

Increasing Impact of Chronic Viral Hepatitis on Hospital Admissions and Mortality among HIV-Infected Patients

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ABSTRACT

To assess the impact of chronic viral liver disease (CVLD) on hospital admissions and death in HIV-infected patients since the introduction of highly active antiretroviral therapy, all hospital charts, from January 1996 to December 2000, in a large HIV/AIDS reference center in Madrid were reviewed. Discharge diagnosis, complications during the inpatient period, and number and causes of death were recorded. A total of 1334 hospital admissions involving 875 HIV-infected individuals was recorded. Up to 82% of them were either active or former intravenous drug users. Overall, 158 (11.8%) were admitted because of complications of CVLD, or developed complications of CVLD during their admission for another reason. The absolute number and proportion of admissions caused by CVLD increased over time, from 9.4% (31 of 330) in 1996 to 16% (46 of 287) in 2000 ($p < 0.05$). Likewise, the total number and proportion of deaths due to CVLD increased from 9.3% (5 of 54) in 1996 to 45% (9 of 20) in 2000 ($p < 0.05$). Chronic hepatitis C was the only etiology in nearly three-quarters of patients who were admitted or died of CVLD. In conclusion, the proportion of hospital admissions caused by liver failure in HIV-infected patients has increased in the last 5 years, accounting for 16% of cases in 2000. End-stage liver disease currently represents 45% of causes of in-hospital death among HIV-infected individuals. Therefore, strategies to prevent infection by hepatitis viruses (hepatitis B vaccine) and specific treatment (interferon plus ribavirin for hepatitis C virus) should be encouraged among HIV-infected persons.

INTRODUCTION

SINCE THE INTRODUCTION of highly active antiretroviral therapy, the incidence of opportunistic infections and death has declined dramatically in developed countries.^{1,2} As consequence, other chronic diseases frequently associated with HIV infection, such as chronic viral hepatitis, have the opportunity to become more apparent. Nearly 2% of the population in developed countries are infected with hepatitis C virus (HCV), which represents the first cause of cirrhosis and liver transplantation.³ Among HIV-positive subjects, the highest rates of HCV coinfection are seen in those who were infected parenterally: 75–90% among injecting drug users (IDUs) and nearly 100% in some hemophiliac series.^{4–6} Since a faster progression to end-stage liver disease, including cirrhosis⁷ and hepatocarcinoma,⁸ occurs in HCV carriers when coinfecting with HIV, we were interested to assess the current impact of HCV-related liver disease in terms of morbidity and mortality at our institution, a large HIV/AIDS reference center located in Madrid, Spain. In

a previous report, which examined hospital records from patients admitted before highly active antiretroviral therapy (HAART) was introduced, we found that chronic viral liver disease (CVLD) was the cause of hospital admission and death in 8.6 and 4.8% of HIV-infected patients, respectively.⁹

PATIENTS AND METHODS

All clinical charts of patients admitted at the hospital of the Instituto de Salud Carlos III from January 1996 to December 2000 were reviewed. For each admission, epidemiologic, immunologic, and virologic information was collected, as well as discharge diagnosis. Liver disease caused by hepatitis B, C, and/or delta viruses was considered on the basis of persistent elevated aminotransferases and circulating hepatitis B surface antigen (HBsAg), HCV antibodies, and the coexistence of HBsAg and delta antibodies, respectively. Significant alcohol

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TABLE 1. MAIN CHARACTERISTICS OF STUDY POPULATION

Characteristic	Year of admission					Total
	1996	1997	1998	1999	2000	
Number of admissions	330	213	255	249	287	1334
Age (years) (mean \pm SD)	34 (\pm 7.5)	35 (\pm 9)	35 (\pm 6.4)	36 (\pm 7)	37 (\pm 6.5)	35.4 (\pm 7)
Sex (male)	274 (83%)	180 (84.5%)	214 (83.9%)	194 (77.9%)	236 (82.2%)	1098 (82.3%)
Risk category						
IV drug user	255 (82%)	143 (73.7%)	200 (80.3%)	186 (91.6%)	205 (83.3%)	989 (82.2%)
Homosexual	31 (10%)	35 (18%)	26 (10.4%)	9 (4.4%)	19 (7.7%)	120 (10.1%)
Heterosexual	20 (6.4%)	15 (7.7%)	17 (6.8%)	8 (3.9%)	21 (8.5%)	81 (6.7%)
Other	5 (1.6%)	1 (0.5%)	6 (2.4%)	0	1 (0.4%)	13 (1.1%)
CD4 ⁺ cell count (cells/ μ l) (mean \pm SD)	146 (\pm 210)	177 (\pm 193)	211 (\pm 235)	273 (\pm 273)	250 (\pm 279)	212 (\pm 246)
Chronic viral hepatitis	270 (82%)	183 (86%)	217 (85%)	217 (87%)	250 (87%)	1137 (85%)
HIV treatment modality						
No treatment	263 (81.9%)	128 (65.3%)	149 (63.4%)	98 (43.9%)	143 (54.2%)	781 (63%)
1 or 2 drugs	53 (16.5%)	25 (12.8%)	5 (2.1%)	9 (4%)	7 (2.7%)	99 (8%)
HAART	5 (1.6%)	43 (21.9%)	81 (34.5%)	116 (52%)	113 (42.8%)	358 (28.9%)

consumption (>60 g/day) was also recorded as a cofactor for liver disease progression.

Admissions due to CVLD were considered when decompensated cirrhosis (encephalopathy, ascites, and jaundice) or complications directly related to it (gastrointestinal bleeding, hepatorenal syndrome, and peritonitis) were recorded as the main cause of admission, or when they developed during the hospitalization period. Admissions due to classic opportunistic infections were diagnosed according to the U.S. Centers for Disease Control and Prevention (CDC, Atlanta, GA) classification.¹⁰

Statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS 98 software; SPSS, Chicago, IL). Results are expressed as medians, means (\pm standard deviation), or percentages.

RESULTS

From January 1996 to December 2000, a total of 1334 admissions involving 875 HIV-infected patients was recorded. Table 1 describes the main characteristics of the study population. The route of infection, sex, and age tended to be unchanged over time, with the majority of patients being IDUs (82%) and male (82%). The median age was 35.4 years. As expected, there was a continuous increase in the number of hospitalized patients receiving HAART, from 1.6% in 1996 to 43% in 2000 ($p < 0.01$). Likewise, the median CD4⁺ cell count increased over time, from 146 cells/ μ l in 1996 to 250 cells/ μ l in 2000 ($p < 0.05$). The overall prevalence of chronic viral hepatitis was 85% among hospitalized patients and did not change during the study period. This high rate of chronic liver disease was in part

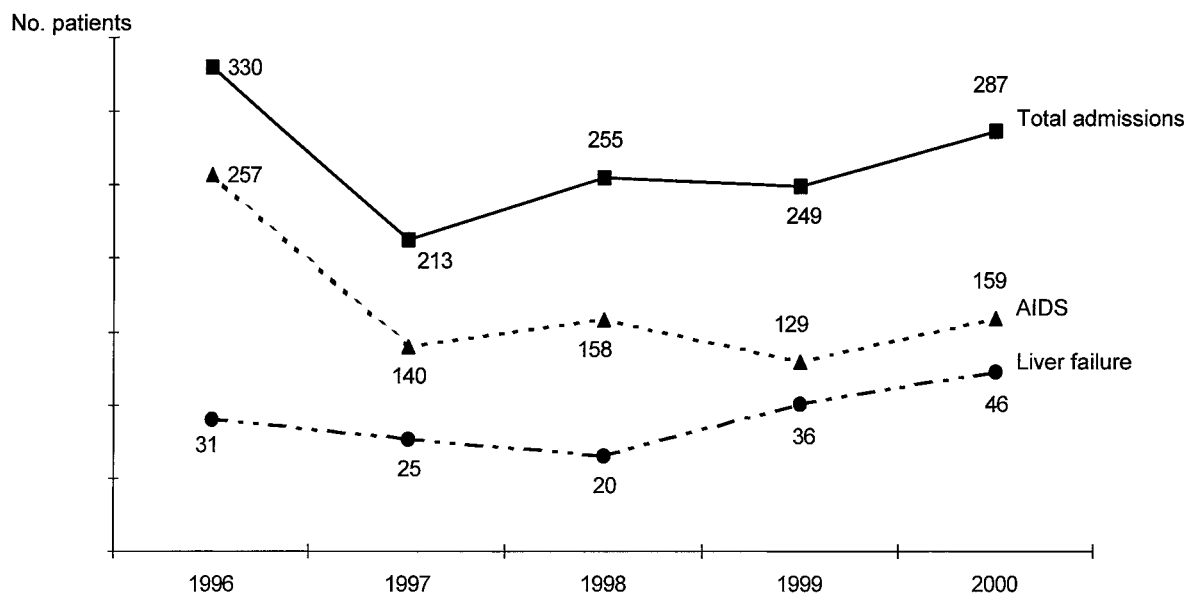


FIG. 1. Trends in the causes of hospital admission.

TABLE 2. ETIOLOGY OF CHRONIC VIRAL HEPATITIS IN PATIENTS BEING HOSPITALIZED WITH LIVER FAILURE

	Admissions (n = 158)	Deaths (n = 27)
HCV	114 (72.1%)	20 (74%)
HBV	6 (3.8%)	1 (3.7%)
HBV + delta	1 (0.6%)	1 (3.7%)
HCV + HBV	30 (18.9%)	4 (14.8%)
HCV + HBV + delta	7 (4.4%)	1 (3.7%)

related to the fact that IDUs were by far the largest group among hospitalized patients. This is in contrast to what is seen in the outclinic of our institution. Homosexual men represent more than one-third of the population on regular follow-up, and the overall prevalence of chronic viral hepatitis in outpatients does not reach 55%.

Admissions due to CVLD

Overall, hospital admissions due to AIDS-defining conditions declined from 73% (n = 241) in 1996 to 61.5% (n = 177) in 2000 (p < 0.05). Decompensated liver failure was either the primary reason for hospitalization or developed during the hospital stage in subjects who were admitted with other illnesses. The proportion of patients admitted to the hospital because of CVLD increased annually during the study period: 9.4% in 1996, 11.7% in 1997, 7.8% in 1998, 14.5% in 1999, and 16% in 2000 (Fig. 1).

Chronic viral hepatitis among hospitalized patients was caused by HCV alone in 72% of patients, by HBV alone in 4%, and by multiple hepatitis viruses in the rest (Table 2). High alcohol consumption was recorded in 19.9% of these patients. Decompensated liver disease occurred as a consequence of the

hepatotoxicity of antiretroviral drugs in 19 subjects, which represented 12% of the total number of admissions due to CVLD during the study period. The drugs more frequently involved as cause of liver enzyme elevation were indinavir, nevirapine, antituberculous agents, cothrimoxazole, and ketoconazole. Overall, liver failure was the third cause of hospital admission, following bacterial pneumonia and tuberculosis.

Mortality due to CVLD

A total of 128 deaths (9.5% of admissions) was recorded during the study period. Rates of global mortality decreased annually since 1996, most likely reflecting the increased use of HAART since the beginning to the end of the study. In contrast, the mortality related to liver failure increased during the study period: 9.3% in 1996, 19.2% in 1997, 22.7% in 1998, 33.3% in 1999, and 45% in 2000 (Fig. 2). Since 1997, CVLD was the leading cause of in-hospital mortality at our institution.

Overall, HCV alone was responsible for 74% of deaths (Table 2). One patient died of fulminant acute hepatitis B, another of chronic delta hepatitis infection, and the rest were infected with multiple hepatitis viruses (Table 2). Of note, two HCV-related deaths were due to hepatocellular carcinoma. Both patients were less than 50 years old, and had a previous diagnosis of decompensated cirrhosis. Overall, high alcohol consumption was recorded in 14.8% of patients who died of CVLD.

DISCUSSION

The growing frequency of chronic viral liver disease as the cause of hospital admission and death in HIV-infected persons is currently of much concern in developed countries.^{9,11-14} Before HAART was widely implemented, 9% of admissions of HIV-infected patients at our institution were due to chronic viral liver disease, and liver failure was just marginally repre-

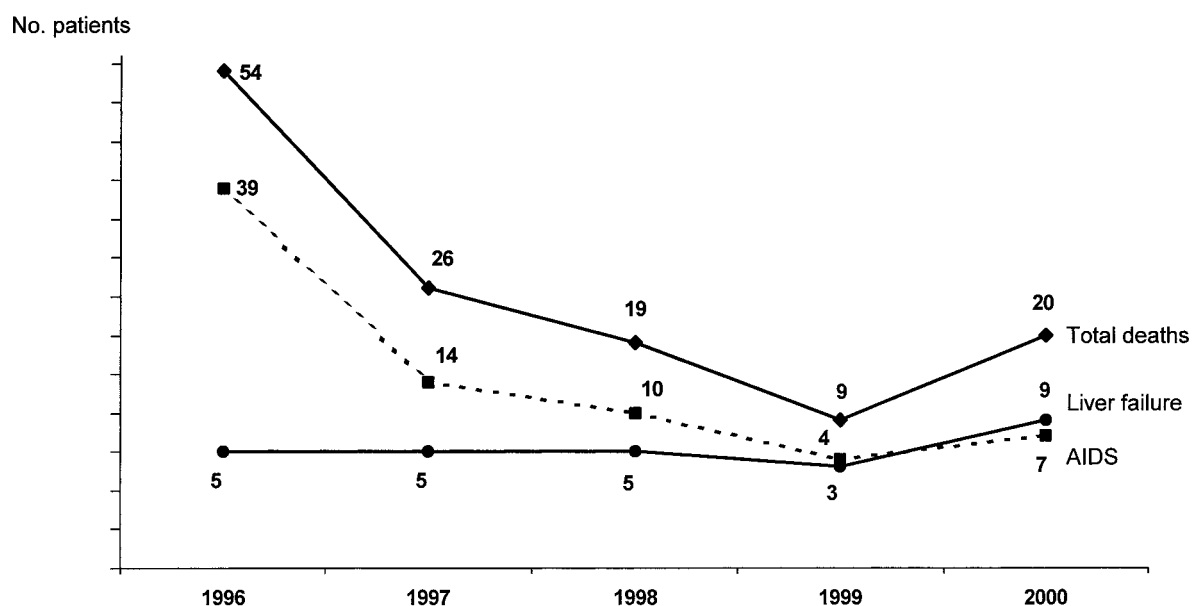


FIG. 2. Trends in mortality of HIV-infected inpatients.

sented in the total number of deaths (5%).⁹ However, since the introduction of HAART, the proportion of patients requiring hospitalization and of those dying from liver failure has increased dramatically. For instance, 16% of admissions in 2000 were due to CVLD, representing the third cause of hospitalization among HIV-infected subjects, just behind bacterial pneumonia and tuberculosis. Of note, in 12% of cases, liver failure occurred as a direct result of drug hepatotoxicity, notably some antiretroviral compounds. It is now well established that the hepatotoxicity of antiretroviral drugs is more frequent in subjects with underlying chronic hepatitis C.^{15,16}

With respect to mortality, liver failure accounted for 45% of in-hospital deaths among HIV-infected persons in 2000. In fact, since 1997, liver failure is the leading cause of in-hospital death among HIV-infected subjects at our institution. Similar figures have been recorded in other places, where drug addicts represent a large proportion of the HIV-positive population.¹¹⁻¹³

Our inpatient population differs significantly from that on regular follow-up at the outclinic of our institution. Currently, more than 80% of outpatients are taking at least three antiretroviral drugs,¹⁷ which contrasts with the 29% recorded among inpatients in this study. Most likely, it reflects the fact that patients without antiretroviral treatment are more prone to be admitted to the hospital for any reason. This observation probably reflects the fact that those patients who are not receiving treatment are at greater risk of worse disease evolution and, consequently, admission to hospital.

In our series, the agent of viral failure was HCV in most instances, alone (71% of cases) or less frequently with either hepatitis B or delta viruses. Likewise, a report from Massachusetts¹² pointed out that end-stage chronic hepatitis C was responsible for half of deaths among HIV-infected patients in 1998. Both HIV and HCV share similar modes of transmission, notably the parenteral route, which explains the high rate of coinfection among IDUs.³⁻⁶ Moreover, chronic hepatitis C adopts a more aggressive course in the setting of HIV infection, increasing the 20% risk of developing cirrhosis within 20 years seen in HIV-negative subjects.^{6,7,13,14} Therefore, our findings of a dramatic impact of liver failure on the current morbidity and mortality of HIV-infected persons should have been expected, once classic HIV-associated opportunistic infections are no longer a problem and survival has been extended dramatically by HAART. The longer HIV-infected persons survive, the greater the risk that they will develop cirrhosis, if they are coinfecting with HCV. Moreover, 2 of the 27 deaths related to liver failure recorded in our study were due to hepatocellular carcinoma, the latest complication seen in the natural history of chronic hepatitis C. What was more striking was the fact that the diagnosis was made in subjects in their forties. In HIV-negative persons, hepatocellular carcinoma is always seen in subjects with long-term chronic hepatitis C, and almost never in people younger than 50 years old. This observation provides further support to the notion that HIV accelerates the course of HCV-related liver disease. Thus, periodic liver ultrasonography and α -fetoprotein measurements should be performed in all HIV/HCV-coinfecting subjects with cirrhosis.⁸ Studies designed to prove the cost-effectiveness of this approach are required.

Up to 20% of patients admitted due to CVLD reported high alcohol consumption. Since high alcohol intake accelerates the course of chronic hepatitis C,¹⁸ patients with HIV infection and

chronic hepatitis C should be strongly advised of the negative impact of drinking.

Efforts to prevent the exposure of risky populations to HCV and/or to treat carriers are warranted. Until recently HIV-positive persons were excluded from anti-HCV treatment protocols. This behavior is no longer appropriate, and the safety and efficacy of new therapies for chronic hepatitis C must be assessed in HCV/HIV-coinfecting patients.^{18,19} Preliminary data suggest that interferon provides similar rates of cure in HIV-positive and HIV-negative subjects, when CD4⁺ cell counts are not below 500 cells/ μ l.²⁰ Rates of sustained response approaching 50% seem to be obtained by using interferon plus ribavirin or PEGylated interferon.^{21,22} Although data on therapy in HCV/HIV-coinfecting patients are still limited,²³ anti-HCV treatment should now be considered a priority in HIV-infected persons with chronic hepatitis C.

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