Increasing Mortality Due to End-Stage Liver Disease in Patients with Human Immunodeficiency Virus Infection

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Highly active antiretroviral therapy has decreased human immunodeficiency virus (HIV)–associated mortality; other comorbidities, such as chronic liver disease, are assuming greater importance. We retrospectively examined the causes of death of HIV-seropositive patients at our institution in 1991, 1996, and 1998–1999. In 1998–1999, 11 (50%) of 22 deaths were due to end-stage liver disease, compared with 3 (11.5%) of 26 in 1991 and 5 (13.9%) of 36 in 1996 ($P = .003$). In 1998–1999, 55% of patients had nondetectable plasma HIV RNA levels and/or CD4 cell counts of >200 cells/mm^3 within the year before death. Most of the patients that were tested had detectable antibodies to hepatitis C virus (75% of patients who died in 1991, 57.7% who died in 1996, and 93.8% who died in 1998–1999; $P =$ NS). In 1998–1999, 7 patients (31.8%) discontinued antiretroviral therapy because of hepatotoxicity, compared with 0 in 1991 and 2 (5.6%) in 1996. End-stage liver disease is now the leading cause of death in our hospitalized HIV-seropositive population.

Highly active antiretroviral therapy (HAART) has slowed the progression of HIV disease and decreased the rate of HIV-associated mortality [1]. With the increased longevity of HIV-infected individuals, other comorbidities, such as chronic liver disease, have assumed greater importance.

Because of the shared routes of transmission, coinfection with hepatitis C virus (HCV) and HIV is very common, especially in injection drug users and hemophiliacs [2–6]. HCV infection leads to chronic hepatitis in 85% of patients, and those patients have a 20% risk of developing cirrhosis during the subsequent 2 decades [7–9]. Several studies suggest that HIV disease modifies the natural history of chronic HCV infection; this leads to an accelerated course of progression from chronic active hepatitis to cirrhosis, end-stage liver disease, and death [5, 10–13].

Most of the published literature on the increased risk of mortality due to end-stage liver disease has involved the hemophiliac population [5, 14–16], among whom rates of coinfection with HIV and HCV range from 60% to 85% [5, 6]. Much fewer data are available regarding mortality due to end-stage liver disease in injection drug users, a population among whom rates of coinfection with HIV and HCV range from 52% to 93% [2–4, 17].

In response to reports of increasing rates of mortality secondary to HCV infection in HIV-infected individuals, we examined the causes of death in HIV-seropositive patients at our institution.

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MATERIALS AND METHODS

We retrospectively reviewed the charts of all HIV-seropositive patients who died at our institution, Lemuel Shattuck Hospital (Jamaica Plain, MA), in 1991, 1996, and 1998–1999 (before, in parallel with, and several years after the introduction of HAART, respectively). Lemuel Shattuck Hospital, a 280-bed facility that provides acute and chronic hospital services to underserved citizens, is an affiliate of the Massachusetts Department of Public Health (Boston) and the Tufts University School of Medicine (Medford, MA).

We obtained death certificates and reviewed all records for any patient who died with an underlying diagnosis of HIV infection or AIDS by use of a structured data collection instrument. Autopsy data were reviewed when available.

We identified 84 HIV-seropositive patients who died during the 3 study periods and compared the following information for the 3 cohorts: causes of death, demographic characteristics, CD4 cell counts, plasma HIV RNA levels, markers of HCV and hepatitis B virus (HBV) infections (when obtainable), history of substance abuse, and information regarding use of antiretroviral medications. The patients who died of spontaneous bacterial peritonitis, hepatic encephalopathy, or gastrointestinal bleeding secondary to esophageal varices or coagulopathy were considered to have died of end-stage liver disease. Statistical comparisons were made by use of the χ^2 goodness of fit, 2-tailed test for proportions, and means were compared by use of the student's *t* test.

RESULTS

A total of 84 HIV-seropositive patients died during the 3 study periods. The number of deaths per year of review was as follows: 26 patients in 1991 (group 1), 36 in 1996 (group 2), and 22 from May 1998 through April 1999 (group 3).

The sociodemographic characteristics of the study groups are presented in table 1. The mean age of the patients in group 1 was 38.3 years old; in group 2, 39.1 years old; and in group 3, 40.1 years old. Men outnumbered women in all 3 groups, but in group 2, women made up a significant minority (30.6%), in contrast to groups 1 and 3 (3.8% and 13.6%, respectively; $P = .02$).

Most patients in all 3 groups had histories of injection drug use as the predominant risk factor for hepatitis B, hepatitis C, and HIV infection (15 [57.7%] of 26 patients in group 1, 27 [75%] of 36 in group 2, and 17 [77.3%] of 22 in group 3). Histories of alcohol consumption were unequally distributed among the 3 cohorts. Rates were similar in groups 1 and 2 (34.6% and 36.1%, respectively) but were higher for group 3 (72.7%; $P = .01$).

Immunologic profiles of the patients in groups 1 and 2 were consistent with advanced HIV infection; these profiles are summarized in table 1. Only 1 patient in these 2 cohorts had a CD4 cell count >200 cells/mm^3. All patients whose CD4 cell counts were not available in the medical record had a history of $\geq$1 opportunistic infections prior to admission to Lemuel Shattuck Hospital, a finding suggestive of advanced HIV disease. In contrast, in group 3, 6 of 11 patients who died of end-stage liver disease had either CD4 cell counts of >200 cells/mm^3 or nondetectable HIV virus loads within 1 year before death.

Discontinuation of antiretroviral therapy. We reviewed the antiretroviral regimens of the patients within the 6 months before admission to Lemuel Shattuck Hospital (table 1); 12 group 1 patients (46.2%), 24 group 2 patients (66.7%), and 10 group 3 patients (45.5%) were receiving antiretroviral therapy at the time of admission to the hospital. All group 1 patients who were receiving antiretroviral therapy were being treated with 1 or 2 nucleoside reverse transcriptase inhibitors. In group 2, 19.4% of the patients were treated with regimens that contained protease inhibitors, and in group 3, 27.3% were treated with regimens that contained protease inhibitors. No patients were being treated with nonnucleoside reverse transcriptase inhibitors. Seven patients (31.8%) in group 3 had recent histories of discontinuation of antiretroviral therapy because of hepatotoxicity, compared with 0 in group 1 and 2 (5.6%) in group 2. Most patients (19 [73.1%], 20 [55.6%], and 17 [77.3%] in groups 1, 2, and 3, respectively) received, along with their antiretroviral therapy, other potentially hepatotoxic agents—namely, fluconazole, trimethoprim-sulfamethoxazole, dapsone, isoniazid, rifabutin, other antimicrobial agents, nonsteroidal anti-inflammatory drugs, phenytoin, and a variety of antidepressants (P = NS; data not shown). We compared the use of prophylaxis for infection due to *Mycobacterium avium* complex and the use of prophylaxis for *Pneumocystis carinii* pneumonia for patients who died of liver disease and those patients who died of all other causes; we did not find a statistically significant difference between the prophylaxis use for the 2 categories of patients during any of the studied years (data not shown).

Serological testing. Serological data were incomplete in all 3 study periods for markers for both HBV and HCV infections. In most cases, the duration of coinfection with HIV and HCV could not be determined from chart review. However, most patients who underwent testing had evidence of antibodies to HCV (3 [75%] of 4 patients in group 1, 15 [57.7%] of 26 in group 2, and 15 [93.8%] of 16 in group 3; P = NS); 11 patients died of end-stage liver disease during 1998–1999, and 9 (90%) of 10 tested for the presence of antibodies to HCV were seropositive. The results of tests for markers for HBV infection (including hepatitis B surface antigen, antibody to hepatitis B surface antigen, and antibody to hepatitis B core antigen) were

Table 1. Demographic characteristics, risk factors for hepatitis, antiretroviral therapy (ART), and CD4 cell counts for human immunodeficiency virus (HIV)–seropositive patients who died at Lemuel Shattuck Hospital (Jamaica Plain, MA) in 1991, 1996, and 1998–1999.

Variable	1991 (n = 26)	1996 (n = 36)	1998–1999 (n = 22)	P
Demographics				
Mean age, y	38.3	39.1	40.1	NS
Male sex	25 (96.2)	25 (69.4)	19 (86.4)	.02
Risk factor for HIV infection[a]				
Injection drug use	15 (57.7)	27 (75)	17 (77.3)	NS
Homosexual sex	6 (23.1)	1 (2.8)	1 (4.5)	.017
Unprotected heterosexual sex	3 (11.5)	11 (30.6)	2 (9.1)	.06
Transfusion(s)	1 (3.8)	0	1 (4.5)	NS
Unknown	2 (7.7)	0	2 (9.1)	NS
Risk factor for liver disease				
Alcohol abuse	9/26 (34.6)	13/36 (36.1)	16/22 (72.7)	.01
Abnormal results of liver function tests[b]	9/24 (37.5)	10/34 (29.4)	13/21 (61.9)	.05
Hepatotoxic drugs other than ART	19 (73.1)	20 (55.6)	17 (77.3)	NS
Antibody to HCV	3/4 (75)	15/26 (57.7)	15/16 (93.8)	NS
HBsAg	2/15 (13.3)	3/25 (12)	2/11 (18.2)	NS
Anti-HBs	8/15 (53.3)	13/25 (52.2)	6/11 (54.5)	NS
Immunologic profile[c]				
CD4 cell count, <200 cells/mm^3	14/14 (100)	35/36 (97.2)	18/22 (81.8)	<.001
CD4 cell count, ⩾200 cells/mm^3	0/14	1/36 (2.8)	4/22 (18.2)	.017
ART within 6 mo before admission				
Did not receive ART	14 (53.8)	12 (33.3)	12 (54.5)	NS
Received ART	12 (46.2)	24 (66.7)	10 (45.5)	NS
Discontinuation of ART because of hepatotoxicity	0	2 (5.6)	7 (31.8)	<.001
Regimen contained NRTIs	12 (46.2)	21 (58.3)	8 (36.4)	NS
Regimen contained PIs	0	7 (19.4)	6 (27.3)	.02

NOTE. Data are no. (%) of patients with variable or no. of patients with variable/total no. tested (%), unless otherwise indicated. Anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NRTI, nucleoside reverse transcriptease inhibitors; PI, protease inhibitors.

[a] One patient may have >1 risk factor for HIV infection.

[b] Alanine aminotransferase levels >2 times the upper limit of normal at admission to Lemuel Shattuck Hospital.

[c] All patients for whom CD4 cell counts were not available had prior opportunistic infections.

found to be positive in 66.7% (in group 1), 64% (in group 2), and 72.7% (in group 3) of the patients tested. Only 7 patients in the entire study cohort tested positive for hepatitis B surface antigen (table 1). Four of these patients were also coinfected with HCV.

Causes of death. The various causes of death are summarized in table 2. In group 3, 11 (50%) of 22 deaths were the direct result of complications secondary to end-stage liver disease ($P = .003$). The causes of death of the remaining 11 patients were sepsis (3 patients), cytomegalovirus disease (2), AIDS dementia complex (1), cryptococcal meningitis (1), progressive multifocal leukoencephalopathy (1), CNS lymphoma (1), gastrointestinal bleeding (1), and end-stage renal disease (1). In contrast, in group 1, only 3 (11.5%) of 26 deaths were associated with end-stage liver disease. The causes of death of the remaining 23 patients were *M. avium* complex disease (5 patients), AIDS dementia complex (5), Kaposi's sarcoma (3), toxoplasmosis (2), cryptococcal meningitis (2), *P. carinii* pneumonia (1), CNS lymphoma (1), bacterial pneumonia (1), sepsis (1), congestive heart failure (1), and Hodgkin's disease (1). In group 2, 5 (13.9%) of 36 deaths were due to end-stage liver disease. The remaining 31 deaths were due to bacterial pneumonia (9 patients), sepsis (5), *P. carinii* pneumonia (5), CNS lymphoma (3), cytomegalovirus disease (3), toxoplasmosis (2), cryptococcal meningitis (1), progressive multifocal leukoencephalopathy (1), *M. avium* complex disease (1), and gastro-

Table 2. Causes of death of human immunodeficiency virus (HIV)–seropositive patients at Lemuel Shattuck Hospital (Jamaic Plain, MA) in 1991, 1996, and 1998–1999.

Cause of death	Deaths by year, no. (%)			
	1991 (n = 26)	1996 (n = 36)	1998–1999 (n = 22)	P
End-stage liver disease	3 (11.5)	5 (13.9)	11 (50)	.003
AIDS dementia complex	5 (19.2)	0	1 (4.5)	.01
CNS toxoplasmosis	2 (7.7)	2 (5.6)	0	NS
Cryptococcal meningitis	2 (7.7)	1 (2.8)	1 (4.5)	NS
Pneumocystis carinii pneumonia	1 (3.8)	5 (13.9)	0	NS
Cytomegalovirus disease	0	3 (8.3)	2 (9.1)	NS
Progressive multifocal leukoencephalopathy	0	1 (2.8)	1 (4.5)	NS
Mycobacterium avium complex disease	5 (19.2)	1 (2.8)	0	.01
CNS lymphoma	1 (3.8)	3 (8.3)	1 (4.5)	NS
Kaposi's sarcoma	3 (11.5)	0	0	NS
Bacterial pneumonia	1 (3.8)	9 (25)	0	<.01
Sepsis	1 (3.8)	5 (13.9)	3 (13.6)	NS
Gastrointestinal bleeding	0	1 (2.8)	1 (4.5)	NS
Congestive heart failure	1 (3.8)	0	0	NS
Hodgkin's disease	1 (3.8)	0	0	NS
End-stage renal disease	0	0	1 (4.5)	NS

intestinal bleeding (1). In all 3 cohorts, only 1 patient with chronic HBV infection alone (who did not have concomitant hepatitis C) did not die of liver disease.

DISCUSSION

In our analysis of causes of death of patients infected with HIV, we found that end-stage liver disease has become the leading cause of death of HIV-seropositive patients at our institution. This trend is occurring in the background of a dramatic decline in the incidence of opportunistic infections and the rate of AIDS-related mortality in the era of HAART [1], as reflected in our 2 most recent cohorts (patients who died during 1996 and 1998–1999). Fifty-five percent of our patients who died of end-stage liver disease had either CD4 cell counts of >200 cells/mm^3 or nondetectable plasma HIV RNA levels within the year before death, which underscores the fact that liver disease led to early death in these patients.

Mortality due to end-stage liver disease occurred in patients with HCV infection, although other cofactors, such as alcohol use, chronic HBV infection, and use of hepatotoxic medications, may have played a contributory role in either progression or decompensation of chronic liver disease.

The use of alcohol, which was more prevalent among patients who died during 1998–1999, may have accelerated the progression of underlying liver disease. However, an alternative hypothesis for the higher prevalence could be an ascertainment bias to obtain more accurate and detailed histories of alcohol consumption in group 3, because of the clinical presentation of liver disease. Regardless, these data emphasize the importance of counseling patients with chronic active hepatitis on the need for abstinence from alcohol ingestion because of its role in the acceleration of the natural history of fibrosis progression [18].

Two of the HCV-infected patients who died of liver disease in 1998–1999 were also chronic HBV carriers, and results of HBV serologic studies were unavailable for 2 patients. However, it is less clear what role chronic HBV infection may have played, since a recent study has shown that even nonreactive HBV serological markers are inadequate to exclude a diagnosis of occult HBV infection for patients with chronic hepatitis C [19].

Our data highlight the fact that almost one-third of patients in group 3 had to discontinue antiretroviral therapy because of abnormal results of liver function tests. Hepatotoxicity was clearly a limiting factor in the use of HAART in this cohort. The likelihood of drug-related toxicities is increased by underlying viral hepatitis [20, 21]. Coinfected patients should have careful assessment of possible underlying liver disease and a close laboratory evaluation when starting HAART, because abnormal transaminase levels and hepatic decompensation during antiretroviral therapy have been reported in the literature [22–24]. However, a recent prospective study of hepatotoxicity in HIV-positive patients who were receiving antiretroviral therapy found that 88% of patients who had concomitant chronic

HCV or HBV infection tolerated their medications without serious adverse effects as evidenced by liver function tests [25].

Because of incomplete serological testing, we cannot rule out the possibility that more patients in group 3 were infected with HCV than were in groups 1 and 2, thus accounting for an increase in liver-related deaths in group 3. However, it is likely that rates of HCV seropositivity were similar because the major risk factor for transmission of both HIV and HCV in all 3 groups was injection drug use, and epidemiological studies have shown a high risk of seroconversion within the first year of substance abuse [26].

Mortality rates associated with end-stage liver disease may now be rising because of several factors. Early deaths due to opportunistic infections in groups 1 and 2 may have masked any morbidity related to underlying chronic viral hepatitis. The use of HAART has led to marked declines in opportunistic infections and acute bacterial infections [27], which may lead to the clinical presentation of other underlying comorbid conditions, such as advanced liver disease. Furthermore, the burden of disease due to past infection with HCV is projected to increase over time, since progression to cirrhosis occurs over an average of 2 decades [7, 9]. Increased longevity of patients with HIV infection in the era of HAART, along with accelerated rates of progression of HCV-related disease, places this group of patients at extremely high risk for liver disease and its complications in the years to come.

The more-accelerated course of hepatitis C in HIV-seropositive patients in the hemophiliac population [5, 10, 17] and, according to our own data, in the injection drug using population, highlights the importance of the recommendation by the United States Public Health Service and the Infectious Diseases Society of America that all patients with HIV infection should undergo testing for antibody to HCV [28]. Furthermore, those patients with clear risk factors for HCV infection who are seronegative should be considered for HCV RNA testing. Loss of antibody to HCV has been described in HIV-infected patients [29], although false-negative results were not found in a recent study when a third-generation EIA was used for screening [30]. Studies are currently under way to determine the efficacy and safety of IFN and ribavirin for treatment of coinfected patients [31, 32]. Clinical trials are also needed to assess whether treatment of hepatitis C should precede or run concurrently with HAART in a certain subgroup of patients.

As HIV-infected patients live longer, prospective studies are needed to clearly define the impact of coinfection with HCV and other viral agents of chronic hepatitis, and to determine the effects of HAART and other potentially hepatotoxic drugs on chronic liver disease.

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