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YEAR BOOK OF MEDICINE® 1990

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The Year Book of MEDICINE®

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Journals Represented

Year Book Medical Publishers subscribes to and surveys more than 700 U.S. and foreign medical and allied health journals. From these journals, the Editors select the articles to be abstracted. Journals represented in this YEAR BOOK are listed below.

APMIS:Acta Pathologica, Microbialogica, et Immunologica Scandinavica
Acta Endocrinologica
Acta Paediatrica Scandinavica
American Journal of Cardiology
American Journal of Human Genetics
American Journal of Kidney Diseases
American Journal of Medicine
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American Review of Respiratory Disease
Annals of Emergency Medicine
Annals of Internal Medicine
Annals of Rheumatic Diseases
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Journal of the American College of Cardiology

Journal of the American Medical Association
Kidney International
Laboratory Investigation
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Nature
New England Journal of Medicine
New Zealand Medical Journal
Oncology
Pain
Quarterly Journal of Medicine
Respiratory Medicine
Science
Seminars in Nephrology
Seminars in Nuclear Medicine
Southern Medical Journal
Surgery
Thorax
Transfusion
Transplantation

Standard Abbreviations

The following abbreviations are used in this edition without expansion: AIDS (acquired immunodeficiency syndrome); CNS (central nervous system); CSF (cerebrospinal fluid); CT (computed tomography); ECG (electrocardiography); and HIV (human immunodeficiency virus).

Publisher's Preface

After 5 years of excellent contribution to the YEAR BOOK OF MEDICINE, Jean D. Wilson, M.D., will be retiring from the YEAR BOOK's Board of Editors with the completion of this edition. His contribution as the Editor of the Endocrinology and Metabolism section has been deeply appreciated by this company, and we wish him the very best in his future endeavors.

We welcome Robert D. Utiger, M.D., Deputy Editor of *The New England Journal of Medicine,* who will be succeeding Dr. Wilson beginning with the 1991 YEAR BOOK OF MEDICINE.

Recent Advances in the Treatment of Human Immunodeficiency Virus Infection and Its Complications

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In the 10-year struggle against the human immunodeficiency virus (HIV) infection and its complications, significant advances have been made on every front. Early clinical experience was dominated by the diagnosis and treatment of opportunistic infections and malignancies. But the isolation of HIV and its subsequent intensive investigation have opened a new era of antiretroviral therapy. Clinicians are no longer faced with treating only the end point of the spectrum of HIV infection, i.e., AIDS. Rather, there is real hope that early intervention with antiretroviral therapy and prophylaxis against opportunistic infection will prevent progression to an AIDS-defining diagnosis. The possibility of HIV infection becoming a chronic, treatable infection, if not a completely curable one, certainly exists. Therefore, it becomes incumbent upon the primary care physician to recognize the entire spectrum of HIV disease and see it as one that is predictably progressive with an average time to the development of an AIDS-defining diagnosis of approximately 10 years (1–3).

It is also important to remember that HIV remains an infection of well-defined risk groups (4). In the United States and Europe these are homosexual and bisexual men, intravenous drug users, hemophiliacs, transfusion recipients, and the sexual partners of these risk group members. In Africa the epidemic is seen in sexually active heterosexuals with multiple partners. Vertical transmission of infection from mother to child is also an important route of infection worldwide.

Our patients and colleagues must be reassured that the transmission of HIV occurs only through previously well-described routes: sexual contact, parenteral exposure to blood or blood products, or perinatally from mother to child. Casual contact, contact with body secretions (other than blood, semen, or cervical secretions), aerosolized saliva or blood, or insect bites have not been identified as routes of viral transmission.

Classification of HIV Infection

Several classification systems for HIV have been proposed in the past 10 years. In understanding our current approach to HIV infection it is helpful to know these previous systems of classification.

The Centers for Disease Control (CDC), responding to this new and mysterious epidemic, proposed surveillance criteria for the diagnosis of AIDS in 1982 (5). This achieved the important goal of defining the clinical end points of the new disease. It focused attention on risk groups and

TABLE 1.—Walter Reed (WR) Staging System

	HIV antibody or antigen	Chronic lymphadenopathy	T-helper cells/mm^3	Delayed hypersensitivity	Oral thrush	Opportunistic infections
WR0	–	–	>400	normal	–	–
WR1	+	–	>400	normal	–	–
WR2	+	+	>400	normal	–	–
WR3	+	±	<400	normal	–	–
WR4	+	±	<400	partial	–	–
WR5	+	±	<400	complete cutaneous anergy and/or thrush	–	–
WR6	+	±	<400	partial to complete	+	+

(Courtesy of Redfield RR, et al: *N Engl J Med* 314:131–132, 1986.)

ultimately helped in identification of the virus. By 1985 the Walter Reed Classification System proposed a model based on immunologic function that is still useful prognostically (6) (Table 1). This system has been used by the military in evaluating several thousand HIV-infected personnel. In

1986 the CDC proposed another classification for HIV that looked at the entire spectrum of disease from the acute infection associated with seroconversion to AIDS-defining diagnoses (7) (Table 2), providing a conceptual framework for the clinician. Although a patient's clinical status could be defined at a given point in time, the system is not useful prognostically and lacks relevance in practical patient management. A more recent attempt at prognostic staging was attempted by Justice et al. (8). This system looked only at the end point of HIV infection, i.e., a group IVc diagnosis, and predicted survival of patients based on "physiologic deficient scores" characterized by neurologic, respiratory, nutritional, and hematologic variables. This system may allow clinicians to develop prognostic information useful in counseling patients and their families as well as in planning future therapy.

The most useful means of classifying a patient clinically and prognostically depends on surrogate markers of HIV infection. Investigators have looked at surrogate markers of HIV infection in an attempt to identify those persons at greatest risk for progressive disease. Clinical predictors of progressive infection include the disappearance or decrease in size of generalized lymphadenopathy (9). The presence of oral candidiasis (10),

TABLE 2.—Centers for Disease Control Classification for HIV Infection

Group I - Acute infection

Group II -Asymptomatic infection

Group III - Persistent generalized lymphadenopathy

Group IV - Other diseases

- Subgroup A - Constitutional disease
- Subgroup B - Neurologic disease
- Subgroup C - Secondary infectious diseases
  - Category C-1 - Specified secondary infectious diseases listed in the CDC surveillance definition for AIDS
  - Category C-2 - Other specified secondary infectious diseases
- Subgroup D - Secondary cancers
- Subgroup E - Other conditions

oral hairy leukoplakia (11), or herpes zoster infection (12) also predicts more rapid progression to a group IV diagnosis.

Multiple laboratory markers for HIV infection have been studied. Low absolute CD_4+ (T_4 or helper lymphocyte) cell counts, low CD_4+/CD_8+ (helper, suppressor lymphocyte) ratios (13–18), p24 antigenemia (17–21), elevated β_2 microglobulin levels (15, 18), and elevated serum or urinary neopterim levels (22) have all been associated with progressive HIV infection. But CD_4+ cell counts remain the most powerful predictor of progressive disease. For example, CD_4+ cell counts of less than 200 cells/mm^3 or CD_4+ counts less than 20% of the total lymphocyte count are clearly associated with the development of opportunistic infections, especially *Pneumocystis carinii* pneumonia (23). Conversely, if patients have more than 200 CD_4+ cells/mm^3, or if more than 20% of their circulating lymphocytes are CD_4+ cells, the risk for this pneumonia developing is very low (approximately 2%). Also, CD_4+ counts of less than 200 have been associated with a 2.7- to 5.5-fold higher risk of contracting any group IVc infection in patients with hemophilia compared with patients with CD_4+ counts from 201 to 500 cells/mm^3, and a 7.3- to 30.3-fold higher incidence than those with cells counts of more than 500 cells/mm^3 (17). Patients with p24 antigenemia have a worse prognosis, and in conjunction with a low CD_4+ count these tests were predictive of a group IVc diagnosis within 12 months that was 6.0-fold higher (17).

Two studies also looked at plasma viremia as a marker of progressive HIV infection and found it to be a more sensitive marker of clinical status than p24 antigenemia (24, 25). These studies are important in that they show virus present at every stage of HIV infection and in greater concentrations than believed previously. A direct correlation was also made between the amount of viral replication and the stage of disease, indicating that early therapy with antiretroviral agents may prevent disease progression. Currently, viral cultures are technically difficult, expensive, and labor intensive, and their use is limited to the research setting.

It is useful to think of patients as having early, middle, or late HIV infection. Early infection would roughly correlate with CD_4+ cell counts of more than 500 cells/mm^3; middle-stage disease, 200–500 CD_4+ cells; and late-stage disease, less than 200 cell/mm^3. This system would provide the clinician with specific guidelines for the initiation of antiretroviral therapy and prophylaxis of opportunistic infections.

Antiretroviral Therapy

Intensive investigation of HIV-1 has led to the development of antiretroviral agents that are specific for difference sites in the life cycle of the virus. These agents are categorized according to their site of action in the virus life cycle. The dideoxynucleosides comprise the most extensively studied group of agents, and all of them are categorized as reverse transcriptase inhibitors.

Reverse transcriptase is an enzyme essential to the life cycle of HIV-1. This enzyme (a viral DNA polymerase) copies the viral RNA into a complementary strand of DNA, which is subsequently incorporated into the

host cell genome. The dideoxynucleosides are activated via phosphorylation. As triphosphates they are used by the reverse transcriptase enzyme and result in defective DNA copies of viral RNA. The best known of these reverse transcriptase inhibitors is zidovudine (3′-azido-2′-3′-dideoxythymidine).

Zidovudine has been used extensively in patients with a group IVc diagnosis or a CD_4+ cell count of less than 200 cells/mm^3, because a prospective, placebo-controlled, phase II trial in 1986 showed significantly fewer opportunistic infections or deaths in patients taking the drug (26). The initial dosage was 1,500 mg per day (usually as 250 mg every 4 hours around the clock). Significant toxicity, primarily anemia or neutropenia, was seen at these dosages (27). Twenty-five percent of group IVa patients and 50% of group IVc required transfusions. Other significant side effects included nausea, stomach discomfort, headache, malaise, irritability, and insomnia.

Long-term follow-up of patients in this phase II trial demonstrated survival benefit at 18 months both in patients initially given zidovudine (68.1%) and in patients who initially received placebo and subsequently were given zidovudine (64.6%). Survival among placebo-treated patients who did not receive zidovudine was 51.5% at 9 months (28).

Three important AIDS Clinical Trials Group (ACTG) studies have further defined the use of this drug.

One study, ACTG 002, looked at more than 500 group IVc patients treated with zidovudine 1,500 mg/day vs. 600 mg/day, and found improved tolerance and decreased toxicity among patients given the lower dose, with 60% taking the drug at 1 year; only 30% of high-dose patients were still being treated at 1 year. Further, there was improved survival among patients given the lower dosage at 1 year. Thus zidovudine, 600 mg/day, proved to be less toxic, and possibly more effective, than 1,500 mg/day (M. Fischl, personal communication.)

A second trial, ACTG 016, studied group IVa patients in a placebo-controlled study of zidovudine, 1,200 mg/day (200 mg every 4 hours around the clock). Patients had at least one symptom of HIV infection (e.g., candidiasis, oral hairy leukoplakia, herpes zoster, weight loss, chronic dermatitis, or severe fatigue). They were stratified into 2 groups on the basis of CD_4+ counts of more than 200 but less than 500 cells/mm^3 and counts of more than 500 cells/mm^3. End points of evaluation included the development of two active symptoms *and* a drop in CD_4+ cell counts to less than 200 cells/mm^3 or a group IVc or IVd diagnosis. There were no differences between zidovudine- and placebo-treated patients with more than 500 cells/mm^3; however, in patients with 200 to 500 cells/mm^3 there were 36 events in the placebo group and only 14 in the zidovudine-treated patients, a statistically significant difference. At 18 months into the study, event-free survival was 76% in placebo-treated patients and 90% among those receiving zidovudine (M. Fischl, personal communication.)

A third important study, ACTG 019, looked at completely asymptomatic patients with more than 500 CD_4+ cells/mm^3 or less than 500

CD_4+ cells/mm^3. In a placebo-controlled fashion, a zidovudine dosage of 500 mg/day was compared with 1,500 mg/day. The zidovudine-treated patients with less than 500 CD_4+ cells/mm^3 had a 50% reduction in rate of progression, compared with the placebo group. There were 38 significant events among placebo-treated patients and only 17 among patients taking 500 mg/day and 19 events in the group given 1,500 mg/day. There was also significantly less toxicity in the low-dose group, with only 3% experiencing significant hematologic toxicity (P. Volberding, personal communication). Data concerning the group of patients with more than 500 CD_4+ cells/mm^3 have not yet been released as that part of the study is ongoing.

Taken together, these three studies indicate a beneficial effect from earlier treatment of HIV infection, equal or even greater efficacy from lower dose zidovudine, and a significantly lower rate of toxicity when zidovudine, 500 to 600 mg/day, is used. This information has led to the earlier initiation of antiretroviral therapy. Essentially any HIV-infected patient with less than 500 CD_4+ cells/mm^3 should be offered zidovudine, regardless of clinical symptoms. The previously cited data regarding viremia also provide theoretical support for this idea of earlier initiation of antiretroviral therapy.

Zidovudine has also been studied with interferon-α (IFN-α) in the treatment of Kaposi's sarcoma. Zidovudine was previously studied alone in a randomized controlled fashion and found to have no effect against Kaposi's sarcoma (29). When combined with IFN-α, however, antitumor and antiviral responses were seen (30). Notably, the dose of both drugs had to be reduced to prevent synergistic toxicity manifest as neutropenia, fatigue, thrombocytopenia, and hepatic dysfunction. The optimal regimen appears to be zidovudine, 100 mg every 4 hours, combined with IFN-α, 5 to 10 million units daily. Complete or partial responses were seen in 11 of 26 (42%) of patients treated with this regimen. This response rate is similar to that previously reported after IFN-α alone but used in much higher doses than in this study. It should also be noted that all but three patients in this study had more than 200 CD_4+ cells/mm^3 and were otherwise well.

Other recently studied dideoxynucleosides include dideoxycytidine (ddC) and dideoxyinosine (ddI). A phase I and II study of ddC in 61 patients with group IVa or IVc disease was conducted using 4 different dosage levels (0.005 mg/kg, 0.01 mg/kg, 0.03 mg/kg, and 0.06 mg/kg) (31). Although p24 antigen suppression occurred consistently at the two higher dose levels, significant toxicity in the form of sensory peripheral neuropathy, fever, aphthous stomatitis, rash, and arthritis was also found. Sensory peripheral neuropathy, the most severe side effect, occurred in all patients at the two highest dose levels. Lower doses of ddC were associated with less toxicity but also less reliably suppressed p24 antigenemia. No hematologic toxicity was seen with ddC. Current studies are being conducted with ddC alternating with zidovudine in an attempt to evaluate a possible synergistic effect while minimizing the toxic side effects of each.

Dideoxyinosine (ddI) showed an antiretroviral effect in a phase I trial of 26 patients with group IVa or IVc disease (32). Patients had persistent elevation of CD_4+ cells, a decrease in p24 antigenemia, and increased responsiveness to skin test antigens. Side effects of the drug included peripheral neuropathy, rash, pancreatitis, seizures, and elevated uric acid levels.

Phase II/III trials are now underway, and ACTG 117 will compare ddI with zidovudine in persons who have been tolerant of zidovudine for more than 12 months. Also, ACTG 118 will compare 2 different doses of ddI in persons who cannot tolerate zidovudine secondary to hematologic toxicity. A phase III study, ACTG 116, will compare ddI and zidovudine in patients who have been taking zidovudine for more than 2 but less than 12 months.

The drug is also available via a "parallel track" basically an open-label regimen for patients with an AIDS-defining diagnosis who have had disease progression despite zidovudine therapy. It will also be available under a Treatment Investigational New Drug (IND) protocol for patients with group IV disease who cannot tolerate zidovudine because of hematologic toxicity (anemia or neutropenia), severe headaches, myositis, or severe nausea and vomiting.

The availability of ddI on the open label of treatment IND protocols represents a precedent-setting break from traditional guidelines for investigational drug use. The aim of these protocols is to make promising new antiretroviral therapies available to persons who may not qualify for any drug study protocols and in whom currently available antiretroviral therapy (e.g., zidovudine) has failed. (The telephone number for enrollment on ddI protocols is 1–800–662–7999 or 1–800–TRIALS–A).

The wider availability of ddI with these protocols is seen as the test case for possible future similar investigational drugs. Therefore, scientists and clinicians at the NIH and FDA will be monitoring these trials very closely and attempting to evaluate their use before extending the program to other drugs.

Other Antiretroviral Agents

The HIV-1 specifically attacks cells with the surface marker known as CD_4. The CD_4 molecule acts as a binding site for HIV-1, initiating the infective process. Molecular biologists have successfully produced this soluble virus receptor, known as recombinant soluble CD_4. It is effective at inhibiting viral growth in vitro. This agent has also been studied in phase I trials and found to be safe, but no in vivo antiviral effect has been demonstrated, perhaps because it has a very short half-life in the serum (33, 34). New forms of the drug, in which it is attached to an IgG molecule, demonstrate a prolonged serum half-life (35). This CD_4-IgG is currently in phase I trials.

Combination therapy using zidovudine and soluble CD_4 have been effective at inhibiting viral replication in the test tube, and this approach is currently under study in humans (36). Another drug that may block the binding of HIV to CD_4+ cells is dextran sulfate. Dextran sulfate is the