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MINIREVIEW

Treatment of Human Immunodeficiency Virus Infections

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The licensure of 3'-azido-3'-deoxythymidine (also known as azidothymidine, AZT, zidovudine, or Retrovir) for certain manifestations of human immunodeficiency virus (HIV) infections will usher in a new era of antiretroviral therapy for acquired immune deficiency syndrome (AIDS). With it will come a new Pandora's box of questions related to the apportionment and proper study of a scarce and incompletely understood commodity in the midst of an epidemic situation. What are the proper roles of the government and the manufacturer (Burroughs-Wellcome Co.) in assuring that optimum quantities of AZT are produced and that those in greatest need are able to receive it? How can the diversion of AZT to unproven indications (e.g., uncontrolled treatment of asymptomatic HIV carriers) be averted? How can properly controlled clinical trials continue so that reliable information can be obtained on appropriate uses of AZT? How should other promising drugs, such as ribavirin and dideoxycytidine (ddC), be compared with AZT? None of these questions has an easy answer, and all are interrelated.

In this context, we will review briefly current approaches to the development of anti-HIV therapeutics from a molecular level to a clinical level. In particular, we will summarize the current status of both laboratory and patient studies of AZT and other promising antiretroviral agents.

HIV REPLICATIVE CYCLE

Within the replicative cycle of HIV there are certain virus-specific steps which are potential targets for antiviral therapy (Table 1). HIV begins replication by binding of the envelope glycoprotein to specific cell receptors on CD4+ target cells. The virus fuses with the cell membrane, penetrates the cell, and is subsequently uncoated, with the release of its genomic RNA. In the cytoplasm, this RNA is transcribed into DNA by the virus-encoded reverse transcriptase enzyme, a target for many antiretroviral drugs, including AZT. The DNA is then circularized, and some of it is integrated into the host chromosomes, where it remains in a quiescent (proviral) form until the infected cell is activated. At that point, proviral DNA is transcribed into viral RNA, which is processed before binding to ribosomes to initiate translation and synthesis of virus-specific proteins. Some of these proteins are cleaved to smaller forms and glycosylated. Viral glycoproteins are synthesized and glycosylated in the rough endoplasmic reticulum and transported through the Golgi apparatus to the plasma membrane. Then the genomic RNA and viral proteins are assembled, and virus particles are released by budding through the plasma membrane. The HIV genome includes the genes *tatIII* and *trs-art*, which code for transactivating factors that regulate viral gene expression. The *tatIII* gene codes for a transactivator protein that increases the rate of synthesis of virus by regulating the transcription of viral RNA or the translation of mRNA into viral proteins or both. The product of the *trs-art* gene may act after transcription to relieve negative regulation of viral RNAs coding for capsid and envelope proteins.

AZT

Initially developed as an anticancer drug in the 1960s, AZT has suddenly emerged as the only drug with proven benefit in the prolongation fo life among patients with AIDS (M. A. Fischl et al., submitted for publication). The activity of AZT in patients is probably a result of its potent anti-HIV effect demonstrated in vitro (16, 17). Within cells AZT is converted by cellular kinases to a triphosphate form which is a strong competitive inhibitor of HIV reverse transcriptase (7). In addition, when AZT monophosphate is incorporated into DNA by HIV reverse transcriptase, its 3' substitution prevents further 5' to 3' phosphodiester linkages and terminates viral DNA chain synthesis. Easily achievable blood concentrations are effective inhibitors of HIV replication in vitro (1 to 5 μM).

AZT is available in both oral and parenteral forms. Bioavailability after an oral dose approximates 60%, and penetration of the blood-brain barrier is sufficient to achieve virostatic concentrations within the central nervous system.

Following phase-1 (dose-finding) studies suggesting a partial reconstitution of immune responses in recipients of oral and intravenous regimens of AZT (26), large multicenter placebo-controlled trials were conducted in patients with AIDS and AIDS-related complex (ARC). AIDS patients were all within the first 4 months after their initial bout with *Pneumocystis carinii* pneumonia, and ARC patients all had either oral thrush or significant weight loss. These studies began in February 1986 and included 282 adult patients (Fischl, submitted; D. D. Richman et al., submitted for publication). Of the AZT recipients (250 mg every 4 h orally), 85 had AIDS and 60 had ARC; in the placebo group were 75 AIDS and 62 ARC patients. The trial was initially designed to treat all patients for 6 months, with study termination planned for December 1986. An independent Data Safety Monitoring Board was established to regularly review differences in morbidity and mortality among the groups. By September 1986, it had become clear that major differences in survival were appearing. At that time, 19 placebo recipients had died (12 with AIDS, and 7 with ARC), as compared with only 1 AZT recipient with AIDS. A number of other parameters were also improved in AZT recipients, including numbers of opportunistic infections, patient weight, skin test reactivity, and T4 lymphocyte

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TABLE 1. Targets of action of some HIV inhibitors

Virus replication step	Inhibitors
Adsorption or penetration	AL-721 and peptide T (?)
Reverse transcription	AZT, ddC, phophonoformate, HPA-23, and suramin
Transactivation	Inactivators of *tatIII* or *trs-art* gene products (?)
Posttranscriptional processing and translation	Ribavirin and interferons (?)
Assembly and release	Interferons (?) and glycosylation inhibitors

numbers in peripheral blood. Given these results, the monitoring board concluded that the study should be terminated and that all placebo recipients should be offered AZT. Preliminary analysis of circulating HIV p24 antigen in the plasma of AZT recipients at one center showed substantial reductions, as compared with values observed in placebo recipients (R. E. Chaisson, J. P. Allain, M. Leuther, and P. A. Volberding, Letter, N. Engl. J. Med. **315**:1610–1611, 1986). If confirmed, these studies will support the concept that the clinical benefits of AZT are mediated through an antiviral effect.

Faced with these preliminary encouraging results, the National Institutes of Health (NIH), Food and Drug Administration, and Burroughs Wellcome launched an unusual and highly successful venture to provide AZT for those most likely to benefit, i.e., patients who have recovered from *P. carinii* pneumonia. In the initial 6 weeks, over 3,000 individuals were treated under this Treatment Investigational New Drug program, a remarkable achievement. In March 1987, licensure of AZT was approved in the United States for adults who have symptomatic HIV infection (AIDS and advanced ARC) and who have a history of cytologically confirmed *P. carinii* pneumonia or an absolute CD4 (T4 helper inducer) lymphocyte count of less than 200/mm^3 in the peripheral blood.

Many important questions regarding AZT remain. How long will improvement be sustained? Can similar beneficial responses be seen in other HIV-associated syndromes, e.g., AIDS dementia? Will asymptomatic HIV carriers be helped or harmed by AZT? In this respect, it is important to point out that AZT has considerable toxicity. Adverse effects of AZT are directed primarily against erythrocyte and granulocyte precursors. Anemia sufficiently severe to require multiple transfusions was observed in over 20% of patients receiving AZT in the controlled trials, and granulocytopenia was observed in approximately 16% (Richman et al., submitted). Headache was the most common adverse symptom observed, and one case of apparent AZT encephalopathy has been reported (D. N. Hagler and P. T. Frame, Letter, Lancet **ii**:1392–1393, 1986). Although these adverse effects are reversible and are tolerable in patients with AIDS or advanced ARC, it is not clear whether in less-ill individuals, e.g., asymptomatic carriers of HIV, the benefits of AZT will outweigh the risks.

For these reasons, it is imperative that further carefully controlled clinical trials of AZT be conducted in a wide variety of populations, including asymptomatic HIV carriers, patients with persistent generalized lymphadenopathy, patients with HIV neurologic disease, patients with Kaposi's sarcoma, and pediatric patients with AIDS or ARC.

Preliminary studies of AZT in HIV neurologic disease suggest some benefit (25). However, the duration and magnitude of the responses need confirmation in carefully controlled trials of more advanced HIV dementia.

The interactions of AZT with agents such as trimethoprim-sulfamethoxazole and rifampin should also be pursued to avoid compounding the bone marrow toxicity of AZT. As is discussed below, AZT may act either synergistically or antagonistically with other antiviral drugs in vitro (10, 11, 15, 23), and these interactions must be explored in vivo.

It is critical that in planning for AZT dispersal in a time of drug scarcity, the two principal aims must be to provide AZT for those in whom benefit has been established and to allow well-controlled studies to proceed in other populations. Burroughs Wellcome has committed itself to establishing a screening program to accomplish these objectives. Private and governmental insurers must also commit the funds necessary to pay for AZT, estimated to cost $7,000 to $10,000 per patient per year.

To facilitate the evaluation of AZT and other agents in patients with HIV infections, the NIH have developed a comprehensive program for drug evaluation. Nineteen university medical centers have now been designated as AIDS Treatment Evaluation Units. Three AIDS Treatment Evaluation Unit multicenter trials are already under way: the first is a placebo-controlled study of AZT in localized Kaposi's sarcoma, the second is a dose comparison study of AZT in patients who have recovered from *P. carinii* pneumonia, and the third is a phase-1 pediatric trial. Many other AZT studies are planned, including trials in HIV neurologic disease, persistent generalized lymphadenopathy, and asymptomatic HIV carriers. Phase-1 pharmacokinetic evaluations of AZT in combination with other agents are also planned.

To expedite the selection of drugs for study and to ensure the implementation of appropriate protocols, the NIH have also established an AIDS Clinical Drug Development Committee comprised of representatives from within the NIH, the Food and Drug Administration, and the AIDS Treatment Evaluation Units. This committee is the principal advisory body to the NIH on candidate drugs to enter extramural clinical trials. In addition, studies of AZT and other interesting agents will be conducted intramurally at the NIH, by other agencies of the government, such as the U.S. Army and the Veterans Administration, and by Burroughs Wellcome. Coordination of these efforts will be necessary, particularly as long as AZT supplies remain limited, to ensure the optimum utilization of this and other drugs.

ddC

AZT is not the only nucleoside with anti-HIV activity. A number of 2′-3′-dideoxynucleosides inhibit HIV replication in vitro; of these ddC is among the most potent (3, 14). Preliminary studies suggest that ddC is phosphorylated by cellular kinases to a triphosphate form that inhibits HIV reverse transcriptase. These effects can be reversed by the addition of deoxycytidine, probably by competition for deoxycytidine kinase (5).

Animal pharmacokinetic studies have already been conducted and phase-1 clinical trials of ddC are currently under way at the National Cancer Institute in patients with AIDS and other HIV-associated disorders. These protocols are analogous to those conducted in 1985 and 1986 with AZT. Plans are under way to rapidly bring ddC into carefully

controlled phase-1 and phase-2 (therapeutic) trials in the AIDS Treatment Evaluation Units during 1987.

RIBAVIRIN

As recently reviewed (8), ribavirin (1-β-D-ribofuranosyl-11-1,2-triazole-3-carboxamide) has broad-spectrum activity against many DNA and RNA viruses. McCormick et al. first demonstrated that ribavirin temporarily suppresses the replication of HIV at concentrations of 50 to 100 μg/ml (13). Others, using a variety of different cell culture systems, have found variable susceptibility of HIV to ribavirin, with some cultures being inhibited at concentrations as low as 4 μg/ml and others being completely resistant to the drug (M. Vogt and M. S. Hirsch, unpublished data). The mechanisms of HIV inhibition by ribavirin remain unclear.

Ribavirin is excreted slowly by renal mechanisms; the half-life in erythrocytes approximates 40 days. Ribavirin can be given orally, and significant levels are obtained in the cerebrospinal fluid after several weeks of therapy, even in the absence of neurologic disease (C. Crumpacker, G. Bubley, D. Lucey, S. Hussey, and J. Connor, Letter, Lancet ii:45–46, 1986). Toxicity has primarily involved anemia secondary to hemolysis and inhibition of hemoglobin synthesis (8).

Phase-1 studies have been conducted in both patients with AIDS and patients with ARC. In one study, seven of nine patients initially positive for HIV became virus-free during treatment, but in five of the seven, HIV cultures became positive once therapy was discontinued (C. Crumpacker, G. Bubley, S. Hussey, L. Schnipper, W. Haegy, R. Finberg, M. F. McLane, J. Allan, and M. Essex, Abstr. Int. Conf. AIDS, Paris, France, 1986). Double-blind, placebo-controlled trials of ribavirin have been conducted in patients with persistent generalized lymphadenopathy (R. Roberts et al., manuscript in preparation). Daily oral doses of 600 or 800 mg were compared with a placebo over a 6-month period in 163 patients. Of 56 patients in the placebo group, 10 (18%) developed AIDS during the period of observation. In the 600-mg group, 6 of 55 (11%) developed AIDS, whereas in the 800-mg group, none of 52 developed AIDS. Few details of these studies have been made public, and results of a similar study in patients with ARC have not yet been reported. Information concerning the comparability of groups and data analysis are being reviewed by the Food and Drug Administration. Nevertheless, the preliminary results indicate that ribavirin should receive extensive evaluation in other populations, including asymptomatic HIV carriers, patients with AIDS, patients with HIV neurologic disease, and children with symptomatic HIV infections. Comparisons with AZT in these populations will be of great interest.

OTHER DRUGS

Several hundred agents have now been evaluated for their activity against HIV in vitro. Of these, few have shown sufficient activity to warrant further investigation in patients. Most of these have been inhibitors of reverse transcriptase, including suramin, HPA-23, and phosphonoformate (2–6, 21, 22). These agents have been or are being tested in clinical trials.

Other nucleoside derivatives are under study; some, e.g., 3′-azido-2′3′-dideoxy-5-ethyluridine (CS-85), 3′-azido-2′3′-dideoxyguanosine, 2′3′-dideoxythymidine, 2′3′-dideoxythymidinene, and 2′3′-dideoxycytidinene, show considerable activity in vitro and will now be studied for safety and tolerance (1, 3; H. Hartman, G. Hunsmann, and F. Eckstein, Letter, Lancet i:40–41, 1987; R. F. Schinazi, C. K. Chu, P. Feorino, and J.-P. Sommadosi, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1092, 1986). Agents have also been developed that act at other sites of viral replication. Peptide T (19) and AL-721 (P. Sarin, R. C. Gallo, D. I. Scheer, F. Crews, and A. S. Lippa, Letter, N. Engl. J. Med. 313:1289–1290, 1985) have been reported to have activity against viral attachment or penetration, but these reports need confirmation. Another approach to the inhibition of HIV replication has been the use of oligonucleotides that have been synthesized as complementary sequences to certain regions of the HIV RNA or mRNA (27). These "hybridons" may act as competitive inhibitors at the level of transcription or translation; this hybridization competition has been called the "antisense RNA" approach. Whether such an approach will be applicable in vivo is unclear.

Interferons appear to act late in the HIV replication cycle. Not only alpha interferon but also beta and gamma interferons, as well as granulocyte-macrophage colony-stimulating factor, have some activity against HIV in vitro (9, 12, 18, 24). In addition, several inhibitors of viral protein glycosylation are currently being investigated. It must be emphasized, however, that in vitro inhibition of HIV does not equate with clinical benefit, and good therapeutic or toxic ratios in lymphocyte cultures may not reflect similar ratios in patients. The list of agents with in vitro activity is growing daily, but translation into proven clinical efficacy will be much slower.

TABLE 2. Interaction of antiviral combinations in vitro

Combination	Action	Reference or source
AZT + alpha interferon	Synergism	11
AZT + ribavirin	Antagonism	23
Phosphonoformate + alpha interferon	Synergism	10
Ribavirin + phosphonoformate	Synergism	M. Vogt, unpublished data
AZT + acyclovir	Synergism	15
Suramin + acyclovir	Synergism (?)	20

COMBINATION THERAPY

Combination chemotherapy has become a hallmark of many infectious diseases, ranging from tuberculosis to gram-negative bacteremia to enterococcal endocarditis. In viral infections, synergism has occasionally been demonstrated in vitro, but combinations of drugs have rarely been used in patients.

Several recent studies have been directed towards exploring drug combinations directed against HIV in vitro (Table 2). Although many combinations show synergistic interactions by strict criteria (10, 11), one combination, AZT plus ribavirin, is reproducably antagonistic under various conditions (23). Ribavirin inhibits the phosphorylation of AZT to its active triphosphate form, probably by increasing deoxythymidine triphosphate levels, resulting in a feedback inhibition of thymidine kinase. Although in vitro interactions may not necessarily reflect conditions in vivo, combinations showing antagonism in the laboratory should be used clinically only under carefully controlled situations. Studies of

pharmacokinetic interactions of the AZT-ribavirin combination in animals are planned.

Combination trials are under way in patients with HIV infections for AZT plus acyclovir and AZT plus alpha interferon. Trials combining an antiviral agent, such as AZT or ribavirin, with an immunomodulator, such as interleukin-2 or isoprinosine, are also planned, as are studies of antiviral agents plus bone marrow transplantation.

CONCLUSIONS

Enormous strides have been made in the development and testing of agents that inhibit HIV in the 3 years since the discovery that this virus causes AIDS. One agent, AZT, has been shown to decrease or delay mortality from AIDS, and a second, ribavirin, has been reported to delay the progression of lymphadenopathy to AIDS. Other exciting compounds, such as ddC, are rapidly being tested in clinical trials.

Mechanisms of developing and evaluating new drugs and drug combinations have now been established which should reduce delays that have held back clinical testing of certain compounds. Although substantial obstacles, such as drug toxicities, lie in the way of adequate control of HIV infections, progress should continue to be made in the months and years ahead.

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LITERATURE CITED

1. **Baba, M., R. Pauwels, P. Herdewijn, E. DeClercq, J. Desmyter, and M. Vandeputte.** 1987. Both 2'3'-dideoxythymidine and its 2'3'-unsaturated derivative (2'3'-dideoxythymidinene) are potent and selective inhibitors of human immunodeficiency virus replication in vitro. Biochem. Biophys. Res. Commun. **142**:128–134.
2. **Balzarini, J., H. Mitsuya, E. De Clercq, and S. Broder.** 1986. Comparative inhibitory effects of suramin and other selected compounds on the infectivity and replication of human T-cell lymphotropic virus (HTLV-III)/lymphadenopathy associated virus (LAV). Int. J. Cancer **37**:451–457.
3. **Balzarini, J., R. Pauwels, P. Herdewijn, E. DeClercq, D. A. Cooney, C. J. Kong, M. Dalal, D. G. Johns, and S. Broder.** 1987. Potent and selective anti-HTLV-III/LAV activity of 2'3'-dideoxycytidinene, the 2'3'-unsaturated derivative of 2'3'-dideoxycytidine. Biochem. Biophys. Res. Commun. **140**:735–742.
4. **Broder, S., J. M. Yarchoan, J. M. Collins, H. C. Lane, P. D. Markham, R. W. Klecker, R. R. Redfield, H. Mitsuya, D. F. Hoth, E. Gelmann, J. E. Groopman, L. Resnick, R. C. Gallo, C. E. Myers, and A. S. Fauci.** 1985. Effects of suramin on HTLV-III/LAV infection presenting as Kaposi's sarcoma or AIDS related complex: clinical pharmacology and suppression of virus replication in vivo. Lancet **ii**:627–630.
5. **Cooney, D. A., M. Dalal, H. Mitsuya, J. B. McMahon, M. Nadkarni, J. Balzarini, S. Broder, and D. G. Johns.** 1986. Initial studies on the cellular pharmacology of 2'3'-dideoxycytidine, an inhibitor of HTLV-III infectivity. Biochem. Pharmacol. **35**:2065–2068.
6. **Dormont, D., B. Spire, F. Barre-Sinousi, L. Montagnier, and J. C. Chermann.** 1985. Inhibition of RNA-dependent DNA polymerases of AIDS and SAIDS retroviruses by HPA-23 (ammonium-21-tungsto-9-antimoniate). Ann. Virol. **136E**:75–83.
7. **Furman, P. A., J. A. Fyfe, M. H. St. Clair, K. Weinhold, J. L. Rideout, G. A. Freeman, S. Nusinoff Lehrman, D. P. Bolognesi, S. Broder, H. Mitsuya, and D. W. Barry.** 1986. Phosphorylation of 3'-azido-3'-deoxythymidine and selective interaction of the 5' triphosphate with human immunodeficiency virus reverse transcriptase. Proc. Natl. Acad. Sci. USA **83**:8333–8337.
8. **Gilbert, B. E., and V. Knight.** 1986. Biochemistry and clinical applications of ribavirin. Antimicrob. Agents Chemother. **30**:201–205.
9. **Hammer, S. M., J. M. Gillis, J. E. Groopman, and R. M. Rose.** 1986. In vitro modification of human immunodeficiency virus infection by granulocyte macrophage colony stimulating factor and γ interferon. Proc. Natl. Acad. Sci. USA **83**:8734–8738.
10. **Hartshorn, K. L., E. G. Sandstrom, D. Neumeyer, T. J. Paradis, T.-C. Chou, R. T. Schooley, and M. S. Hirsch.** 1986. Synergistic inhibition of human T-cell lymphotropic virus type III replication in vitro by phosphonoformate and recombinant alpha-A interferon. Antimicrob. Agents Chemother. **30**:189–191.
11. **Hartshorn, K. L., M. W. Vogt, T.-C. Chou, R. S. Blumberg, R. Byington, R. T. Schooley, and M. S. Hirsch.** 1987. Synergistic inhibition of human immunodeficiency virus in vitro by azidothymidine and recombinant alpha A interferon. Antimicrob. Agents Chemother. **31**:168–172.
12. **Ho, D. D., K. L. Hartshorn, T. R. Rota, C. A. Andrews, J. C. Kaplan, R. T. Schooley, and M. S. Hirsch.** 1985. Recombinant human interferon alpha A suppresses HTLV-III replication in vitro. Lancet **i**:602–604.
13. **McCormick, J. B., J. P. Getchell, S. W. Mitchell, and D. R. Hicks.** 1984. Ribavirin suppresses replication of lymphadenopathy associated virus in cultures of human adult T lymphocytes. Lancet **ii**:1367–1369.
14. **Mitsuya, H., and S. Broder.** 1986. Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides. Proc. Natl. Acad. Sci. USA **83**:1911–1915.
15. **Mitsuya, H., M. Matsukura, and S. Broder.** 1987. Rapid in vitro systems for assessing activity of agents against HTLV-III/LAV, p. 303–333. *In* S. Broder (ed.), AIDS, modern concepts and therapeutic challenges. Marcel Dekker, Inc., New York.
16. **Mitsuya, H., K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry, and S. Broder.** 1985. 3'-Azido-3'-deoxythymidine (BWA509U): 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.
17. **Nakashima, H., T. Matsui, S. Harada, N. Kobayashi, A. Matsuda, T. Ueda, and N. Yamamoto.** 1986. Inhibition of replication and cytopathic effect of human T cell lymphotropic virus type III/lymphadenopathy-associated virus by 3'-azido-3'-deoxythymidine in vitro. Antimicrob. Agents Chemother. **30**:933–937.
18. **Nakashima, H., T. Toshida, S. Harada, and N. Yamamoto.** 1986. Recombinant human interferon gamma suppresses HTLV-III replication in vitro. Int. J. Cancer **38**:433–436.
19. **Pert, C. B., J. M. Hill, M. R. Ruff, R. M. Berman, W. G. Robey, L. O. Arthur, F. W. Ruscetti, and W. L. Farrar.** 1986. Octapeptides deduced from the neuropeptide receptor-like pattern of antigen T4 in brain potently inhibit human immunodeficiency virus receptor binding and T-cell infectivity. Proc. Natl. Acad. Sci. USA **83**:9254–9258.
20. **Resnick, L., P. D. Markham, K. Veren, S. Z. Salahuddin, and R. C. Gallo.** 1986. In vitro suppression of HTLV-III/LAV infectivity by a combination of acyclovir and suramin. J. Infect. Dis. **154**:1027–1030.
21. **Sandstrom, E., J. C. Kaplan, R. E. Byington, and M. S. Hirsch.** 1985. Phosphonoformate inhibits HTLV-III replication in vitro. Lancet **i**:1480–1482.
22. **Vogt, M., and M. S. Hirsch.** 1986. Prospects for the prevention and therapy of infections with the human immunodeficiency virus. Rev. Infect. Dis. **8**:991–1000.
23. **Vogt, M. W., K. L. Hartshorn, P. A. Furman, T.-C. Chou, J. A. Fyfe, L. A. Coleman, C. Crumpacker, R. T. Schooley, and M. S. Hirsch.** 1987. Ribavirin antagonizes the effect of azidothymidine

on HIV replication. Science 235:1376–1379.
24. **Yamamoto, J. K., F. Barre-Sinoussi, V. Bolton, N. C. Pederson, and M. B. Gardner.** 1986. Human alpha- and beta-interferon but not gamma suppress the in vitro replication of LAV, HTLV-III and ARV-2. J. Interferon Res. 6:143–152.
25. **Yarchoan, R., G. Berg, P. Brouwers, M. A. Fischl, A. R. Spitzer, A. Wichman, J. Grafman, R. V. Thomas, B. Safai, A. Brunetti, C. F. Perno, P. J. Schmidt, S. M. Larson, C. E. Myers, and S. Broder.** 1987. Response of human-immunodeficiency-virus-associated neurological disease to 3′-azido-3′-deoxythymidine. Lancet i:132–135.
26. **Yarchoan, R., R. W. Klecker, K. J. Weinhold, P. D. Markham, H. K. Lyerly, D. T. Durack, E. Gelmann, S. Nusinoff-Lehrman, R. M. Blum, D. W. Barry, G. M. Shearer, M. A. Fischl, H. Mitsuya, R. C. Gallo, J. M. Collins, D. P. Bolognesi, C. M. Myers, and S. Broder.** 1986. Administration of 3′-azido-3′-deoxythymidine, an inhibitor of HTLV-III replication, to patients with AIDS and AIDS-related complex. Lancet i:575–580.
27. **Zamecnik, P. C., J. Goodchild, Y. Taguchi, and P. S. Sarin.** 1986. Inhibition of replication and expression of human T-cell lymphotropic virus type III in cultured cells by exogenous synthetic oligonucleotides complementary to viral RNA. Proc. Natl. Acad. Sci. USA 83:4143–4146.