

AIDS Report

Problems in Treating the HIV-Infected Patient

BY SIMSON L. GARFINKEL

A middle-aged patient complaining of a persistent cough sits on your examination table. Under his arms, you feel enlarged lymph nodes. On the side of his tongue, you spot a white patch indicative of hairy leukoplakia. Does he have the acquired immunodeficiency syndrome (AIDS)? Probably not, says Dr. Neal

Rzepkowski, at the Fenway Community Health Center in Boston. But almost certainly the patient is infected with human immunodeficiency virus (HIV), he says, maintaining that he has never seen hairy leukoplakia on a patient who was not infected with the virus. When the diagnosis is confirmed by

the HIV antibody test, the most important thing for the physician to do is to assure the patient that HIV—and even full-blown AIDS—is not a death sentence,” says Dr. Rzepkowski. Indeed, says Dr. Rzepkowski, patients who are developing HIV-related symptoms that haven't yet been tested for HIV “are living in the past. If they

haven't had the test in the last four years, either they don't realize that they are at risk, or they don't realize that there is anything they can do about it.” Although fear and denial also play a role in preventing patients from getting tested, he says, many patients now developing symptoms of the disease are less informed than the well-networked, upper-middle-class homosexuals who were the first to develop the disease. Infection with the virus is increasingly cutting across cultural and economic lines.

Once Dr. Rzepkowski assures the patient that he is not going to die, he hand draws blood for a preliminary laboratory work-up and gives the patient a page entitled “AIDS Resources.” He then schedules a follow-up appointment and encourages the patient to “do the research” and become an expert on the disease that will probably affect him for the rest of his life.

Dr. Rzepkowski estimates that he has seen at least 250 HIV-infected patients since the disease was first reported in 1981. The Fenway Community Health Center is well known in the Boston area for its work with the homosexual community.

Physician Recognition

Do physicians who work in practices that do not primarily cater to homosexual men or intravenous drug abusers need to conceal themselves with the proper treatment of an HIV-infected person?

Definitely, says Dr. Sandy Pomerantz, a medical consultant to the State of California's Office of AIDS. Although many physicians believe that they do not have patients who are at risk for the disease, the real issue is that many physicians have not spoken frankly with their patients about the disease and the practices that cause its transmission. “They are in the practices already, so taking a detailed sexual and drug use history should be done on all patients,” he says.

Many physicians who discover HIV-infected patients “are sending patients to other physicians who are known to be knowledgeable about HIV.” This is a trend that Dr. Pomerantz says cannot continue.

“The number of HIV-infected individuals far outnumber the number of so-called AIDS specialists,” he says. “All primary-care physicians, to be sure, and in general, all clinicians, need to become more knowledgeable about HIV.

“It is ironic that many HIV-infected individuals have gotten to the point of understanding that HIV infection

Advertisement for Atenolol (Tenormin) with tagline 'A right start for the long run.' Includes product name 'TENORMIN (atenolol)' and 'ONE TABLET A DAY'.

A beta<sub>1</sub>-selective (cardioselective) blocking agent

DESCRIPTION: TENORMIN (atenolol), a synthetic, beta<sub>1</sub>-selective (cardioselective) adrenergic receptor blocking agent, may be chemically described as benzeneacetamide 4-[2'-(hydroxy-3'-(11-methyl-ethyl)amino)propoxy]-Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 50 mg and 100 mg tablets for oral administration. Inactive ingredients: magnesium stearate, microcrystalline cellulose, powder, sodium starch glycolate.

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

CONTRAINDICATIONS: TENORMIN is contraindicated in patients with a known hypersensitivity to any of the components of the formulation, including atenolol, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyethylene glycol, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 800, polyethylene glycol 1000, polyethylene glycol 1500, polyethylene glycol 2000, polyethylene glycol 3000, polyethylene glycol 4000, polyethylene glycol 6000, polyethylene glycol 8000, polyethylene glycol 10000, polyethylene glycol 15000, polyethylene glycol 20000, polyethylene glycol 30000, polyethylene glycol 40000, polyethylene glycol 60000, polyethylene glycol 80000, polyethylene glycol 100000.

Cessation of Therapy With TENORMIN: Patients with coronary artery disease who are being treated with TENORMIN should be advised against abrupt discontinuation of therapy. Sudden discontinuation of atenolol may precipitate angina pectoris and/or myocardial infarction. Antihypertensives have been reported to precipitate the abrupt discontinuation of therapy with other beta-blockers. The last two complications may occur with or without preceding overdosage of the beta-blocker. If a patient has been on atenolol for a prolonged period of time, an attempt should be made to gradually reduce the dose of TENORMIN over a period of one to two weeks. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinitiated, at least temporarily. (See Dosage and Administration.)

BRONCHOSPASTIC DISEASE: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta<sub>1</sub>-selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta<sub>1</sub>-selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg, and a beta<sub>2</sub>-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anaesthesia and Major Surgery: As with all beta<sub>1</sub>-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anaesthesia. If treatment is continued, care should be taken when using anaesthetic agents which depress the myocardium such as ether, cyclopropane, and trichloroethylene.

TENORMIN like other beta-blockers is a competitive inhibitor of beta<sub>1</sub>-adrenergic agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see section on Overdosage). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta<sub>1</sub>-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and unlike nonselective beta-blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of thyrotoxicosis. Abrupt withdrawal of beta-blockade might precipitate a thyroid storm. Therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See Dosage and Administration.)

Drug Interactions: Calcium channel blocking drugs (eg, verapamil) may have an additive effect when given with beta-blocking agents. Salivary glands tested with TENORMIN plus a calcium channel blocker should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta-blockers and clonidine concurrently, the beta-blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female rats at tested dose levels of atenolol (at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrophic degeneration of hearts of male rats at 300 mg/kg but not 150 mg/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.3 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were self-reported by the patient (US studies) or elicited (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN (atenolol) and placebo-treated patients, than when these reactions were self-reported. The adverse effects for TENORMIN and placebo are similar; causal relationship to TENORMIN is uncertain.

The following adverse reaction data present frequency estimates in terms of percentages, first from the studies (both on- and off-therapy) and then from both US and foreign studies (volunteered and elicited, as applicable).

US STUDIES (% ATENOLOL-% PLACEBO): cold extremities (0% 0.5%), postural hypotension (2% 1%), leg pain (0% 0.5%), dizziness (1% 1%), headache (1% 1%), fatigue (3% 1%), lethargy (1% 0%), drowsiness (0.6% 0%), depression (0.6% 0.5%), dreaming (0% 0%), GASTROINTESTINAL: diarrhea (2% 0%), nausea (4% 1%), flatulency (see WARNINGS), indigestion (0% 0%), dyspepsia (0.6% 1%). TOTALS US AND FOREIGN STUDIES: CARDIOVASCULAR: bradycardia (3% 0%), cold extremities (10% 5%), postural hypotension (4% 1%), leg pain (1% 1%), dizziness (13% 6%), vertigo (2% 0.2%), light-headedness (3% 0.7%), weakness (26% 13%), fatigue (6% 5%), lethargy (3% 0.7%), drowsiness (2% 0.5%), depression (10% 8%), dreaming (3% 1%), GASTROINTESTINAL: diarrhea (3% 2%), nausea (3% 1%), flatulency (see WARNINGS), indigestion (3% 3%), dyspepsia (6% 4%), MISCELLANEOUS: There have been reports of sinus bradycardia and/or dizziness associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of other so-called adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential adverse effects of TENORMIN.

HEMATOLOGIC: Argyropoiesis, nonthrombocytopenic purpura, thrombocytopenic purpura, ALLERGIC: Fever, combined with angina and/or congestive heart failure and respiratory distress, CENTRAL NERVOUS SYSTEM: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, partial memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometric tests.

GASTROINTESTINAL: Mesenteric arterial thrombosis, ischemic colitis, BRADYCARDIA: Atropine or another anticholinergic drug, HEPATITIS: A patient who had been treated with atenolol for hypertension was transferred to TENORMIN therapy with subsequent resolution of a reaction that was characterized by jaundice, fever, malaise, and myalgia. OVERDOSAGE: In data, there is no known case of an overdose, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypothermia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

BRADYCARDIA: Atropine or another anticholinergic drug, HEPART BLOCK (SLO-CLEF) OR THIRD-DEGREE: Isoproterenol or transvenous cardiac pacemaker, CONGESTIVE HEART FAILURE: Concomitant therapy, HYPOTENSION (DEPRESSION ASSOCIATED FACTORS): Epinephrine (at a higher rate than isoproterenol) or norepinephrine may be useful in addition to atropine and digitalis, BRONCHOSPASM: Aminophylline, ephedrine, or atropine, MYOCLONIC MIGRAINES: Chlorazepate.

DOSE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day, either alone or added to diuretic therapy. The full effect of this dose will usually be seen within 1 to 2 weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect. Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate antihypertensive effect. The maximum daily dose of TENORMIN is 100 mg with dosing of 50 to 100 mg, but the therapeutic effect is maintained, averaging about 50% to 75% of that observed with once a day dosing of 200 mg.

Patients with Renal Impairment: Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN or current plasma clearance falls below 35 mL/min. 1.73 m<sup>2</sup> (normal range is 100 mL/min, 1.73 m<sup>2</sup>). Therefore, the following maximum dosages are recommended for patients with renal impairment.

Table with 3 columns: Creatinine Clearance (mL/min/1.73 m<sup>2</sup>), Atenolol Elimination Half-life (h), Maximum Dosage. Values: 15-35, 16-27, 50 mg daily; <15, 16-27, 50 mg every other day.

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under the usual supervision as marked below. If a dialysis procedure occurs during the period of therapy, it will not affect the TENORMIN therapy. Patients should be carefully observed and advised to limit physical activity to 8 hours daily.

HOW SUPPLIED: Tablets of 50 mg atenolol, NDC 0310 0105 (round flat, uncoated white tablets, identical with ICI) dispensed on one side and 100 mg tablets on the other side, bisected; are supplied in bottles of 100 tablets and unit dose packages of 100 tablets. Tablets of 100 mg atenolol, NDC 0310 0101 (round flat, uncoated white tablets, identical with ICI) dispensed on one side and 101 dispensed on the other side, are supplied in bottles of 100 tablets and unit dose packages of 100 tablets. Protect from heat, light, and moisture.

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doesn't mean necessarily death, whereas many physicians still hold on to that concept." HIV-infection really represents a spectrum of disease, says Dr. Pomerantz, that can be monitored and managed with prophylactic treatments by the primary-care physician for "long, long periods of time."

#### "AIDS Docs"

Dr. Kathleen Nolan, a physician and ethicist at the Hastings Institute in New York, amplifies the point: "The primary-care physician has to change his or her mind set and begin to see HIV infection as a problem that will be routinely handled in the private office or general clinic.

"I don't think that shift in mind set has really occurred. I think that there is still, in many people's mind, the idea of AIDS as a very difficult disease to manage, which it can become, and also the idea of AIDS as a very frightening disease that should be somebody else's responsibility," says Dr. Nolan. "What is needed is for people to realize that HIV-disease is a long-term disease where the patient can be managed by a nonspecialist for perhaps many years, and there is a responsibility for people to carry their share of the burden in terms of managing their share of the patients who are infected."

So far, that does not seem to be happening. In every state of the country, says attorney Ben Schatz, Director of National Gay Rights Advocates, there are physicians who are denying care to patients "because the person has or is perceived to have HIV." Doing so, says Mr. Schatz, is illegal under the laws of many states or if the physician is a recipient of Medicare.

Nevertheless, there is talk in the medical community of the growing number of "AIDS Docs"—physicians who have large parts of their case loads devoted in part or entirely to people who test positive for HIV.

Dr. Gary Blick is such a physician. Although his practice is in Greenwich, Connecticut, he draws his patients from nearly a quarter of the state: "I see people from Southbury, Connecticut, about an hour away. I see people from the other side of New Haven. If they are driving an hour and a half, it's because they can't get appropriate care—they don't find physicians who are open-minded to treating them and will sit down and give them any kind of discussion."

Once an HIV diagnosis is shared with the patient, the first thing that Dr. Blick does is sit down with the patient and spend 45 minutes finding out who they are, how they are psychologically approaching the diagnosis, and how they are caring for themselves. The most important thing, says Dr. Blick, is to give the patient a sense of hope.

"It's a totally different feeling now

than it was two years ago," says Dr. Blick, adding that the hundred HIV-positive patients he treats make up roughly 10 percent of his workload. "It's just a chronic virus: we can treat HIV today. We couldn't say that several years ago. It's not a death sentence."

Although it is important to begin medical treatment early, says Dr. Blick, it is more important to deal with psychological issues first. "The mind is three-fourths of the battle dealing against this virus. The psychological issues have to be dealt with. You have to get the people into positive thinking."

Next, Dr. Blick focuses the patient's attention on nutrition and exercise. A lot of HIV-infected people do not have a balanced diet; some are on "fad diets" to lose weight, he notes. Between 35 and 47 percent of the patients may be deficient or borderline deficient in vitamin B-6 or B-12.

As for exercise, Dr. Blick recommends "aerobics exercise—getting that heart beating for a steady 20 or 25 minutes, three times a week, is very important in stimulating that immune system." Other physicians agree that aerobic exercise three times a week is one of the most important things to recommend to a presymptomatic HIV-infected patient.

Basic laboratory work, says Dr. Blick, ranges from T-cell profiles, beta-2-microglobulin, HIV-P24 antigen, and the anti-HIV-P24 antibody test, all of which can give indications of the progression of the disease. While the patient's T4 count remains above 500, Dr. Blick is comfortable simply moni-

toring the patient every six months. When the patient's T-cell count drops below 500, Dr. Blick begins T-cell monitoring every three months or less. He starts a low-dose regimen of zidovudine (azidothymidine, or AZT) when the count dips between 300 and 400, in contrast to the Food and Drug Administration's approved regimen of high-dose AZT when the T-cell count drops below 200. It is also vital that the patient begins prophylactic measures against *Pneumocystis carinii* pneumonia. Commonly used prophylaxes include trimethoprim-sulfamethoxazole and aerosolized pentamidine.

Instead of having his patients wake up in the middle of the night to take their medication, as was once common

practice, Dr. Blick has his patients get a full night's sleep and take the drug at 7AM, 11AM, 3PM, 7PM, and 11PM. "It's very important to have a full night of sleep," he says.

Many other treatments are available. "I am very open minded to any therapy people want to use," says Dr. Blick. "I will follow people in any therapy people want to use as long as it is not going to harm them. If you believe in a therapy, I'll be the last to tell you that it's not going to do you any benefit." Just believing in a self-prescribed, self-administered therapy, Dr. Blick says, is often enough to get positive results.

#### Physician Confidentiality

Because of the mechanisms of transmission and the groups that have most often been infected, a physician's obligation of confidentiality holds new importance when AIDS and HIV infection is involved.

"Physicians need to be extremely careful about patient confidentiality and need to make sure they instruct their staff about confidentiality," says Mr. Schatz. Many of the cases that he handles involve situations in which a nurse or clerical personnel learned of a patient's infection.

In Arkansas, for example, a nurse learned that a hairdresser had tested positive for HIV infection: "The nurse and her husband took it upon themselves to call his customers and told them not to go to him any more because [the hairdresser] had HIV," Mr. Schatz says.

Indeed, he says, "the majority of the calls I receive have been the result of someone on the staff making phone

#### PATIENTS AT HIGH RISK OF HIV INFECTION

Nearly all physicians have patients in their practices who are at risk for AIDS, says Dr. Sandy Pomerantz, a medical consultant to the State of California's Office of AIDS. In particular, patients considered at high risk include:

- Any man who has engaged in sex with another man since 1977.

- Any person who has had heterosexual (vaginal) or anal intercourse with an unknown partner since 1977, and more so since the mid-1980s

- Any person who has used intravenous drugs since 1977.

- Any person who has had sex with an intravenous drug abuser.

- Any person who had a blood transfusion or received blood products, especially products containing blood factors 8 and 9, between 1977 and 1985 (the year in which the blood supply started being tested for HIV).

[well be used] to deny insurance, even though neither has a particular medical significance."

But once a patient tests positive for HIV, says Dr. Rzepkowski, it becomes unreasonable to try to keep that information out of the patient's records. Although he knows of some physicians who maintain lists of their patients who have tested HIV-positive, such lists present confidentiality problems of their own. And, says Dr. Rzepkowski, when patients begin to develop opportunistic diseases that are nearly synonymous with AIDS, the fact that a patient's HIV status is not in the chart becomes meaningless.

#### Current Clinical Trials

At the National Institute of Allergy and Infectious Diseases' AIDS Clinic, Dr. Clifford Lane says that there is a growing interest in the AIDS-research community on conducting long-term studies on HIV-infected patients with healthy immune systems in an attempt to find ways of staving off the disease. A national toll-free hotline for information about these and other trials has been established (800-TRIALSA). A quarterly updated directory of trials is also published by the American Foundation for AIDS Research and can be ordered by calling 800-458-5231. Physicians with patients interested in such trials can also call Dr. Lane at 301-496-9054.

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