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AIDS: MEDICAL AND SCIENTIFIC ASPECTS

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TABLE OF CONTENTS

Page

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ISSUE DEFINITION

Acquired Immune Deficiency Syndrome (AIDS) was first described in the United States in the summer of 1981 and was initially associated with cases of *Pneumocystis carinii pneumonia* (PCP) and Kaposi's sarcoma (KS) in homosexual men who were also immunocompromised. The first case of AIDS in Canada was reported in February 1982. Since then the incidence of AIDS has grown significantly. **Worldwide 36.1 million people are infected with HIV, and more than 14,000 new infections occur daily.** The vast majority of those infected live in the developing world, particularly in sub-Saharan Africa, southeast Asia and the Asian sub-continent. **It is estimated that nearly 22 million people have died from AIDS and 13.2 million children have been orphaned by the disease**. However, exact numbers are difficult to obtain because of under-diagnosis, incomplete reporting and reporting delays in many countries.

As its name suggests, AIDS involves the breakdown of the body's immune system, leaving the victim vulnerable to unusual and fatal diseases. The human immunodeficiency virus (HIV) – the virus that is now known to cause AIDS – was discovered in 1983. HIV is not highly contagious and its transmission is easily preventable, but prevention is predicated on behavioural change among populations at risk. The virus is unusual: it has a very high mutation rate and, although it is the subject of intense research scrutiny, its mode of action is not fully understood. An effective vaccine against HIV is not expected for a number of years and, until relatively recently, no effective therapies existed. In mid-1996, the results of a number of clinical trials investigating the effect of mixtures of multiple anti-HIV drugs were reported. Early observations show that drug"cocktails" of three or more drugs can overcome the rise of drug-resistant mutants; in many cases, HIV concentrations in the blood have fallen below the level of detection. It is too soon to say that a cure for HIV/AIDS is at hand; however, it now appears that it may be possible to transform HIV disease into a chronic, controllable condition.

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* The original version of this Current Issue Review was published in November 1993; the paper has been updated regularly since that time.

BACKGROUND AND ANALYSIS

In the years that have passed since the identification of AIDS in 1981, many advances have been made in understanding the disease, how it is spread, and how it may be prevented. The disease will be discussed under the following headings: epidemiology of HIV/AIDS; the human immunodeficiency virus (HIV); the immune system and the etiology of HIV infection; associated diseases; HIV vaccines; and anti-HIV drugs.

A. Epidemiology of HIV/AIDS

Since the first AIDS case was diagnosed in Canada in 1982, the disease has spread widely. **By 31 December 2000, a total of 17,594 Canadians had been diagnosed with full-blown AIDS and 70.6% (12,419) of those had died.** Health Canada states that the significant delay in the reporting of AIDS cases, together with under-reporting, affects the accuracy of the figures quoted above. Following initial infection, HIV disease is characterized by a long asymptomatic period that can last for ten years or more before full-blown AIDS develops. **In 2000, 2,104 positive HIV tests were reported in Canada, bringing the cumulative total of reported tests between 1985 and the present to 48,014. It is estimated that at the end of 2000, there were well over 50,000 HIV-positive (HIV^+) people in Canada (including those living with AIDS). Of these, an estimated 30% are unaware of their infection.**

Health Canada now reports statistics on the incidence of HIV and AIDS in the publication *HIV and AIDS in Canada.* This document, published biannually, covers material formerly presented in two separate reports: *HIV in Canada* and *AIDS in Canada*; it reflects an integrated approach to HIV and AIDS surveillance.

Among other statistics, *HIV and AIDS in Canada* allocates all reported Canadian AIDS cases to an exposure/risk category. **As of 31 December 2000, of all adult AIDS cases attributed to identifiable risk categories, 72.3% were attributed to homosexual activity and a further 4.8% consisted of men who identified a combination of homosexual activity and intravenous drug use as risk factors. The balance of adult cases attributed to identifiable risk categories were allocated as follows: intravenous drug use, 6.5%; recipient of blood,**

1.6%; recipient of clotting factor, 1.7%; and heterosexual contact, 11.6%. For adults with no identifiable risk factors, 581 cases of AIDS have been reported (3.3% of total cases). Children under 15 years of age accounted for 203 cases of AIDS (1.2%).

The above data serve only as a snapshot of the Canadian HIV epidemic; they do not identify which Canadian groups are being infected today. Only in Canada and the developed nations of Europe and Australasia does AIDS remain a disease where the majority of those afflicted are gay. The incidence of new HIV infections among Canadian gay men has fallen, with the most significant decrease taking place among older gay men who have witnessed the deaths of friends and loved ones. Unfortunately, young gay men are less likely to practise safe sex and they continue to have a relatively high rate of infection. As the epidemic in the gay population slackens, it is intensifying among young heterosexuals. **By the end of 2000, women accounted for 7.7% of the total cumulative adult cases of AIDS.** They represent an increasing proportion of the HIV infections and AIDS cases reported each year among adults. **In 2000, 22.9% of new HIV infections reported in adults were in women**. Between 1985 and 1994, HIV infections in women accounted for only 9.8% of the total.

The profile of newly diagnosed HIV infections has changed considerably since it was first identified. Essentially three-quarters of all infections between 1984 and 1995 were due to the high-risk activity of men who have sex with men. **This changed over subsequent years as the proportion of females infected rose and the contribution of intravenous drug use to the spread of the virus increased. Between 1994-1995 and 1999 general trends of decline were observed in the number of: HIV infections reported; AIDS diagnoses; and AIDS-related deaths. However, in 2000, the number of new AIDS cases reported increased for the first time since 1994. Additionally, there has been an increase in both the reported number and relative proportion of positive HIV tests attributed to men who have sex with men, corroborating the increased HIV incidence reported for this group in 1999.**

In the United States, AIDS ceased being primarily a disease of gay men in the early 1990s. Data from the United States Centers for Disease Control and Prevention show that the proportion of newly reported HIV cases among homosexual/bisexual men steadily decreased from 43% in 1996 to 41% in 1997 to 40% in 1999. However, this tread reversed in 2000 and the rate jumped back to 43%. The percentage of new cases for white adults,

which had in the past declined and then remained constant at 32% between 1998 and 1999, has now increased to 37.3%. At the same time, the rate of infection among women and minority groups has continued to rise, similar to the situation in Canada. AIDS cases among women have been increasing over the years, accounting for 13.0% of all total AIDS cases in 1993, and rising to 17.4% in 2000. The percentage of U.S. blacks with AIDS continues to increase, rising steadily from 31.8% of all cases in 1993 to 37.8% in 2000. These are alarming statistics, given that only 12.3% of the population is black. Similarly, Hispanic Americans accounted for only 12.5% of the population, but 18% of AIDS cases in 2000. For Americans aged 25-44, HIV was the fifth leading cause of death in 1999; among blacks it was the number one cause of death in this age group.

Sexual intercourse is the principal means of HIV transmission. Unprotected anal or vaginal intercourse poses the greatest risk of infection as the epithelial tissue of both the vagina and anus/rectum contain cells that are susceptible to invasion by HIV. Scientific studies have shown that in heterosexual transmission of HIV, women are at least twice as susceptible as men; however, lack of circumcision increases the risk for men. Oral sex is believed to be a less risky sexual practice because viral entry is limited to access through oral cuts, abrasions or inflamed areas; however, HIV has been found capable of infecting Langerhans cells present on tonsil epithelial tissue. The virus is destroyed by stomach acids. The use of non-latex condoms for all sexual acts involving the exchange of body fluids significantly reduces the risk of HIV transmission.

Although only 6.5% of all AIDS cases diagnosed up to 31 December 2000 were directly attributable to intravenous drug use, it is a high-risk activity when shared needles are involved. This means of transmission is increasing in Canada's major urban centres. Canadian studies have shown that low-income inner-city residents with unstable housing are twice as likely to become infected with HIV than are wealthier drug users. It has also been observed that people who inject cocaine more than four times a day are 2.4 times more likely to become infected than are those who inject other drugs. In the United States, intravenous drug use is a major cause of new HIV infections. A February 1995 analysis conducted by the United States Centers for Disease Control and Prevention found that approximately 75% of the 40,000 newly infected with HIV in the United States in 1994 "self-medicated" with illegal drugs.

The AIDS virus can be transmitted in whole blood and blood products. Factor VIII, a coagulation product originally prepared from blood plasma, has been responsible for a large number of HIV infections. Approximately 1,200 Canadians were infected by HIV from contaminated blood and blood products in the 1980s. By 1 November 1985, the Canadian Red Cross had fully instituted testing of all donated blood for HIV antibodies. Earlier, the Red Cross had instituted donor screening to eliminate persons in high-risk groups. The Canadian blood system now is as safe as any in the world. Canadian Blood Services, in operation since September 1998, tests all blood donations for the most common strains of HIV (HIV-1 and HIV-2), using a very sensitive test; this test produces no "false negatives," i.e., no infected samples are missed. However, the test can produce infrequent "false positives."

Infants born to mothers infected with HIV are at risk of contracting the virus. Mother-to-infant transmission of HIV – "perinatal transmission" – may occur in three ways: (1) infection *in utero* in cases where the virus moves across the placenta; (2) exposure of the baby to infectious blood and vaginal secretions during labour and delivery; and (3) postpartum transmission through breast-feeding. The rate of infection varies considerably, but may be as low as 13% or as high as 40%. In a U.S. study, the incidence of perinatal transmission was reduced from 25.5% to 8.3% when AZT was administered to HIV^+ women during pregnancy and delivery and to newborns for eight weeks after birth. It is believed that further improvement can be achieved by means of combination therapy using three or more anti-HIV drugs. **By 31 December 2000, a total of 158 cases in which perinatal transmission of HIV had progressed to AIDS had been recorded in this country. This mode of transmission accounts for by far the largest proportion of AIDS cases in children less than 15 years of age (83.6%).**

Occupational transmission of HIV is of greatest concern in the medical and dental professions and, to some extent, also in areas of emergency assistance where persons come into contact with blood. HIV transmission has occurred in hospitals, usually through "needle-stick" injuries with contaminated syringes. Invasive surgical procedures also involve some risk of transmission through cuts caused by surgical instruments or bone fragments, but the incidence of infection by this means is very low. No instances of HIV transmission from a health-care worker to a patient have been recorded.

The transmission of HIV by dentists to patients has been given prominence as a result of the case of a (now-deceased) Florida dentist who may have infected as many as five patients. Dentistry is not thought to be a major risk to the public, however, and procedures have been developed to sterilize dental equipment to protect patients. As in the medical profession, the risk is greater for dentists and their assistants who treat HIV-infected persons, but this risk is regarded as very small.

The AIDS virus has been isolated in many body fluids, including saliva, but transmission of HIV by this route is very low-risk, if it exists at all.

B. The Human Immunodeficiency Virus (HIV)

HIV is unlike most of the viruses that infect human beings in that it is a retrovirus whose genetic material is ribonucleic acid (RNA), rather than deoxyribonucleic acid (DNA). There are two major types of HIV: HIV-l is the commonest strain worldwide, while HIV-2 is prevalent in West Africa. Of the two, HIV-l produces the more severe disease. To date, nine genetically distinct subtypes of HIV have been identified and designated subtypes A through H, and O.

HIV is the most studied virus in history but much remains to be learned about it. A single HIV virus particle, or *virion*, is roughly spherical in shape. It has an outer coat, or *envelope*, consisting of a double layer of lipid (fat) molecules. The envelope is studded with proteins. Some of these are of human origin and are known as *major histocompatibility complex* (MHC) protein molecules, which are important components of the human immune system.

The virion envelope also has numerous protein "spikes," each of which contains a protein called gp120 on the outside and gp41 embedded in the envelope. The prefix "gp" stands for glycoprotein, meaning that the proteins are linked to sugars. The number refers to the mass of the protein. The gp120 envelope glycoprotein is derived from a precursor molecule called gp160. The gp120 protein is known to bind tightly to the CD4 molecule on the surface of immune cells, thus facilitating entry of HIV into the cell. Recent research has suggested that a second protein on the cell surface, an enzyme designated CD26, may serve as the actual entry point for HIV into the cell. Within the gp120 protein is a loop structure called the "V3 loop" and this is believed to be important in the infective process of HIV. Two other proteins have been identified inside the envelope, and designated p17 and p24. The core, or *capsid*, of the virion contains the genetic material of the virus,

in the form of two strands of RNA. A number of enzymes essential to the infective cycle of HIV have been identified. These are described in detail in a later section.

C. The Immune System and the Etiology of HIV Infection

A major impediment to a full understanding of HIV's role in the development of AIDS is the fact that the functioning of the human immune system is still incompletely understood. A brief discussion of the immune system follows.

The human immune system consists of two sub-systems: *humoral immunity* and *cell-mediated immunity*. Humoral immunity is based on the production of antibodies by B lymphocytes, or B cells, which are produced in the bone marrow and circulate in the bloodstream. The B cells are extremely versatile and, in total, represent millions of antibody genes which direct the production of equal numbers of different antibodies. These lymphocytes, carrying any one of millions of different antibodies on their individual cell surfaces, constantly roam the body, ready to meet an invading *antigen*. (An antigen is a foreign protein or carbohydrate toxin, which may be produced by a pathogenic organism.) When an antigen meets a B cell carrying a matching antibody, that B cell is stimulated to divide rapidly and to secrete large numbers of antibodies to attack the invader. The antibody need not match the antigen exactly to be effective.

Cell-mediated immunity involves a type of lymphocyte, known as the T-cell, that originates in the thymus gland. Unlike a B cell, a T-cell cannot "see" the entire antigen, but receptors on its cell surface recognize protein fragments of antigens called peptides. These peptides, which are short linear sequences of amino acids, may even include the inner part of a microbe's structure. A major histocompatibility complex (MHC) protein molecule processes and "presents" the antigen fragment to the T-cell.

T-cells comprise two sub-populations, the CD4 helper and CD8 killer T-cells. The latter also are known as "cytotoxic T-cells" because they literally kill infected cells, thus limiting the spread of a virus. The CD4 helper T-cells respond to the chemical signal from the antigen fragment on the MHC protein and produce a large amount of chemicals called cytokines (or lymphokines). Interferons and interleukins are two of the various classes of cytokines produced. These chemicals stimulate the immune system and the inflammatory response of body tissue that is a part of the immune reaction.

The *complement system* is another important part of the immune system. This sub-system involves the interaction of more than 18 protein fractions which augment the body's immune defences when antibodies combine with invading antigens. Among other things, the complement system facilitates the *lysis* (break-up) of cells of invading pathogens.

The B and T-lymphocytes form a tightly interwoven system which has positive and negative feedback loops. The T-cells stimulate the B cells into an active state where they divide rapidly and produce large quantities of antibodies. In turn, the B cells process antigens into a form to which T-cells most readily respond, stimulating the T-cells into an active state.

Some understanding of the immune system is necessary in a discussion of AIDS because the dominant theory of the disease is that the CD4 T-lymphocytes are affected by the virus, producing functional abnormalities and reduced numbers of cells, leading eventually to the profound immunosuppression that characterizes advanced HIV disease. Other cell types, notably large scavenger cells called *macrophages*, are also infected by HIV, and these may serve as important reservoirs of HIV outside the blood, and as carriers of the virus to other organs (the "Trojan horse" effect).

It is generally accepted that HIV infection proceeds through a number of stages leading up to the condition known as AIDS. In 50 to 70% of persons with primary HIV infection, after three to six weeks an acute syndrome develops which is similar to mononucleosis and is marked by fever and general malaise. There is also a high level of *viremia* (virus in the blood) at this time.

Within a week to three months after initial infection, the body mounts an immune response to HIV. At the same time, it is possible that the virus becomes widely disseminated in the body, particularly in the lymphoid organs. The immune reaction results in a large decline in viremia but is unable to suppress HIV reproduction completely. The virus becomes almost undetectable in the peripheral blood cells, but remains detectable in the lymph nodes.

The mechanism(s) leading to the dysfunction and decline of CD4 T-cells is not well understood. The simplest hypothesis is that the T-cells are directly killed by the virus after infection. It also has been shown, *in vitro*, that an infected T-cell will fuse with a number of uninfected cells to form clusters called *syncytia*, a process which leads to the death of all the affected cells. Syncytia formation has rarely been seen *in vivo*, however.

CD4 T-lymphocytes also may be killed through an HIV-specific immune response involving both the humoral and cellular sub-systems. A number of viral proteins have been identified which stimulate antibody formation; HIV-infected T-cells that express these proteins on their surfaces may be selectively killed by cytotoxic T-cells. The immune system also may be disrupted without actual cell death: infected cells may not function properly, the result being a compromised immune system. It has also been hypothesized that some sort of *auto-immune reaction* may be causing the death of the CD4 T-cells.

There is evidence that a significant number of individuals infected by HIV do not progress to AIDS; in some studies, about half the persons remain free of AIDS 10 years after becoming infected by the virus. One study in San Francisco found that 8% of men infected for between 10 and 15 years remain clinically normal, exhibiting only minor abnormalities of the blood and immune systems. A research group in Britain suggests that up to 25% of persons infected with HIV will survive for 20 years without developing AIDS.

There is evidence that "viral burden" – the amount of virus in the body – is an important factor in progression to AIDS. Persons with a high viral burden, both initially and as the infection continues, seem to progress more rapidly to AIDS. Why some people have a higher viral burden than others is not known, but the answer to that question may produce important insights into the etiology of the disease and could point the way to improved therapies.

In summary, despite a number of hypotheses about how HIV produces the pathogenic events that eventually lead to AIDS, there is no completely satisfactory explanation as yet. The emerging majority view of AIDS is that the disease is caused by a progressive HIV burden in the infected person, involving an incompletely effective activation of the immune system, followed by the eventual destruction of that system by the virus.

D. Associated Diseases

It is now recognized that HIV infection leads to a continuous disease process that starts with the initial exposure and terminates in the advanced forms of immune deficiency, the state typically known as AIDS. Death results from the complex interactions between the HIV infection itself and the secondary opportunistic infections and cancers that are commonly associated with the syndrome.

The first stage of infection is known as the "acute retroviral syndrome" and is characterized by fevers, pharyngitis, headache, malaise and a rash. The symptoms are often mistaken for influenza or infectious mononucleosis. This phase begins about one to three weeks after infection and may last for one to two weeks. During this period, there is a burst of viremia in the person, who is now infective. It is important therefore that counselling be initiated immediately to prevent HIV transmission.

In the next stage of the disease, most people enter a period of "clinical latency." In a large study of homosexual men, the median time from estimated initial infection to the development of full-blown AIDS was 10.8 years. This period varied from as little as 12 months to more than 11 years. In fact, the virus is not really inactive during this period, so the term latency is not really appropriate. Virtually all infected persons suffer a gradual deterioration of their immune system, particularly depletion of CD4 T-cells in the peripheral blood; also, *lymphadenopathy* – swelling of the lymph nodes – typically occurs at this time.

In January 1995, a review article on the population dynamics of HIV in infected persons suggested that the long period of "clinical latency" associated with HIV/AIDS is a period of great activity during which cells are being infected and dying at a high rate and in large numbers. A "steady-state model" is suggested, during which infection, cell death, and cell replacement are in balance. This further suggests that the virus goes through an extraordinarily large number of replication cycles, a turnover that drives both the pathogenic process and the development of great genetic variation within the virus. The great accumulation of mutations accounts for the resistance that invariably develops to antiviral drugs.

The next stage of the disease is called "early symptomatic HIV disease." This designation has largely replaced the older "AIDS-related complex" (ARC) terminology. In this stage, the CD4 T-cell count has dropped significantly, and there is an increase in infectious diseases, although these are usually not life-threatening. A variety of chronic or intermittent symptoms may occur, and almost every organ system may be affected. The observed symptoms include: fever, night sweats, chronic diarrhoea, fatigue, minor oral infections, and headache.

Another factor that can be important in this phase is the development of adverse effects to antiretroviral drugs such as zidovudine (AZT). At this stage also, the virus may become increasingly resistant to such drugs.

In the late symptomatic stage of HIV disease, the CD4 T-cell count declines even further, and the infection rate for serious opportunistic diseases increases. Antibiotics are available to treat most diseases effectively, but these drugs often have side effects, and there is a risk of drug resistance by the various pathogens. *Pneumocystis carinii pneumonia* (PCP) is common during this stage but is susceptible to treatment. Treatments for other infections including cryptococcal meningitis, cytomegalovirus (CMV) retinitis, central nervous system toxoplasmosis, and *Mycobacterium avium-intracellulare* tuberculosis are under development or in the experimental stage.

The final stage of the illness is familiarly referred to as "full-blown AIDS." Some medical workers prefer "advanced HIV disease" as more appropriate. In this stage, the CD4 T-cell count drops to below 50 cells/ml and the probability of death rises greatly. Opportunistic diseases remain as the greatest threat for morbidity and mortality. Careful and regular expert medical care is essential at this stage.

E. HIV Vaccines

Vaccines are the most cost-effective means of reducing infectious disease; the ideal solution to the HIV/AIDS epidemic would be an effective and affordable vaccine for general use in all countries and among all population groups. Although HIV transmission is almost completely preventable through the use of appropriate prophylaxis, this approach requires major behavioural modification in the areas of sexual activity and intravenous drug abuse, where this is notoriously difficult to achieve. The international vaccine research program is very active; currently, more than 20 experimental AIDS vaccines are in various stages of human testing.

When HIV was first discovered in 1983, there was a burst of optimism about possible vaccines; however, because HIV is different from most viruses for which vaccines have been developed, it presents special challenges. The body mounts an early immune response to acute HIV infection but lasting immunity does not develop and the immune system eventually is destroyed.

HIV is perhaps the most genetically variable virus yet discovered. HIV-l, the predominant viral group in most of the world, differs greatly from HIV-2, the viral group responsible for AIDS in West Africa. Worldwide, there are at least nine distinct subtypes of HIV-l.

Within the subtypes the genetic diversity of HIV is vast, and any given population of virus within a host includes a large proportion of defective viral genomes. An asymptomatic HIV^+ person might have at least one million genetically distinct variants of HIV; a person living with AIDS might have 100 times that number. The source of the variation lies in the enzyme reverse transcriptase which has no "editing mechanism" to correct the errors in transcription which occur during viral reproduction. Thus, a vaccine effective against one strain of HIV will not necessarily confer immunity against the mixture of strains encountered in nature.

Experimental animals ("animal models") are needed for vaccine development, as well as for study of the disease process in AIDS. The ideal animal model would be an inexpensive laboratory animal in which HIV induces an AIDS-like condition. At present, there is no such model. Chimpanzees can be infected with HIV, but they have to be infected with the most virulent strains before they develop AIDS-like symptoms. Their use is held to be valuable for vaccine development. The simian immunodeficiency virus (SIV) is related to HIV, and is very closely related to HIV-2. SIVs occur naturally in a number of African nonhuman primates but the virus is not normally pathogenic. However, SIV will cause an AIDS-like condition in macaques, a simian group that includes the familiar rhesus monkey.

Various types of HIV vaccine are currently under development. The standard approach is the use of a *prophylactic* vaccine to prevent individuals becoming infected. Another approach is the use of a *therapeutic* vaccine to modify the disease in infected persons. An additional approach is to develop a vaccine to prevent transmission of HIV from mother to fetus during pregnancy, an important consideration because more women are becoming infected with the virus.

There are two classic approaches to vaccine development for virus diseases:

- First, the vaccine may be based on a live virus that has been genetically altered, or "attenuated," to eliminate its ability to cause disease. Examples include vaccines to prevent polio and measles. This option has some potentially serious safety problems with HIV. The virus, as noted, mutates extremely rapidly and is known to recombine with other HIV strains, and potentially with other viruses, raising the possibility that the altered virus could regain its pathogenicity. Further, because there is no reliable animal model in which to study HIV disease, an attenuated strain of the virus cannot be tested for pathogenicity.

- Second, vaccines also may be based on inactivated, or "killed," whole virus. Testing of inactivated SIV vaccines in nonhuman primates has yielded some success in producing a protective response, but the protection has been brief and has been effective only against virus delivered by intravenous inoculation. Also, there is no evidence that any such HIV vaccine has generated the cytotoxic-T-lymphocyte response believed to be necessary for successful immunity to HIV.

A number of novel approaches to vaccine development are also being pursued with HIV/AIDS. Recombinant DNA (rDNA) technology is being used to produce large quantities of viral proteins and peptides, and even viral genes, which can be used as immunogens for vaccine production. Their new approaches include the use of various attenuated microorganisms, such as the vaccinia virus, containing an HIV gene encoding an HIV protein.

Only one such vaccine has entered trials so far and is described as a "gp120 subunit" vaccine. The designation "gp120" refers to a subunit of the envelope glycoprotein produced by the virus which it uses to latch on to susceptible cells. The vaccine has been shown to be safe for humans on the basis of small-scale trials in Europe and the United States. However, recent research suggests that the current generation of gp120 immunogens (i.e., antibodies to gp120) may not be effective against HIV. Instead, scientists are producing a better antibody to gp120. What is needed is a line of cells that mimic HIV by having the gp120 protein on their outer membranes. The hybrid cells are then "activated" by mixing them with cells susceptible to HIV. The hybrid cells are then "fixed" at this point with formaldehyde in a fusion-competent form which is then used to produce antibodies in mice. It has been shown to neutralize several strains of HIV.

Much research is still needed to surmount the numerous problems that exist with HIV vaccines. In animal studies, vaccine protection lasts only for a short period and only against a virus identical to the one used to make the vaccine. This is a major problem, given the huge genetic variation among HIV populations: vaccines will have to provide immunity against the extreme genetic diversity of HIV observed in humans, a property known as *cross-reactivity*. It remains to be determined whether a special type of immunity is required to protect against mucosal exposure to HIV, such as would occur during sexual intercourse, as opposed to exposure through the bloodstream. Also, protective immunity will need to be achieved against both cell-free and cell-associated virus particles because humans are rarely infected by cell-free virus.

Finally, the trials of any prophylactic HIV vaccine will be both difficult and controversial. To provide a "good" test of vaccine efficacy, an unprotected control group would have to be involved. The prospect of using such a group, without doing everything possible to prevent their becoming infected by the virus, raises very difficult ethical and moral issues.

F. Anti-HIV Drugs

The most publicized news out of the 1996 XI International Conference on AIDS was in regard to the successes achieved in combating HIV by means of combination therapies consisting of two to four anti-HIV drugs given at one time. There is now a good indication that HIV infection will become a controllable chronic condition, and there is also the hope that a real cure may actually be possible in the future.

The genetic material of HIV contains nine genes, three of which code for essential enzymes. The first enzyme, reverse transcriptase (RT), copies the viral RNA into the more common genetic material DNA. The second enzyme, integrase, snips the host's DNA and inserts the viral DNA sequence. Thus, through the normal operations of the host cell, the HIV sequence is read and translated into a long HIV protein strand. Finally, the third enzyme, protease, cuts the protein strand at the correct points releasing all the protein subunits needed for the virus to self-assemble a new virus particle. In this manner, one infected CD4 cell can produce and release hundreds of new HIV particles.

The focus of anti-HIV drug development has been the design of drugs that specifically target the function of one of these enzymes. To date, most work has focused on two classes of drugs to defeat RT. The most common RT drugs, the nucleoside analogues, include AZT, ddI, ddC, 3TC, and d4T. In addition, there is also a group of non-nucleoside RT inhibitors, of which nevirapine, loviride, and delavirdine have been studied in most detail. Some success also has been achieved in developing drugs to inactivate the protease enzyme. The major protease inhibitors include saquinavir, ritonavir, indinavir, amprenavir and nelfinavir. As yet, only a few drugs have been designed to interfere with integrase activity. These anti-integrase drugs, as well as a number of additional RT and protease inhibitors, are in the early stages of testing. As many as 20 anti-HIV drugs can be used in a large number of effective therapeutic combinations.

Since the first anti-HIV drug, AZT, came on to the market, the HIV virus has been able to defeat drug challenges by developing drug-resistant mutants. It has been estimated that each time HIV genetic material is duplicated, at least one, and perhaps even two or more, duplication mistakes are made. Every progeny virus that is different from the parent virus is a mutant. Some mutations are deleterious to the virus, making it less infectious or able to replicate; other mutations may benefit the virus. However, the vast majority of mutations have little or no effect. Due to the rapid rate of viral reproduction and the huge quantity of virus that may be present in the body, a few viral particles that are resistant to a specific drug may already exist in the body, even though the virus has never come in contact with that drug. When this happens, the drug may kill off the susceptible virus and the amount of virus in the blood (viral load) will drop dramatically. The resistant virus, however, is given a selective advantage; after a few months, it proliferates and previous viral levels are again attained. Alternatively, no resistant mutants may be present, but the anti-HIV drug may not completely suppress viral replication. Viral load will drop, but a low level of viral reproduction continues and eventually a drug-resistant mutant appears and proliferates.

Mathematical analyses have shown that drug resistance to monotherapy (use of one drug) can arise in only a few months. There is also a high possibility of a double mutation that results in drug resistance to combined two-drug therapy; however, there is an extremely low to negligible chance of a triple or quadruple mutation that would lead to drug resistance to combination therapies of three or more drugs. If HIV is challenged with high doses of three or more drugs, viral replication should be completely arrested so that reproduction cannot take place and triple or quadruple mutations cannot accumulate over time. It is now recommended that aggressive combination therapy be initiated as soon after initial infection as possible, before the immune system has been severely degraded and while the viral load is still relatively low and a wide variety of mutants have not yet accumulated. This is called Highly Active Anti-Retroviral Therapy (HAART).

It is now recognized that any combination of drugs should include both AZT and 3TC. AZT is a very potent anti-HIV drug. Although 3TC is less potent, the 3TC-AZT combination acts as a toggle switch against resistance. AZT resistance may arise, but 3TC keeps viral replication in check until resistance to it occurs. Luckily, the mutation that confers

resistance to 3TC is the reverse of the mutation that gave AZT resistance, and the HIV becomes susceptible to AZT again. AZT and 3TC combined with ddI or the non-nucleoside RT inhibitor, nevirapine, have been found to reduce viral load to nearly non-detectable levels; however, even better results may be possible if AZT and 3TC are combined with a protease inhibitor. On their own, the protease inhibitors have been found to be very potent against HIV replication; however, resistant mutants quickly arise. Resistance does not appear to be a problem when optimum levels of protease inhibitor, AZT, and 3TC are used. For example, in clinical trials, the continued use of a combination of indinavir, AZT, and 3TC resulted in a sustained drop in viral load below detection level and a sustained gradual increase in CD4 count.

It is theorized that an early aggressive attack on HIV will stop replication, allow the immune system to heal and, over time, allow the body to clear itself of virus. There is some indication that severely damaged immune systems may not completely heal, which leaves the difficult option of remaining on the harsh drug therapies for a lifetime. A more appealing alternative is to restore the immune system; this is being pursued by work on interleukin-2 and granulocyte-macrophage colony stimulating factor (IL-2 and GM-CSF). Although combined therapy of these drugs is believed to invigorate the immune system, substantial work remains to be done in this area.

No one yet knows how long it will take to clear HIV from the body, if indeed this is possible. Some long-lived body cells can function for three years before they are replaced, and dormant HIV might shelter in them. In addition, some clinicians fear that dormant HIV might shelter indefinitely in certain specialized nerve cells or in the brain. Accordingly, only trial and error experimentation in humans will tell when or if combination therapy can be terminated. On a positive note, no evidence of HIV was seen when lymph node biopsies were conducted on six patients after 78 weeks on a combination of AZT, 3TC, ddI, ddC and interferon-alpha therapy.

In spite of the good news, it is estimated that combination therapy will cost more than $13,000 per patient per year, which will put a financial strain on the health-care budgets of developed nations. This is a minor concern, however, when compared to the plight of those living with HIV in developing nations. The developing countries of the world contain 90% of all HIV infections, and the poor who live there have no hope of ever affording anti-HIV therapies.

Unless the cost of anti-HIV drugs can be drastically reduced, the recent successes in combination drug therapy will have virtually no effect in stemming the world AIDS pandemic.

G. The Krever Commission

In September 1993, following the annual meeting of federal-provincial-territorial ministers of health in Edmonton, it was announced that the alleged failures of the Canadian blood system to protect Canadians adequately from HIV infection would be the subject of an inquiry. Mr. Justice Horace Krever, Justice of the Ontario Supreme Court and Member of the Ontario Court of Appeal, was named commissioner of the inquiry, which began 22 November 1993 and was conducted pursuant to Part I of the federal *Inquiries Act*.

On 14 February 1994, testimony began at the inquiry into Canada's blood system. Public hearings were held in every province. Prior to the start of the public hearings, however, Canada's deputy health ministers suggested that major changes be made to the blood system and recommended that the Canadian Red Cross no longer control the purchases of blood products. A report by the deputy ministers suggested that the Canadian Blood Agency assume this responsibility.

The Krever Inquiry's 485-page Interim Report was released on 24 February 1995. In addition to making recommendations for improving the safety of Canada's blood system, the report recommended that hospitals should contact individually the estimated 3.5 million Canadians who had received blood transfusions between 1978 and 1985, to inform them of the risks of HIV infection from the transfusions and of the advisability of being tested.

In December 1995, as required by section 13 of the *Inquiries Act*, Judge Krever issued notices to a number of individuals informing them that the final Commission report might assign blame to them. The right of the Commission to assign blame was challenged in the Federal Court of Canada by the Canadian Red Cross, the federal government, six provinces, five pharmaceutical companies, and a number of individuals. In June 1996, Mr. Justice John Richard allowed allegations of potential misconduct to stand against 17 Red Cross and federal officials; however, he forbade the inquiry to assign blame to 47 other people, including former health ministers and senior bureaucrats.

When the Commission was established, its mandate was to investigate and assess the problems and shortcomings of the Canadian blood system and make recommendations. The Commission's recommendations were then to be used by the federal and provincial governments to reorganize the Canadian blood system to help ensure that such a tragedy would not occur again. Due to the many delays experienced by the Commission, federal, provincial and territorial health ministers felt the safety of the Canadian blood supply could not wait until receipt of the final report. On 10 September 1996, these ministers announced that a new national authority would be established within one year, at arm's length from all governments, to operate the blood system.

On 26 November 1997, the Health Minister released the final report of the Krever Commission, on behalf of the federal government. Judge Krever's report dealt with major topics related to the AIDS crisis, including:

- the Canadian response to threats to the safety of the blood supply caused by the emergence of AIDS;
- safety in blood products and plasma derivatives;
- international responses to the risk of HIV in the blood supply; and
- the need for reform of the current blood system.

In response to the Krever Commission's recommendations, Canadian Blood Services (CBS) was set up as a charitable, not-for-profit organization, to provide a safe and reliable blood supply for Canadians. (Quebec has established its own blood supply system called Héma-Québec.) CBS assumed responsibility for the operation of Canada's blood supply system on 28 September 1998.

On 28 May 1998, the Health Minister announced details of the new Canadian Strategy on HIV/AIDS (CSHA). A significant feature of the new strategy is that, unlike previous HIV/AIDS initiatives (Phases I and II of the National AIDS Strategy), it will not be time-limited and will receive annual funding of $42.2 million from the government's A-budget. Other elements of CSHA include:

- a new policy to make promising drug products available sooner to Canadians;

- additional funding for Correctional Service of Canada (CSC), directed toward the prevention of the spread of HIV infection and the treatment of inmates in federal correctional institutions who have AIDS; and

- the establishment of a 15-member Ministerial Council on HIV/AIDS, with membership drawn from all areas of HIV/AIDS and representing broad expertise. The Council is intended to provide the Minister of Health with advice on the effective and efficient implementation of a shared national HIV/AIDS strategy and will replace the National Advisory Committee on AIDS.

PARLIAMENTARY ACTION

Parliament has produced several reports on AIDS. In May 1986, the House of Commons Standing Committee on National Health and Welfare tabled a report entitled *AIDS in Canada*. In June 1990, the Parliamentary Ad Hoc Committee on AIDS released its report, *Confronting A Crisis*. In November 1992, the House of Commons Standing Committee on Health and Welfare, Social Affairs, Seniors and the Status of Women held public hearings in the form of a roundtable discussion with the Parliamentary Ad Hoc Committee on AIDS to focus on renewed federal funding for the national AIDS strategy.

On 26 November 1992, the Sub-Committee on Health Issues of the House of Commons Standing Committee on Health and Welfare, Social Affairs, Seniors and the Status of Women began public hearings on a "study of HIV-infected blood and other related matters." The Sub-Committee's report, entitled *Tragedy and Challenge: Canada's Blood System and HIV*, was tabled in the House of Commons in May 1993 and made nine recommendations. The principal recommendation was for a public inquiry into Canada's blood system. The efficiency and safety of the system was the primary focus of the report, which included a full examination of the events of the 1980s when the blood supply became contaminated by HIV.

The House of Commons Sub-Committee on HIV/AIDS was formed in December 1994; its first report, entitled *A Study of the National AIDS Strategy: Report of the Sub-Committee on HIV/AIDS*, was presented to Parliament one year later. The report contained 23 recommendations aimed at strengthening the federal government's response to the AIDS epidemic. The Sub-Committee then examined the issue of compassionate access to experimental

drugs for people who are catastrophically ill and, in October 1996, submitted their findings to Parliament in the report entitled *Compassionate Access to Investigational Therapies: Second Report of the Sub-Committee on HIV/AIDS*. This document made eight recommendations focused on developing mechanisms to liberalize access to unproved drugs while still maintaining the rigour of clinical drug trials.

CHRONOLOGY

June 1981 -	AIDS was first reported by the Centers for Disease Control (CDC) in the United States and was incorrectly attributed only to promiscuous homosexual activity among males.
February 1982 -	AIDS was first reported in Canada.
June 1982 -	CDC reported that 20% of the U.S. patients were heterosexual IV drug abusers of both sexes.
July 1982 -	CDC reported that hemophiliacs had contracted AIDS through blood products.
May 1983 -	AIDS virus – LAV (lymphadenopathy associated virus) – was discovered in France.
September 1983 -	National Advisory Committee on AIDS was established in Canada.
April 1984 -	AIDS virus HTLV-III (human T-cell lymphotropic virus III) –believed to be the same as the LAV virus – was discovered in the U.S.
March 1985 -	U.S. approval of the first commercial screening test for the presence of AIDS virus antibodies in blood.
May 1985 -	Heat treatment for hemophilia blood complexes was initiated in Canada (100% in place by June 1985).
November 1985 -	Blood screening of donated blood for AIDS virus antibodies began in Canada.
1 May 1986 -	Minister of National Health and Welfare announced a $39-million, five-year plan to support activities dealing with AIDS in Canada.
8 June 1988 -	The Minister of National Health and Welfare allocated an additional $129 million over five years to the federal government's AIDS program.

16 October 1989 - The Minister of National Health and Welfare announced that a new HIV Clinical Trials Network would be developed in Canada by the University of British Columbia at St. Paul's Hospital in Vancouver. The Network would improve the access of patients and physicians to clinical trials of drugs and vaccines for treatment of AIDS and HIV infection.

24 April 1990 - The Minister of National Health and Welfare announced the federal government's intention to establish a National Treatment Registry for persons with HIV/AIDS. The Registry would be known as the Treatment Information System for AIDS and HIV Infection (TISAH) and be based at the University of Toronto.

28 June 1990 - The Minister of Health and Welfare, Mr. Beatty, presented the National Strategy on AIDS. The Strategy did not include any new federal funding; existing funds were re-allocated.

October 1990 - Anonymous blood testing of 67,078 newborn babies born in Ontario between October 1989 and July 1990 showed that 21 tested positive for HIV antibodies, for an indicated infection rate of 3.1 per 10,000. This rate was about double that anticipated. Where a blood test indicates that the mother is infected with HIV, the newborn has a 30-50% probability of being infected also.

30 October 1991 - The Minister of Health and Welfare, Benoît Bouchard, announced that the Federal Centre for AIDS would be phased out and its duties assumed by other units of the department. A national AIDS Secretariat was created to serve as the departmental focal point of HIV/AIDS issues. The Laboratory Centre for Disease Control would carry out AIDS surveillance and epidemiological research as well as biomedical/laboratory research. The Health Services and Promotion Branch would handle AIDS education and prevention strategies and funding for national and community-based groups as well as for non-governmental organizations. A new unit of the Branch would be created to address care and treatment issues.

January 1992 - The Ontario Ministry of Health set up anonymous HIV-testing centres across the province. The program was to cost $600,000 and be part of a $2.1 million AIDS program announced by the government in October 1991. Many AIDS workers believed that the anonymity of the testing would encourage persons at risk to come forward to be tested.

July 1992 - At the VIII International Conference on AIDS in Amsterdam, a topic of major interest was the possibility that AIDS, or a condition similar to

AIDS, may occur in the absence of infection by either HIV-l or HIV-2, the viruses believed to be responsible for the disease.

15 April 1993 - The Hospital for Sick Children in Toronto announced that it would notify the families of children who received blood transfusions between 1980 and 1985 that they might have been exposed to HIV. It was estimated that some 17,000 former patients might be involved. The program was to start by sending letters to some 1,700 families of former pediatric heart patients. The program was to be expanded if the initial effort was successful. In mid-June, the Hospital announced that six former patients had been found to be HIV^+.

24 November 1993 - The Hospital for Sick Children in Toronto announced that 17 of the 1,700 pediatric heart patients contacted in April 1993 had tested positive for HIV. This 1% infection rate was higher than had been expected. The hospital set up a "hot line" for parents seeking information on transfusions during the 1980-1985 period.

7 June 1994 - At its annual meeting in Halifax, the Canadian Hospital Association announced that it would develop a national campaign urging persons who had received blood between 1978 and 1985 to be tested for HIV. The campaign would involve individual hospitals, and the federal and provincial governments. Three weeks later, the Ontario Hospital Association launched a province-wide campaign urging blood recipients from the period in question to be tested for HIV.

25 June 1994 - After two years of discussion and debate, the Canadian Red Cross Society formally announced plans to construct a $150-million blood-processing plant near Halifax. The plant would be run jointly by the Red Cross and Miles Incorporated, a subsidiary of the German pharmaceutical company, Bayer AG. The plant was scheduled to open by 1997.

July 1994 - A paper in the journal *Science* quoted a WHO estimate that, worldwide, at least 3 million people had developed AIDS and that, cumulatively, at least 15 million people had been infected by HIV. It was estimated that, cumulatively, by the year 2000, a total of 30 to 40 million people would have been infected by HIV since the start of the epidemic.

19 July 1994 - A Reuter report in *The Globe and Mail* stated that the U.S. National Task Force on AIDS Drug Development had been told that some medical firms planned to terminate their AIDS research if the current approach to finding a therapy proved fruitless. The most recent avenue of research focused on "protease inhibitors"; protease is an enzyme essential to the

replication of HIV. This announcement was in line with information presented at the X International Conference on AIDS (see below).

7-12 August 1994 - The X International Conference on AIDS was held in Yokohama, Japan, the first ever in Asia. The conference included few reports on new results of AIDS drugs or therapies, and no indication that vaccine development was a realistic hope for the near future. One important announcement was that zidovudine (AZT), given to HIV-positive pregnant women, can protect their babies from infection. The dominant theme of the conference was that more resources needed to be directed to basic research on the virus and on the human immune system. There was an indication that the U.S. National Institutes of Health might divert some funds away from clinical trials of AIDS drugs towards basic research, although vaccine research and testing might not be affected. The conference organizers planned to stage the conference every two years in future, instead of continuing the annual format.

31 August 1994 - A report in *The Globe and Mail* stated that the federal Laboratory Centre for Disease Control "estimates that in Canada between 940 and 1,440 persons became infected due to transfusion in the period 1978-85" and that as many as 245 persons might still be unaware of their HIV-positive status. The figure of 1,440 was described as the "worst case estimate."

16 December 1994 - The WHO announced that the first major human tests of AIDS vaccines would be carried out with heterosexual male drug users in Thailand and homosexual men in Brazil as the key volunteers.

1 May 1995 - The Secretary-General of the Canadian Red Cross Society stated that, although Canada's blood supply today is as safe as that of any developed country, blood recipients still have approximately a 1-in-50,000 chance of contracting HIV through blood and blood products. This continuing small risk of infection is in part due to the fact that a blood donor may be infected by HIV but test negative for HIV antibodies at the time of donation.

29 June 1995 - Health Minister Diane Marleau announced funding for a national HIV/AIDS Treatment Information Network to be administered by CATIE, the Community AIDS Treatment Information Exchange of Toronto. The network would provide information on: the diagnosis and treatment of HIV and AIDS; clinical advances in the field; drug and non-drug therapies; medical and complementary therapies; and where to obtain care. Health Canada would provide $4.9 million over three years to establish the Network, which would be operational by the end of 1995.

7-12 July 1996 - Vancouver hosted the XI International Conference on AIDS. Data presented at this conference showed that it should be possible to transform HIV/AIDS from a terminal disease to a chronic controllable condition through the use of "drug cocktails" of three or more anti-HIV drugs.

10 September 1996 - Federal, provincial and territorial Ministers of Health agreed to establish, within one year, a new national authority to operate Canada's blood system. The new blood authority would operate at arm's length from all governments and be responsible for managing all aspects of an accountable and fully integrated blood system. Quebec decided to establish a separate agency of its own.

September 1997 - Health Canada – in close collaboration with national stakeholders involved in HIV/AIDS issues and under the direction of the Minister of Health, Allan Rock – began a national consultation process to obtain input, suggestions and advice, from both organizations and individuals, to help Health Canada shape the direction and priorities for Phase III of the National AIDS Strategy which became known as the Canadian Strategy on HIV/AIDS (CSHA). CSHA was to begin in April 1998 and continue for a further five years following that date.

September 1998 - Canadian Blood Services took over the operation of Canada's blood supply.

SELECTED REFERENCES

"AIDS: The Unanswered Questions." *Science*, Vol. 260, 28 May 1993, pp. 1219, 1253-1293.

Canada, Health and Welfare. *Building an Effective Partnership: The Federal Government's Commitment to Fighting AIDS*. Ottawa, 1990.

HIV and AIDS: Canada's Blueprint. Ottawa, 1990.

Canada, House of Commons, Standing Committee on National Health and Welfare. *Report on AIDS In Canada*. 9 May 1986.

DeVita, Vincent T. Jr., Samuel Hellman, and Steven A. Rosenberg. *AIDS – Etiology, Diagnosis, Treatment and Prevention*. Third Edition. J.B. Lippincott Company, 1992.

Greene, Warner C. "AIDS and the Immune System." *Scientific American*, Special Issue, September 1993, pp. 98-105.

MacDonald, Hon. David. Chairperson. *Confronting A Crisis: The Report of the Parliamentary Ad Hoc Committee on AIDS*. June 1990.

Nossal, Sir Gustav J.V. "Life, Death and the Immune System." *Scientific American*, Special Issue, September 1993, pp. 52-63.

Pantaleo, Giuseppe, Cecilia Graziosi, and Anthony S. Fauci. "The Immunopathogenesis of Human Immunodeficiency Virus (HIV) Infection." *The New England Journal of Medicine*, Vol. 228, No. 5, 4 February 1993, pp. 327-335.

Royal Society of Canada. *AIDS: A Perspective for Canadians*. Summary Report and Recommendations, Ottawa, 1988.