight? J. Expert. Rev. ant. Infect. Ther. 12(7): 783-91.
5. Mayer K.H., Venkatesh K.K., (2010), Antiretroviral Therapy as HIV Prevention: Status and Prospects. Am. J. Public Health. 100(10): 1867-1876.
6. Zyl G.V., Bale M.J., Kearney M.F., (2018), HIV evolution and diversity in ART treated patients. J. Retrovirology. 15(1): 14.
7. Simonetti F.R., Kearney M.F., (2015), Review: Influence of ART on HIV genetics. J. Curr. Opin. HIV AIDS. 10 (1): 49-54.
8. Taylor B.S., Tien H.V., Jones J., Wilkin T.J., (2019), CROI 2019: Advances in Antiretroviral Therapy J. top. Antivir. Med. 27(1): 50-68.
9. Volarevic V., Markovic B.S., Gazdic M., Volarevic A., Jovicic N., Arsenijevic N., armstrong L., Djonov V., Lako M., Stojkovic M., (2018), Ethical and Safety Issues of Stem Cell Based Therapy. Int. J. Med. Sci. 15(1): 36-45.
10. Choudhery M.S., Harris D.T., (2020), Stem Cell Therapy for Covid-19: Possibilities and Challenges. J. Cell Biol. Int. 44(11): 2182-2191.

11. Kitchen S.G., Zack J.A., (2011), Stem Cell Based Approaches to Treating HIV Infection. J. Curr. Opin. HIV AIDS. 6(1): 68-73.
12. Seitz R., (2016), Human Immunodeficiency Virus (HIV). J. Transfus. Med. Hemother. 43(3): 203-222.
13. Turner B.G., Summer M.F., (1999), Structural Biology of HIV. J. Mol. Biol. 285(1): 1-32.
14. Verma P., Shanmugam G., Bansode S., (2018), Challenges to Cure: Transmission, Virulence and Pathogenesis of HIV infection. Int. J. Life. Sci. Scienti. Res. 4(1): 1614-1619.
15. Moir S., Chun T.W., Fanci A.S., (2011), Pathogenic Mechanism of HIV Disease. J. Annu. Rev. Pathol. 6(1): 223-248.
16. Lucas S., Nelson A.M., (2015), HIV and the Spectrum of Human Disease. J. Pathol. 235: 229-241.
17. Belasio E.F., Raimondo M., Suigoi B., Butto S., (2010), HIV Virology and Pathogenetic mechanism of infection: A brief overview. J. Ann. Ist. Super Sanita. 46(1): 5-14.
18. Kurapati K.R.V., Samikkannu T., Atluri V.S.R., Nair M.P.N., (2015), Cell Cycle Checkpoints and Pathogenesis of HIV-1 infection: A brief overview. J. Basic. Clin. Physiol. Pharmacol. 26(1): 1-11.
19. Chen B., (2019), Molecular Mechanism of HIV-1 Entry. J. Trends. Microbiol. 27(10): 878-891.
20. Wilen C.B., Tilton J.C., Doms R.W., (2012), HIV: Cell Binding and Entry. J. Cold Spring. Harb. Perspect. Med. 2(8): a006866.
21. Fergusson M.R., Rojo D.R., Lindern J.J., O'Brien W.A., (2002), HIV-1 replication cycle. J. Clin. Lab. Med. 22(3): 611-635.
22. Turlure F., Devroe E., Silver P.A., Engelman A., (2004), Human Cell Proteins and Human Immunodeficiency Virus DNA Integration. J. Front. Biosci. 9: 3187-3208.
23. Huges J.R. HIV: Structure, Life Cycle, and Pathogenicity. Chancellor's Honors Program Project. (2002).
24. Naif H.M., (2013), Pathogenesis of HIV Infection. J. Infect. Dis. Rep. 5(1): e6.
25. Biehl J.K., Russell B., (2009), Introduction to Stem Cell Therapy. J. Cardiovasc. Nurs. 24(2): 98-105.
26. Falzarano M.S., Ferlini A., (2019), Urinary Stem Cells as Tools to Study Genetic Disease: Overview of the literature. J. Clin. Med. 8(5): 627.
27. Aly R.M., (2020), Current State of Stem cell-based: An overview. J. Stem Cell. Investig. 7:8.
28. Nadig R.R., (2009), Stem Cell Therapy – Hype or Hope? A review. J. Conserv. Dent. 12(4): 131-138.
29. Hűtter G., (2016), Stem Cell Transplantation in Strategies for curing HIV/AIDS. J. AIDS. Res. Ther. 13(1): 31.
30. Allers K., Hűtter G., Hofmann J., Loddenkemper C., Rieger K., Thiel E., Schneider T., (2011), Evidence for the cure of HIV infection by CCR5Δ32/Δ32 Stem Cell Transplantation. J. Blood. 117(10): 2791-9.
31. Becker Y., (2005), The Molecular mechanism of human resistance to HIV-1 infection in persistently infected individuals – a review, hypothesis and implications. J. Virus. Genes. 31(1): 113-9.
32. Jabri A.A., (2007), Mechanism of Host Resistance Against HIV infection and Progression to AIDS. Sultan Qaboos Univ. Med. J. 7(2): 82-96.
33. Gupta R.K., Peppa D., Hill A.L., Galnez C., Salgado M., Pace M., EMc.Coy L., Griffith S.A., Thornhill J., Alrubayyi A., Huyveneers L.E.P., Nastouli E., Grant P., Edwards S.G>, innes A.J., Frater J., Nijhuis M., Wensing A.M.J. Martinez-Picado J., Olavarria E., (2020), Evidence for HIV-1 cure after CCR5Δ32/Δ32

allogenic haemopoietic Stem cell transplantation 30 months post analytical treatment interruption: a case report. J. Lancet. HIV. 7(5): 340-347.

34. Brown T.R., (2015), I am the Berlin Patient: A personal reflection. J. AIDS. Res. Hum. Retroviruses. 31(1): 2-3.
35. Prator C.A., Donatelli J., Henrich T.J., (2020), From Berlin to London: HIV-1 Reservoir Reduction Following Stem Cell Transplantation. J. Curr. HIV/AIDS. Rep. 17(4): 385-393.
36. Kiem H.P., Jerome K.R., Deeks S.G., McCune J.M., (2013), Hematopoietic Stem cell-based gene therapy for HIV disease. J. cell stem cell. 10(2): 137-147.
37. Kuritzkes D.R., (2016), Hematopoietic Stem Cell Transplantation for HIV cure. J. Clin. Investig. 126(2): 432-437.
38. Gupta P.K., Saxena A., (2021), HIV/AIDS: Current Updates on the Disease, Treatment and Prevention. J. Proc. Natl. Acad. Sci. India. Sect. B. Biol. Sci. 23: 1-16.
39. Haworth K.G., Peterson C.W., Kiem H.P., (2017), CCR5 – edited gene therapies for HIV cure: Closing the door to viral entry. J. Cytotherapy. 19(11): 1325-1338.
40. Cornu T.I., Mussolino C., Bloom K., Cathomen t., (2015), Editing CCR5: a novel approach to HIV gene therapy. J. Adv. Exp. Med. Biol. 848: 117-30.
41. Armijo E., Soto C., Davis B.R., (2014), HIV/AIDS: Modified Stem Cells in the spotlight. J. Cell. Mol. Life. Sci. 71(14): 2641-9.
42. Gupta R.K., Jawad S.A., McCoy L.E., Mok H.P., Peppa D., Salgado M., Picado J.M., Nijhuis M., Wensing A.M.J., Lec H., Grant P., Nastouli E., Lambert J., Pace M., Salasc F., Monit C., Lever A.M.L., Edwards S.G., Gabriel I.H., Olavarria E., (2019), HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. J. Nature. 568(7751): 244-248.