Attacks Beware of Future HAART (and Heart) Attacks

Few modern diseases have experienced as dramatic a change in prognosis and treatment as HIV. Once considered uniformly fatal, HIV may now be effectively treated with highly active antiretroviral therapy (HAART).1 HAART has led to a decline in the morbidity and mortality associated with HIV infection and a decrease in the incidence of opportunistic infections.2,3 Unfortunately, not all patients have been able to benefit from HAART, particularly those without access to health care, those who are unable to adhere to or tolerate antiretroviral regimens, and those infected with drug-resistant virus. Furthermore, patients receiving HAART are subject to metabolic complications, including lipid abnormalities and glucose intolerance, which may impact the development of coronary artery and cerebrovascular disease.1

Whether the changes in the epidemiology of HIV have been reflected in admission patterns and outcomes in the ICU is an important question. Throughout the AIDS epidemic, ICU utilization has been influenced not only by the epidemiology of the complications of the disease, but also by patient and provider attitudes toward utility of ICU care.4 ICU admission and mortality rates have shifted multiple times during the course of the AIDS epidemic, with initial decreases in admissions in response to high mortality rates followed by increases as improvements in HIV care, particularly in the treatment of Pneumocystis pneumonia, improved ICU prognosis.5,7 Since the widespread availability of HAART, few studies exist to guide clinicians in the ICU care of patients with HIV infection.

The current study by Narasimham and colleagues (see page 1800) explores the changes in ICU care during the era of HAART (1996 to present). They compared hospital admissions of patients with HIV infection in the first 6 months of 2001 to a 1-year period of time 10 years earlier. In contrast to their original hypothesis, the authors found an increase in the number of ICU admissions for patients with HIV infection in the HAART era (1996 to present). They speculated that this increase might be due to an increasing number of patients living with HIV. Two other studies have examined single-institution ICU admission rates in the era of HAART.8 Nuesch and colleagues8 reported in a series from a Swiss hospital that ICU admissions as a percentage of total hospital admissions of patients with HIV infection increased from 6.3% (from 1994 to 1996) to 11.8% (from 1997 to 1999). In contrast, we found a decrease in the number of ICU admissions for patients with HIV infection in the HAART era (from 1996 to 1999) compared to the 4-year period immediately preceding (from 1992 to 1995) in San Francisco.7,9 These differences may result from variations in local populations or practices or from the slightly different time periods examined by the studies.

Despite an increase in the number of ICU admis-

Intensive Care of Patients With HIV Infection

HAART Warming Improvement but Beware of Future HAART (and Heart) Attacks

Intensive Care of Patients With HIV Infection

HAART Warming Improvement but Beware of Future HAART (and Heart) Attacks

Few modern diseases have experienced as dramatic a change in prognosis and treatment as HIV. Once considered uniformly fatal, HIV may now be effectively treated with highly active antiretroviral therapy (HAART).1 HAART has led to a decline in the morbidity and mortality associated with HIV infection and a decrease in the incidence of opportunistic infections.2,3 Unfortunately, not all patients have been able to benefit from HAART, particularly those without access to health care, those who are unable to adhere to or tolerate antiretroviral regimens, and those infected with drug-resistant virus. Furthermore, patients receiving HAART are subject to metabolic complications, including lipid abnormalities and glucose intolerance, which may impact the development of coronary artery and cerebrovascular disease.1

Whether the changes in the epidemiology of HIV have been reflected in admission patterns and outcomes in the ICU is an important question. Throughout the AIDS epidemic, ICU utilization has been influenced not only by the epidemiology of the complications of the disease, but also by patient and provider attitudes toward utility of ICU care.4 ICU admission and mortality rates have shifted multiple times during the course of the AIDS epidemic, with initial decreases in admissions in response to high mortality rates followed by increases as improvements in HIV care, particularly in the treatment of Pneumocystis pneumonia, improved ICU prognosis.5,7 Since the widespread availability of HAART, few studies exist to guide clinicians in the ICU care of patients with HIV infection.

The current study by Narasimham and colleagues (see page 1800) explores the changes in ICU care during the era of HAART (1996 to present). They compared hospital admissions of patients with HIV infection in the first 6 months of 2001 to a 1-year period of time 10 years earlier. In contrast to their original hypothesis, the authors found an increase in the number of ICU admissions for patients with HIV infection in the HAART era (1996 to present). They speculated that this increase might be due to an increasing number of patients living with HIV. Two other studies have examined single-institution ICU admission rates in the era of HAART.8 Nuesch and colleagues8 reported in a series from a Swiss hospital that ICU admissions as a percentage of total hospital admissions of patients with HIV infection increased from 6.3% (from 1994 to 1996) to 11.8% (from 1997 to 1999). In contrast, we found a decrease in the number of ICU admissions for patients with HIV infection in the HAART era (from 1996 to 1999) compared to the 4-year period immediately preceding (from 1992 to 1995) in San Francisco.7,9 These differences may result from variations in local populations or practices or from the slightly different time periods examined by the studies.

Despite an increase in the number of ICU admis-
visions, the authors reported an encouraging increase in hospital survival from 49% from 1991 to 1992 to 71% in 2001. Similarly, Nuesch and colleagues8 (from 71 to 75%) and our series (from 63 to 71%) also found improvements, albeit modest, in survival. Knowledge of the improved survival of patients with HIV infection is useful for clinicians in discussing prognosis and in deciding utility of care with their patients.

Of importance to clinicians caring for these patients, the authors reported an increase in the number of non-AIDS–associated admission diagnoses. Similar to our study, this study found that non-AIDS–associated diagnoses account for a higher proportion of ICU admissions than AIDS–associated diagnoses. Cardiac (myocardial infarction, unstable angina), GI (GI bleeding, hepatic encephalopathy), renal (renal failure), and neurologic disease as well as drug overdose (reflecting the changing epidemiology of HIV infection with increases in injection drug users) are now frequent admission diagnoses in patients with HIV infection. Although respiratory failure is still common, it accounted for less than one fourth of all ICU admissions in the current study, and respiratory failure secondary to Pneumocystis pneumonia was quite rare (<5% of admissions). These proportions represent dramatic changes from all published series prior to the HAART era.

Clinicians also need to be acutely aware of complications that may result directly or indirectly from the use of HAART. Patients may acquire drug hypersensitivity reactions (more common with certain antiretrovirals than others), resulting in fever, hypotension, and acute interstitial pneumonitis with respiratory failure.10 Fatal lactic acidosis from nucleoside reverse transcriptase inhibitors has been described.1,10 Concurrent use of zidovudine and corticosteroids may result in severe myopathy and respiratory muscle dysfunction.10 In addition, reports have documented several cases of respiratory failure related to HAART initiation and immune reconstitution resulting in a paradoxical worsening of Pneumocystis pneumonia.11 Distinguishing HAART-associated immune reconstitution with paradoxical worsening from Pneumocystis pneumonia treatment failure or a superimposed respiratory infection is often clinically challenging.

In addition to these “HAART attacks,” clinicians need to be aware of future heart attacks. The impact of HAART on decreasing HIV-associated morbidity and mortality has resulted in an ever-aging population of patients with HIV infection, subject to the entire spectrum of associated medical illnesses. The combination of increasing age with HAART-associated metabolic complications including hypertriglyceridemia, hypercholesterolemia, insulin resistance, and type 2 diabetes mellitus portends an increase in future coronary and cerebrovascular events that may result in ICU admission.

Although the current findings of an improved mortality for patients with HIV infection receiving intensive care in the era of HAART are heartening, it is important that research in this area continue. There may be significant differences in regional mortality rates depending on the populations served and physicians’ familiarity with HIV-associated complications. The question of whether initiating HAART in critically ill patients with HIV infection improves mortality remains unanswered and is currently being studied in a prospective, randomized, multicenter study. There may also be future changes in the epidemic resulting from drug resistance, both in the HIV virus and in the HIV-associated opportunistic infections. Drug-resistant HIV may lead to decreases in the effectiveness of HAART, which may, in turn, lead to increases in opportunistic infections. If so, then reports suggesting that opportunistic pathogens such as Pneumocystis may also be developing drug resistance become increasingly concerning.12–15

Studies of ICU epidemiology and outcomes serve to guide clinicians in offering appropriate care to their patients and in providing complete and accurate differential diagnoses. The current study suggests that ICU outcomes in patients with HIV infection are improving. However, clinicians need to be familiar with HAART-related complications and to remember to include non-AIDS–associated diagnoses in their differential when caring for those with HIV infection in the current era.

**Alison Morris, MD, FCCP**
Los Angeles, CA

**Laurence Huang, MD, FCCP**
San Francisco, CA

Dr. Morris is Assistant Professor of Medicine University of Southern California, Keck School of Medicine Division of Pulmonary and Critical Care Medicine, and Adjunct Assistant Professor of Medicine University of Pittsburgh Division of Pulmonary, Allergy, and Critical Care. Dr. Huang is Associate Professor of Medicine University of California, San Francisco Division of Pulmonary and Critical Care Medicine and Positive Health Program.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

**Correspondence to:** Laurence Huang, MD, FCCP, Associate Professor of Medicine University of California, San Francisco Division of Pulmonary and Critical Care Medicine and Positive Health Program, 955 Potrero Ave, Ward 84, San Francisco, CA 94110; e-mail: lhhuang@php.ucsf.edu

**REFERENCES**

1 Yeni PG, Hammer SM, Carpenter CC, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recom-
Malignant Pleural Mesothelioma

The Puzzling Role of Gene-Environment Interaction

Malignant pleural mesothelioma is a relatively uncommon and yet incurable tumor that is aggressive and highly lethal. After the occurrence of mesothelioma was first reported in 1960 in workers exposed to blue asbestos crocidolite, a huge number of experimental and epidemiologic studies has proved causality between asbestos mineral fibers and mesothelioma, whereas relatively few efforts have been made to understand the mechanisms underlying the pathogenesis of and the susceptibility to this tumor. Yet, in the last 2 decades geographic clusters of mesothelioma have been reported in populations with nonprofessional environmental exposure to asbestos, and other mineral fibers including zeolite and fluoro-edenite, a new amphibole end-member, which is chemically different from known asbestos types.

According to current knowledge, mesothelioma derives from multipotent mesothelial stem cells, which differentiate into malignant epithelial or mesenchymal elements. However, the mechanisms determining this differentiation as well as the local invasiveness of mesothelioma, despite extensive investigation, still remain poorly understood. Mesotheliomas with a predominantly epithelial growth pattern have a better prognosis than the sarcomatoid mesothelioma and the mixed or biphasic types, consisting of both epithelial and sarcomatous foci. Thus, the phenotype appears to be highly important for the biological behavior of the tumor, but little is known about the mechanisms and genetic determinants of different phenotypes. The mesothelioma occurs in selected individuals among population groups with known exposure to asbestos, either in the workplace or in the community. Interestingly, the evidence of a background incidence of this tumor, along with the description of familial clustering, suggest that the occurrence of asbestos-induced mesothelioma in some individuals, but not in others, may not be a matter of chance and points to the existence of genetic predisposition. Furthermore, although malignant mesothelioma has received much attention, benign pleural diseases, including pleural plaques, pleural effusion, diffuse pleural thickening, and rounded atelectasis, induced by asbestos and nonasbestos fibers, are also common in clinical practice and often produce difficulties in the differential diagnosis. Hence, an understanding of the genetic profiling of malignant mesothelioma and other asbestos-induced pleural diseases is pivotal importance and can be viewed from the perspective of how normal mesothelial cells respond to injury, how they transform into malignant cells, and how they proliferate so aggressively.

In this issue of CHEST (see page 1843), Hoang and coworkers explore the expression of matriptase, a trypsin-like protease, in freshly dissected human malignant mesothelioma and cultured mesothelioma cell lines, and find a mean 826-fold overexpression of