

Changes in liver-related hospital admissions and hospital mortality among HIV-infected patients (1998 to 2005)

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Liver-related disease has increased as a cause of hospitalization and in-hospital death in HIV-infected patients since the introduction of highly active antiretroviral therapy (HAART). Better clinical management of these diseases may contribute to decreasing their incidence. Admissions due to liver-related disease in HIV-infected patients in our institution increased from 2.9% in 1998-1999 to 11.3% in 2004-2005 ($P = 0.001$). In-hospital deaths due to this cause increased from 2.7% in 1998-1999 to 26% in 2002-2003 ($P = 0.02$), with a subsequent decrease to 22% in 2004-2005. Hospitalization of HIV-infected patients for liver-related disease continues to increase, whereas the rate of in-hospital deaths from this cause appears to have changed since 2003.

Key words: HIV infections. Liver disease. HAART. Morbidity. Mortality.

Evolución de los ingresos y la mortalidad por hepatopatía en pacientes infectados por el VIH entre 1998 y 2005

La hepatopatía ha aumentado como causa de ingreso y muerte intrahospitalaria en pacientes infectados por el virus de la inmunodeficiencia humana (VIH) tras la aparición de la terapia antirretroviral de gran actividad (TARGA). Un mejor manejo clínico de la hepatopatía podría ayudar a disminuir su incidencia. En nuestro centro, los ingresos por hepatopatía aumentaron del 2,9% en 1998-1999 al 11,3% en 2004-2005 ($p = 0,001$). Las muertes intrahospitalarias debidas a hepatopatía aumentaron del 2,7% en 1998-1999 al 26% en el período 2002-2003 ($p = 0,02$) y disminuyeron al 22% en 2004-2005. Si bien el número de ingresos por hepatopatía en pacientes infectados por el VIH todavía sigue aumentando, parece que la mortalidad intrahospitalaria ha sufrido un cambio desde 2003.

Palabras clave: Infección por VIH. Hepatopatía. TARGA. Morbilidad. Mortalidad.

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Introduction

Highly active antiretroviral therapy (HAART) has changed the natural history of human immunodeficiency virus (HIV) infection in patients who have access to it¹. The decrease in hospital admissions and deaths due to acquired immunodeficiency syndrome (AIDS) in this population has paralleled an increase in the number of hospitalizations and deaths due to other causes². Thus, the importance of liver-related diseases (LRD) as a cause of hospital admission and death has increased in HIV-infected patients^{3,4}.

In recent years, however, increasingly more patients are being effectively treated for hepatitis C virus (HCV) and hepatitis B virus (HBV) infections. In addition, HAART has been found to slow down the progression of liver fibrosis and reduce liver-related mortality in HIV/HCV-coinfected patients^{5,6}. Based on these facts, we hypothesized that liver-related morbidity and mortality in HIV-infected patients has declined in the last few years.

Methods

HIV-infected patients hospitalized from January 1998 to December 2005 were retrospectively analyzed in this serial cross-sectional study. All the discharge and the in-hospital death reports in our institution are codified using the International Classification of Diseases, 9th edition (ICD-9).

The patients analyzed met the following criteria: 1) 18 years old or older; 2) ICD-9 codes corresponding to HIV infection (042 and V08) at discharge or on the in-hospital death report; 3) ICD-9 codes referring to LRD at discharge or on the in-hospital death report (chronic liver disease, cirrhosis, chronic and acute HBV infection, chronic HCV infection, chronic HCV with hepatic coma, non-alcoholic liver cirrhosis, gastrointestinal bleeding, esophageal varices with bleeding, ascites, pharmacological liver toxicity, alcoholic liver disease, hepatic encephalopathy, congestive gastropathy in portal hypertension, hepatorenal syndrome, hepatocellular carcinoma, portal vein thrombosis, acute liver failure and spontaneous bacterial peritonitis: 070.9, 070.30, 070.32, 070.44, 070.54, 155.0, 452, 456.20, 537.89, 567.9, 571.2, 571.5, 571.9, 572.2, 572.4, 573.3, 573.8, 578.9 and 789.5).

Only one admission per patient and year was computed to avoid repeated inclusion of the same patient in one calendar year. Data were analyzed in 4 periods of 2 years. The statistical analysis was performed using the chi-square test for linear trends, and a chi-square test was applied to compare mortality among biennia. Associations with a P value of ≤ 0.05 were considered significant. Statistical analyses were carried out using Stat-Cal (EpiInfo 3.3.2, Centers for Disease Control and Prevention, Atlanta, Georgia, USA) and SPSS 11 (SPSS Inc., Chicago, Illinois, USA).

Results

Over the study period, 1138 HIV-infected patients were hospitalized, and 72 (6.3%) were admitted for LRD. Liver disease was the reason for admission in 9 (2.9%) of 311 patients in the 1998-1999 period, which was used as the reference period for comparisons. In the 2000-2001 biennium, there were 14 (4.7%) LRD admissions out of a total of 300 (Odds ratio [OR] 1.64, 95% confidence interval [95% CI] 0.70-3.85, $P = 0.254$). In the 2002-2003 period, 21 (7.5%) of 279 admissions were due to LRD (OR [95%CI]: 2.73 [1.23-6.07], $P = 0.014$). And in the 2004-2005 period, 28 (11.3%) of 248 patients were admitted for LRD (OR [95%CI]: 4.27 [1.98-9.23], $P < 0.001$).

Between 1998 and 2005, 124 HIV-infected patients died in the hospital. Twenty (16%) deaths were due to LRD. Total deaths and liver-related deaths by biennia are summarized in table 1. In-hospital mortality due to LRD increased significantly from the 1998-1999 period to 2002-2003. However, in the last period, LRD mortality showed a tendency to decrease. There were no significant differences between the last 2 biennia ($P = 0.8$).

Discussion

Liver-related disease as a cause of hospitalization has continued to increase in HIV-infected patients in our institution. However, the trends in hospital mortality due to LRD seem to have changed in the last few years. In fact, after a striking increase in the 2000-2001 period, in-hospital mortality increased less markedly in the following biennium and presented a non-significant decreasing trend since 2003.

Since 1998, the number of HIV-infected patients admitted to our hospital has progressively decreased, a fact that likely reflects the effect of HAART, interferon plus ribavirin treatment for HCV coinfection, and better management of chronic liver disease. However, LRD admissions continue to increase. The findings of this study do not support our hypothesis of a decrease in LRD admissions in the late HAART era and are consistent with previously reported data^{2,3}. Nonetheless one Spanish group reported an increase in LRD hospital admissions and deaths among HIV-infected patients from 1996 to 2001, followed by a significant reduction since 2001⁷. Another study describing data on mortality related to end-stage liver disease in HIV-infected patients reported stable rates between the years 2001 and 2003⁸. In this regard, we observed a later decreasing trend in in-hospital deaths attributable to LRD between 2003 and 2005.

There are some possible explanations for these results. First, HIV/HCV-coinfected patients with end-stage liver disease have very limited survival⁹. HAART exposure can extend their survival, but their life expectancy remains short¹⁰. These patients are being admitted and it is reasonable that there be significant in-hospital mortality. Second, some patients hospitalized for LRD may have certain peculiarities. They may be a minority group of HIV-infected patients who do not adhere properly to HAART and follow-up. These patients do not benefit from HAART or HCV infection treatment, and consequently, they will not survive. Third, we may be observing a para-

TABLE 1. In-hospital deaths due to liver-related disease (LRD)

Years	LRD deaths n (%)	Total deaths n	Odds Ratio (95% confidence interval)*
1998-1999	1 (2.7)	37	1 (-)
2000-2001	5 (17.9)	28	7.83 (0.86-73.3)
2002-2003	7 (25.9)	27	12.6 (1.44-109.8)
2004-2005	7 (21.9)	32	10.08 (1.16-87.07)

*Chi-square for linear trends ($P = 0.02$). The reference period for the comparisons is 1998-1999.

doxical increase of patients admitted for LRD that is derived from an ultimate decrease in LRD mortality. Better LRD management may decrease mortality. However, the surviving patients will be at risk of experiencing another episode of hepatic decompensation and being readmitted.

This was a cross-sectional, retrospective study of admissions and in-hospital mortality. Hence, the conclusions are limited. The effect of treatment interventions can only be evaluated in longitudinal studies, with data on patient follow-up. The descriptive results of the present study show the trends of admissions and in-hospital deaths in the recent past. The frequency of admissions due to LRD is increasing while in-hospital LRD mortality may be reaching a plateau or starting a fall. The underlying reasons for this new clinical pattern should be clarified in future cohort studies.

References

- Mocroft A, Monforte A, Kirk O, Johnson MA, Friis-Moller N, Banhegyi D, et al; EuroSIDA Study Group. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362:22-9.
- Mocroft A, Monforte A, Kirk O, Johnson MA, Friis-Moller N, Banhegyi D, et al. EuroSIDA study group. Changes in hospital admissions across Europe: 1995-2003. Results from the EuroSIDA study. *HIV Med*. 2004;5:437-47.
- Mocroft A, Soriano V, Rockstroh J, Reiss P, Kirk O, de Wit S, et al; EuroSIDA Study Group. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? *AIDS*. 2005;19:2117-25.
- Macías J, Melguizo I, Fernandez-Rivera FJ, García-García A, Mira JA, Ramos AJ, et al. Mortality due to liver failure and impact on survival of hepatitis virus infections in HIV-infected patients receiving potent antiretroviral therapy. *Eur J Clin Microbiol Infect Dis*. 2002;21:775-81.
- Qurishi N, Kreuzberg C, Luchters G, Effenberger W, Kupfer B, Sauerbruch T, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet*. 2003;362:1708-13.
- Bonacini M, Louie S, Bzowej N, Wohl AR. Survival in patients with HIV infection and viral hepatitis B or C: A cohort study. *AIDS*. 2004;18:2039-45.
- Sánchez-Somolinos M, Martín-Carbonero L, Valencia ME, Samaniego J, Romero M, Núñez MJ, et al. Reduction in liver-related hospital admissions and deaths in HIV patients since year 2001. 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment. Rio de Janeiro, Brazil. July 2005. Abstract 2177343.
- Rosenthal E, Pialoux G, Bernard N, Pradier C, Rey D, Bentata M, et al. Liver-related mortality in human-immunodeficiency-virus-infected patients between 1995 and 2003 in the French GERMIVIC Joint Study Group Network (MORTAVIC 2003 Study). *J Viral Hepat*. 2007;14:183-8.
- Merchante N, Girón-González JA, González-Serrano M, Torre-Cisneros J, García-García JA, Arizcorreta A, et al. Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease. *AIDS*. 2006;20:49-57.
- Pineda JA, Romero-Gómez M, Díaz-García F, Girón-González JA, Montero JL, Torre-Cisneros, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. *Hepatology*. 2005;41:779-89.