Hepatocellular Carcinoma in HIV-Infected Patients: Clinical Characteristics and Prognostic Factors

Antonio Díaz-Sánchez1, Pilar Miralles2,3, Ana Matilla3,5, Teresa Aldámiz-Echevarría2,3, Oscar Núñez, Ana Carrero2,3, Beatriz Merino3,5, Cristina Díez2,3, Rafael Bañares3,6, Gerardo Clemente3,5 and Juan Berenguer2,3*

1Servicio de Aparato Digestivo, Hospital Universitario del Sureste, Arganda del Rey, Spain
2Unidad de Enfermedades Infecciosas/VIH, Hospital General Universitario Gregorio Marañón, Spain
3Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Spain
4Unidad de Hepatología, Hospital General Universitario Gregorio Marañón, Spain
5Centro de Investigación Biomédica en el Área Temática de Enfermedades Hepáticas y Digestivas (CIBEREHD), Spain
6Facultad de Medicina, Universidad Complutense de Madrid, Spain

*Corresponding author: Juan Berenguer, Unidad de Enfermedades Infecciosas/VIH (4100), Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Madrid, Spain, Tel: +34-91-586-8592; Fax: +34-91-426-5177; E-mail: jbb4@me.com

Abstract
We analyzed 53 HIV-infected patients with hepatocellular carcinoma (HCC) diagnosed at our institution from 1998 to 2012. All patients were coinfected with hepatitis virus (77% HCV; 12% HBV; 11% HCV+HBV), and 95% had liver cirrhosis. HCC was diagnosed under surveillance in 41% of patients. Potentially curative therapy was given to 32% of patients and palliative therapy to 30% patients. Median survival was 2 months in those diagnosed from 1998 to 2005, and 11 months in those diagnosed from 2006 to 2012; P=0.16. Survival was independently associated with HCC stage, alpha-fetoprotein serum levels, MELD score, and any treatment.

Keywords
Hepatocellular carcinoma; Human Immunodeficiency Virus; Hepatitis C Virus; Chronic Hepatitis C; Liver Cirrhosis

Introduction
Each year, more than half a million people worldwide are diagnosed with hepatocellular carcinoma (HCC), and approximately 20,000 of these cases are diagnosed in the United States [1]. Major risk factors for HCC include infection with HBV or HCV, alcoholic liver disease, and nonalcoholic fatty liver disease [1]. It is noteworthy that this neoplasm usually appears in patients with underlying cirrhosis.

Since the introduction of combination antiretroviral therapy (cART), the incidence of HCC has increased steadily in HIV-infected individuals, driven primarily by HCV infection [2-4]. Recent reports indicate that HCC is an increasingly frequent cause of death among patients with HIV infection [5].

In comparison with non–HIV–infected patients, some reports suggest that at diagnosis of HCC, patients with HIV infection are younger and more frequently symptomatic with advanced tumors [6,7]. Little is known however about HCC surveillance practices in at-risk HIV-infected patients and about prognostic factors of HCC in this population group. Our objective was to assess clinical characteristics, treatment, and survival in HIV-infected patients with a particular emphasis on identification of prognostic factors.

Methods
We reviewed the Minimum Basic Data Set (MBDS) of our institution to identify all HIV-infected patients diagnosed with HCC at our institution from 1998 to 2012. The MBDS is a computerized database of clinical and administrative data generated from the medical records of discharged patients that is used in hospital management processes and clinical and epidemiological research. Patient medical records were reviewed, and data were extracted according to a protocol and recorded in a working database.

Diagnosis of HCC was based on noninvasive imaging tests or pathology findings according to well-defined criteria [8]. HCC was staged following the Barcelona/Clínic Liver Cancer (BCLC) classification [9]. We compared patients with HCC diagnosed before and after 2005, when the new HCC guidelines of the American Association for the Study of Liver Diseases were published [10]. For the purposes of the study, we...
Within the 12 months before the diagnosis of HCC, ultrasonography of the liver (with no evidence of HCC) was performed. Hepatocellular carcinoma by Cox regression analysis. Variables associated with survival of HIV-infected patients with hepatitis B or C (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cox regression analysis</th>
<th>Multivariate Cox regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>CDC category C</td>
<td>0.76</td>
<td>0.38-1.53</td>
</tr>
<tr>
<td>cART</td>
<td>0.75</td>
<td>0.27-2.14</td>
</tr>
<tr>
<td>CD4 cells (%)</td>
<td>0.99</td>
<td>0.95-1.02</td>
</tr>
<tr>
<td>Detectable HIV-RNA</td>
<td>1.89</td>
<td>0.97-3.67</td>
</tr>
<tr>
<td>HCV infection</td>
<td>1.16</td>
<td>0.35-3.80</td>
</tr>
<tr>
<td>Child-Pugh (A vs. BC)</td>
<td>0.87</td>
<td>0.45-1.69</td>
</tr>
<tr>
<td>Decompensation</td>
<td>0.87</td>
<td>0.45-1.67</td>
</tr>
<tr>
<td>MELD score</td>
<td>1.09</td>
<td>1.01-1.67</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>1.09</td>
<td>1.01-1.67</td>
</tr>
<tr>
<td>BCLC (CD vs. OAB)</td>
<td>1.68</td>
<td>0.62-4.73</td>
</tr>
<tr>
<td>AFP &gt; 200 ng/ml</td>
<td>3.58</td>
<td>1.83-6.99</td>
</tr>
<tr>
<td>Screening of HCC</td>
<td>0.69</td>
<td>0.35-1.33</td>
</tr>
<tr>
<td>Diagnosis after 2006</td>
<td>0.64</td>
<td>0.33-1.22</td>
</tr>
</tbody>
</table>

Abbreviations: CD4, helper T lymphocytes; CDC, Centers for Disease Control and Prevention; BCLC, Barcelona-Clinic Liver Cancer staging system; MELD, Model for End-stage Liver Disease; CD, Cole and Dye; DEB, drug-eluting balloon; IQR, interquartile range; HR, hazard ratio; CI, confidence interval; 95%, 95% confidence interval; P, P value; 0.01, 0.05; <0.01, <0.05; <0.001, <0.01.

HCC was diagnosed during surveillance in 41% of patients, with no significant differences between the periods (Table 1).

A nonsignificant trend towards tumors with better prognostic characteristics was found in the second period in comparison with the first period (Table 1). A solitary lesion was found in 38% of patients, and lesions greater than 5 cm in diameter were found in 52% of patients. Portal vein invasion was detected in 36% of patients, and metastases in 15%. The tumor was advanced (BCLC stage C or D) in 55% of patients, and alpha-fetoprotein serum levels were above 200 ng per ml in 38% of patients.

Sixty percent of patients received treatment for HCC. Of note, patients in the second period received treatment for HCC more frequently than patients in the first period. Potentially curative therapy was given to 32% of patients and noncurative therapy to 30% of patients.

The median (IQR) duration of follow-up was 10 (1-23) months. The median (IQR) survival was 2 (1-27) months in the first period and 11 (3-23) months in the second period; P=0.16. A nonsignificant trend towards improved survival during the first 3 years after diagnosis of HCC was observed in the second period (1-year survival, 62%; 2-year survival, 37%; and 3-year survival, 28%) in comparison with the first period (1-year survival, 37%; 2-year survival, 26%; and 3-year survival, 14%).

Variables associated with survival by univariate and multivariate Cox regression analysis are shown in (Table 2). Survival was independently associated with BCLC stage, serum alpha-protein levels, MELD score, and any treatment (Figure 1).

**Discussion**

We analyzed the characteristics, treatment, and outcome of 53 HIV-infected patients with HCC attended in our institution over a 14-year period (1998 to 2012). HCV-related cirrhosis was the most frequent underlying disease, although in a large number of patients, profound immunosuppression and alcohol consumption - well-known enhancers of fibrosis progression in HIV/HCV-coinfected individuals [3,11,12] - were associated with advanced liver disease.

Of note, only 40% of tumors were detected in surveillance programs, irrespective of the period analyzed; this figure differs little from data reported elsewhere [13]. It must be remembered that ours is a referral center for liver-transplantation and that a substantial proportion of patients were already diagnosed with HCC when first seen by us. We found that HCC was more frequently diagnosed...
monthly intervals [14]. However, it must be taken into consideration that the ideal surveillance interval is not known; and that a surveillance interval of 6-12 months has been proposed based on tumor doubling times [14]. Moreover, a retrospective study has reported that surveillance is no different in patients screened at 6 or 12 monthly intervals [15]. Nevertheless our results reflect the experience of a single institution in which a multidisciplinary team reviewed HCC cases and outlined treatment plans. Our findings allow us to draw some conclusions that we believe are relevant for clinical practice. First HCV-related cirrhosis was by far the most frequent underlying disease in patients with HCC many of whom had a history of severe immunosuppression and/or alcohol consumption. Consequently, key preventive measures for HCC among HIV/HCV-coinfected individuals should include interventions that modify the natural history of HCV infection such as antiviral therapy for HCV [16] and HIV [17] and avoidance of alcohol and injection drugs. Second most cases of HCC were detected outside surveillance programs. Third at the time of diagnosis, half of the patients already had decompensated liver disease and the tumor was frequently advanced. These findings highlight the need to prioritize identification of patients at risk of HCC particularly those with liver cirrhosis. Patients can be identified accurately using noninvasive methods such as transient elastography and serum tests [18]. Following current guidelines patients at risk should be screened for HCC with 6-monthly liver ultrasound with or without serum alpha-fetoprotein testing [10], a procedure that is associated with significant improvements in early tumor detection, administration of curative therapy and overall survival in patients with cirrhosis [19].

Shortening the interval for HCC screening has been proposed for HIV-infected patients with liver cirrhosis since development of HCC could be more rapid in this group than in cirrhotic patients without HIV-infection [20]. This approach warrants further analysis in prospective studies, particularly in patients at high risk of developing liver-related events such as those with liver-stiffness values ≥40kPa [21,22].

Acknowledgements
This work was supported by Red de Investigaciónen SIDA [AIDS Research Network] (RIS). Ref RD12/00017. J Berenguer is an investigator from the Programa de Intensificación de la ActividadInvestigadora en el Sistema Nacional de Salud (ISSNIS). Ref INT10/009 and INT12/154.

The authors thank Thomas O’Boyle for writing assistance during the preparation of the manuscript.

References


