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► To cite this version:

Moana Gelu-Simeon, Maïté Lewin, Maria Ostos, Tatiana Bayan, Maria Beso Delgado, et al.. Prognostic factors of survival in HIV/HCV co-infected patients with hepatocellular carcinoma The CARCINOVIC Cohort. *Liver International*, 2019, 39 (1), pp.136-146. 10.1111/liv.13921 . hal-01874554

HAL Id: hal-01874554

<https://univ-rennes.hal.science/hal-01874554>

Submitted on 20 Sep 2018

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Article type : Original Articles

Editor : Jürgen Rockstroh

Prognostic factors of survival in HIV/HCV co-infected patients with hepatocellular carcinoma: the CARCINOVIC Cohort

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List of abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HIV/HCV co-infected patients, HIV+/HCV+ patients; HCV mono-infected patients, HIV-/HCV+ patients; cART, combined anti-retroviral therapy; AFP, α -foetoprotein; US, ultrasonography; AASLD, American Association for the Study of Liver Disease; CT, computed tomography; MRI, magnetic resonance imaging; LT, liver transplantation; MELD, Model for End-Stage liver disease; CTP, Child-Turcotte-Pugh; BCLC, Barcelona Clinic Liver Cancer; PA, percutaneous ablation; TACE, transarterial chemoembolization; IQR, InterQuartile Range; aRR, adjusted rate ratio; SVR, sustained virological response.

Conflict of interest: No conflict of interest by authors for this study

Financial support: This study was sponsored and funded by the French National Institute for Health and Medical Research - French National Agency for Research on Aids and Viral Hepatitis (Inserm-ANRS).

Author's contributions: study concept and design, study supervision, obtained funding (JCDV); acquisition of data, administrative, technical, or material support (MGS, MO); analysis and interpretation of data (MGS, JCDV, ML, MO, TB, MBS, LM, PN, RL, FRT); drafting of the manuscript (MGS, JCDV, ML, MO); critical revision of the manuscript for important intellectual content (all authors); statistical analysis (TB, MBS, LM).

Abstract

Background and Aims: HIV/HCV co-infected patients with hepatocellular carcinoma (HCC) have poorer survival than HCV mono-infected patients. We aimed to evaluate the prognostic factors for survival. **Methods:** From 2006 to 2013, 55 incident HCCs among HIV+/HCV+ patients, from three ANRS cohorts, were compared with 181 HCCs in HIV-/HCV+ patients from the ANRS Cirvir cohort. **Results:** HIV+/HCV+ patients were younger (50 years [IQR: 47–53] vs. 62 [54–70], $P<0.001$), male (89% vs. 63%, $P<0.001$) than HIV-/HCV+ patients. At HCC diagnosis, both groups had a majority of non-responders to anti-HCV-therapy, and HIV+/HCV+ patients had more frequently known a previous cirrhosis decompensation (31% vs. 14%, $P=0.005$). At diagnostic imaging, there were more infiltrative forms of HCC in HIV+/HCV+ group (24% vs. 14%, $P<0.001$), associated with tumour portal thrombosis in 29%. During a median follow-up period of 11.96 [5.51–27] months since HCC diagnosis, a majority of

palliative treatments were decided in HIV+/HCV+ patients (51% vs. 19%, $P<0.001$). The 1 and 2-year crude survival rates were 61% vs. 78% and 47% vs. 63%, $P=0.003$, respectively. In a Cox model multivariate analysis adjusted for the cohort, age and sex, the most important prognostic factor for survival was the infiltrative form of the tumour (aRR: 8.10 [4.17-15.75], $P<0.001$). **Conclusions:** The radiological aggressiveness of the tumour is the best prognostic factor associated with poorer survival of HCC in HIV+/HCV+ patients. High α -foetoprotein level and decompensated cirrhosis are other ones. This justifies a particular attention to the detection and the management of small nodules in this high-risk population.

Keywords: HIV/HCV co-infected patients; hepatocellular carcinoma; prognostic factors; therapeutic strategy.

Key points

- HIV+/HCV+ patients with HCC have poorer survival than HIV-/HCV+ patients.
- In a HIV+/HCV+ cirrhotic cohort with HCC, prospectively followed, the majority of patients presented an infiltrative form of HCC, associated with poorer access to curative therapies than HIV-/HCV+ patients.
- The radiological aggressiveness of the tumour was the best prognostic factor for survival.
- A particular attention should be given to this high-risk population in order to propose early detection of small nodules whose evolution may be rapidly at risk of a poor prognosis.

Introduction

Hepatocellular carcinoma (HCC), a primary liver cancer, is the third leading cause of cancer deaths worldwide and the sixth most common malignancy (1). Before new oral hepatitis C virus (HCV) agents, the frequency of HCC in human immunodeficiency virus (HIV)-infected patients has increased worldwide in parallel with improvements of HIV treatment regimens and HCV co-infection, estimated in 16% to 33% of HIV-infected patients (2,3). Recently, the D:A:D study, which followed 49,000 HIV positive persons in Europe, United States and Australia calculated an incidence rate of end-

stage liver disease and HCC of 1 per 1,000 person-years, including a third of HCC (4). In the Era of Direct-Acting Antiviral Agents, there is no data concerning the incidence of HCC in HIV/HCV co-infected (HIV+/HCV+) patients but it is likely to fall in this population, in line with its predicted decline in HCV mono-infected (HIV-/HCV+) patients (5, 6).

Some studies have shown that HIV+/HCV+ patients with HCC have poorer survival than HIV-/HCV+ patients with a more advanced tumour stage at diagnosis (7-11). Nevertheless, the clinical course of HCC in an HIV-infected setting is still not clearly defined; most studies have involved small samples and many of the HIV patients included were not receiving combined antiretroviral therapy (cART). Two case-control studies reported that HCC occurred at a younger age, with more infiltrating and metastatic tumours in HIV+/HCV+ than HIV-/HCV+ patients (7,8). Moreover, elevated α -foetoprotein (AFP) levels were quite common in the HIV+/HCV+ group, independently of the HCC staging score and the severity of cirrhosis (8, 9). We recently demonstrated that HCC present with more severe radiological features at diagnosis in HIV+/HCV+ than HIV-/HCV+ cirrhotic patients because of the frequent infiltrative types HCC with portal vein tumour thrombosis (11). The overall survival of patients who develop HCC is also significantly worsened in HIV+/HCV+ than HIV-/HCV+ patients (7-11). However, the therapeutic management and the analysis of prognostic factors for survival in prospective studies have not been taken into account to date. We therefore constructed a large Carcinovic collaboration from three ANRS cohorts (Prethevic, HepaVih, CirVir), to include all HIV+/HCV+ patients diagnosed with HCC in order to analyze the prognostic factors for survival and to evaluate their therapeutic management.

Patients and methods

Patients

The Carcinovic collaborative study recruited HCC in HIV+/HCV+ patients, from three prospective ANRS (France Recherche Nord&Sud Sida-hiv Hépatites) cohorts: 1) the ANRS HP25-Prethevic cohort included 98 HIV+/HCV+ patients with end-stage liver disease between 2009 and 2012 (12); 2) the ANRS CO13 HepaVih cohort started in 2005, studying the outcomes of 1225 HIV+/HCV+ patients at various stages of fibrosis (13); 3) the ANRS CO12-CirVir cohort included 1823 HCV and/or HBV-infected patients with compensated cirrhosis between 2006 and 2012, some being also HIV-co-

infected (14). All patients included in these three cohorts were evaluated every 3 or 6 months for HCC, screened by ultrasonography (US) and AFP levels.

Cases of HCC diagnosed at imaging in HIV+/HCV+ patients until January 2013 were prospectively included in the Carcinovic collaboration. A control group of HIV-/HCV+ cirrhotic patients with HCC was included from ANRS CO12-Cirvir.

Diagnosis of HCC

All patients included in this study had cirrhosis, the diagnosis was established histologically or by transient elastometry (Fibroscan threshold value 12 kPA). In the event of a focal nodule identified by US examination, with or without elevated AFP levels, the diagnosis of HCC was confirmed on imaging according to the updated 2011 American Association for the Study of Liver Disease (AASLD) criteria (15): the presence of a nodule larger than 1 cm in diameter with arterial phase hyper-enhancement and portal venous or delayed phase washout at either computed tomography (CT) or magnetic resonance imaging (MRI) (15). Image analysis was performed unblinded on a picture archiving and communication system station jointly by two expert abdominal radiologists (ML and OS) in the Carcinovic collaboration. Image analysis evaluated the type of HCC (nodular or infiltrative), the nodule's largest diameter and the presence/absence of a tumour portal obstruction, defined as a distension of the portal vein lumen by the enhancement of a thrombus (9). Reports of imaging techniques showing liver focal lesions were secondarily reviewed by two senior hepatologists (MGS and PN).

All patients were evaluated from the date of first vascular imaging with radiological evidence of HCC, from which started the follow-up.

Virological analysis

HCV and HIV positivity was identified by the presence of serum HCV and HIV antibodies, plus HCV and HIV ribonucleic acid, respectively. The first positive serological tests were considered as the initial dates of viral infection.

Data collection

Follow-up was ensured every 3 months until death, loss to follow-up, or liver transplantation (LT) in the Carcinovic collaboration. At each visit, a physical

examination, Model for End-Stage liver Disease (MELD) score, Child-Turcotte-Pugh (CTP) score, CDC score, and virological, immunological, biochemical and drug toxicity assessments were carried out. The treatment histories and patient's responses to previous treatments of HIV and HCV infections were recorded at the diagnosis of HCC and during follow-up.

Twenty-six Infectious Diseases or Hepatology units in France participated in the Carcinovic collaboration. A common database with, patients' demographics, radiological and biological features, modality of therapy and survival, was created, which represented the support for analysis.

Data on HIV-/HCV+ patients from ANRS CO12-Cirvir were extracted and integrated into the whole database for the analysis.

Therapeutic management of HCC

The treatment of HCC, defined according to the Barcelona Clinic Liver Cancer (BCLC) staging system was recorded at initiation and at each modification during follow-up (16). Liver transplantation, percutaneous ablation (PA) and surgical resection were considered as curative treatments. Percutaneous ablation included radiofrequency ablation or alcoholization. Transarterial chemoembolization (TACE) was also considered as a curative treatment when associated with PA or surgical resection.

First, the eligibility to LT was evaluated through the application of Milan criteria at diagnosis of HCC; retrospectively compared with secondly the AFP score (17,18). The access to LT was completed at each visit by a questionnaire about the indications, contraindications, enrolment on waiting list and LT.

Palliative treatments consisted of TACE, chemotherapy or anti-angiogenic therapy given alone or in combination.

Statistical Analysis

The characteristics and outcomes of HCC were analyzed, as were the therapeutic strategies employed, survival rates, prognostic factors for survival and the causes of death. Kaplan-Meier methods were used to calculate the 1 and 2-year survival rates since the first confirmed diagnosis of HCC by MRI or CT. Survival was studied from the date of confirmed diagnosis until death, censoring or LT. The censoring date for patients who were neither deceased nor transplanted was the date of the last visit until

January 2014. The relationships between overall survival and the following parameters were studied: gender, age at HCC diagnosis, AFP level, HIV and HCV viral loads, diabetes mellitus, type (infiltrative or nodular) of tumour, venous portal thrombosis, alcohol and tobacco consumption. Univariate and multivariate Cox regression models were used to assess prognostic factors for survival. All analyses were performed using SAS v9.3 software (SAS Institute, Inc, Cary, NC). A *P* value <0.05 was considered to denote statistical significance.

Ethical aspects

The three cohorts were implemented according to the Declaration of Helsinki and the French law relative to biomedical research, with written informed consent obtained from all patients. The three cohorts were approved by their relevant Ethics Committee (CPP Ile-de-France) and the French Agency for the Safety of Medicines and Healthcare Products (ANSM).

Results

Characteristics of the study population

Fifty-five HIV+/HCV+ patients diagnosed with HCC between 2006 and 2013 were included in the Carcinovic collaboration. Thirty-five (64%) patients were recruited from the ANRS HP25-Prethevic cohort, 19 (34%) from the ANRS CO13-HepaVih cohort and 1 (2%) from the ANRS CO12-CirVir cohort.

They were compared with 181 cases of HCC developed in HIV-/HCV+ patients with histologically proven cirrhosis from the ANRS CO12-CirVir cohort.

The relevant characteristics concerning these populations are shown in Table 1.

HIV+/HCV+ patients were more often male and younger than HIV-/HCV+ ones (male: 89% vs. 63%, *P*<0.001; median age: 50 years [IQR: 47–53] vs. 62 [54–70], *P*<0.001). The main mode of HIV/HCV acquisition was intravenous drug use (87%), which was associated with alcohol intake in 76% of cases and tobacco intake in 89%. HCV genotype 1 was the most frequent in both groups (55% vs. 80% in HIV+/HCV+ and HIV-/HCV+, *P*<0.001, respectively), followed by genotype 4 (22%) in HIV+/HCV+, and 3 (12%) in HIV-/HCV+ subjects.

In the HIV+/HCV+ Carcinovic collaboration, 40 patients (77%) had received at least one anti-viral C therapy before the diagnosis of HCC, and in 18 cases (33%),

treatment was still ongoing at the diagnosis of HCC, essentially Peg-Interferon-ribavirin, with a majority of non-responders in 29 cases (72.5%). With a protease inhibitor-based combination used as cART strategy (96%), HIV viral load was below 50 copies/mL in 39 (71%) patients, and median CD4 count was 379/mm³ [203–531]. The median times elapsing between the first positive serological test and the diagnosis of HCC was 15 years [11–18] for HCV and 20 years [15–23] for HIV; it was 5 years [1–8] between the diagnosis of cirrhosis and HCC.

The rate of at least one episode of cirrhotic decompensation before the diagnosis of HCC was recorded in 17 (31%) in the HIV+/HCV+ Carcinovic collaboration, vs. 25 (14%) in HIV-/HCV+ ones, $P=0.0046$, including ascites in 82% of cases ($n=14$). In the Carcinovic collaboration, CTP score was evaluated A in 64%, B in 29% and C in 7%, and the median MELD score was 12 [8–14]. In the ANRS CO12-CirVir cohort, CTP score was recorded in 105 patients, with similar results as CTP score A in 79%, B in 18% and C in 3%.

There was no difference in AFP levels at the time of diagnosis between HIV+/HCV+ and HIV-/HCV+ patients, with a majority of low AFP levels below 200 ng/mL (Table 1).

Radiological characteristics of HCC at presentation in the two cohorts

All cirrhotic patients were prospectively followed at least every 6-months as currently recommended. In the HIV+/HCV+ patients, HCC was mostly diagnosed as a result of this regular follow-up (78% in HIV+/HCV+ cohort and 100% in HIV-/HCV+ cohort); except for 5 patients (9%), thanks to incidental imaging in addition to the screening programme, and for 7 patients (13%), in the context of suggestive clinical symptoms. The median delay between the first suspicion of a hepatic nodule by US (suspected date of HCC) and the vascular imaging that confirmed the diagnosis of HCC according to AASLD radiological criteria (diagnostic date of HCC) was 0.56 months [0–1.81]. In 49 (89%) patients, this period (defined as the diagnostic interval) was 3 months or less, while in 6 (11%) patients, it was longer than 6 months (with a maximum of 15 months). Long diagnostic interval > 6 months was due to an atypical nodule on vascular imaging that did not comply with AASLD criteria in four patients, while in two other patients there was a lack of compliance.

Vascular imaging revealed an infiltrative HCC in 24% of HIV+/HCV+ patients vs. 14% of HIV-/HCV+ patients, $P<0.001$, respectively, and a nodular form in 76% vs. 96% of cases, $P<0.001$, respectively, which largest diameter was 23.5 mm [17–30] in HIV+/HCV+ cohort and 20 [10–100] mm in HIV-/HCV+ cohort. The 13 HIV+/HCV+

patients with infiltrative forms also suffered from a tumour portal thrombosis, which accounted for 81% of all tumour portal thrombosis observed.

Therapeutic management of HCC in the two cohorts and access to liver transplantation in HIV+/HCV+ patients

As reported in Table 1, overall by the end of follow-up, HIV+/HCV+ patients had received less curative treatment than HIV-/HCV+ ones (38% vs. 61%, $P < 0.001$, respectively) however, LT tended to be more frequent in HIV+/HCV+ than HIV-/HCV+ patients in 9 (16%) vs. 11 (6%), respectively.

According to the BCLC classification, HCC at diagnosis in the Carcinovic collaboration was assessed as stage A, B, C, D in 31 (56%), 7 (13%), 13 (24%) and 4 (7%) patients, respectively.

The access to LT was evaluated in 39 (71%) HIV+/HCV+ patients without an infiltrative form or tumour portal thrombosis (Fig. 1). Finally, 33 (60%) and 36 (65%) patients, respectively met the Milan criteria and AFP score at diagnosis of HCC. For patients in Milan criteria, LT was finally contraindicated in 17 (31%) patients: this was due to a tumour extension during follow-up in 5 patients (4 with the development of new hepatic nodules and 1 with haemorrhagic ascites) leading to a fatal outcome, severe alcoholism in 7 patients, advanced age in 1 (74 years old), lymphoma in 2 and psychiatric disease in 2. Seven of these 17 patients received an alternative curative treatment. Among the 16 (29%) patients eligible for LT, three died before LT from liver failure or bacterial septicaemia. As the latter patients had received TACE during the waiting period, they belonged to the palliative group at the end of follow-up. Among the 13 listed patients, four were treated with alternative curative treatments without recurrence of HCC and didn't need LT; only nine underwent LT, while still complying with the Milan criteria and AFP score. Six (67%) of the latter, required pre-operative treatment (PA in five or TACE + PA in one) during the waiting period.

Palliative treatment was initiated in 51% vs. 19% of cases in HIV+/HCV+ and HIV-/HCV+ patients, respectively. It consisted of TACE 13% vs. 11% of patients, chemotherapy or anti-angiogenic therapy in 13% vs. 4%. A combination of multiple palliative treatments (chemotherapy, radio-embolization and/or TACE) was applied in 25% vs. 4%, while 11% vs. 20% received supportive care only.

Causes of death and prognostic factors

In the Carcinovic collaboration, the median follow-up period since the diagnostic date of HCC was 11.96 months [5.51–27], 34 (62%) patients died and two were lost to follow-up. At the end of follow-up, 19 still received ongoing care, with (n=9) or without LT (n=10). The median survival times were 22.3 months from the suspected date and 20.6 months from the diagnostic date. The causes of death were liver failure in 20 (59%), non-AIDS-related bacterial or fungal infections in 7 (21%), (septicaemia due to Gram-negative bacillus in most cases and one case of *Candida* infection), progression of HCC in four (12%), and the three (8%) remaining causes were one head trauma and two complications of LT.

HIV+/HCV+ patients with HCC had worse survival than HIV-/HCV+ patients, (Fig 2). The 1-year and 2-year overall survival rates were 61% vs. 78% and 47% vs. 63%, $P=0.003$, respectively. Factors that predicted mortality in the univariate analysis in both cohorts were AFP ≥ 200 ($P=0.005$ and $P=0.003$, respectively) and type of tumour (infiltrative form) ($P<0.001$ and $P<0.001$, respectively). Moreover, previous decompensation was significantly associated with survival in the Carcinovic collaboration ($P=0.001$). In a multivariate Cox model, the infiltrative form of the tumour (adjusted rate ratio (aRR): 8.10 [95% Confidence Interval: 4.17–15.75], $P<0.001$), adjusted for the cohort, age and gender, was independently associated with the probability of death (Table 2).

Discussion

This is the largest multicentre prospective cohort of HIV/HCV co-infected patients with HCC to have been studied. We were able to confirm that the latter have poor survival (61% and 47% at 1 and 2 years) and poor access to curative therapies (38%), compared to HCC in HIV-/HCV+ patients. Trinchet *et al.* reported that curative treatments were implemented in 71.3% of HIV-/HCV+ patients, with PA in 50% of cases (14). Moreover, in their study, only 9.1% of patients (n=9) were transplanted, although 78% met the Milan criteria, as the data were given in intent to treat (14). Supporting our data, Merchante *et al.* found that only 30% of their HIV+/HCV+ cohort met the Milan criteria for LT at diagnosis of HCC; finally, 13% received potentially curative treatments (19). In addition, these two studies highlighted that a minority of HCC in HIV+/HCV+ patients achieve curative treatments unless they are potentially curable at diagnosis (14,19). In fact, in our cohort, where 60% of patients met the Milan criteria, nearly half of them were not eligible for LT because of extra-hepatic

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contraindications or death (10%) while on the waiting list from hepatic causes (mainly liver failure). Another curative treatment than LT was implemented in 10% and nearly 30% of the patients falling within the Milan criteria were transplanted. Currently, these data support the idea that the diagnosis of HCC in HIV+/HCV+ patients is globally performed in too advanced stages of cirrhosis and HCC, which lead to a poor access to curative treatment.

First, the poor prognosis for HCC in HIV+/HCV+ patients may be explained by a late diagnosis. However, our results, which suggest that the diagnostic interval, i.e., between the date of suspicion of a nodule and its confirmation, is not particularly long (median diagnostic interval: 0.56 months [0-1.81] in reference centres and a 6-months follow-up interval), do not support this hypothesis. Surprisingly, the individuals with longer diagnostic interval had not necessarily poorer survival. Unfortunately, we have no data about the diagnostic interval in the mono-infected Cirvir cohort, prospectively followed by a physical exam and US every 6 months.

Second, the problem should be a more rapid progression of HCC in HIV+/HCV+ patients. Indeed, our group previously reported a more advanced radiological presentation at diagnosis in HIV+/HCV+ than in HIV-/HCV+ cirrhotic patients, related to more infiltrative tumours (23%) and tumour portal thrombosis (28.5%) (11). Here, on the basis of a larger sample, the infiltrative form of HCC, which affected 24% of HIV+/HCV+ patients, was a strong prognostic factor for death (adjusted RR of 8.10 [4.17-15.75], $P < 0.001$). Puoti et al. previously described tumour portal thrombosis as being a prognostic factor for death, along side a tumour diameter greater than 5 cm and an AFP level higher than 400 ng/mL (7). Merchante *et al.* also reported portal thrombosis in 29% of HIV+/HCV+ patients, without making a distinction between tumour and cruric thrombosis (19).

The reasons why HCC might be more aggressive in HIV+/HCV+ patients should rely on multiple factors. First, the immunodeficiency associated with HIV infection accelerates the course of HCV by lowering the viral immune response through a quantitative decline of T-cells (20). In HIV patients, there is also an alteration in the balance between CD4 and CD8 T-cell activities, with a predominant CD8-cell response mediated by cytokines such as IL-4, IL-5, and TGF- β , which increases liver inflammation and fibrosis (20). It appears that HIV proteins (tat, gp120), or HIV itself, promotes pro-inflammatory cytokines by binding (and possibly entering) hepatic stellate cells on its CCR5 receptors, which is also involved in hepatocarcinogenesis (21,22). Finally, there is the role of metabolic syndrome associated with HIV infection.

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These data therefore argue for an earlier diagnosis of HCC in HIV+/HCV+ patients, and a new screening policy could be proposed because of the rapidly evolving form of these tumours. Current international guidelines that recommend US screening every 6 months in cirrhotic patients seem to be inappropriate in the latter patients. Some authors proposed a 3-month interval for US screening in HIV/HCV patients, rather than 6 months. However, no prospective studies have validated such a strategy and European guidelines recommended 6-monthly liver US and AFP testing in HIV+/HCV+ patients with cirrhosis (23). Admittedly, the sensitivity of the US is too limited to detect both infiltrative and nodular types of HCCs, MRI is frequently required to confirm the diagnosis. Indeed, MRI or CT scan have been proposed for screening HCC in particularly high-risk population in Asia (24).

In cases where MRI fails to conclude, biopsy remains the last resort. Obtaining an earlier HCC diagnosis in HIV+/HCV+ patients should improve access to, and the efficacy of, curative treatments. This is especially true regarding the treatment of infiltrative type HCC, which is limited to palliative approaches (25).

As well as radiological prognostic factors, immunosuppression, well known to accelerate tumour progression, has been confirmed as constituting a higher risk of HCC (10), which was not supported by our study.

We acknowledge that one limitation of our study is the lack of a prospective evaluation of radiological tumour progression in order to give more precision in the prognostic imaging factors.

In conclusion, particular attention should be given to HIV+/HCV+ cirrhotic patients because of the specific radiological aggressiveness of the tumour, and specifically high rate of infiltrative forms. Regarding the previous cirrhotic decompensation or elevated AFP levels, the physician must be particularly careful in the detection of small nodules in this high-risk population in order to prevent the development of infiltrative forms with poorer survival.

Acknowledgements

† This study is dedicated in the memory of Prof. Jean-Claude Trinchet

The authors thank Prof. Jean-François DELFRAISSY who supported the project and all members of the ANRS HC EP 25 Prethevic, ANRS CO13 HepaVih, and ANRS CO12 CirVir Study Groups, Laetitia JOHNSON and Messad OULD RABAH (Clinical Research Assistants), Anne PERSOZ (senior data manager).

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Table 1 : General characteristics of the study population at diagnosis of hepatocellular carcinoma according to HIV+/HCV+ or HIV-/HCV+ status: the ANRS Carcinovic and Cirvir cohort studies

Characteristics	HIV+/HCV+ Cohort N=55	HIV-/HCV+ Cohort N=181	P value
Male gender	49 (89)	112 (63)	<0.001
Age (years)	50.0 [47.0 – 53.0]	61.9 [54.4 – 70.2]	<0.001
Co-morbidities			
Alcohol (Never/Past or Present)(%)	24/56 or 20	37/63	NA
Tobacco (Never/Past/Present) (%)	11/29/60	41/28/31	<0.001
Diabetes mellitus	11 (20)	48 (27)	0.299
HIV parameters			
CD4 (/mm ³)	379 [203 – 531]	–	–
On going cART	53 (96)	–	–
HCV parameters	N=55	N=173	
Positive HCV viral load	39 (70.9)	140 (81)	0.371
Genotype 1	30 (55)	138 (79.8)	<0.001
2	1 (1.8)	6 (3.5)	

	3	10 (18.2)	20 (11.6)	
	4	12 (21.8)	8 (4.6)	
	5	2 (3.6)	1 (0.6)	
Response to HCV treatment		N=40	N=126	0.09
	NR	29 (72.5)	75 (60)	
	RR	3 (7.5)	23 (18)	
	SVR	8 (20)	28 (22)	
Cirrhosis				
	CTP score (A/B/C) (%)	64/29/7	79/18/3 (N=105)	NA
	Previous episode of decompensation	17 (30.9)	25 (13.8)	0.0046
AFP >200 (ng/mL)		9 (16.4)	18 (13.9)	0.658
Imaging presentation				
	Nodular form	42 (76)	158 (96)	<0.001
	Infiltrative form	13 (24)	6 (14)	<0.001
	Tumour portal thrombosis	16 (29)	13 (8) N=159	NA
Treatment of HCC at the end of follow-up				
	Curative treatment			
	Liver transplantation	21 (38)	109 (61)	
	PA (+/_ TACE)	9 (16)	11 (6)	
	Surgical resection (+/_ TACE)	7 (13)	72 (40)	Curative/
	PA + surgical resection	5 (9)	24 (13)	Palliative/
	Palliative treatment	0	2 (1)	No
	TACE	28 (51)	34 (19)	Treatment
	Chemotherapy	7 (13)	19 (11)	<0.001
	Multiple palliative treatments	7 (13)	8 (4)	
	No treatment	14 (25)	7 (4)	
	No treatment	6 (11)	36 (20)	

For qualitative values, results are expressed in n (%), for quantitative values, results are expressed in median with range.

Abbreviations : HCC, Hepatocellular carcinoma ; CTP, Child Turcotte Pugh ; cART ; combined antiretroviral therapy ; PA, percutaneous ablation ; TACE, transarterial chemoembolization; NA: Not applicable.

Table 2 : Factors associated with death according to HIV+/HCV+ (N=55) and HIV-/HCV+ (N=181) status: the ANRS CO12 Cirvir and CARCINOVIC cohort studies

	Univariate analysis		Multivariate analysis	
	Hazard ratio [95% CI]	<i>P</i> value	Adjusted Hazard ratio [95% CI]	<i>P</i> value
Cohort				
ANRS CO12 Cirvir	1		1	
Carcinovic	1.34 [0.84-2.15]*	0.223	1.42 [0.88-2.30]**	0.154
Type of the tumour				
Nodular	1		1	
Infiltrative	7.66 [3.99-14.73]***	<0.001	8.10 [4.17-15.75]****	<0.001

*Adjusted by the type of the tumour

** Adjusted by the type of the tumour, sex and age

*** Adjusted by the cohort

**** Adjusted by the cohort, sex and age

Figure legends

Fig. 1: Therapeutic management of HCC and access to liver transplantation according to the Milan criteria in HIV/HCV co-infected patients

Abbreviations: HCC, hepatocellular carcinoma; CI, contraindication; LT, liver transplantation; PA, percutaneous ablation; TACE, transarterial chemoembolization; supp. care, supportive care.

Fig. 2: Probabilities of death in patients with hepatocellular carcinoma according to HIV+/HCV+ (Carcinovic cohort) or HIV-/HCV+ (ANRS CO12 Cirvir cohort) status.

APPENDIX

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Table 1 : General characteristics of the study population at diagnosis of hepatocellular carcinoma according to HIV+/HCV+ or HIV-/HCV+ status: the ANRS Carcinovic and Cirvir cohort studies

Characteristics	HIV+/HCV+ Cohort N=55	HIV-/HCV+ Cohort N=181	P value
Male gender	49 (89)	112 (63)	<0.001
Age (years)	50.0 [47.0 – 53.0]	61.9 [54.4 – 70.2]	<0.001
Co-morbidities			
Alcohol (Never/Past or Present)(%)	24/56 or 20	37/63	NA
Tobacco (Never/Past/Present) (%)	11/29/60	41/28/31	<0.001
Diabetes mellitus	11 (20)	48 (27)	0.299
HIV parameters			
CD4 (/mm ³)	379 [203 – 531]	–	–
On going cART	53 (96)	–	–
HCV parameters			
Positive HCV viral load	39 (87)	140 (81)	0.371
Genotype 1	30 (55)	138 (79.8)	<0.001
2	1 (1.8)	6 (3.5)	
3	10 (18.2)	20 (11.6)	
4	12 (21.8)	8 (4.6)	
5	2 (3.6)	1 (0.6)	
Response to HCV treatment	N=40	N=126	0.09
NR	29 (72.5)	75 (60)	
RR	3 (7.5)	23 (18)	
SVR	8 (20)	28 (22)	
Cirrhosis			
CTP score (A/B/C) (%)	64/29/7	79/18/3 (N=105)	NA
Previous episode of decompensation	17 (30.9)	25 (13.8)	0.0046
AFP >200(ng/mL)	9 (16.4)	18 (13.9)	0.658
Imaging presentation			
Nodular form	42 (76)	158 (96)	<0.001

Infiltrative form	13 (24)	6 (14)	<0.001
Tumour portal thrombosis	16 (29)	13 (8) N=159	NA
Treatment of HCC at the end of follow-up			
Curative treatment	21 (38)	109 (61)	
Liver transplantation	9 (16)	11 (6)	
PA (+/_ TACE)	7 (13)	72 (40)	Curative/
Surgical resection (+/_ TACE)	5 (9)	24 (13)	Palliative/
PA + surgical resection	0	2 (1)	No
Palliative treatment	28 (51)	34 (19)	Treatment
TACE	7 (13)	19 (11)	<0.001
Chemotherapy	7 (13)	8 (4)	
Multiple palliative treatments	14 (25)	7 (4)	
No treatment	6 (11)	36 (20)	

For qualitative values, results are expressed in n (%), for quantitative values, results are expressed in median with range.

Abbreviations : HCC, Hepatocellular carcinoma ; CTP, Child Turcotte Pugh ; cART ; combined antiretroviral therapy ; PA, percutaneous ablation ; TACE, transarterial chemoembolization; NA: Not applicable.

Table 2 : Factors associated with death according to HIV +/-HCV+ (N=55) and HIV-/HCV+ (N=181) status: the ANRS CO12 Cirvir and CARCINOVIC cohort studies

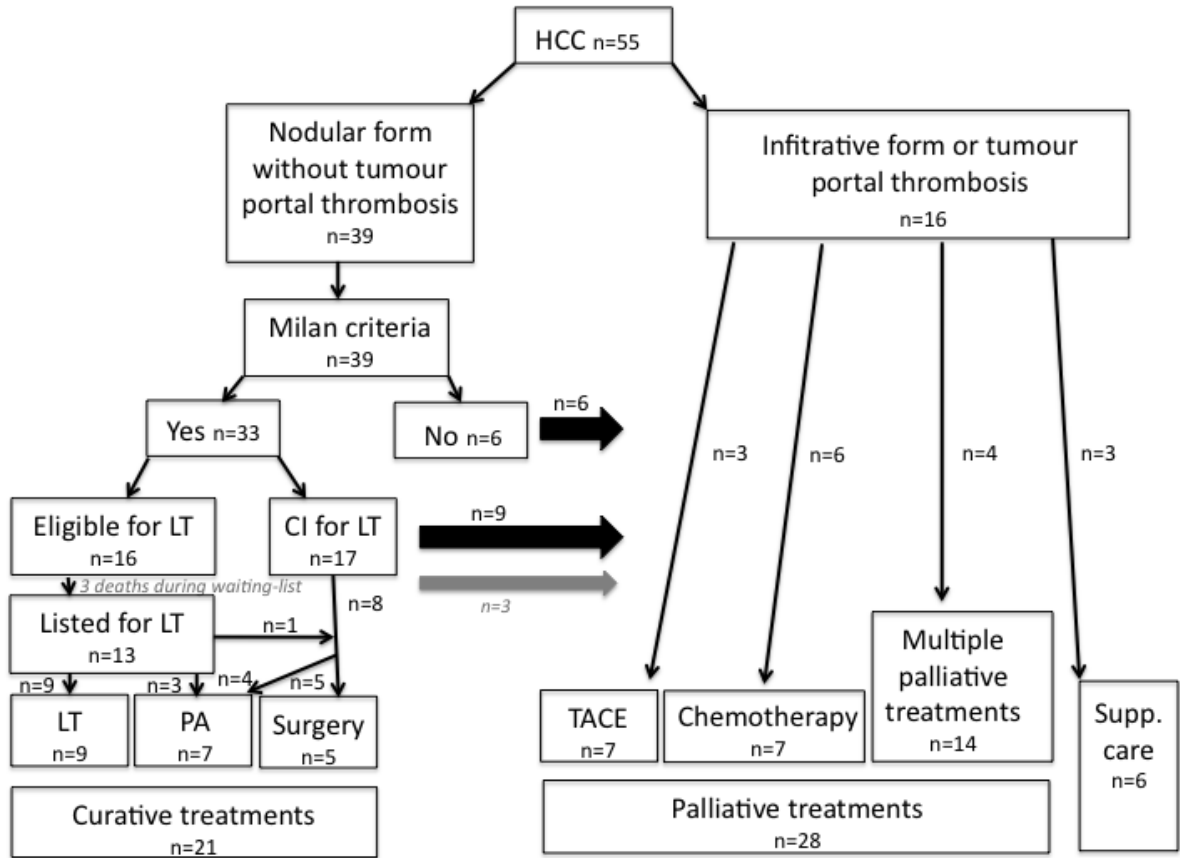
	Univariate analysis		Multivariate analysis	
	Hazard ratio [95% CI]	P value	Adjusted Hazard ratio [95% CI]	P value
Cohort				
ANRS CO12 Cirvir	1		1	
Carcinovic	1.34 [0.84-2.15]*	0.223	1.42 [0.88-2.30]**	0.154
Type of the tumour				
Nodular	1		1	
Infiltrative	7.66 [3.99-14.73]***	<0.001	8.10 [4.17-15.75]****	<0.001

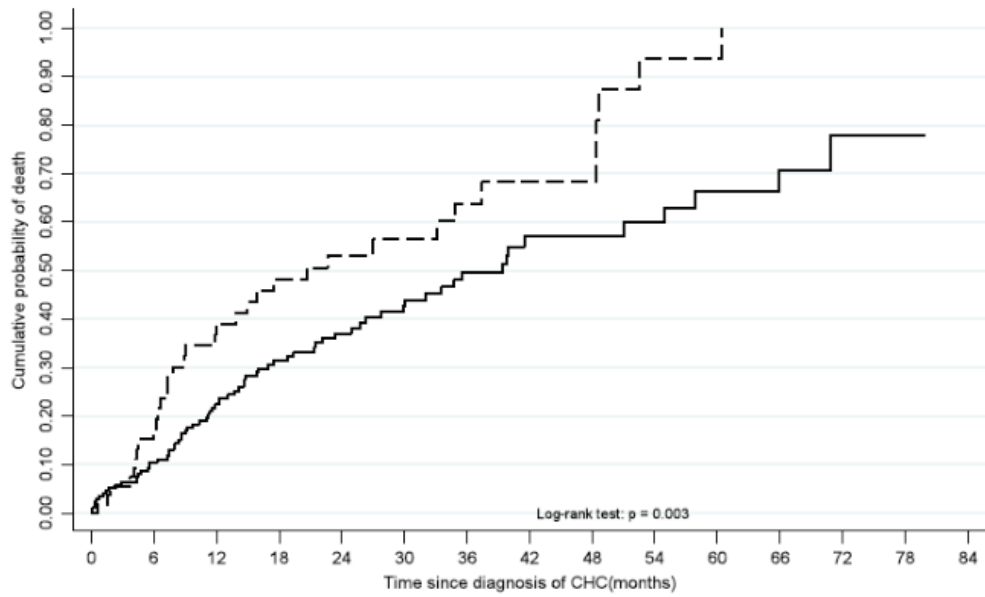
*Adjusted by the type of the tumour

** Adjusted by the type of the tumour, sex and age

*** Adjusted by the cohort

**** Adjusted by the cohort, sex and age





Patients at risk

Cirvir	178	146	111	79	60	48	34	20	18	13	9	7	2	1	0
Carcinovic	55	40	27	23	17	13	10	5	5	1	1	0	0	0	0

Cirvir ——— Carcinovic - - - - -