Increasing Incidence of Hepatocellular Carcinoma in HIV-Infected Patients in Spain

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Background. To report the clinical and epidemiological characteristics of hepatocellular carcinoma (HCC) diagnosed in a cohort of human immunodeficiency virus (HIV)–infected patients in Spain.

Methods. All HIV-infected patients diagnosed of HCC in 18 hospitals in Spain before 31 December 2010 were included. The main characteristics of HCC cases are described and comparisons between cases according to the year of diagnosis are presented.

Results. Eighty-two cases of HCC in HIV-infected patients were included, all of them related to viral hepatitis coinfection: hepatitis C virus (HCV) in 66 (81%), hepatitis B virus (HBV) in 6 (7%), and HBV/HCV in 10 (12%). From 1999, when the first case of HCC was diagnosed, a progressive increment in the incidence of HCC in the cohort has occurred. In patients coinfected with HIV/HCV-coinfected patients, the incidence HCC increased from 0.2 to 2.8 cases per 1000 person-years between 2000 and 2009. Death occurred in 65 patients (79%), with a median survival of 91 days (interquartile range, 31–227 days). Three of 11 patients (28%) who received potentially curative therapy died, compared with 62 of 71 patients (87%) who did not receive curative therapy ($P = .0001$). Compared with cases of HCC diagnosed before 2005, cases diagnosed later did not show a higher survival rate.

Conclusions. HCC is an emerging complication of cirrhosis in HIV-infected patients. A sharp increase in its incidence has occurred in those also infected by HCV in the recent years. Unfortunately, HCC is frequently diagnosed at an advanced stage, and mortality continues to be very high, with no significant changes in recent years. Earlier diagnosis, which may allow potentially curative therapy, is necessary.

Keywords. HIV; hepatitis C virus; hepatocellular carcinoma; cirrhosis; liver transplantation.

With the introduction of highly active antiretroviral therapy (ART) and the subsequent reduction of AIDS-associated mortality, human immunodeficiency virus (HIV) infection has become a chronic illness. This has been accompanied by an increase of end-stage liver disease (ESLD)–related mortality in Western countries, mainly due to chronic hepatitis C virus (HCV) infection [1–3]. Solid evidence from the last decade has highlighted that the natural history of

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HCV-related ESLD is accelerated in the setting of HIV infection [4, 5], with poor rates of survival [6].

Hepatocellular carcinoma (HCC) is mainly driven by hepatitis coinfection in the HIV-infected patient. It has been suggested that the time from HCV infection to the development of HCC is shorter in the setting of HIV infection [7–9]. However, it remains controversial whether the incidence of HCC is higher in HCV-infected patients also infected with HIV. In one retrospective cohort study, HIV did not increase the risk of developing HCC [10]. In another survey, among 1217 patients with HCV-related ESLD, 180 of them coinfected with HIV, the incidence of HCC was significantly lower in the HIV-coinfected group [11]. Another cohort study has shown similar results [12].

The reasons for this low incidence of HCC among HIV/HCV-coinfected patients are unclear. There is some consensus [13–15] that HIV probably shortens the survival of patients with HCV-related ESLD enough that HCC, a late complication of liver cirrhosis [16–18], hardly has a chance to emerge. For this reason, some experts have suggested that the incidence of HCC could increase in the next years as a consequence of the effect of highly active ART on survival [19]. The Mortalité Study in France [20] has reported a 10-fold increase in the mortality attributable to HCC in HIV-infected individuals from 2000 to 2005. In contrast, we have reported in a previous analysis of the HEPAVIR cohort of HIV/HCV-coinfected patients from Andalusia (Spain) that HCC represented only 2% of the initial decompensations of ESLD and 3% of liver-related deaths in 2005 [3]. The objective of our study was to report the clinical and epidemiological characteristics of the cases of HCC diagnosed in a cohort of HIV-infected patients in Spain.

METHODS

Study Design, Patients and Data Collection

This study includes the cases of HCC diagnosed in 18 hospitals from 2 regions of Spain before 31 December 2010. Patients were included in this study if they met the American Association for the Study of Liver Diseases (AASLD) 2005 criteria for the diagnosis of HCC [21]. HCC cases were identified from specific databases of HIV-infected patients from the participant centers and by using the database of the clinical documentation services of each institution. In addition, a systematic search of the local cancer registry for cases of HCC was performed in each hospital. Information obtained from clinical records was included in a common database, specifically created for this study. Vital status and causes of death were established from database and clinical records. Patients lost to follow-up or their next of kin were contacted via telephone to assess their vital status.

Statistical Analysis

The incidence density rate of HCC was calculated as the number of registered new cases per 1000 person-years in each calendar year. The date of HCC diagnosis was the date when the patient first met the AASLD 2005 criteria for HCC.

The main characteristics of HCC cases were further analyzed. For these analyses, the following variables were collected and included: age, sex, risk factor for HIV infection, known or estimated date of HIV transmission, positive anti-HCV antibodies, HCV genotype and HCV viral load, previous therapy against HCV and type of response, hepatitis B virus (HBV) surface antigen, previous alcohol consumption, CD4 cell count, previous ART, clinical, radiological, or histological evidence of cirrhosis at the moment of HCC diagnosis and Child-Turcotte-Pugh stage, α-fetoprotein level, number of liver mass lesions, diameter of the largest lesion, presence of an infiltrating mass, evidence of portal thrombosis or extrahepatic metastases, Milan criteria for liver transplantation [22], stage of HCC at diagnosis as established by the Barcelona Clinic Liver Cancer (BCLC) staging system [23], modality of therapy against HCC given, including absence of therapy and vital status. For analyses, HCC diagnosis was divided into 2 categories: diagnosis made by screening or clinical diagnosis. For the first category, HCC diagnosis had to be established on the basis of an initial abnormal finding on a routine α-fetoprotein determination or ultrasound examination in the absence of symptoms. Otherwise, the HCC diagnosis was considered clinical. HCC surveillance was done according to the caring physician criteria, based on consensus recommendations in effect during the study period. Recommendations from the AASLD 2005 practice guidelines [21] were adopted in the cohort after their publication. Therapy against HCC was categorized as curative or noncurative, as established by the updated AASLD practice guidelines [24].

Continuous variables are expressed as medians (interquartile range [IQR]). Categorical variables are presented as numbers (percentage; 95% confidence interval). A comparison was made between the characteristics of HCC cases diagnosed before or after 31 December 2004. Continuous variables were compared using the Student *t* test or Mann-Whitney *U* test, depending on the normality of distributions. Categorical variables were compared using the χ^2 test or the Fisher test, when appropriate.

Finally, the survival of HCC case patients was analyzed. For this analysis, the baseline time point was considered to be the date of HCC diagnosis, defined as the date when the patient first met AASLD 2005 criteria of HCC. The time to event was computed as the months elapsed from this time point to the date of death, loss to follow-up, or 31 December 2010. Kaplan-Meier estimates of the cumulative probability of survival were used, and survival curves were compared using the log-rank test. The statistical analysis was carried out using the SPSS 19 Statistical Software Package (SPSS) and Stata SE 9.0 (Statacorp).

Table 1. Characteristics of the Study Population (n = 82)

Parameter	Value
Age, median (IQR), years	47 (45–51)
Male sex, No. (%)	74 (90)
Daily alcohol intake >50 g/d, No. (%)	33 (40)
Previous intravenous drug users, No. (%)	64 (78)
Hepatitis coinfection, No. (%)	
Hepatitis C	66 (81)
Hepatitis B	6 (7)
Hepatitis B and C	10 (12)
HCV genotype, No. (%)[a]	
1	28 (50)
2	1 (2)
3	20 (36)
4	6 (11)
CD4 cell count, median (IQR), cells/mL[b]	273 (194–385)
Previous ART, No. (%)	68 (83)
α-fetoprotein, median (IQR), ng/mL[c]	152 (9–931)
Child-Turcotte-Pugh class, No. (%)[d]	
A	33 (43)
B	24 (31)
C	20 (26)
BCLC stage, No. (%)[e]	
A	24 (33)
B	15 (20)
C	27 (36)
D	8 (11)

Abbreviations: ART, antiretroviral therapy; BCLC, Barcelona Clinic Liver Cancer; HCV, hepatitis C virus; IQR, interquartile range.

[a] Data available in 55 patients.

[b] Data available in 68 patients.

[c] Data available in 79 patients.

[d] Data available in 77 patients.

[e] Data available in 74 patients.

Ethical Aspects

The study was designed and conducted following the Helsinki declaration. The ethics committee of the Hospital Universitario de Valme approved this study.

RESULTS

Features of the Study Population

Eighty-two cases of HCC in HIV-infected patients were diagnosed in the participant hospitals before 31 December 2010. The main characteristics of the population are depicted in Table 1. In all instances, HCC was related to viral hepatitis coinfection. Namely, 66 patients (81%) were coinfected by HCV, 6 (7%) by HBV, and 10 (12%) by both HBV and HCV. Twenty-two (29%) of 76 HIV/HCV-coinfected patients had previously been treated for HCV. Six of these patients had achieved sustained virological response (SVR), with a median of 28 months (IQR, 18–33 months) elapsed from SVR to HCC diagnosis. None of these patients reported previous excessive alcohol consumption, and only 1 was also infected by HBV. At the time of HCC diagnosis, 77 patients (94%) had clinical, sonographic, or histological evidence of liver cirrhosis. Forty-four patients (56%) had an α-fetoprotein <200 ng/mL at the time of HCC diagnosis.

Incidence Density Rate of HCC Over Time

Since 1999, when the first case of HCC in an HIV-infected patient in the participant hospitals was reported, the frequency of such diagnosis has steadily increased, with a dramatic increment in the last few years. In fact, whereas only 16 cases of HCC (19.5%) were diagnosed in HIV-infected patients before 31 December 2004, 66 new cases (80.5%) have been diagnosed

Table 2. Incidence Density Rate of Hepatocellular Carcinoma in the Overall Human Immunodeficiency Virus (HIV)–Infected Population and in HIV/Hepatitis C Virus–Coinfected Patients by Calendar Year (n = 82)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
HIV-infected population												
HCC cases, No.	1	1	1	3	2	8	7	8	10	17	16	8
Patients at follow-up, No.	10 138	10 397	10 688	10 851	11 237	11 373	12 331	13 182	13 401	13 728	13 866	14 258
HCC incidence density rate, cases/1000 person-years	0.1	0.1	0.1	0.3	0.2	0.7	0.6	0.7	0.7	1.2	1.1	0.6
HIV/HCV-coinfected patients												
HCC cases, No.	0	1	1	3	2	8	6	7	10	15	15	8
Patients at follow-up, No.	4623	4740	4776	4818	4936	4901	5146	5414	5451	5420	5439	5386
HCC incidence density rate, cases/1000 person-years	0	0.2	0.2	0.6	0.4	1.6	1.3	1.4	1.8	2.8	2.8	1.4

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

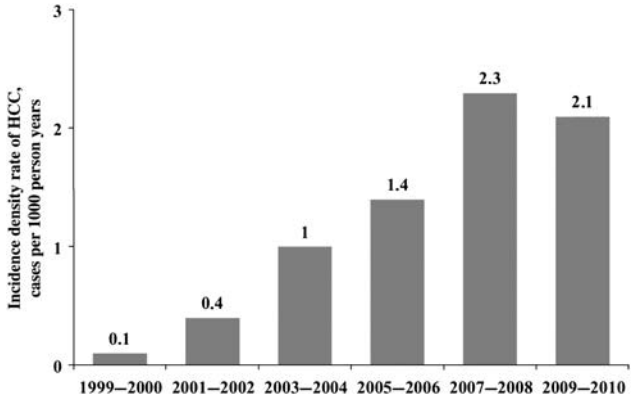

Figure 1. Evolution of the incidence density rate of hepatocellular carcinoma in patients coinfected with human immunodeficiency virus and hepatitis C virus during the study period (n = 76). Abbreviation: HCC, hepatocellular carcinoma.

since this date. Consequently, the incidence density rate of HCC in the overall HIV-infected population has increased during the last decade (Table 2). This increment was more evident in the HIV/HCV-coinfected population (Table 2 and Figure 1). Thus, whereas the incidence density rate of HCC was between 0 and 0.6 cases per 1000 person-years until 2003, the respective figure in 2008 and 2009 was 2.8 cases per 1000 person-years (Table 2).

Staging, Management, and Prognosis

The main characteristics of HCC staging and treatment are depicted in Table 3. HCC was diagnosed in the majority of cases on the basis of symptoms. In fact, HCC was diagnosed at routine screening in only 26 patients (32%). HCC was diagnosed at an advanced stage in a large proportion of patients. Thus, HCC was multifocal at diagnosis in 49 patients (60%) and was complicated by portal thrombosis or extrahepatic metastases in 24 (29%) and 13 (16%), respectively. Consequently, only 25 patients (30%) met the Milan criteria for liver transplantation at diagnosis. Finally, 35 (47%) showed advanced stages (C or D) with the BCLC staging system at initial presentation.

After diagnosis, 33 patients (40%) received therapy for HCC. Of these patients, 11 received potentially curative therapy (surgical resection in 1, liver transplantation in 6, radiofrequency ablation in 1, and ethanol injections in 3) and 22 received noncurative therapy (transarterial chemoembolization in 16 and sorafenib in 6).

The prognosis for HCC was very poor in almost all cases. Thus, 65 patients (79%) died after diagnosis of HCC, with a median survival of 91 days (IQR, 31–227 days). Death was HCC related in all except 2 patients, who died of septic shock and *Pneumocystis jiroveci* pneumonia, respectively. Three of 11 patients (28%) who received potentially curative therapy died, compared with 62 of 71 (87%) who did not receive curative therapy. The median survival after HCC diagnosis was significantly shorter in those individuals who did not receive therapy or received noncurative therapy than in those who received potentially curative therapy (Figure 2). The median survival was 22 months (IQR, 6–42 months) in patients whose HCC diagnosed at screening, compared with 2 months (IQR, 0–7 months) in those whose HCC was diagnosed on the basis of symptoms ($P < .0001$).

Comparison Between HCC Cases Before or After 2005

Table 3 summarizes the main characteristics of HCC cases according to the calendar year of diagnosis. Compared with cases diagnosed before 2005, HCC cases diagnosed later were more likely to be unilocular at presentation, meet Milan criteria, and receive therapy, although these differences did not reach statistical significance. However, HCC prognosis did not improve in the second period. Namely, the probability of survival at 3, 6, and 12 months was 69%, 50%, and 38%, respectively, in patients with HCC diagnosed before 2005, compared with 57%, 41%, and 27% in those with HCC diagnosed in 2005–2010 ($P = .6$). Figure 3 shows the probability of survival according to the period of HCC diagnosis.

DISCUSSION

This study suggests that the incidence of HCC is increasing in HIV-infected patients in recent years in Spain. In fact, whereas only 16 cases of HCC were diagnosed in our cohort before 31 December 2004, there have been 66 new diagnosis of HCC in the last 6 years. This has resulted in a progressive increase in the incidence of HCC among our study population during the last decade. This observation was mainly driven by a notable rise of the incidence of HCC among HIV/HCV-coinfected patients. Remarkably, the incidence of HCC in this population has increased by a factor of 14 from 2000 to 2009. These results are in agreement with a previous report in France indicating that HCC is emerging as a leading cause of liver-associated death in HIV/HCV-coinfected patients [20]. In fact, HCC due to HCV infection has become the fastest rising cause of cancer-related death in the United States, and its incidence has tripled during the past 2 decades [25]. Our results confirm that HCC is an emerging complication of chronic liver disease in HIV-infected patients, especially in those also infected by HCV.

The increasing incidence of HCC in HIV-infected patients may be due to multiple factors, as has been hypothesized by some experts [13]. First, potent ART has improved the survival of HIV-infected individuals long enough to allow HCC, a late complication of cirrhosis [16–18], to emerge in patients with known risk factors for HCC, such as prolonged ethanol

Table 3. Main Features of Hepatocellular Carcinoma Cases According to Date of Diagnosis (n = 82)

Parameter	Patients With HCC, No. (%)			*P* Bivariate
	Overall Population (n = 82)	Diagnosis Before 2005 (n = 16)	Diagnosis in 2005–2010 (n = 66)	
Age				
<50 years	54 (66)	8 (50)	46 (70)	.1
≥50 years	28 (34)	8 (50)	20 (30)	
CD4 cell count[a]				
<200 cells/mL	22 (32)	4 (31)	18 (33)	.9
≥200 cells/mL	46 (68)	9 (69)	37 (67)	
Previous therapy against hepatitis C				
No	46 (67)	8 (57)	38 (70)	.3
Yes	22 (32)	6 (43)	16 (30)	
Child-Turcotte-Pugh class[b]				
A	33 (43)	6 (46)	27 (42)	.8
B or C	54 (57)	7 (54)	37 (48)	
Diagnosis at screening				
No	56 (68)	12 (75)	44 (67)	.5
Yes	26 (32)	4 (25)	22 (33)	
Nodules at diagnosis				
Solitary	33 (40)	4 (25)	29 (44)	.1
Multiple	49 (60)	12 (75)	37 (56)	
Size of largest lesion				
<5 cm	25 (30)	2 (12)	23 (35)	.08
≥5 cm	57 (70)	14 (88)	43 (65)	
Portal thrombosis				
No	58 (71)	14 (87)	44 (67)	.08
Yes	24 (29)	2 (13)	22 (33)	
Extrahepatic metastases				
No	69 (84)	14 (87)	55 (83)	1.0
Yes	13 (16)	2 (13)	11 (17)	
Milan criteria				
No	57 (70)	14 (87)	43 (65)	.08
Yes	25 (30)	2 (13)	23 (35)	
α-fetoprotein level[c]				
<200 ng/mL	44 (56)	10 (67)	34 (53)	.3
≥200 ng/mL	35 (44)	5 (33)	30 (47)	
BCLC stage[d]				
A–B	39 (53)	5 (42)	34 (55)	.4
C–D	35 (47)	7 (58)	28 (45)	
Therapy against HCC				
Potentially curative	11 (13)	1 (6)	10 (15)	.1
Noncurative	22 (27)	3 (19)	19 (29)	
None	49 (60)	12 (75)	37 (56)	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.

[a] Data available in 68 patients.

[b] Data available in 77 patients.

[c] Data available in 79 patients.

[d] Data available in 74 patients.

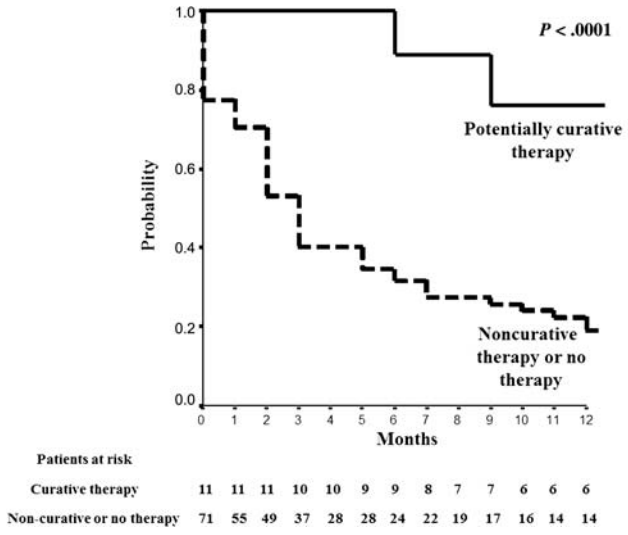

Figure 2. Probability of survival according to the therapy received for hepatocellular carcinoma.

consumption or chronic viral hepatitis. Second, the efficacy of antiviral therapy against HCV in persons living with HIV has been low across all studies, with overall rates of SVR ranging to 41% to 52% [26]. Third, in vitro and animal studies have suggested that HIV may play a role in viral hepatitis and alcohol-induced hepatocarcinogenesis mediated via the Tat protein [27]. Finally, the management of liver cirrhosis by clinicians attending HIV-infected patients has probably improved in the last decade with the increasing burden of liver disease in the HIV-infected population. This may lead to a better management and prevention of other liver decompensations, resulting in longer survival of HIV-infected patients with cirrhosis, which enables HCC to develop.

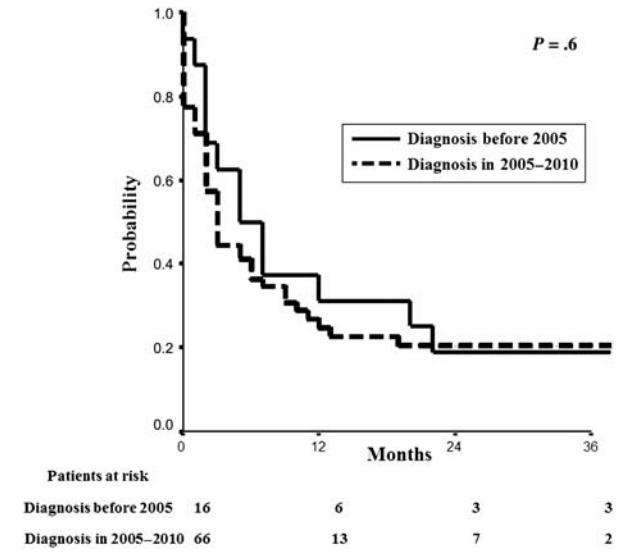

Figure 3. Probability of survival according to the year of hepatocellular carcinoma diagnosis.

Previous reports have suggested that, compared with findings in patients without HIV infection, HCC in HIV-infected patients is more frequently symptomatic, multilocular or invasive, and advanced in stage at the time of diagnosis [9, 28]. HCC cases were diagnosed at an advanced stage in a large proportion of patients in our study, in line with previous data [28]. Consequently, only a minority of patients could receive potentially curative therapy and more than half of the patients did not receive any therapy, a rate similar to that reported by Puoti and coworkers [9]. Thus, the mortality rate was extremely high in our cohort, with a median survival of 3 months, markedly lower than the median survival of 7 months reported in a US-Canadian study [28]. These differences probably reflect the more frequent use of curative therapy in that study.

The proposed management of HCC in HIV-infected patients is the same as that of in patients not infected with HIV. The choice of therapy is mainly driven by cancer stage, with BCLC classification [23] the most widely accepted staging system [18, 21, 24]. Our study confirms that survival increases in HIV-infected patients receiving potentially curative therapy, in agreement with preliminary data from other cohorts [28, 29]. Unfortunately, only a third of our patients had a BCLC classification of stage A at diagnosis, partly because HCC was diagnosed at screening in only a small proportion of patients. Moreover, screening-based diagnosis was only slightly more frequent in the later period compared with older cases. In our opinion, these data reflect the need for clinicians caring for persons with HIV infection to adhere to screening programs for HCC in order to achieve earlier diagnoses. Although there is no definitive evidence for the cost-effectiveness of screening for HCC in patients with HIV infection and cirrhosis, most experts recommend liver ultrasound evaluations at least every 6 months [13–15, 30, 31]. The rationale of this recommendation is that it would facilitate the diagnosis of HCC at earlier stages, thus permitting more effective therapeutic interventions. Furthermore, new approaches are reasonable, such as sequential measurements of liver stiffness by transient elastography in HIV/HCV-coinfected patients, which may allow earlier, more reliable diagnosis of cirrhosis [32] and earlier initiation of HCC surveillance measures.

Patients who have cleared HBV or HCV with therapy have a reduced risk for developing HCC that has been quantified for HCV-monoinfected individuals [33]. However, this risk reduction is not immediate and probably increases with time. Thus, guidelines of clinical practice recommend continuing to undergo surveillance in patients with cirrhosis in whom HCV is eradicated [24]. SVR has been associated with a lower incidence of liver decompensations and liver-related death in

HIV/HCV-coinfected patients in a previous retrospective study [34]. Although a statistically significant reduction in the incidence of HCC could not be proved by the investigators; there were no subsequent cases of HCC among 218 coinfected patients who achieved SVR [34]. Interestingly, there were 6 cases of HCC in patients with previous SVR in our cohort. This finding reinforces the need to continue performing ultrasound examinations in patients who respond to anti-HCV therapy to rule out late emergence of HCC.

This study has a few limitations. First, cases of HCC were mainly collected retrospectively. Thus, we cannot exclude underreporting of HCC cases in the first years of the HIV epidemic. However, HCC was an infrequent liver event in most previous reports of cohorts of HIV/HCV-coinfected patients with cirrhosis [3, 4, 6, 12], in line with our results. Moreover, the majority of recent HCC diagnoses have also been made on the basis of symptoms, not screening, which suggests that prior underreporting is improbable. Second, analyses of survival should be interpreted with caution owing to the retrospective design, because potential biases may have occurred. Conversely, our results represent one of the largest published series of HCC cases in HIV-infected patients and provide additional evidence that this entity is increasing in incidence.

In summary, HCC is an emerging complication of chronic liver disease in HIV-infected patients, especially in those who are also infected by HCV, with a dramatic increase in its incidence in recent years. Unfortunately, HCC is still frequently diagnosed at an advanced stage, and mortality continues to be very high, with no significant changes in recent years. Earlier diagnosis in time to offer potentially curative therapy continues to be the main challenge for clinicians caring for HIV-infected patients with HBV or HCV coinfection. Treatment for HCV infection should also be offered to all potential candidates, in order to achieve SVR, which may prevent the emergence of HCC.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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