HIV and AIDS

Could stem cell transplants provide a cure?

Human immunodeficiency virus causes acquired immunodeficiency syndrome (AIDS) — a major human health problem. This *Interface* outlines how the virus infects white blood cells and examines whether recent research on stem cell transplants might provide hope of a cure

Key words

Stem cell
Disease
White blood cell
Retrovirus

HIV infection/AIDS is a disease of the immune system that is transmitted predominantly through sexual intercourse. In 2010, it affected more than 34 million people worldwide and is considered to be a major health problem in many parts of the world, especially sub-Saharan Africa and south Asia. There is currently no cure for the disease, which resulted in almost 2 million deaths in 2010 (see Figure 1).

In developed countries the disease is controlled using antiviral therapy, which usually inhibits key enzymes important for viral replication. A variety of drugs that target different stages in the virus life cycle must be taken in combination for the therapy to be effective. Antiviral therapy in developing countries is less widespread owing to its high cost and the complexity of the treatment regimes.

What is HIV?

Human immunodeficiency virus (HIV) is a retrovirus. This class of virus contains RNA as its genetic material. When a retrovirus infects a cell, the RNA is transcribed to DNA by the enzyme reverse transcriptase. This viral DNA is then incorporated into the **genome** of the host cell (see Figure 2). Once incorporated, viral genes are converted to messenger RNA (mRNA) by transcription. The mRNA then travels to the ribosomes of the host cell where the process of translation results in the formation of new viral proteins. The

Terms explained

Co-receptor A cell surface protein that forms an additional bond with a signalling molecule already attached to a primary receptor.

Genome The complete set of genetic material of an organism.

Glycoprotein A protein containing covalently attached carbohydrate.

Homozygous Bearing two copies of the same allele at a particular gene locus.

Pathogen A microorganism that causes disease.

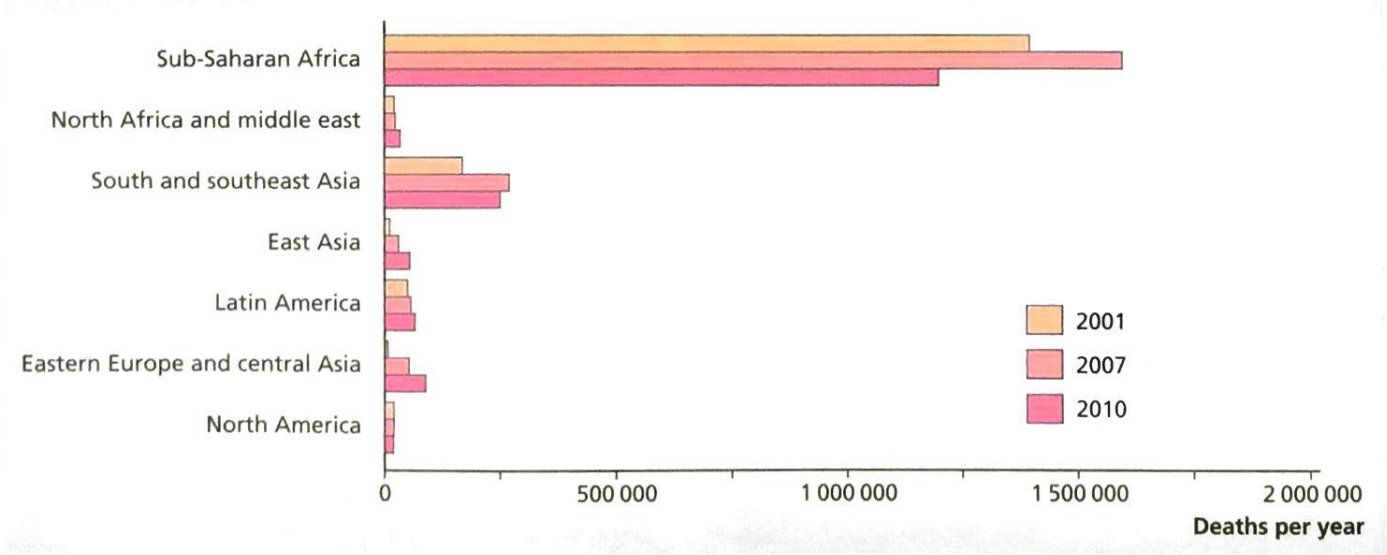


Figure 1 Worldwide deaths per year due to AIDS

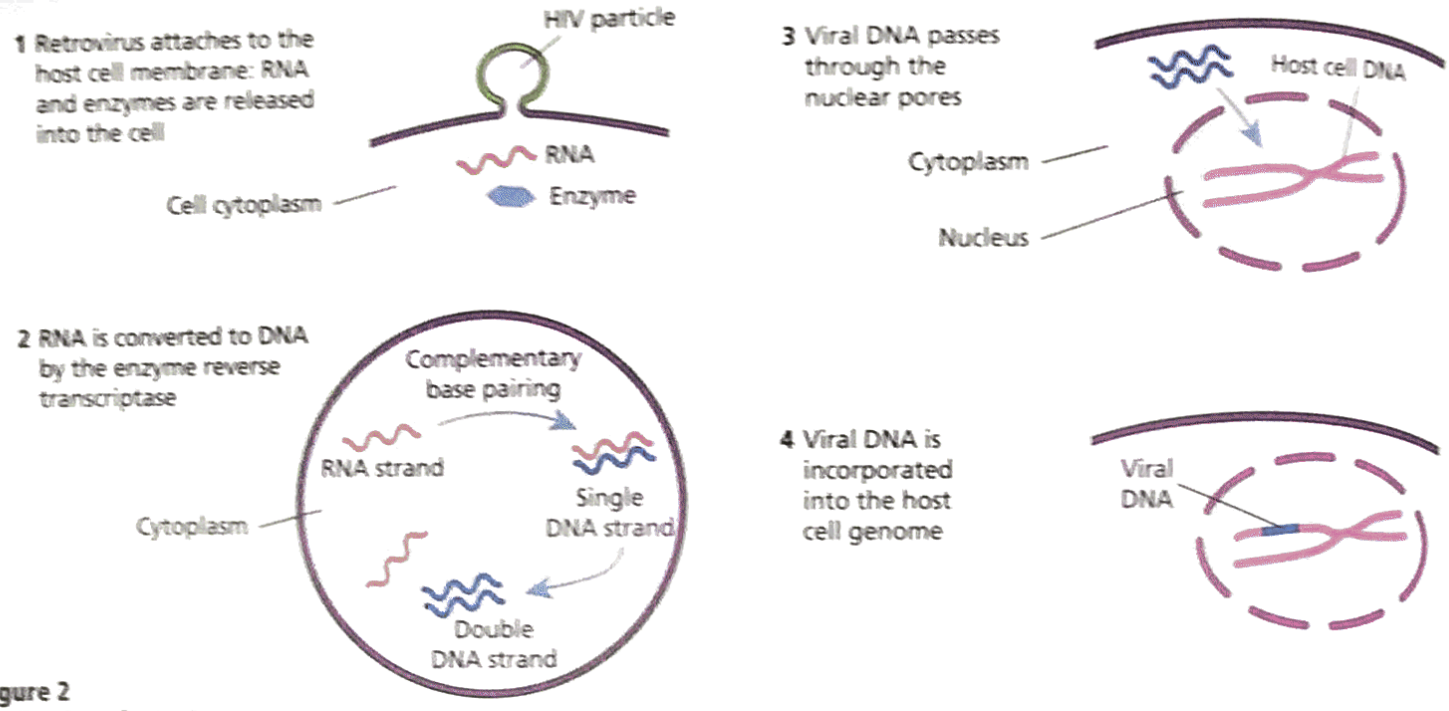


Figure 2
Replication of HIV virus

viral DNA is also replicated and passed on to daughter cells whenever the infected cell divides.

HIV particles are spherical and measure around 120 nm (see Figure 3). They are surrounded by a viral envelope. The envelope is a complex structure consisting of a phospholipid bilayer taken from the host cell membrane. The envelope is formed when the phospholipid layer surrounds the virus particles as they are released from the host cell. The whole structure becomes detached from the host cell membrane in a process called budding. **Glycoproteins** embedded in the viral envelope enable the virus particles to bind with and infect new host cells.

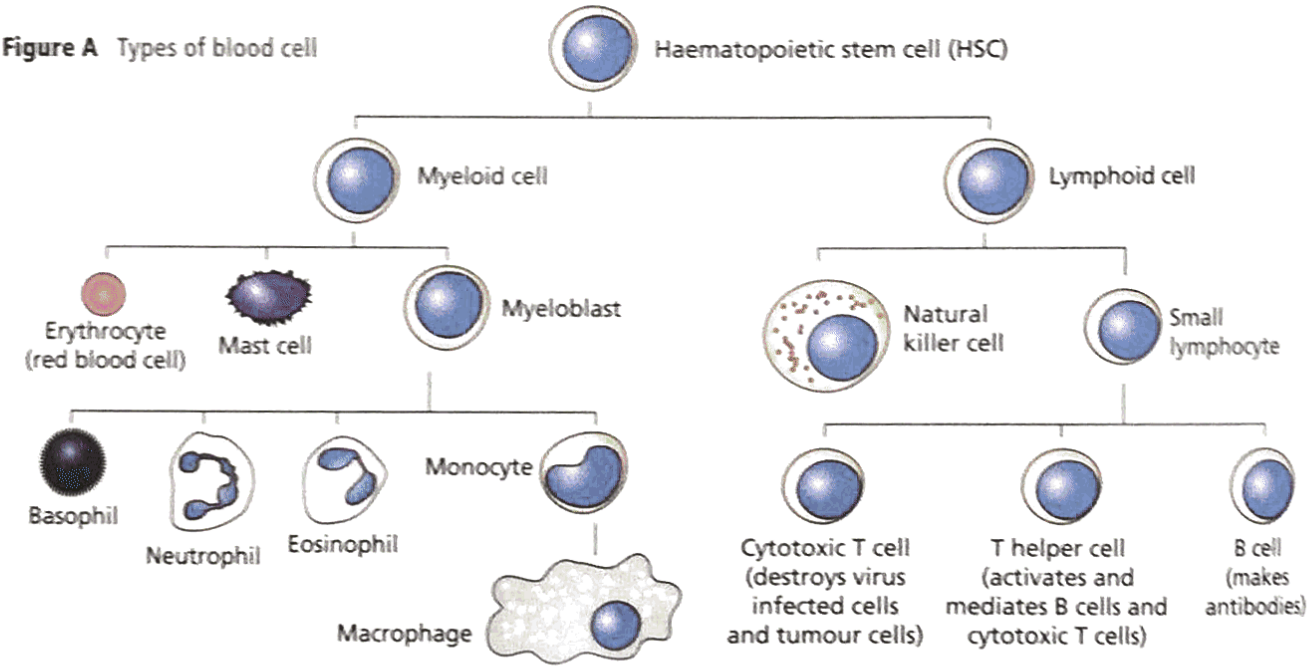
Box 1 Types of blood cell

All the components of the blood originate from haematopoietic stem cells (HSC). Two main cell lines arise from these stem cells:

- myeloid cells
- lymphoid cells

The myeloid cell line gives rise to basophils, eosinophils and neutrophils, named after their staining characteristics; and monocytes, which develop into macrophages (see Biological Sciences Review Vol. 25, No. 4, pp. 2–6). The lymphoid cell line produces lymphocytes, which include B cells, T helper cells (CD4+) and cytotoxic T cells (CD8+). B cells produce antibodies, whereas T cells are involved in activation of other lymphocytes. T cells also destroy cells that have become infected with viruses or are cancerous.

Figure A Types of blood cell



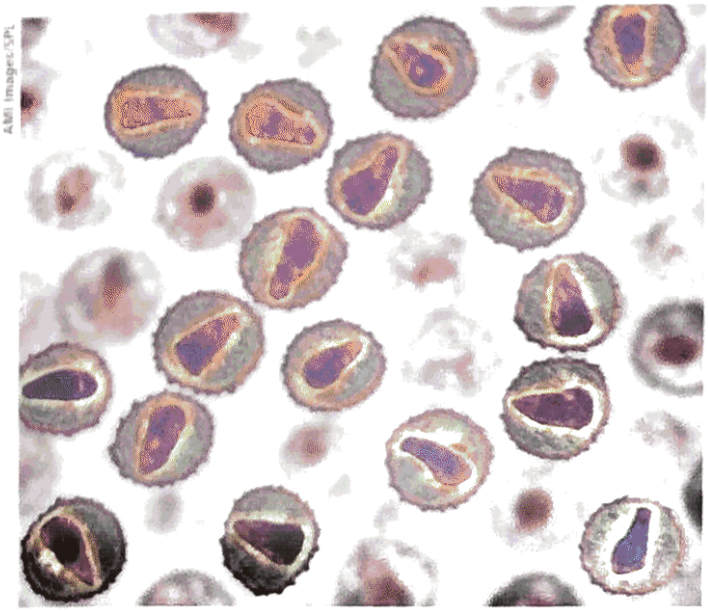


Figure 3 Coloured transmission electron micrograph of HIV particles. The central purple areas are RNA, which are surrounded by a protein coat (yellow) (×100)

How does HIV cause disease?

HIV targets a type of white blood cell known as a T helper cell or CD4+ T cell (see Box 1). T helper cells express a receptor on their cell surface membrane known as CD4. The CD4 receptor enables T helper cells to bind with other white blood cells and stimulate the biochemical pathways involved in a normal immune response. T helper cells play an important part in the immune response. Their functions include:

- activation of B cells resulting in antibody production
- regulation of CD8+ T cells (cytotoxic T cells) which attack virus-infected and tumour cells

Infection with HIV leads to a reduction in the number of working CD4+ T cells. If the number of these cells falls too low, the immune system of the patient will be unable to respond normally to other **pathogens**, and acquired immunodeficiency syndrome (AIDS) will develop. Death is usually due to the development of cancer, or infection with other pathogens that occurs as a result of the failure of the patient's immune system.

How does HIV infect white blood cells?

HIV virus particles bind to white blood cells by means of a viral envelope protein called gp120. This glycoprotein recognises the CD4 receptors on the surface of T helper cells. Binding of gp120 to the CD4 receptor fixes the virus particle in the correct position relative to the cell membrane. This enables it to interact with **co-receptors** such as CCR5, a protein with seven membrane-spanning sections (see Figure 4). Once the viral envelope interacts with both the CD4 receptor and the CCR5 co-receptor, it can fuse with the cell surface membrane of the host cell, and viral RNA is released into the host cell cytoplasm (see Figure 5).

Resistance to HIV infection

Some people are resistant to infection with HIV, despite being exposed to the virus through sexual contact. These

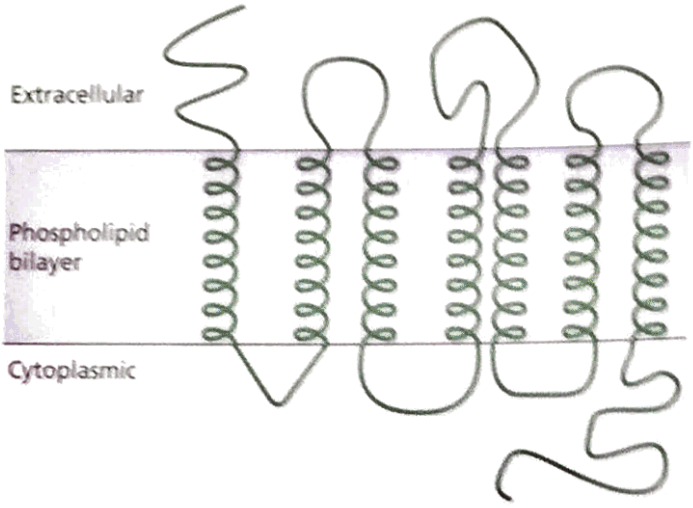


Figure 4 Structure of the CCR5 co-receptor

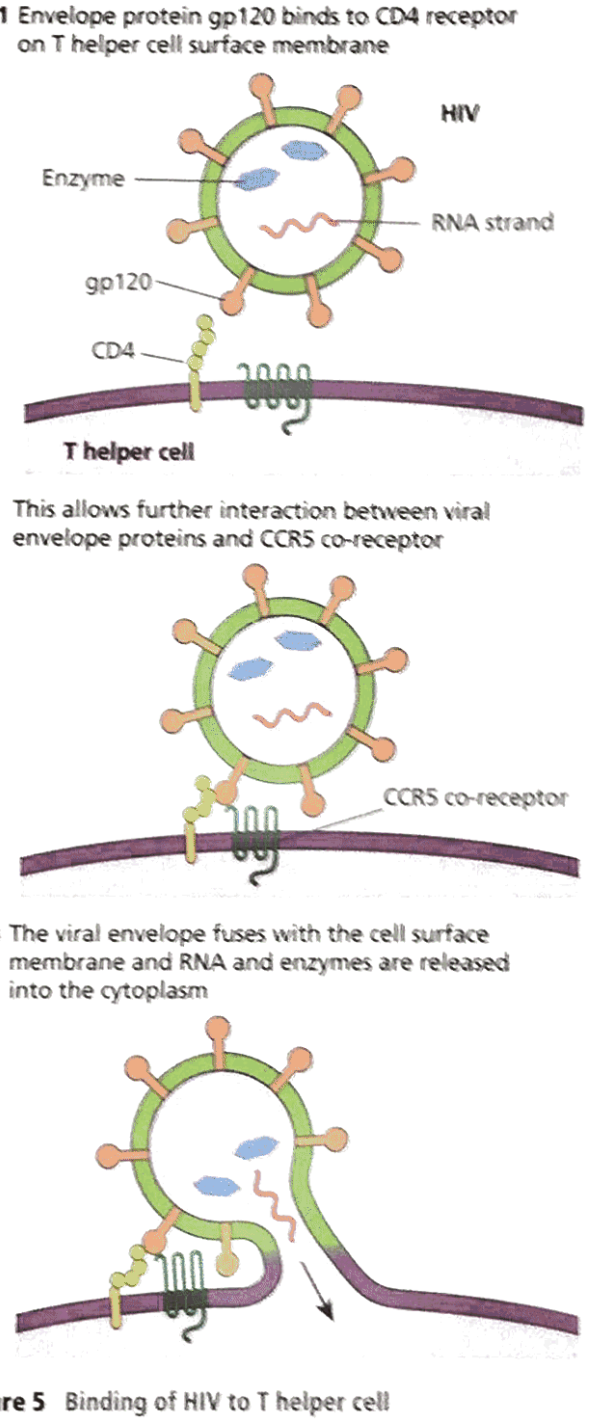


Figure 5 Binding of HIV to T helper cell

The father of these African children died of AIDS and the children are HIV positive. Might stem cell transplants hold hope for their future?

individuals have a mutation in the gene coding for the CCR5 co-receptor. About 1% of the Caucasian population is **homozygous** for this mutation. This mutation is given the name CCR5 delta32 allele and involves the deletion of 32 base pairs from the DNA sequence. As a result, the mutant CCR5 co-receptor protein is missing the last three membrane-spanning sections, and so cannot function. This is why homozygous individuals who have two copies of the CCR5 delta32 allele cannot make functional CCR5 receptors. These individuals are resistant to HIV — they do not become infected, even when exposed to the virus on several occasions.

CCR5 delta32 and HIV/AIDS treatment

The discovery of a gene conferring resistance to HIV infection opens up the possibility of using various novel techniques to treat or prevent HIV infections. Gene therapy involves the introduction of a new gene to an individual. This procedure is most appropriate in treating conditions such as cystic fibrosis, in which a *healthy functional protein* is missing. It is easier to use gene therapy to introduce a missing protein than to eliminate a healthy allele. An effective treatment involving the CCR5 delta32 allele would require the *normal CCR5* genes to be absent from the treated cells. This would render them unable to make functional CCR5 co-receptors. This could only be achieved by transplanting stem cells homozygous for CCR5 delta32 into the affected individual.

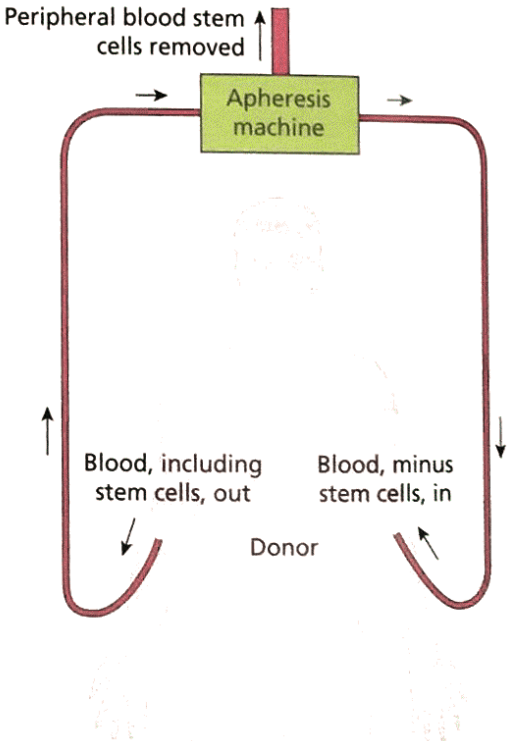


Figure 6 Apheresis. How white blood cells are removed from the donor's blood

What are stem cells?

Stem cells are undifferentiated cells that can give rise to several different types of differentiated cell. Due to these special abilities, stem cells have a great deal of potential in medical science (see Biological Sciences Review, Vol. 23,

No. 4, pp. 22–25). Stem cells can be harvested from a number of sources including the developing embryo, umbilical cord, and some adult tissues. Currently, the most clinically useful adult stem cells are haematopoietic stem cells (HSCs, see Box 1) which are found in the bone marrow. HSCs have been used successfully in transplants for several years, particularly in the treatment of cancers of the blood such as leukaemia.

How do stem cell transplants work?

HSC transplants usually involve a healthy donor with a tissue type that matches that of the patient. Stem cells can be extracted directly from the bone marrow in a surgical procedure, or can be obtained from the blood. The second method is now the most widely used. The donor is first treated with granulocyte-colony stimulating factor, which causes HSCs to move from bone marrow into the circulation. The stem cells are then collected by a process called apheresis (see Figure 6).

The recipient usually undergoes a course of treatment before receiving the transplant. The treatment destroys the diseased white blood cells, including HSCs, using chemotherapy or irradiation. Donor HSCs are then injected into the patient's blood. The transplanted stem cells migrate to the bone marrow and begin to replicate, eventually repopulating the blood with healthy white blood cells. Because the new cells originate from the transplanted HSCs, they contain genetic material from the donor rather than the patient's own DNA.

Stem cell transplants can be hazardous. During the process, the patient does not have a functioning immune system and so is at risk of serious illness or death from other infections. There is also a high incidence of graft-versus-host disease, in which the transplanted cells begin to attack the host's own body cells. Due to these risks, stem cell transplants are usually only considered in the treatment of life-threatening conditions such as leukaemia.

In theory, similar techniques could be used to treat patients infected with HIV. The donor would need to be homozygous for the CCR5 delta32 mutation. Following transplantation of donor cells into the HIV patient, the patient's T helper cells — which will now be derived from the transplanted stem cells — will not express functional CCR5 co-receptors and so will be resistant to infection by the HIV virus.

A cure for AIDS?

Highly active anti-retroviral therapy (HAART) has greatly improved survival of patients with HIV since its introduction in 1996, but it does not cure the disease. In 2000, a pioneering medical treatment took place on a patient who had been infected with HIV more than 10 years previously. The patient had been treated with HAART for several years and showed no signs of illnesses associated with AIDS.

Unrelated to his HIV status, the patient developed acute myeloid leukaemia (AML), which is a cancer of blood cells belonging to the myeloid line (see Box 1). Rapid production of abnormal white blood cells leads to their build-up in bone marrow, which prevents the development of normal white blood cells. Treatment for AML is usually either chemotherapy or stem cell transplantation. In this case, a stem cell transplant was deemed to be the appropriate treatment. The selected donor had a matching tissue type to minimise the chances of rejection.

The donor was also screened to ensure homozygosity for the CCR5 delta32 allele so that white blood cells produced from the grafted stem cells would not express the CCR5 co-receptor, thus rendering them resistant to infection with HIV. The leukaemia returned and a second transplant from the same donor was required 7 months later, but since then the patient has shown no further relapses. Despite the discontinuation of HAART treatment, there has also been no evidence of active replicating HIV in this patient. This finding suggests that the patient's new white blood cells remain resistant to infection by HIV, and the transplant has effectively provided a long-term cure for the condition.

Stem cell transplants and HIV

Although this case shows that stem cell transplants can be used successfully in the treatment of HIV, there are several reasons why this therapy is not widespread in its use. So far, the therapy has only been tried on one patient. This is because it is only ethical to perform stem cell transplants on patients with life-threatening conditions such as AML, and the number of HIV patients developing such conditions is extremely low. In addition, the chance of finding donors with tissue types matching the prospective patient and also demonstrating homozygosity for the CCR5 delta32 allele is low.

Until more studies show that stem cell transplants can prevent HIV disease progression, it is unlikely that a more widespread clinical trial will be authorised. Even then, it may still be considered too risky for HIV patients to be routinely offered stem cell transplants as a treatment option, particularly given the success of the current HAART regime. However, this case has reinforced the importance of the CCR5 co-receptor in disease progression of AIDS, and encourages further development of anti-retroviral treatments targeting this membrane protein.

Further reading

AVERT international HIV and AIDS charity:
www.avert.org/hiv-aids-science.htm
UK Stem Cell Foundation:
www.ukscf.org/research/index.html

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