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Current Findings and Developments in AIDS Research: A Review Article

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INTRODUCTION

The year of 1995 brought a considerable amount of research on Human Immunodeficiency Virus (HIV) infection and Acquired Immune Deficiency Syndrome (AIDS). Current investigations cover several major areas of therapy potential and seek understanding of the mechanisms of this particular type of retroviral infection.

Of underlying importance to AIDS research is a comprehensive understanding of the pathophysiology of the virus. Its interaction with the cells of the immune system at both cellular and molecular levels is highly complex and only partially understood. HIV belongs to a class of viruses called retroviruses because it is composed of RNA rather than DNA. When it initially enters the body, it infects two major types of immune cells: helper T cells and macrophages. The virus latches onto a protein on the cell membrane and releases its contents into the target cell. HIV uses the enzyme reverse transcriptase to copy its RNA into DNA. The viral DNA is then inserted into the genome of the host cell. This virus uses the infected cell's genetic machinery to produce copies of viral RNA and proteins, which are assembled into viral particles and released from the cell to infect more cells. In the case of macrophages, the viral particles are ingested and broken down into small peptides (epitopes). These epitopes are displayed on the surface of the macrophage in combination with a protein, forming a unit that can be recognized by other immune cells.

It is known that CD8+ cytotoxic T lymphocytes (CTLs) and anti-HIV antibody production are critical components of the immune reactivity against the virus (Haynes et al., 1996). However, the natural activation of the immune system in response to the virus may actually render the immune cells more susceptible to HIV infection. In other words, as the body tries to fight off the virus, it may actually be increasing viral activity. An example which demonstrates the cunning nature of the HIV virus and the problems it poses for the body is the CD8+ CTL response. These cells are particularly important during the latent phase of viral infection because they literally kill virally infected cells and, in effect, help control the viral load. However, HIV-specific CD8+ CTLs may contribute to the immunopathogenesis of the virus either by depleting the amount of antigen-presenting cells through direct killing, or by tissue damage due to the release of certain cytokines (chemicals secreted by immune cells). Antigen-presenting cells are necessary for the recognition of the virus and the subsequent cell-mediated immune response. Furthermore, it has been found that certain cytokines actually induce HIV expression.

Adding complexity to the search for AIDS therapies is the fact that HIV variants emerge over time, evading highly-specific neutralizing antibodies which are key to fighting off infection. The virus, as evidenced by drug studies, is also capable of rapidly developing resistence to antivirals. Scientists originally thought that the virus entered a latency stage, as those infected remain asymptomatic for many years. Many researchers now believe that the immune system is continually fighting off the virus (Nowak and McMichael, 1995). Its high rate of mutation may be what enables it to eventually evade the host's immune defenses. The reverse transcription of the RNA is very error prone, making HIV the most variable virus known. Research also indicates that during this asymptomatic stage of infection the virus is stored, and builds up in the germinal centers of lymph nodes (Fox, 1996). The virus may be covered with antibody, but is still able to infect T cells which enter the lymph nodes. This partially explains the resistance of HIV to antiviral drugs, as it is "sheltered" by the antibodies and lymph nodes.

Most of the antiviral drug therapies and gene therapies in use for AIDS attempt to inhibit some stage of viral replication. Other therapies are aimed at enhancing the immune response, either with chemicals or through vaccination. Some have also tried alternative methods for healing, but the antiviral drugs are by far the most commonly used today.

ANTIVIRALS

Nucleoside Analogs

Nucleoside analogs are compounds similar to the building blocks of genetic material, which interfere with transcription or reverse transcription of the virus. The virus incorporates them in the production of the DNA copy, but these molecules stop transcription because they differ slightly from the bases of DNA. AZT, the most common and widely used antiviral, is a nucleoside analog. Many nucleoside analogs have FDA approval or are in clinical trials. These compounds, however, are not able to completely eradicate the virus and the development of viral resistance to nucleoside analogs is common (Project Inform, 1996). Today, antivirals are most beneficial when used in combination therapy.

Protease Inhibitors

A newer class of drugs, called protease inhibitors, attempts to prevent replication of the virus at a later stage, after the cell has been infected. These compounds block the activity of a protease enzyme that the virus needs to make copies of itself. They have been shown to substantially reduce the amount of virus in the bloodstream of infected individuals, even in the late stages. Like nucleoside analogs, the effects of

Table 1: Antiretroviral drugs available for treatment of HIV infection and AIDS.

Drug	Mode of Action, Status
AZT ZDV	NARTI; used as initial therapy and in combination therapy; increases survival 6-21 mo.; reduces dementia and mother-child transmission; resistance develops rapidly.
ddI	NARTI; works best after AZT treatment; unpleasant side effects; resistance develops.
ddC	NARTI; similar to ddI; used in combination w/ AZT; slows progression of disease; mild side effects.
3TC	NARTI;combined w/ AZT, has best results of current combination therapy, longest period of improved CD4 counts and reduced viral load.
d4t	NARTI; used w/ AZT, delays progression; possibly harmful side effects; more studies underway.
Nevirapine Delavirdine	Non-NARTI; resistance develops quickly; may have possibility in combination therapy.
NVP	Currently in clinical trials.
Saquinavir	PI; poor bioavailabilty when taken orally; difficult/expensive to manufacture; minimal side effects; works well in 3-drug combination.
MK639 ABT538	PI; substantial decrease in viral load observed, but short-lived (12-18 wks.); effective in late-stage.
Indinavir Ritonavir	PI; modest decreases in viral load observed; minimal side effects; works better in combination therapy.
KNI272	PI; currently in development.

NARTI = nucleoside analog reverse transcriptase inhibitor; PI = protease inhibitor

protease inhibitors are short-lived and offer the most potential in combination therapy with other drugs (Cohen, 1996). Table 1 lists a number of antivirals which are currently being used or tested.

GENE THERAPY

The most notable development in HIV gene therapy is antisense. Antisense drugs are composed of oligonucleotides (segments of about 20 DNA bases) which are complementary strands of a viral gene. These bind to the target gene or RNA segment and block the transcription and/or translation of the gene to viral protein. An example is a drug called GEM91, which targets a viral life cycle gene called *gag* (Gura, 1995). Researchers have encountered problems with getting the antisense into target tissues because enzymes in the body break down nucleic acids. Also, if the antisense passes into cells, it often gets trapped in endosomes rather than entering the nucleus where the DNA or RNA target resides. To overcome these obstacles, researchers have made modifications to the oligonucleotides. For instance, the attachment of a sulfa-moiety to the antisense prevents degradation by cellular enzymes (Cimoch, 1995). Pharmaceutical companies are also generating fat-soluble delivery molecules called cationic liposomes. GEM91 and a similar drug, ISIS5320, are currently in clinical trials and preliminary results show no development of viral resistance (Project Inform, 1996).

IMMUNOTHERAPY

Because the immune system is capable of initially suppressing the virus, some researchers believe that it can be therapeutically manipulated to assist pharmacologic interventions. Immunotherapeutics can be divided into active and passive immunotherapy. Active immunotherapy involves vaccine development, while passive immunotherapy involves adoptive immune reconstitution and cytokine therapy.

Critically important to the development of vaccines are the studies of individuals who live with HIV. Certain characteristics of the virus may render it susceptible to control by the immune system. Scientists have been studying particularly weak strains of the virus, and have found deletions in the *nef* gene, which is needed for full-scale viral replication (Cohen, 1995). Scientists have already created a vaccine for the macaque model virus, simian immunodeficiency virus (SIV), where the *nef* gene has been deleted. It was found to protect monkeys from subsequent infection with SIV.

Another breakthrough in vaccine development came when researchers found a much less virulent strain of the virus called HIV-2, which was thought to be in West Africa long before HIV-1, the common form. Those infected with HIV-2 rarely develop symptoms and most are immune to HIV-1 (Richardson, 1996). A newly-developed antiviral called PMPA may also have a potential role in prophylaxis against early HIV infection (Tsai, et al., 1995). When PMPA, an acyclic nucleoside phosphonate analog, was administered to macaques either 24 or 48 hours prior to inoculation with SIV, they were protected from infection, with no toxicity of the drug, whereas all of the controls became infected.

Most vaccines are made from viral proteins and require the patient to be in the early, immuno-competent stage of infection. A compilation of several vaccines in development appears in Table 2.

Table 2. Therapeutic HIV vaccines currently in clinical studies.

Vaccine	Company	Type/strain
gp160	MicroGeneSys	subunit/LAI
gp160	Immuno AG	subunit/LAI
gp160	Pasteur Merieux	recombinant/MN
gp120	Chiron Biocene	subunit/SF2
gp120	Genentech	subunit/LAI
Salk	Immune Products	whole/HZ321

Another area of immunotherapeutics involves the cryopreservation and/or expansion of immune cells taken from patients prior to full-blown AIDS or from other sources. Researchers in Hamburg, Germany have shown that T lymphocytes could be preserved for up to a year before reinjected into the patients (Cimoch, 1995). The purpose of adoptive immunotherapy is to artificially activate healthy immune cells, such as CD8 + T cells, grow them in culture, and reinject them into the patient to fight off the virus. Although some studies have shown this technique to produce a dramatic decrease in viral load, the effect is typically of short duration due to the high mutation rate of the virus.

Some have used large quantities of those compounds naturally produced by the immune system to "hyperactivate" immune cells to divide and grow more than they ordinarily would. Cytokines such as interleukins, interferons, and thymic peptides have been used for this purpose, but have not produced any outstanding results. A better understanding of the interactions between HIV and the immune system will bring more possibilities for this type of therapy. For instance, researchers have found three major HIV-suppressor factors produced by the immune system during infection (Balter, 1995). These compounds, called RANTES, MIP1-α, and MIP1-β are produced by CD8 cells and may prove to be very useful in immunotherapy.

In the search for new and better therapies to treat HIV infection and AIDS, the future will likely bring improvements in existing drugs and development of new drugs. Some antiviral approaches that are being pursued include glucosidase inhibitors, which inhibit sugar coating of HIV, cyclophilin inhibitors, which prevent fusion of infected and uninfected cells, a synthetic formulation of the Chinese bitter melon, integrase inhibitors, and wider usage of antisense gene therapy. HIV has developed some form of resistance to all current treatments; it may be a very long time before the goal of a sustained benefit from treatment is achieved, but possibilities and hope live with each new experiment.

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