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CURRENT TRENDS IN RESEARCH REGARDING A CONTROL FOR THE HUMAN IMMUNODEFICIENCY VIRUS

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ABSTRACT

The focus of this paper is explaining what current research is ongoing in AIDS and HIV treatment. The biomedical treatment of HIV and AIDS is based on three separate but integrated steps: use of antiviral drugs that will interfere with continuation of the HIV cycle; restoration of the immune system, and treatment of opportunistic infections and cancers. With improved treatment, growing experience among health professionals in caring for HIV-infected patients, improved access to health care, and the decrease in number of new HIV infections in the United States, Canada and Western Europe due to health education is part of the success in the fight against HIV.

Key words: AIDS, HIV, Azidothymidine, protease inhibitors, HIV vaccine, prevention, health education

In the summer of 1981, Dr. Michael Gottlieb of the University of California, Los Angeles described a rare form of pneumonia that was appearing in homosexual men. Along with this rare pneumonia, other reports of rare forms of cancers were appearing in homosexuals. This "syndrome" was at first dismissed as the "gay plaque" by the media and was believed it would soon vanish as fast as it emerged. That was twenty years ago.

Origins and Course of the Human Immunological Virus

It is believed by the established scientific and medical community (6,7) that the origins of the human immunodeficiency virus (HIV) based on recent molecular epidemiological data identified that HIV type 1 (HIV-1) evolved with a subspecies of chimpanzee, *Pan troglodytes troglodytes*, and was present with them for centuries. In this subspecies of chimpanzees, HIV-1 does not cause disease. The jump from the chimpanzees to humans most likely occurred in the sub-Sahara region of Africa where chimpanzees are butchered and consumed as a source of protein. The most likely mechanism of transmission of the virus would have been contamination of an open wound by butchering process or the eating of under-cooked meat with open wounds in the mouth. This mode of transmission would have been sporadic and have escaped detection over the years, perhaps centuries.

This intermittent HIV infection in rural Africa might have been passed on to an infected person's sexual partner and probably have resulted in the deaths of both victims, without the further spread of the virus. Furthermore the onslaught of the opportunistic infections may have masked the AIDS and HIV infection. These diseases are often rare in manifestation in a healthy individual.

Human social and demographic conditions have changed for Africa, and world hence an epidemic was unleashed. These conditions are: migration from the rural regions to the urban centers, disintegration of the family due to the migratory nature of employment, with its attendant sexual promiscuity and extensive frequency of prostitutes, and contamination of blood supplies. Frequent civil uprisings and warfare in Central Africa most likely hasten the spread of this disease and others (7).

The introduction of the epidemic to developed countries such as the United States, Canada and Western Europe has its roots in the "sexual revolution". The high-risk sexual practices, drug use and travel to "exotic" locations made free targets among the young adults in the 1970s and early 1980s. The demographics for those effected from the HIV and AIDS epidemic in the United States has shifted from young homosexual males, intravenous drug users and hemophiliacs to the heterosexual population.

Fauci (7) reports that it is believed that the HIV and AIDS epidemic in the United States and most developed countries has reached a plateau, because the level of new cases is no longer increasing exponentially. In fact, in the United States, Western Europe and Australia the number of cases of AIDS (per 100 000 population) has decreased overall 48 %. The Center for Disease Control, Atlanta, GA, estimates that the half of the new cases of infection are young people of 25 years, or younger and are infected sexually. However, this reported plateau is deceptive. The number of infections among young heterosexual males and females is accelerating.

Globally, we have a pandemic, no populated area is escaping this infection and the sub-Saharan region is presently experiencing the greatest burden of the infection. The coun-

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tries formed from the former Soviet Union are experiencing an escalated number of new AIDS and HIV cases. If dramatic preventive steps are not taken, the infection rate in the Indian subcontinent and Southeast Asia will eclipse the Black Death Plagues of Europe (1,3,4).

Azidothymidine (AZT)

The first drug to show significant benefit in treatment of AIDS patients was Azidothymidine (AZT). It is still one of the primary drugs used in the treatment of AIDS. AZT or commercially known as *Retrovir* is a *nucleoside analog* that blocks viral replication by inserting it's self in place of thymidine during DNA assembly. This inhibits viral DNA function and growth. Without AZT, the average life expectancy of an individual with opportunistic infections is less than six-seven months (6). AZT has been proven in clinical tests and numerous studies show that the life expectancy for the patients generally will increase to one-two years, treatment with AZT for some individuals has led to some recovery of the immune system function.

This partial recovery is owed to the increased number of T_{helper} lymphocytes, opportunistic infections occur and some patients gain weight. AZT is seldom used by itself today as a "monotherapy". In the beginning of the AIDS outbreak it was the only effective drug. However, the use of AZT has not had its critics, in the mid 1990's the Concorde trial, held in England and France showed that in a blind study of HIV-infected individuals treated with AZT and a group that received no treatment. There was difference in the rate of deaths between the AZT-treated and untreated individuals (6). The benefit of this drug is in the psychological well-being of the patients and improving their perceived quality of life. The value of treating asymptomatic individuals in statistical analysis has resulted with a value of no significance according to these authors (6).

Although AZT has been effective in AIDS treatment, it has limitations:

a) *toxic side effects.* The basis of this drug is to disrupt process of the DNA polymerase. However, in prolonged treatment some AZT is incorporated into the cell's DNA leading to the death of the cell. Anemia results from killing red blood cells are a common side effect of AZT treatment.
b) *inability to prevent the progression of HIV infection to full blown AIDS.* This is due to the fact that the virus can mutate within its host. AZT-resistant HIV develops in the individuals who have been taking AZT.
c) *development of AZT-resistant variants.* HIV has a rapid mutation capacity. Normally, the mutations take place in the *pol* gene, because this slows the growth rate down in the virus. However, the *pol* gene is less sensitive to AZT.

Even though AZT has limitations, the effectiveness in slowing down the progression of the virus has given patients and researcher time to study the HIV virus and improve patients' quality of life. Additionally, the AZT drug has provided us with a mechanism that can inhibit HIV replication and serve as model for future research to improve the *nucleoside analog* drugs. The nucleoside analogs incorporate different DNA bases in the HIV DNA to inhibit its transcription. In a sense this acts to misspell the genetic instructions of the virus and hence halting its ability to function.

Protease Inhibitors

In 1996 a new class of anti-HIV drugs were developed and released for therapy: *protease inhibitors* (PI). This process is different from AZT; this agent inhibits HIV replication. PI targeted the viral enzyme protease. They work by binding to the HIV-protease enzyme and directly block its function. Protease inhibits the maturation of immature virus particles to maturity. Immature viral particles themselves are not infectious. Thus, drugs that inhibit the protease will inhibit the production of infectious HIV. A major advantage of using protease inhibitor is the reduction of the viral load in the blood to that below detection (6).

Highly Affective Antiretroviral Therapy (HAART)

When the protease inhibitors are combined with another regimen, highly affective antiretroviral therapy (HAART), the effect is remarkable when compared to the nucleoside analog reverse transcriptase inhibitors (NRTIs) of the late 1980s and early 1990s. The NRTIs therapy would consist of 1 or 2 nucliosides. The HAART regimen consists of three antiretroviral drugs approved by the United States Food and Drug Administration (USFDA). This enhanced therapy consists of a nonnucleoside, a nucleoside and a protease inhibitor (9).

Gallant (9) considers HAART as a revolutionary treatment of HIV. HAART will change the treatment of HIV to that of a manageable and chronic condition. The success of this therapy depends on early decisions that the patient and physician make together. The treatment should be delayed until the patient is educated and is willing to take responsibility to follow a strict schedule. Patient's discipline is crucial for the success of this therapy. Even with HAART and strict patient's regimen it will be impossible to achieve significant viral suppression. The problem with this combination of antiretroviral drugs is the rapid mutations that occur with the HIV.

PI interfere with the cleavage of polyprotein by the viral protease, which results in the production of noninfectious virions (9). On the other hand, the HAART regimen suppresses the viral load, which increases the CD4 cell count, improves the immunological function, delays clinical progression of the HIV and enhances patient's survivability.

Presently, HAART is considered to be one of the most effective therapies for control of the HIV infection and AIDS symptoms (6,7,9,10). Studies by the former listed researchers have determined that HAART is one of the most cost-effective medical innovations. Gallant (9) claims HAART has significantly reduced mortality, hospitalizations, the incidence of opportunistic infections, and the use

home care resources, skilled nursing homes and hospices. Like any medical treatment, HAART has shortcomings. The short-term and long-term side complications include: hepatotoxic effects, diabetes, and a number of metabolic deviations that appear with no reason.

Finally, other strains of drug resistant viruses are emerging and antiretroviral failure of some the antireretroviral agents has also emerged. Fauci (7) cites that the reason for HAART failure is due to the unfounded promise of success. The hope for success in his opinion encourages promiscuity and a return to unsafe sexual practices.

Furthermore, patients with HIV-1 are being found to harbor up to 12 mutated strains with in themselves. Fauci (7) declares that the HAART itself is problematic in that many HIV-infected people cannot tolerate the toxic effects of the chemicals, or comply with the strict regimen that requires large numbers of pills, complicated dosage schedules to be considered with personal diets and fluid intakes, and chemical interactions between the drugs and other materials ingested. Even if the patients are willing to comply with the scheduling and chemical concerns concerning HAART, they must have a low level of HIV-1 in their plasma. Testing for the HIV-1 virus is difficult, as it is notorious in its ability to hide in other tissues, and become latent. In a latent form no drugs so far can treat it.

Finally, HIV-1 is constantly in a mutable form. HIV-1 is able to change its phenotype, develop new strains that can evade the new drugs. The persistence of latent HIV misleads the detectable HIV-1 levels in the plasma. The actual level of the HIV-1 level may be actually much greater that indicated. This fact necessitates in the simplest case that lifelong treatment may be necessary. The drugs used to treat HIV are expensive and difficult for the patient to tolerate for long periods.

Other areas of research

Current research conducted in other areas to make HIV treatment more patient-friendly is being directed towards: a) preventing the virus from entering the cell and preventing the integration of the provirus from entering the nuclear DNA; b) purging the latent virus from its latent reservoirs in cells and tissues, and c) finally, to boost HIV-specific immune responses with in the body.

Early diagnosis and treatment is important in controlling the HIV infection. The decision to start therapy for early stage patients must be made by the physician and patient together. The needs of the patient should be evaluated in accordance with advantages and disadvantages of treatment.

Advantages of early treatment:

1) Prevents loss of immune function and allows for effective immune reconstitution.
2) Viral mutation is reduced, and the potential for drug resistance is decreased.
3) Patients with low baseline viral loads respond better to HAART, and "healthier patients" tolerate treatment easier.

Disadvantages of early therapy:

1) Early treatment will not make an asymptomatic patient feel better.
2) The daily reminder of treatment may psychologically harm patients who can benefit from denial when it may be beneficial.
3) Resistance to the drugs may develop earlier, therefore eliminating therapeutic options later.

Predictions for patients who are started are not definite how effective their treatment will be if it is delayed until symptoms if full blown AIDS appear. Patients who begin their treatment early lock themselves into a regimen that is demanding and may not be the best for them later. Many patients exhaust their treatment options prematurely, before they are able to show definite signs of improvement (9).

The HIV vaccine

Vaccines described by some authors (6) are being developed as those that will induce cellular mediated immunity and vaccines that are made from recombinant RNA that would induce the humoral immune response. Experiments with killed Simian immunodeficiency Virus (SIV) prevented infection at low doses of live SIV virus, yet it was unsuccessful against higher doses or repetitive doses of live SIV. This situation, high doses, and repetitive doses is probably closer to natural routes of HIV infection.

Research in development of the live vaccine against HIV is centered on the inactivation of the *nef*-gene, which is shared with the SIV and HIV virus (6). The immunity induced by the shared *nef*-mutant gene in an attenuated virus is stronger than those induced by the killed SIV. This indicates the safety of an attenuated HIV vaccine that will not induce AIDS. Vaccines designed to induce cellular immunity to HIV are also underway. Several trials are using combinations of vaccines designed to induce cellular immunity with those that will initiate humoral immune responses. Fauci (7) reports that the National Institute of Health has recently assessed a series of vector vaccines from harmless viruses (e. g., canary pox) that has been altered to make HIV proteins. The vectored vaccine with the purified HIV envelope protein has had encouraging results. The combination approach has appeared safe and has evoked both cellular and humoral immune responses that may provide protection from HIV infection.

The development of a vaccine for HIV is not likely in the near future as there are many theoretic reasons that will be effective. HIV evades the immune system in an infected individual because of: the high mutation rate of the virus, particularly the *en* gene sequences; the ability of the virus to become latent in cells and to proliferate by cell to cell contact.

Additionally, there are differences between the HIVs found in various geographical regions. A successful vaccine would have to be tailor made for each strain.

Biomedical efforts in research

The biomedical efforts to treat HIV-infected individuals will continue to focus on three main points (6): antivirals

that will interfere with continued HIV infection; restoration of the immune system, and treatment of opportunistic infections and cancers.

All of the approved anti-HIV drugs work by interference with the processes carried out by the virus in protein transcription and translation. This process reduces the viral load in patient's blood below the levels of detection, yet the fear of latency of the virus persists. The virus persists in the lymph nodes and macrophages much longer.

Another direction of research in antiviral therapy is to interfere with the ability of the virus to enter cells. Recombinant DNA procedures have been used to produce large quantities of CD4 proteins that will attract the HIV before it would enter the cell. This reduces the viral load but does not prevent further infection in HIV individuals.

t has been discovered that cells require a co-receptor, CCR5, to allow for HIV infection. A small percentage of he population lacks this receptor because of a genetic mution. Epidemiological studies have found that these indiiduals are resistant to HIV infection despite repeated expoures. Therefore an effective anti-viral therapy could be tareting the CCR5 co-receptor to prevent the spread of IIV-infection.

wo new classes of potential antiviral agents recently deeloped and directed at the molecular level are antisense olecules and ribozymes. The antisense molecules are eces of RNA or DNA molecules that will be inserted into e viral RNA of HIV. This disruption of the viral RNA ads to the destruction of the HIV, because the virus would t be able to replicate and build protein or other particles. bozymes are specialized antisense RNA molecules that mbine with HIV RNA, attack the RNA and cut the strand various sites destroying the virus.

Restoration of the immune system

e second targeted research area, restoration of the imne system, is important. Most of the symptoms resulting m AIDS are caused by the destruction of T-helper cells. ood cell growth factors are currently being studied to nulate and regenerate the immune system. Interluekin 2 -2) is the most promising in the restoration of the imne systems. This is logical as IL-2 is necessary for the wth of both T-helper and T-killer cells. However, there two serious drawbacks. When administered it causes a fever and shock. Second, the treatment requires hospiation, which is costly, and not feasible for developing ons to care for large number of patients. Bone marrow splants and blood transfusions are other avenues of inigation with limited expectations. The greatest technical blem that lies here is that the HIV-infected individual's y generally attacks and destroys the healthy tissue.

reatment of opportunistic infections and cancers

third area of research is important as it improves the h of AIDS patients and enables their system to better age the HIV infection. In terms of working with many e opportunistic infections and cancers that develop it is allenge, because many of these were diseases and infections that were rarer than the HIV virus prior to the AIDS epidemic.

Medical research reformed as a result of the HIV panemic

The AIDS epidemic has left its indelible mark in many facets of science and society. Research has been effected by AIDS. Research is now perceived as a global and public concern. In the past, the Food and Drug Administration of the United States government would require years of research and testing before an experimental drug would have been developed and implemented to be tested. Another reform in medical research is the parallel track. This allows patients to participate in research trials, even though they are unable to be at research centers. The patient is allowed to stay at home, his physician monitors his progress and reports it to a medical research center. The local physicians record and report the results to a central pool. This greatly enhances the test population and brings the physicians in the mainstream of medical research.

The parallel track of research provides the medical researcher and the community a greater stake in the investigation and search for an answer in working with AIDS and HIV.

Finally, the AIDS crisis has influenced upon medical research in the development of surrogate endpoints. In clinical trials, endpoints or standards are development to mark and compare the results of the research. When a disease is used, its cure or death of the individual has been traditionally used. A clinical study of AIDS could take years to complete. To assist in the preliminary evaluation of HIV drugs, alternative measures have been developed and adopted. The most common surrogate endpoints are the patients' CD4 (T-helper) lymphocyte cell count, the amount of viral protein (antigen) present in the blood, and the viral RNA that is present in the blood. The overall level of each of the surrogate endpoints reflects the overall health of the individual.

Specifically targeted educational programs

The role of public health education to appropriate populations does work. AIDS prevention campaigns to practice "safer-sex" in high-risk populations in the United States and Canada have resulted in a decrease in new cases of HIV infection. Addressing specific populations is strongly endorsed by the National AIDS Commission.

Populations targeted for education:

a) intravenous drug users. These individuals may be a conduit for spread of the infection into the heterosexual population. Clean needle programs have met resistance in many regions, for various reasons. Yet programs directed to this population had been underfunded and thus had limited success.
b) ethnic groups. In the United States, Black-Americans and Hispanics represent a disproportionate number of AIDS patients as compared to those of European descent. In Europe, minority populations reflect the

same trend as the United States in HIV-infection incidence rates.

c) reduction of backsliding behaviour. It is important to remind the general public continued adherence of safer behaviour.

Continued education for health workers is important in this crisis. Uganda, one nation that has been especially affected by HIV-AIDS now provides for government sponsored warnings about AIDS. Schools and the public media openly discuss the promotion of safer-sex. The journal *Natural Medicine* (2) reported that the foreign-financed non-governmental organizations are given free reign to educate people about AIDS. UNAIDS is sponsoring research in a tropical microbiocide substance that a woman can use before intercourse as well as the female condom. These interventions may help women to protect themselves from acquiring or passing the HIV infection if there is no other choice. Uganda and South Africa are establishing a collaborative AIDS policy that will apply pressure to the pharmaceutical industry to reduce the cost of medications. A single regimen of HAART consists of over 20 tablets, and will cost the individual thousands of dollars annually.

CONCLUSION

This epidemic will require partnerships between public and private sectors as well as stronger political bonds between the nations of the world. Control of the HIV-AIDS pandemic will not be an easy task. No nation will be untouched. Education, behaviour modification, continued research and development of understanding and compassion for the victims of this disease will be the key to ending this "new age plague" (5-8,11). Free communication and unfettered medical care for citizens regardless of nationality is vital. Unless methods of prevention, with or without a vaccine, are successful, the worst pandemic will occur in this century.

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