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EDITORIAL

GENERAL ARTICLES

Contents continued

CONTENTS *Continued*

DEPARTMENTS

THE AIDS BROCHURE

PROGRAMS, PRACTICES, PEOPLE

AIDS POSTERS

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Progress in Drug Therapies for HIV Infection

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Synopsis

The discovery of effective therapies for HIV requires a fundamental knowledge of retroviral infections. Research by the Public Health Service and collaborating organizations on oncogenic viruses, including retroviruses, has provided much of the basic understanding of retroviruses in general and anti-retroviral therapeutic strategies in particular.

Early work by the Viral Cancer and Developmental Therapeutic Programs of the National Cancer Institute and the Intramural Research Program of the National Institute of Allergy and Infectious Diseases has contributed much of the current understanding of AIDS and its therapy.

This paper describes the progress that has been made in the treatment of AIDS and the programs that have been created to develop future therapies. These programs include efforts to screen existing compounds for activity against HIV, to design new anti-HIV therapies, and to test potential agents in controlled clinical trials.

As a result of these activities, researchers have identified one drug, AZT, that has proven effective in prolonging the lives of some patients with AIDS, and are developing several other promising compounds. The key question no longer is whether HIV infection can be treated, but what is the best and fastest way to develop new therapies and improve existing ones.

As WITH ANY VIRUS, the different stages in the life cycle of the human immunodeficiency virus (HIV) present targets of opportunity for new retroviral agents. However, because viruses are so intimately associated with cells during their life cycle, drugs that interrupt the viral life cycle may be toxic to the host's cells.

Effective (and possibly curative) therapy for HIV infection may depend on a combination of strategies which, because they are directed at similar or multiple steps in the viral life cycle (*1*), help minimize possible toxic effects on the patient. Combination approaches may help make the emergence of drug-resistant strains less likely, as well.

Although the way that HIV enters the brain and causes neurologic damage is not known with certainty, successful therapeutic strategies must address the consequences of viral replication within the central nervous system. Similarly, investigators must consider the ability of HIV to remain latent in lymphocytes or macrophages for long periods of time (*2*).

National Institutes of Health (NIH) research takes two approaches to the development of anti-retroviral drugs, widespread screening of existing compounds and targeted development of new agents. Much of the emphasis to date has been on screening existing compounds because screening offers the best hope of near-term success and because a massive drug screening effort was already in place for anti-cancer drugs.

Screening Compounds for Anti-HIV Activity

The early identification of new anti-retroviral agents has been facilitated by the availability of rapid and sensitive *in vitro* screening systems that determine whether a putative drug can inhibit the replication and T-cell-killing activities of HIV (*3*). The goal of the acquired immunodeficiency syndrome (AIDS) screening and preclinical drug development program is to discover and develop expeditiously the most promising anti-HIV agents for clinical testing. This program has been implemented primarily to support the acquisition, testing, bulk production, pharmacology, and toxicology of potential candidates for clinical evaluation. Government laboratories, university cen-

ters, and private companies have been invited to submit agents to be screened for anti-retroviral activity. About 3,000 agents were screened in 1987.

The anti-retroviral properties of 3′-azido-2′, 3′-dideoxythymidine, or AZT, were discovered by the drug screening program for anti-HIV agents. The development of AZT is an example of a partnership among the Public Health Service (PHS); a private pharmaceutical organization, Wellcome Research Laboratories; and academic centers. AZT was first synthesized in 1964 as a possible therapy for cancer at the Michigan Cancer Foundation under a grant from the National Cancer Institute (NCI) (*4*). The activity and expected therapeutic concentration of AZT against diverse strains of HIV was demonstrated by PHS workers in February 1985 (*5*). AZT was first administered to a patient on July 3, 1985 (*6*), at the Warren G. Magnuson Clinical Center at NIH. In February 1986, a multi-center, randomized, placebo-controlled trial of AZT involving about 280 patients (*7*) was begun. Within 7 months, an independent data safety monitoring board recommended that the study be terminated and that patients previously randomized to placebo be offered the drug under an open-label arrangement.

NIH was able to expedite the drug distribution very quickly. When it became apparent that AZT was effective in certain AIDS patients, NIH, in collaboration with the Burroughs Wellcome Company, quickly set up a system to distribute the drug to all patients who might benefit from it. Existing NIH mechanisms were used to distribute the drug in 90 days to nearly 5,000 patients free of cost. By March 1987, the Food and Drug Administration (FDA) licensed AZT for general distribution.

AZT has been shown to prolong survival in patients with AIDS and to confer certain other clinical benefits. While AZT is not a cure and can cause prominent side effects in some patients, the development of this drug has proved that AIDS and the retrovirus which causes the disease are not inherently beyond the reach of therapeutic intervention. Many of the lessons learned from the AZT experience are likely to have value in developing new anti-retroviral drugs.

Targeted Drug Development

Targeted drug development applies information gained about the properties of HIV to the process of designing agents to interfere with the life cycle of the virus or with structural components of the virus (see table). Drugs are being identified or designed to prevent specific viral proteins from folding or working properly, and stopping viral replication. Development of such drugs depends heavily on comparatively recent advances in microcomputers, computer modeling, chemistry, and gene cloning techniques for the production of cellular or viral proteins.

NIH has begun programs to promote targeted drug development. Among these is the National Cooperative Drug Discovery Groups for the Treatment of AIDS (NCDDGs). The 18 NCDDGs are organized according to one of four specific therapeutic approaches: immunologic (either the humoral or cellular arm of the immune system); biologic (the biochemical or biophysical properties of HIV or host cell proteins needed for viral replication); synthetic (synthesizing or altering natural products to interfere with a particular step in viral replication); and comprehensive (all three areas). The 18 groups represent an expanded, coordinated effort to use the capabilities of academic institutions, pharmaceutical companies, biotechnology and bioengineering companies, NIH intramural scientists, and international organizations, in cooperation with the Federal Government, to develop anti-HIV drugs.

Since immunologists and virologists predominantly have been involved in AIDS research, NIH has earmarked funds to bring intramural investigators trained in various scientific areas into AIDS research. NIH has established six program project grants to encourage the organization of multidisciplinary extramural research groups to focus on studies related to the structural biology of HIV.

Progress in targeted drug development includes recent *in vitro* data suggesting that genetically engineered CD4 molecules can bind to HIV virions and provide high-affinity false attachment sites for the virus, thereby blocking virus replication (*8–12*). We can expect that in the future a genetically engineered CD4 molecule will be adapted as a novel experimental treatment for AIDS.

Preliminary data suggest that certain specially modified compounds ("anti-sense" oligodeoxynucleotides) can be constructed to bind to an HIV-specific gene transcript, art/trs mRNA, and interfere with its function *in vitro* (Makoto Matsukura, NCI, and Broder, unpublished data, 1987). Thus, it may be possible to reduce viral expression even in chronically infected cells *in vivo*.

The final steps of viral replication involve secondary processing of the viral proteins. Second-

Stages of HIV replication that may be targets for therapeutic intervention

Stage	*Possible intervention*
Binding to target cell	Antibodies to virus or cellular receptor; genetically engineered, soluble CD-4 receptors; dextran-sulfate?
Entry into target cell and uncoating of RNA	Drugs (by analogy with calmodulin antagonists for Epstein-Barr infection or amantadine for type A influenza virus infection)
Transcription of RNA to DNA by reverse transcriptase	Reverse transcriptase inhibitors (AZT and other dideoxy- or didehydro-nucleoside congeners)
Degradation of RNA by RNase activity (encoded by viral pol gene)	RNase H inhibitors
Integration of DNA into host genome	Agents that inhibit pol-encoded integrase function may be found
Transcriptional efficiency/translation of viral RNA	Inhibitors of tat-III or art-trs; "anti-sense" constructs
Ribosomal frameshifting	Possibly specific "frameshift inhibitors" can be found
Viral component production	Myristylation, glycosylation, or protease inhibitors (aspartyl proteinase-specific inhibitors)
Viral budding	Interferons; antibodies to a viral antigen

ary processing systems could be targets for anti-retroviral therapy. For example, castanospermine, a novel drug that inhibits the proper trimming of the sugars on the HIV envelope glycoproteins, may interfere with virus entry into the target cell. Castanospermine reduces cell fusion, which may inhibit cell-to-cell transmission of the virus. These findings have inspired several related studies of this and analogous compounds as an entirely new class of AIDS drugs that work at a different stage in the replicative cycle of HIV than, for example, AZT.

Agents that inhibit reverse transcriptase, an enzyme essential for the replication of the virus, probably will have an immediate clinical impact. Several potent agents that inhibit the enzyme either are already available, having been developed for the therapy of conventional viral diseases (such as phosphonoformate) (*13*), or are being developed specifically for AIDS treatment on the basis of *in vitro* screening systems for activity against HIV. The dideoxynucleoside analogues (which include AZT) are of special interest because they prove that a simple chemical modification of the sugar moiety can predictably convert a normal substrate for nucleic acid synthesis into a compound with a potent capacity to inhibit the replication and cytopathic effect of HIV, at least *in vitro* (*14*). 2′, 3′-dideoxycytidine (ddC), the most potent anti-viral nucleoside now available, is currently being evaluated in AIDS patients. Three new nucleoside analogues, CS-87, D4C, and D4T, have been identified by NCDDG investigators and are currently undergoing *in vitro* testing. Drugs that are currently undergoing preclinical development as potential AIDS therapies are CD4, D4C, D4T, CS-87, phosphonoformate, and castanospermine.

Several other approaches to anti-retroviral therapy are being considered. Interferons, and drugs which induce interferons (such as ampligen), are being studied at many centers. Interferons are thought to inhibit viral replication by interfering with the assembly and release of mature virions. Another example is the use of monoclonal antibodies to the envelope protein, which could have a therapeutic role.

Drug Evaluation

The evaluation of promising therapeutic agents is a crucial part of the AIDS drug development process. The experience with AZT underscores the principle that relying on a controlled clinical trial need not retard drug development, but rather can greatly accelerate the development and availability of a therapeutic agent. AZT became an FDA-approved drug available on a prescription basis about 2 years after its identification as an agent that could suppress the AIDS virus in a test tube. The usual time for drug development would range from 7 to 10 years. The development of AZT would certainly have taken longer, and it is very likely that the drug would have been dismissed altogether, without the information gained in the multi-center controlled trial.

NIH has established a clinical trials network to determine the safety and efficacy of both anti-retroviral and immunomodulatory therapies for the

treatment and control of HIV infection, and specific therapies (including prophylaxis) for the opportunistic infections and malignancies associated with HIV infection. Two NIH advisory groups, the AIDS Decision Network Committee (ADNC) and the AIDS Clinical Drug Development Committee (ACDDC), review data on proposed experimental drug treatments from any source and set priorities for those drugs to be developed preclinically (ADNC) and to enter clinical trials (ACDDC).

Promising drugs are tested at institutions that are participating in the AIDS Clinical Trials Cooperative Group. The first major initiative in this effort was the establishment of the AIDS Treatment Evaluation Units. A group of 19 contracts support 35 separate sites for clinical investigation. Another initiative, the Clinical Study Groups, established 17 additional clinical investigation sites. All these institutions are now participating in the AIDS Clinical Trials Cooperative Group. As of January 1988, 26 clinical protocols of a group of therapeutic agents, alone or in combination, were being conducted with more than 2,700 patients.

Clinical trials of promising agents are in progress in NIH intramural programs. The first clinical trial has begun of ddC to treat patients with AIDS and AIDS-related complex. Preliminary clinical results show that ddC can suppress viral replication *in vivo*, but it is too early to say that it has efficacy as a new therapy (*15*). The dose-limiting toxicity is a peripheral neuropathy which results in pain in the feet. The neuropathy can be drastically reduced or eliminated by building in rest periods during which the drug is briefly withheld. Combining ddC with drugs with nonoverlapping profiles of toxicity, or with bone-marrow stimulants, could minimize the potential for cumulative toxicity.

Because HIV attacks and destroys the host's immune system, immunologic reconstitution (drugs and techniques to help restore the damaged immune defenses) is another component of AIDS treatment. Immunologic reconstitution is still highly experimental. This approach, together with specific anti-retroviral therapy, provides a two-pronged attack aimed at suppressing viral replication as the damaged immune system is rebuilt.

Researchers at NIH have conducted clinical trials with biological response modifiers, such as alpha-interferon and interleukin-2, and have performed bone-marrow transplantation combined with antiviral therapy in sets of identical twins.

AIDS therapeutics currently being tested in NIH-supported clinical trials

Anti-HIV therapies:
AZT
ddC
Acyclovir[1]
AL-721
Foscarnet
Desiclovir[1]
Interferon-alpha[1,2]
Interferon-gamma[1,2]
IL-2[1,2]
Tumor necrosis factor[1,2]
Ampligen (to be tested)
Ribavirin (to be tested)
Therapies for opportunistic infections:
Aerosol pentamidine
DHPG[1]
Trimetrexate
Amphotericin B
Fluconazole
Trimethoprim-sulfamethoxazole
Therapies for AIDS-associated malignancies:
Radiotherapy[1]
Doxorubicin
Biological response modifiers:
Bone marrow transplantation[1]
Muramyl tripeptide

[1]In combination with AZT.
[2]Functions also as a biological response modifier.

NIH grantees have found that a recombinant preparation of the human growth factor, granulocyte macrophage-colony stimulating factor (GM-CSF), boosted white blood cell counts in adult AIDS patients. Scientists believe that increasing the number and function of white blood cells may reduce illness and death from the infections that AIDS patients develop. An intramural trial of GM-CSF and AZT has started.

Drugs being studied in NIH-sponsored clinical trials are listed.

Considerations for the Future

An important question is whether a drug can prevent the onset of AIDS in asymptomatic carriers of HIV. In theory, it might be easier to prevent HIV-induced damage than to repair it after damage has occurred. Any therapy which significantly reduces the proportion of infected individuals who develop AIDS, or which meaningfully delays the onset of the disease, could fundamentally alter the course of the AIDS pandemic. However, because of the toxic side effects, AZT (or any drug) could do more harm than good. To

help resolve this issue, the NIH Clinical Trials Cooperative Group has initiated a placebo-controlled AZT early intervention trial involving about 1,500 asymptomatic HIV-seropositive volunteers. Similar trials could be initiated as other agents with comparable clinical activity become available. It is possible that an answer will be known within 2 to 3 years.

AZT, and essentially every other treatment now under study or proposed, is predicated on a strategy of slowing the pace of HIV replication in a person with established infection, making some immune system regeneration possible, or at least preventing further deterioration. The virus would remain in the body despite therapy. If therapy were stopped, as might be necessary in the case of drug toxicity, the virus could pick up where it left off.

It is theoretically possible, based on work with animal models, to initiate drug or biologic therapy to block the establishment of certain retroviral infections, provided the therapy is given at the time of infection or shortly after the viral inoculation. This, at least in theory, has established that exposure to a retrovirus need not lead to the development of a life-time infection if the cycle of replication is interrupted early. We might be able to obtain useful information by studying individuals who receive a known exposure to HIV, such as by a needle stick while caring for patients or in a laboratory accident.

Studies to answer whether an anti-retroviral intervention (AZT) works in such a clinical setting are in the planning stages. The premise is that for optimal effects an individual might not need to receive long-term treatment in this setting. Other drugs could be tested in a comparable way. At the conclusion of such studies, the information gathered might teach us about the value of prophylactic therapy in a more general setting (for example, treatment to prevent the establishment of infection following a sexual contact with a virus carrier).

At present, one can say only that prophylactic therapy for persons who do not yet have an established infection might be possible at some future time. But there is insufficient information to say when such a prophylactic therapy might be possible or practical. Education and appropriate public health measures are the only ways to protect uninfected individuals. No technology is ever likely to be more reliable and cost effective for a person or for society than a commitment to mutually monogamous sexual relations and elimination of intravenous drug abuse. The development of anti-retroviral agents should not be viewed as a reason to reduce our commitment to prevent viral transmission in the first place.

Conclusions

PHS agencies have attacked HIV on a number of fronts, and there have been some successes in anti-retroviral chemotherapy. We are cautiously optimistic that new and better strategies for treating diseases caused by pathogenic human retroviruses will be possible.

The future of AIDS therapy will depend on how well we have absorbed the lessons of developing new therapies. New therapies for AIDS can be accelerated (or retarded) by the methods used to select and test experimental treatments. In particular, the principle of studying the life-cycle of HIV and developing new treatments to attack specific points in the replicative cycle has been extremely useful in identifying new experimental agents.

This approach will continue to be useful in the future. But identifying new drugs and biologic therapies is only a first step. We need to make a commitment to the controlled trial methodology for developing new therapy, including the use of placebo-controls (such as an early intervention study), where the risk-to-benefit ratio is not clear and cannot be established or when a promising experimental agent might be otherwise discarded.

Three years ago we faced the unthinkable: there was no certainty that any anti-retroviral therapy would ever be successful. While there is much that still needs to be done, we now face a totally different future.

References

1. Gallo, R. C., and Fauci, A. S.: The human T-lymphotropic viruses. *In* Harrison's principles of internal medicine, edited by E. Braunwald, et al. McGraw-Hill, New York, NY, 1987, pp. 1550–1553.
2. Fauci, A. S.: AIDS: immunopathogenic mechanisms and research strategies. Clin Res 35: 503–510 (1987).
3. Mitsuya, H., Matsukura, M., and Broder, S.: Rapid *in vitro* systems for assessing activity against HTLV-III/LAV. *In* AIDS: modern concepts and therapeutic challenges, edited by S. Broder. Marcel Dekker, Inc., New York, NY, 1987, pp. 303–333.
4. Horwitz, J. P., Chua, J., and Noel, M.: The monomesylates of 1-(2′-deoxy-b-D-lyxofuranosyl) thymine. J Org Chem 29: 2076–2078 (1964).
5. Mitsuya, H., et al.: 3′-azido-3′-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*. Proc Natl Acad Sci USA 82: 7096–7100 (1985).

6. Yarchoan, R., et al.: Administration of 3′-azido-3′-deoxythymidine: an inhibitor of HTLV-III/LAV replication, to patients with AIDS or AIDS-related complex. Lancet No. 8481: 575–580, Mar. 15, 1986.
7. Fischl, M. A., et al.: The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 217: 185–191, July 23, 1987.
8. Smith, D. H., et al.: Blocking of human immunodeficiency virus infectivity by a soluble, secreted form of the CD4 antigen. Science 238: 1704–1707, Dec. 18, 1987.
9. Deen, K. C., et al.: A soluble form of CD4 (T4) protein inhibits AIDS virus infection. Nature 331: 82–84, Jan. 7, 1988.
10. Fisher, R. A.: HIV infection is blocked *in vitro* by recombinant soluble CD4. Nature 331: 76–78, Jan. 7, 1988.
11. Hussey, R. E. et al.: A soluble CD4 protein selectively inhibits HIV replication and syncytium formation. Nature 331: 78–81, Jan. 7, 1988.
12. Traunecker, A., Luke, W., and Karjalainen, K.: Soluble CD4 molecules neutralize human immunodeficiency virus, type 1. Nature 331: 84–86, Jan. 7, 1988.
13. Sandstrom, E. G., et al.: Inhibition of human T-cell lymphotropic virus type III *in vitro* by phosphonoformate. Lancet No. 8444: 1480–1482, June 29, 1985.
14. Mitsuya, H., and Broder, S.: Inhibition of the *in vitro* infectivity and cytopathic effect of human T-cell lymphotropic virus, type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2′, 3′-dideoxynucleosides. Proc Natl Acad Sci USA 83: 1911–1915 (1986).
15. Yarchoan, R., et al.: Phase I studies of 2′, 3′-dideoxycytidine in severe human immunodeficiency virus infection as a single agent and alternating with zidovudine (AZT). Lancet No. 8577: 76–81, Jan. 16, 1988.