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Lack of evidence of an effect of Direct Acting Antivirals on the recurrence of hepatocellular carcinoma

The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT cohorts)

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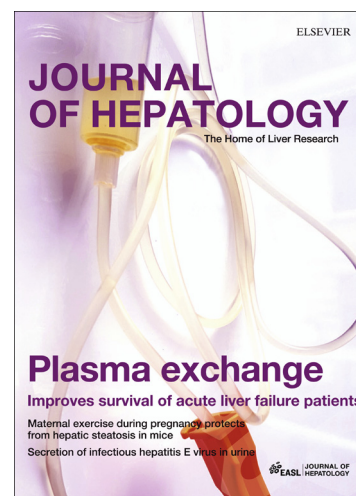
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**Lack of evidence of an effect of Direct Acting Antivirals on the recurrence of hepatocellular carcinoma**

**The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT cohorts)**

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**Abbreviations**

ANRS (France REcherche Nord&sud Sida-vih Hépatites)

HCV : Hepatitis C Virus

RNA : RiboNucleic Acid

DAA : Direct Acting Antivirals

HCC : HepatoCellular Carcinoma

SVR : Sustained Virological Response

RR : Relative Risk

INF : Interferon

US : Ultra-Sound

CT-scan : Computer Tomodensitometry

MRI : Magnetic Resonance Imaging

SD : Standard Deviation

Vs : Versus

Cuml : Cumulative Incidence PLC : Primary Liver Cancer

LT : Liver Transplantation

**ABSTRACT**

**Background and aims :** Sustained virological response following antiviral interferon- based treatment of chronic hepatitis C is associated with decreased long-term risk of hepatocellular carcinoma (HCC) in advanced liver fibrosis. An unexpected high rate of HCC recurrence following antiviral treatment using direct acting antiviral (DAA) has been recently reported.

**Methods:** We analyzed data individually from three French prospective multicenter ANRS cohorts including more than 6,000 patients treated with DAA and we focused on HCC patients who underwent curative procedures before DAA treatment. The aim was to assess the rates of HCC recurrence in these patients according to antiviral treatment regimen.

**Results :** In the ANRS CO22 HEPATHER cohort, 267 patients with CHC who were previously treated for HCC were analyzed, among whom 189 received DAA and 78 did not. The rates of recurrence were 0.73/100 and 0.66/100 person-months, respectively. In the ANRS CO12 CIRVIR cohort, 79 cirrhotic patients in whom HCC was diagnosed and treated, 13 received DAA and 66 did not. The rates of recurrence were 1.11/100 and 1.73/100 person-months, respectively. In the ANRS CO23 CUPILT Cohort, 314 liver transplant recipients for HCC who were subsequently treated with DAA were analyzed. Seven HCC recurrences were reported after a median time of 70.3 months after liver transplantation. The rate of recurrence was 2.2 %.

**Conclusions :** In three distinct prospective cohorts, we did not observe an increased risk of HCC recurrence after DAA treatment, notably in patients who underwent curative HCC treatment including liver transplantation.

## INTRODUCTION

Currently, high rates of sustained virological response (SVR) are achieved in patients with chronic hepatitis C treated with direct-acting antivirals (DAAs) (1-3).

Viral eradication is associated with a reduced risk of liver complications, including the occurrence of HCC, as reported in a recent meta-analysis: Relative Risk (RR) = 0.24 in all stages of fibrosis ; RR = 0.23 in advanced liver disease (4). These results were only supported by studies with IFN-based regimens.

Surprisingly, a high rate of tumor recurrence has been recently reported after antiviral treatment of chronic hepatitis C using DAAs in 16 of 58 patients (28%) with apparent complete remission after HCC treatment (5). Most of these patients had previous surgical resection or radio-frequency ablation and had favorable prognostic factors with an expected low rate of HCC recurrence (<4-5%) (6). Another study of 59 patients with HCC remission at start of DAA therapy reported a 29% rate of early HCC recurrence within 6 months of therapy (7). Similar data has not been suggested by pivotal controlled trials performed in the population of patients with cirrhosis, however patients with a history of HCC had been systematically excluded.

This data prompted us to assess the risk of HCC recurrence in three distinct prospective cohorts of the French ANRS (France REcherche Nord&sud Sida-vih Hépatites) agency including HCV-infected patients with or without cirrhosis who received DAA therapy. The current analyses are focused on HCC patients who underwent curative management for their liver tumor based on hepatic resection, percutaneous ablation or liver transplantation before starting DAA therapy. The rates of HCC recurrence were assessed in this population according to antiviral therapy.

## PATIENTS AND METHODS

The present work analyzed three distinct prospective cohorts, sponsored and funded by the ANRS (France REcherche Nord&Sud Sida-HIV Hépatites), namely, ANRS CO22 HEPATHER, ANRS CO12 CIRVIR, ANRS CO23 CUPILT.

**ANRS CO22 HEPATHER cohort**

The ANRS CO22 HEPATHER cohort « Therapeutic options for hepatitis B and C: a French cohort » is a multicentre observational cohort which aims to include 15 000 HCV- and 10 000 HBV-infected patients, to quantify the clinical efficacy and safety of new hepatitis treatments in real-life, and to identify, at the patient level, which treatment will most likely improve overall health (ClinicalTrials.gov, NCT01953458). HCV-positive patients are defined as patients with positive HCV-RNA or positive anti-HCV antibodies. Each patient gave written informed consent before enrollment and the protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the "CPP Ile de France 3" Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM). By December 31st, 2015, 14,379 participants with past or active chronic hepatitis C infection had been recruited; among whom 5,458 had begun a Direct Acting Agent (DAA) therapy from entry. We selected all participants with chronic active hepatitis C and a history of treated hepatocellular carcinoma (HCC) prior to inclusion (n=307), and we excluded patients with progressive or active recurrence of HCC upon inclusion (n=40).

**ANRS CO12 CIRVIR cohort**

The ANRS CO12 CirVir cohort is a multicentre observational cohort which aims to characterize the incidence of complications occurring in biopsy-proven compensated cirrhosis and to identify the associated risk factors using competing risks analysis (8). Patients were recruited in 35 French clinical centres between 2006 and 2012. Inclusion criteria were: histologically proven cirrhosis due to HCV or HBV; Child-Pugh A; and no previous hepatic complications (8). Patients were seen by physicians every 6 months, and the usual clinical and biological data were recorded. Examination by Doppler US was performed every 6 months. When HCC diagnosis was established, treatment was determined using a multidisciplinary approach according to AASLD guidelines for HCC.(6, 9)

All events occurring during follow-up, liver-related or not, were recorded based on information obtained from patient medical files from each centre. Likely cause(s) of death were established.

A total of 1,822 cirrhotic patients were included. Among them, 151 were subsequently excluded from analysis after reviewing individual data either due to non-compliance with inclusion criteria (n=142) or consent withdrawal (n=9). Consequently, 1,671 patients among whom 1,354 had HCV-related compensated cirrhosis, were selected for further analysis. On January 5, 2016, after a median follow-up of 58.6 [36.5-79.1] months, a first hepatic focal lesion was observed in 409 patients (30.2%) with a 5-year cumulated incidence (CumI) estimated at 32.3%. Following a diagnostic procedure, more than half of these focal liver lesions remained indeterminate or were considered benign (n=214, 52.3%). A definite diagnosis of primary liver cancer (PLC) was established in the remaining 195 patients: HCC (n=189) and intra-hepatic cholangiocarcinoma (n=6). HCC 5-yr CumI was 13.9%.

#### **ANRS CO23 CUPILT cohort**

The ANRS CO23 “Compassionate use of Protease Inhibitors in viral C Liver Transplantation” (CUPILT) study is a multicentre, cohort study implemented in 24 French and one Belgian liver transplant (LT) centres (ClinicalTrials.gov number NCT01944527). To be enrolled in this cohort, patients must comply with the following associated criteria, which include: (1) having received a liver transplant for an HCV infection, (2) having experienced an HCV recurrence in any stage of fibrosis, (3) having been treated with second-generation DAAs. All patients provided their informed consent before inclusion.

Among the 699 liver transplant recipients enrolled between October 2013 and December 2015, 330 (47%) received LT for HCC. We excluded patients receiving Peg-interferon concurrently with their DAA regimen (n=12) and those presenting with active HCC recurrence at baseline (n=4). Finally, 314 patients were included in the analysis.

## **RESULTS**

The flow charts of the 3 cohorts are depicted in figure 1 and the main patient characteristics are summarized in table 1.

**ANRS CO22 HEPATHER cohort**

In the ANRS CO22 HEPATHER cohort, our analysis focused on 267 patients with a history of treated hepatocellular carcinoma (HCC) prior to inclusion among whom 189 received DAA from inclusion (DAA group), 78 did not receive DAA (untreated group). Overall, 147 (78%) patients from the DAA group were male versus 57 (73%,  $P=0.4107$ ) in the untreated group. In comparison, patients from the DAA group were younger (mean (+/- SD) age of 62 (+/-9) years versus (vs) 66 (+/- 10) years,  $P=0.0047$ ) and prior HCV interferon-based therapy was more frequent (80% vs 69%,  $P=0.0529$ ). Severe fibrosis or cirrhosis was also more frequent in the DAA group (78% vs 63%,  $P=0.0148$ ). No other difference was noticed between the two groups in regards to time between HCC discovery and inclusion (Median 1.8 years, Interquartile Range (IQR) 0.7-4.4 years), time between last assessment of HCC and inclusion (Median 1.1 (IQR 0.4-3.2) years), duration of HCV infection (Median 15.3 (IQR 9.2-20.1) years) or HCV Genotype (65 % genotype 1).

Survival time in patients treated with DAA was considered as time-dependent to distinguish between the time from inclusion in the cohort to therapy initiation (untreated period) and the time from therapy initiation to end of follow-up (treated period). The median follow-up was 1.4 months before DAA initiation, 20.2 months after DAA initiation and 26.1 months for untreated patients. Overall, 24 recurrences of HCC were reported in 3,292 treated person-months (at a rate of 0.73/100 person-months), while 16 recurrences of HCC were reported in 2,438 untreated person-months (at a rate of 0.66/100 person-months,  $P=0.8756$ , Figure 2). The estimated hazard ratio (HR) for time-dependent DAA treatment was 1.21 (95%CI (0.62-2.34),  $P=0.5782$ ). Multivariate adjustments on age, past treatment experience and severe fibrosis or cirrhosis did not modify the findings (multivariate adjusted HR for time-dependent DAA treatment (1.04 (95%CI (0.53-2.07),  $P=0.9060$ ). We did not find an increase in HCC recurrence rate during the first 3 months of the treated period (which corresponds to active treatment intake in most patients) compared with the period following the first 3 months (1.27/100 person-months vs 0.62/100 person-months,  $P=0.1831$ ). Recurrences of HCC occurred in 5 patients who received sofosbuvir+peginterferon±ribavirin (at a rate of 1.52/100 person-months) and in 19 patients who received other combination therapies (at a rate of 0.64/100 person-months,  $P=0.1715$ ), suggesting that interferon did not modify the risk of early HCC recurrence.



**ANRS CO12 CIRVIR cohort**

In the ANRS CO12 CIRVIR cohort, 79 HCC patients were considered to be in remission at least 3 months following the implementation of at least one curative procedure. Overall, most of these patients met Milan criteria (Table 2). Thirteen patients subsequently received a DAAs-based regimen after anti-tumoral treatment. One patient (7.7%) experienced HCC recurrence after 37.1 months while 31 recurrences occurred among the remaining 66 patients (47.0%) who did not received DAAs.

Overall, 31 recurrences occurred in 1789 untreated person-months (at a rate of 1.73/100 person-months) and 1 recurrence was reported in 90 treated person-months (at a rate of 1.11/100 person-months,  $P=0.748$ ). The hazard ratio for time-dependent DAA treatment intake was 0.41 (95% CI [0.05-3.08],  $P=0.386$ ). The estimation of the hazard ratio was not modified by adjustment for age at the first HCC diagnosis (0.40, 95% CI [0.05-3.03]),  $P=0.377$ ).

**ANRS CO23 CUPILT cohort**

In the ANRS CO23 CUPILT cohort, 314 liver transplant recipients for HCC were treated with DAA. The mean time between LT and the initiation of DAA was  $67 \pm 60$  months. The planned durations of treatment were as follows: 12 weeks,  $n=109$  (35%); 24 weeks,  $n=198$  (63.7%); 16 weeks,  $n=3$  (1.0%) and 26 weeks,  $n=1$  (0.3%). Among the 248 patients who reached 12 weeks of follow-up, the overall SVR12 rate was 96.8%. A recurrence of HCC was observed in seven patients (2.2%) (mean age  $58.0 \pm 8.4$  years) within mean time after LT of  $70 \pm 64$  months,  $7 \pm 3$  months,  $21 \pm 14$  weeks following the introduction of DAAs and after obtaining viral clearance, respectively. Five of the seven patients (71%) died  $58 \pm 47$  months after LT.

The characteristics of the seven patients are detailed in Table 3. At inclusion, six of the seven patients (86%) met Milan criteria. Five patients displayed factors predictive of a recurrence based on histological criteria in the native liver. However, microvascular invasion in the native liver was present in two (28%) of the seven patients, and in two others, without vascular invasion a large number of active nodules was observed (patient 2,  $n=4$ ; patient 5,  $n=8$ ).

Moreover, we observed that two patients (patients 4 and 7) experienced a first episode of recurrence when they were considered to be in complete remission after LT and before the introduction of DAA.

## DISCUSSION

These three prospective multicentre cohorts, dealing with different patient profiles including cirrhotic and non cirrhotic patients and liver transplant recipients, do not support any evidence of an increased risk of HCC recurrence in patients treated with DAA.

The strength of this present work is the large size of patients treated with DAA and that each cohort contributes unique information that gives consistent results.

The HEPATHER, CirVir and CUIILT cohorts are all characterized by prospective rigorous multicenter protocol-driven systematic data collection and analysis of predefined outcomes. The HEPATHER cohort included a large number of patients treated with DAAs ensuring a high statistical power to identify an increased risk of events during treatment, while the analyses conducted in the CirVir cohort were performed in incidental cases of well-phenotyped HCC occurring during follow-up of patients, thus ensuring the unbiased record of tumors and their evolution after therapeutic management. The CUIILT cohort included only DAA-treated patients after liver transplantation among whom almost half were transplanted for HCC. The expected risk of recurrence following LT range from 8 to 20% within the first 2 years after LT (10).

Another strength of our work is our focus on patients previously treated for HCC using curative procedures (hepatic resection, percutaneous ablation or liver transplantation) as we excluded patients treated with chemoembolization. Indeed, the recent Spanish study suggesting an high risk of HCC recurrence have included patients with non curative therapies such as chemoembolization, characterized by high early recurrence rates (5). With an annual rate of recurrence reaching 20% after resection or percutaneous ablation (6), it is tempting to speculate that incomplete treatment or mistaken initial staging of tumour burden might also introduce interpretation biases in those retrospective studies. This may

lead to an erroneous attribution of DAAs being responsible for HCC recurrence. The prospective design of the cohorts allowed us to cautiously select patients according to tumoral response, in particular those who achieved complete remission after the implementation of a curative procedure and before the introduction of DAA.

Moreover, in 2 of these cohorts (HEPATHER and CIRVIR) we compared HCC patients who received DAA to those who did not. In both cohorts there was no evidence of an increased risk of HCC recurrence in treated compared with untreated patients. Similarly, in the CUPILT cohort which included treated patients only, the observed recurrence rate of 2.2% was lower than the expected rate according to previous studies with Interferon regimen.

DAAs are associated with a SVR in more than 90% of patients and SVR is a variable usually associated with a decreased risk of both HCC occurrence and HCC recurrence. What could explain the paradox of an increased risk of HCC? Authors hypothesized that the rapid control of inflammatory state could impact anti-tumoral immune control allowing for tumor clones emergence (5). The qualitative and quantitative immune alterations which are associated with chronic HCV infection may be restored in a time-dependent fashion (11) but persists an imbalance between different cytokines/chemokines which may decrease the regional immune control of tumoral clones (12, 13).

Overall, the analyses performed in these prospective cohorts did not underline a specific link between DAA treatments and the risk of HCC recurrence after the implementation of curative procedures including liver transplantation.

In conclusion, we did not find any evidence that DAA treatment increases the risk of recurrence of HCC in DAA-treated patients compared with untreated patients. In another study, we have also observed a decreased risk of HCC over time in cirrhotic or non cirrhotic patients achieving SVR after DAAs (14).

The prospective follow-up of a large number of patients included in three distinct cohorts of patients reflecting various clinical profiles ensures the quality of our analyses and the confidence in our conclusions.

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**For the ANRS CO 12 CIRVIR Cohort**

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**Legends to figures**

**Figure 1.** Flow-chart of the 3 multicentre prospective ANRS cohorts.

Part A : ANRS CO22 HEPATHER; PART B : ARNS CO12 CIRVIR; Part C : ARNS CO23 CUPILT

**Figure 2.** Recurrence of HCC according to DAA treatment in the ANRS CO22 Hepather cohort.

Pseudo-survival curves were plotted for time-dependent DAA treatment.

ACCEPTED MANUSCRIPT

**Table 1** - Characteristics of the patients who developed HCC from the 3 ANRS cohorts

	HEPATHER (n=267)		CIRVIR (n=79)		CUPILT (n=314)
	DAA + (n=189)	DAA - (n=78)	DAA + (n=13)	DAA - (n=66)	DAA + (n=314)
<b>Age years</b> mean $\pm$ sd	62 $\pm$ 9	66 $\pm$ 10	61 $\pm$ 10	65 $\pm$ 9	61 $\pm$ 8
<b>Sex M n (%)</b>	147 (78)	57 (73)	11 (85)	39 (59)	257 (82)
<b>DAA regimen n (%)</b>		NA		NA	
SOF + RBV + PEGIFN	17 (9)		-		-
SOF +DCV $\pm$ RBV	94 (49.7)		8 (62)		190 (60.5)
SOF + LDV $\pm$ RBV	38 (20.1)		2 (15)		83 (26.4)
SOF + RBV	17 (9)		-		27 (8.7)

SOF + SMV ± RBV	20 (10.6)		2 (15)		12 (3.8)
3D Abb ± RBV	3 (1.6)		1 (8)		-
SMV + DCV	-		-		1 (0.3)
SOF + LDV + RBV and SOF +DCV	-		-		1 (0.3)
<b>SVR</b>	n=148 91.9%		n=8 100%		n=248 96.8%
<b>Fibrosis stage</b>					n=198
cirrhosis	152 (80)	55 (72)	13 (100)	66 (100)	49 (15.6)
<b>Previously IFN therapy</b> n (%)	150 (80)	54 (69)	12 (92)	59 (89)	71 (23)
<b>Genotyp 1</b> n (%)	121 (65)	46 (66)	11 (85)	53/63 (84)	212 (67.5)
<b>Recurrence HCC</b> n (%)	24 (12.7)	16 (20.5)	1 (7.7)	31 (47)	7 (2.2)
Person-months	0.73/100	0.66/100	1.11/100	1.73 (100)	

<b>Delay HCC diagnosis/inclusion</b> med (IQR)	1.9 (0.6-4.5)	1.6 (0.8-4.4)			
<b>&lt; 1yr</b>	67 (35)	25 (32)			
<b>1-3 yr</b>	57 (30)	25 (32)			
<b>3yr</b>	65 (34)	28 (36)			
n (%)					
<b>Delay last assessment</b> <b>HCC/inclusion</b> med (IQR)	1.2 (0.3-3.2)	1 (0.4-3.3)			
<b>&lt; 1yr</b>	87 (46)	39 (50)			
<b>1-3 yr</b>	51 (27)	18 (23)			
<b>3yr</b>	51 (27)	21 (27)			
n (%)					
<b>Duration HCV infection</b> med (IQR)	15.3 (9.8- 19.9)	15.2 (7.6- 21.3)			n=278  17 (12-24)

**Table 2-** Characteristics and outcome of 79 incidental HCC occurring in 1354 patients with HCV cirrhosis treated by percutaneous ablation or hepatic resection (CO12 CirVir cohort)

	Number of patients	All patients (n = 79)	Recurrence after HCC treatment [n = 32 (40.5%)]	No Recurrence after HCC treatment [n = 47 (59.5%)]	P-value
<b>Male gender</b>	79	50 (63.3)	20 (62.5)	30 (63.8)	0.90
<b>Age (years)</b>	79	63.9 [56.1 – 72.3]	62.6 [56.7 – 72.9]	64.1 [55.7 – 71.2]	0.71
<b>HCV genotype</b>	76				
1		64 (84.21)	25 (80.65)	39 (86.7)	
2		3 (3.95)	2 (6.45)	1 (2.2)	
3		6 (7.89)	2 (6.45)	4 (8.9)	0.69
4		3 (3.95)	2 (6.45)	1 (2.2)	
5		0	0	0	
6		0	0	0	



<b>Number of nodules</b>	78	1 [1-1]	1 [1-1]	1 [1-1]	0.49
<b>Number of nodules (class)</b>	78				0.53
1		64 (82.0)	25 (78.1)	39 (84.8)	
2-3		13 (16.7)	7 (21.9)	6 (13.0)	
> 3		1 (1.3)	0	1 (2.2)	
<b>Diameter of the largest nodule</b>	76	18.5 [15.0 – 23.5]	20.0 [15.5 – 22.5]	17.0 [14.5 – 23.5]	0.40
<b>Diameter of the largest nodule</b>	76				0.22
≤ 30		68 (89.5)	27 (84.4)	41 (93.2)	
31-50		5 (6.6)	4 (12.5)	1 (2.3)	
> 50		3 (3.9)	1 (3.1)	2 (4.5)	
<b>In-Milan</b>	76	72/76 (94.7)	31/32 (96.9)	41/44 (93.2)	0.63
<b>AFP at HCC diagnosis</b>	60	9.9 [4.1 – 19.3]	13.0 [6.0 – 35.0]	8.5 [4.0 – 12.0]	0.12
<b>AFP at HCC diagnosis (log10)</b>	60	1.0 [0.6 – 1.3]	1.1 [0.8 – 1.5]	0.9 [0.6 – 1.1]	0.12
<b>Last imaging before diagnosis (months)</b>	79	6.4 [5.6 – 7.5]	6.3 [5.5 – 7.5]	6.4 [5.6 – 7.4]	0.65

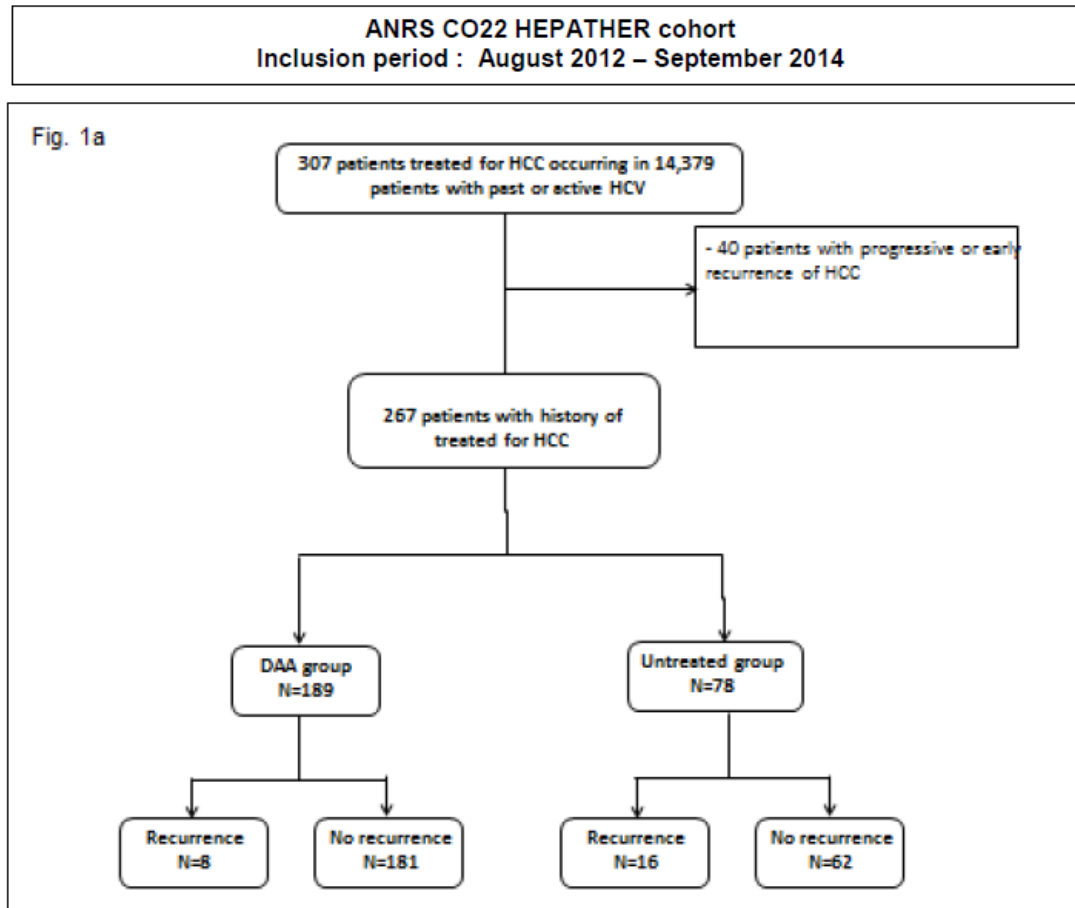
<b>Therapeutic procedure</b>	79				0.15
Percutaneous ablation		62 (78.5)	27 (84.4)	35 (74.5)	
Hepatic resection		16 (20.2)	4 (12.5)	12 (25.5)	
Both		1 (1.3)	1 (3.1)	0	
<b>Median time to recurrence (months)</b>	32	16.5 [12.7 – 32.2]	-	-	-
<b>Median follow-up (months)</b>	79	21.3 [13.0 – 33.5]	16.5 [12.7 – 32.2]	22.1 [14.6 – 34.0]	0.26

**Table 3** - Characteristics and outcome of 7 recurrence HCC after liver transplantation  
(CO23 CUPILT cohort)

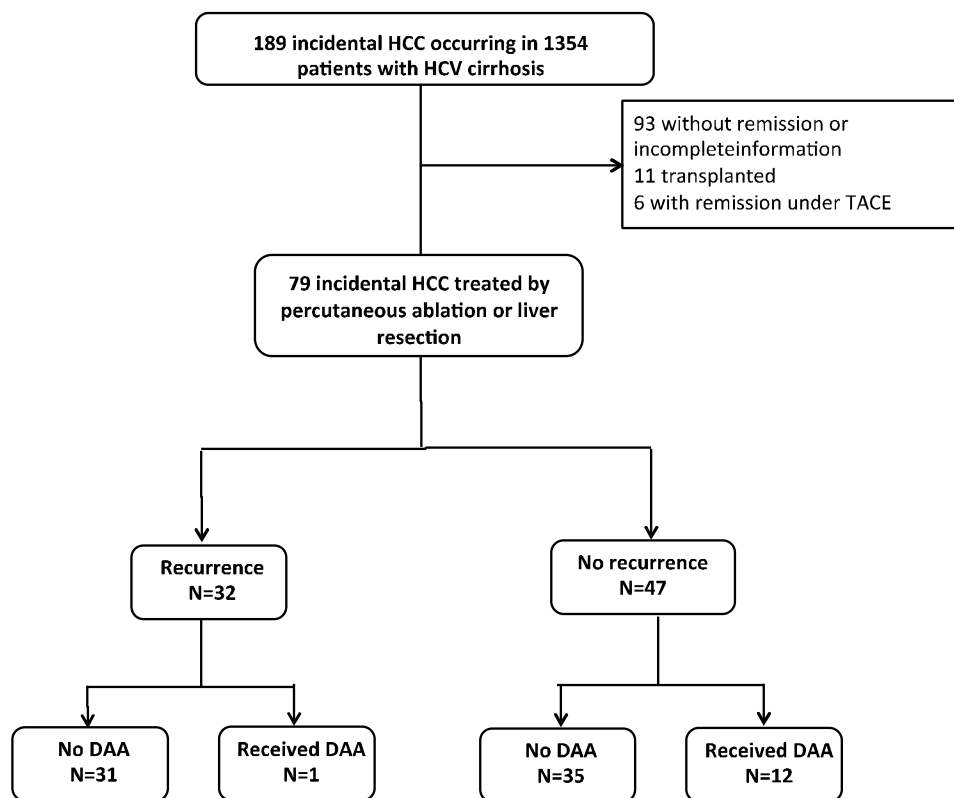
Pt	MELD score before LT	Indication LT	Therapy during waiting time	Milan criteria at inscription *	Characteristics of native liver	Delay LT/DAA (months)	DAA-based therapy	Duration of DAA therapy (weeks)	Characteristics of recurrence Site/ Nodule(s)	Delay LT/recurrence (months)	Delay DAA/recurrence (months)	Delay viral clearance / recurrence (weeks)	Response	Delay recurrence /SVR (weeks)	Status at last news	Delay LT / last news (months)	Delay recurrence / last news (months)
1	NA	HCC	None	W	1 nodule 12 mm No vascular invasion	84	SOF+RBV	17	Liver 1 nodule, 8 mm diameter	88	4	9	SVR24	26	re-LT alive	106	18
2	7	HCC	Resection TACE	W	6 nodules (2 completely necrotic, 5 10 < 15 mm) Vascular invasion	128	SOF+RBV	24	Liver 1 nodule 22 mm diameter	136	8	31	SVR24	7	dead	141	6
3	NA	re-LT for HCC	TACE	W	1 nodule 5 cm with capsule rupture No vascular invasion	173	SOF+DCV	24	Liver >5 nodules - Larger nodule: 6 cms	175	2	2	EOT	NA	alive	188	13
4	17	HCC	RF	W	3 nodules (8,9 and 10 cm) 2 micronodules (3 and 7 mm) No vascular invasion	18	SOF+DCV +RBV	24	Liver 1 nodule, 9 mm diameter	28	10	35	SVR24	5	dead	45	17
5	26	HCC	TACE	B	8 nodules (larger 7 cm) No vascular invasion	6	SOF+DCV +RBV	24	Pulmonary metastasis	16	10	35	SVR24	4	dead	26	10
6	9	HCC	TACE chemotherapy RF	W	3 nodules (7 to 30 mm) No vascular invasion	12	SOF+RBV	25	Pulmonary metastasis and thoracic lymph nodes	17	4	13	relapse at FUW4	NA	dead	32	15
7	17	HCC	TACE / RF	W	5 nodules (0,6 to 1,8 cm) Vascular invasion	25	SOF+DCV +RBV	12	Liver Multinodular recurrence	32	7	26	breakthrough at W12	NA	dead	44	13

**Figure 1**

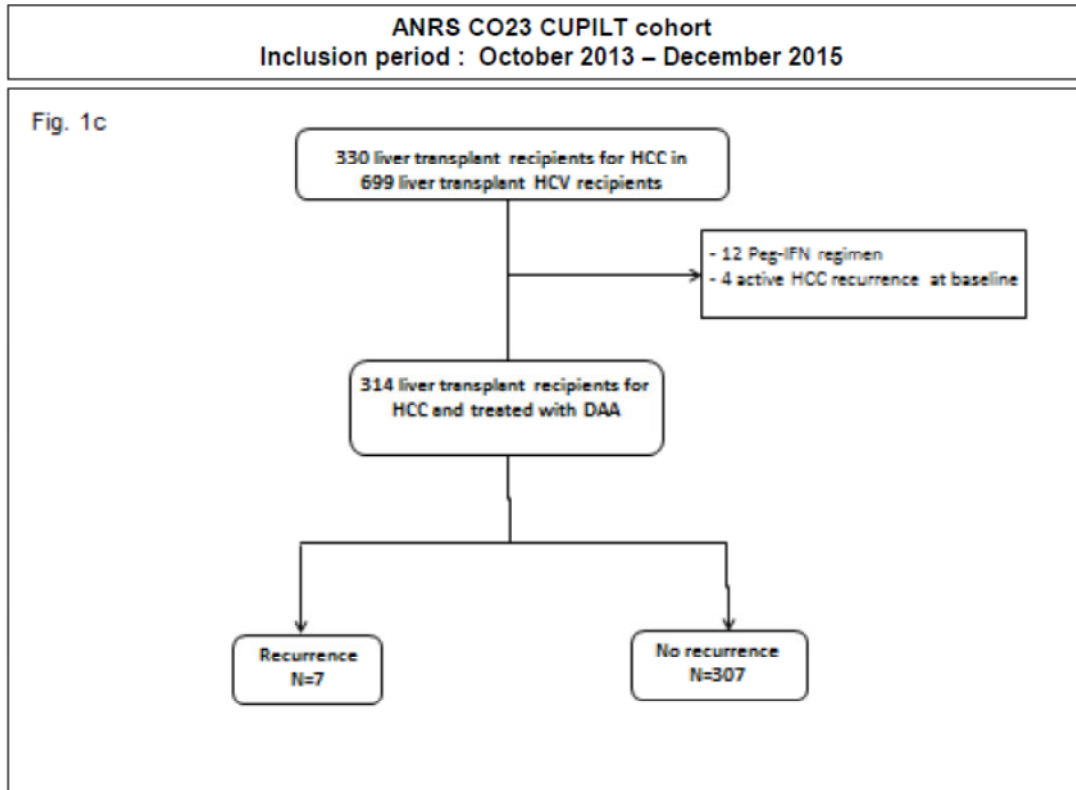
Part A. Fig 1a



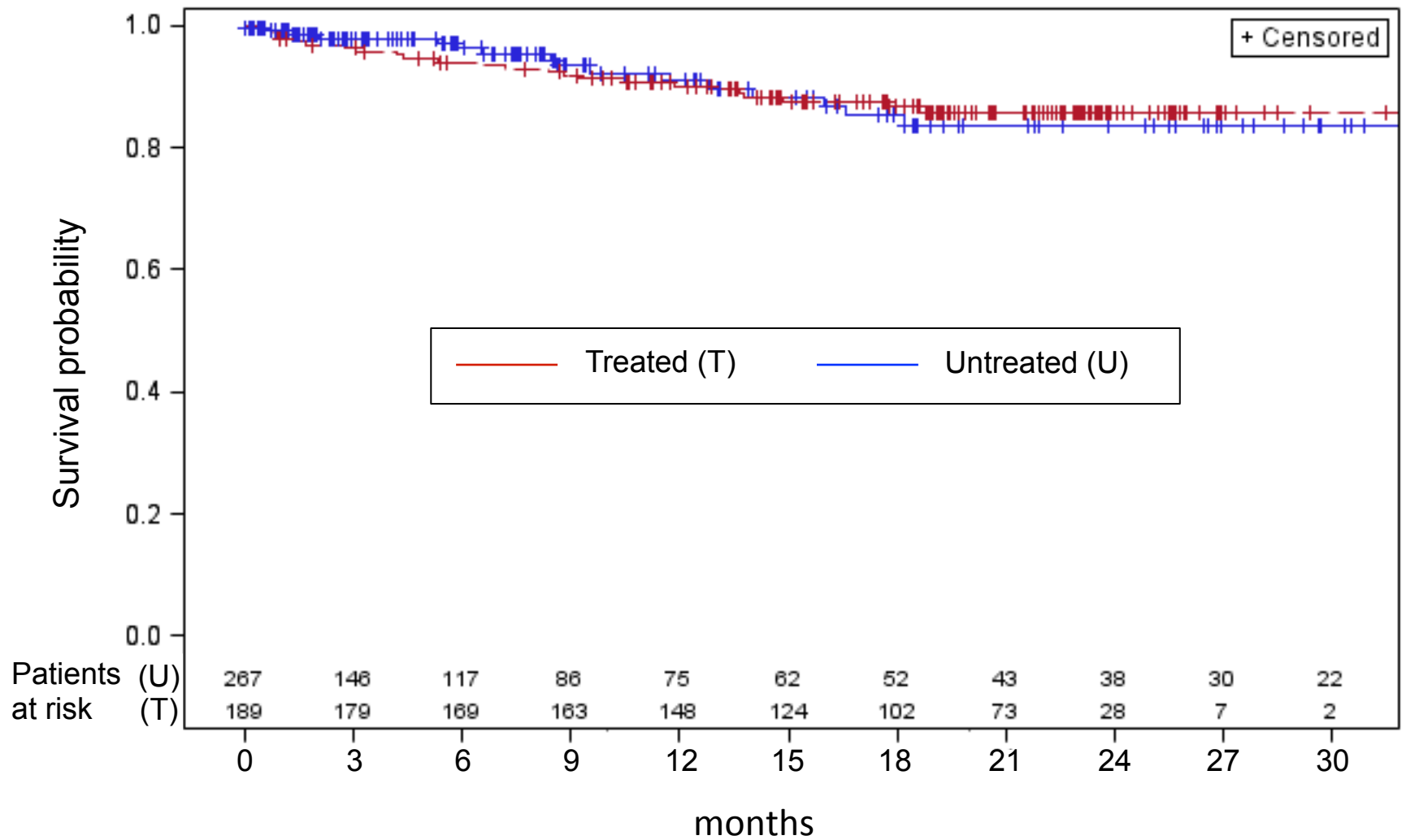
Part B. Fig 1b



Part C. Fig 1c



# Survival-free of HCC recurrence



**Lay summary**

Since an unexpected high rate of hepatocellular carcinoma (HCC) recurrence after direct acting antiviral (DAA) treatment has been suggested in a retrospective study, we analyzed data from three French prospective multicenter ANRS cohorts of > 6,000 DAA treated patients who underwent curative HCC therapies.

We did not observe an increased risk of HCC recurrence after DAA treatment: the rates of recurrence were similar in treated and untreated patients (0.73/100 and 0.66/100 person-months in in the ANRS CO22 HEPATHER cohort including 189 DAA+ and 78 DAA- and 1.11/100 in 13 DAA+ and 1.73/100 person-months in 66 DAA- in the ANRS CO12 CIRVIR cohort), respectively. Finally, in the ANRS CO23 CUPILT Cohort, HCC recurred in only 7 among 314 (2.2 %) liver transplant recipients for HCC subsequently treated after 70 months after liver transplantation



# Survival-free of HCC recurrence

