HIV / AIDS

AIDS is caused by HIV which destroys important cells in the immune system. It was first described in 1979 and the virus was identified in 1983. Then, patients died because there was no treatment. Today there are many medicines. These allow people with AIDS to lead more normal lives. Extensive research is underway into even better medicines for the future.

What is AIDS?

AIDS is the acronym for Acquired Immunodeficiency Syndrome, a name given to a collection of symptoms arising from the infection with the human immunodeficiency virus (HIV), first identified in 1983. Infection with this retrovirus results in destruction of the patient's immune system - especially a group of blood cells called T lymphocytes (T cells).

As the number of T cells falls, the body becomes increasingly susceptible to infectious agents such as *Pneumocystis carinii*, almost unknown in a healthy person. Other opportunistic pathogens such as *Candida spec.*, *Mycobacterium tuberculosis*, *Cytomegalovirus* and *Herpes simplex* virus cause serious, often life-threatening infections. HIV / AIDS patients have an increased risk of developing tumours such as Kaposi's sarcoma and non-Hodgkin's lymphoma. Death usually results from overwhelming infection.

Who does HIV / AIDS affect?

Since it was first described in 1981, HIV / AIDS has reached epidemic proportions in parts of the developing world, especially sub-Saharan Africa and south-east Asia. The WHO estimates that 65 million people have been infected worldwide since 1980, over four million of them in 2005 alone. In early 2003, United Nations´ demographers projected that by 2050, the populations of the countries hit hardest will suffer a marked reduction in their birth rate. Currently, about twice as many men become infected as women, but this ratio has been declining for several years.

Present treatments

Some 20 chemically distinct anti-retroviral compounds are licensed for use. This is an enormous increase on the three compounds that were approved in 1995, indicating the strenuous and continuing efforts being made by the pharmaceutical industry to develop improved treatments. As the range of medicines for HIV / AIDS is much greater and the disease is more treatable than it was fifteen years ago, as a result, life expectancy after sero-conversion has increased from about two to three years in 1984 to over 10 years today.

According to their therapeutic action, the antiviral medicines can be classified into RTIs or reverse transcriptase inhibitors (the enzyme reverse transcriptase is central to the route by which HIV spreads to infect new cells), PIs or protease inhibitors (these help block key stages in the assembly of the virus structure), FIs or fusion inhibitors and further compounds that block the distinct steps of entry of the virus into T-cells, as opposed to preventing viral replication after infection. FIs act by binding to a glycoprotein (gp41) on the HIV particle's surface and prevents it binding to the T-cells that it would otherwise enter and infect. In this way, spread of the virus is inhibited.

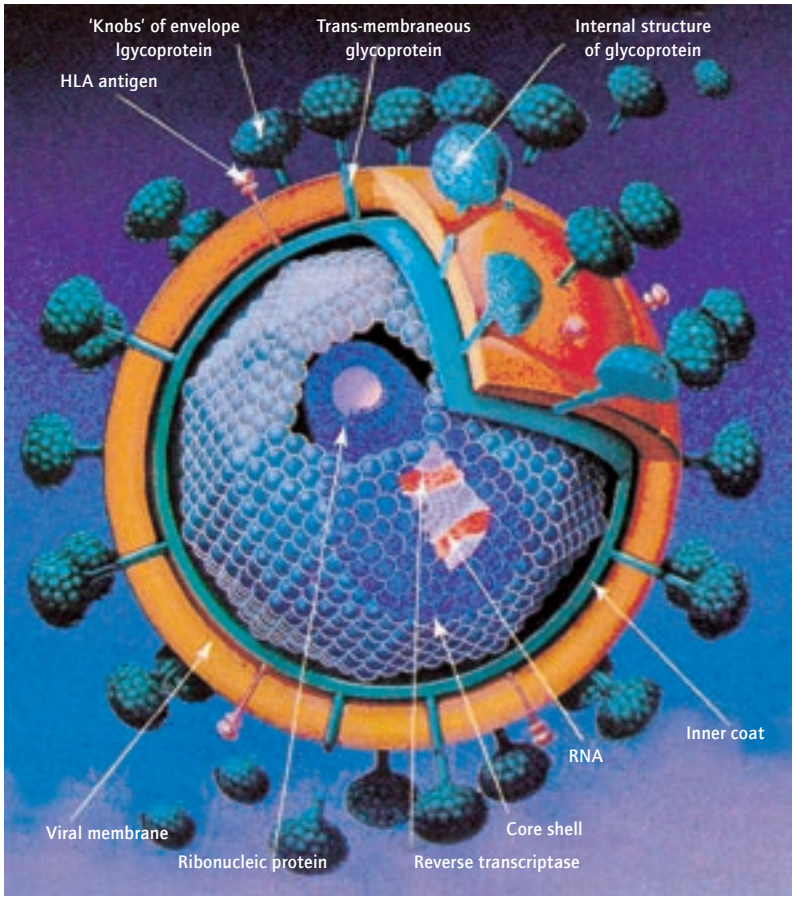

FIGURE 1: Structure of a Human Immunodeficiency Virus (HIV)

Although various RTIs have already been authorised for use, new antivirals of this type continue to be developed. Inhibiting the enzyme reverse transcriptase as effectively as possible (and with the fewest possible side-effects) is still seen as a key to preventing disease progress. Two principal types of medicines are used: nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs).

Combinations of antivirals have been found to be very effective in reducing viral load and a great variety of different treatment regimens are known. Such combinations commonly include PIs combined with other PIs, PIs combined with NRTIs, PIs combined with NNRTIs, and almost every combination of all three.

The problem with such approaches has been the large number of pills that need to be taken at different times during the day, which has led to difficulties for patients in adhering to required schedules. Newer medications that need only be taken once or twice a day and pills containing combinations of two or three antivirals make it easier to comply with dosing schedules, which should make therapy more effective.

Highly active antiretroviral therapy (HAART) for the treatment of HIV infection was introduced about a decade ago. Virological response, i.e., reaching 500 or less HIV RNA copies per ml blood and the change in counts of helper T-cells after starting HAART has indeed improved but, so far, such improvement has not translated into a decrease in patients' mortality. Until today, none of the compounds is able to eliminate HIV. Rather, they reduce the viral load in the body, improve the immune status and considerably slow down the development of more serious symptoms.

The major problems with these medicines are side effects, complicated administration schedules and the development of resistance. HIV multiplies quickly and resistant forms constantly emerge. This extreme changeability also makes it difficult to design a protective vaccine. Newer medications that need only be taken once or twice a day and pills containing combinations of antivirals make it easier to comply with dosing schedules, making therapy more effective.

What is in the development pipeline?

Major efforts are underway to improve therapies for HIV / AIDS and its complications. Medicines being developed fall into four categories:

(i) new antivirals and combinations of antivirals to inhibit the binding or replication of HIV;
(ii) immuno-modulators and cytokines which may boost the immune system of patients with HIV / AIDS;
(iii) compounds to treat opportunistic infections and other complications in more advanced AIDS; and
(iv) vaccines for HIV / AIDS prevention and treatment.

New approaches include medicines known as integrase inhibitors that decrease viral load in patients with significant HIV drug resistance. Other new compounds bind themselves to a receptor protein found on the surface of human cells and block the HIV virus from entering the cell.

If AIDS develops, there is a need for medicines to treat the opportunistic infections and other complications such as cancers which may occur. For example, CMV eye infections (retinitis) can occur in 10 to 40 per cent of those with AIDS. A new compound has been approved in this indication and further medicines are being developed.

New medicines are also being sought for other late-stage complications. An interesting approach may be a tyrosine kinase inhibitor of angiogenesis to treat Kaposi´s sarcoma, another avenue is the research of an amino acid analogue for its efficacy in relieving the painful peripheral neuropathy that may develop with prolonged antiviral treatment.

The longer-term future:

Research continues on RTIs, PIs, FIs and other compounds that may have a broader spectrum and longer period of action in the human body. Compounds that support or stimulate the immune response continue to be of interest. One example is the cytokine interleukin-10, another is interleukin-2. Elimination of the virus from infected people remains the ultimate goal, and prevention of the spread of HIV infection would be much aided by the discovery of a successful vaccine.

Future approaches may include the switching-off of CD4- and CXCR4-genes of T-cells via small interfering ribonucleic acids (RNAs). Scientists are intensively investigating the removal of the HIV genome from the T-helper cell genome by means of specific enzymes known as recombinases. Research is also being continued to find new virus inhibiting molecules, e.g., VIRIP, a 20 residue peptide corresponding to the C-proximal region of alpha-1-antitrypsin which interferes with HIV gp41 fusion protein.

The development of vaccines or monoclonal antibodies against HIV fusion protein gp120 is considered to be of major therapeutic value. Many companies are trying to develop protective or therapeutic AIDS vaccines. One principle consists of a combination of DNA snippets from HIV with a protein that boosts the immune response. At present, therapeutic vaccines look more promising than preventive vaccines, but the next few years can be expected to bring progress in applying immunological approaches to the conquest of this disease.

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