Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study

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Summary

Background Although direct-acting antivirals have been used extensively to treat patients with chronic hepatitis C virus (HCV) infection, their clinical effectiveness has not been well reported. We compared the incidence of death, hepatocellular carcinoma, and decompensated cirrhosis between patients treated with direct-acting antivirals and those untreated, in the French ANRS CO22 Hepather cohort.

Methods We did a prospective study in adult patients with chronic HCV infection enrolled from 32 expert hepatology centres in France. We excluded patients with chronic hepatitis B, those with a history of decompensated cirrhosis, hepatocellular carcinoma, or liver transplantation, and patients who were treated with interferon-ribavirin with or without first-generation protease inhibitors. Co-primary study outcomes were incidence of all-cause mortality, hepatocellular carcinoma, and decompensated cirrhosis. The association between direct-acting antivirals and these outcomes was quantified using time-dependent Cox proportional hazards models. This study is registered with ClinicalTrials.gov, number NCT01953458.

Findings Between Aug 6, 2012, and Dec 31, 2015, 10 166 patients were eligible for the study. 9895 (97%) patients had available follow-up information and were included in analyses. Median follow-up was 33·4 months (IQR 24·0–40·7). Treatment with direct-acting antivirals was initiated during follow-up in 7344 patients, and 2551 patients remained untreated at the final follow-up visit. During follow-up, 218 patients died (129 treated, 89 untreated), 258 reported hepatocellular carcinoma (187 treated, 71 untreated), and 106 had decompensated cirrhosis (74 treated, 32 untreated). Exposure to direct-acting antivirals was associated with increased risk for hepatocellular carcinoma (unadjusted hazard ratio [HR] 2·77, 95% CI 2·07–3·71) and decompensated cirrhosis (3·83, 2·29–6·42). After adjustment for variables (age, sex, body-mass index, geographical origin, infection route, fibrosis score, HCV treatment-naive, HCV genotype, alcohol consumption, diabetes, arterial hypertension, biological variables, and model for end-stage liver disease score in patients with cirrhosis), exposure to direct-acting antivirals was associated with a decrease in all-cause mortality (adjusted HR 0·48, 95% CI 0·33–0·70) and hepatocellular carcinoma (0·66, 0·46–0·93), and was not associated with decompensated cirrhosis (1·14, 0·57–2·27).

Interpretation Treatment with direct-acting antivirals is associated with reduced risk for mortality and hepatocellular carcinoma and should be considered in all patients with chronic HCV infection.

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Introduction

WHO's Global Hepatitis Report[1] states that hepatitis C virus (HCV) has infected 1% of the population worldwide (71 million) and caused approximately 400 000 deaths annually, mainly from cirrhosis and hepatocellular carcinoma. This substantial public health burden can be improved by HCV treatments, because this chronic viral infection is the only one that can be cured, as defined by a sustained virological response.[2,3] Combining two or three direct-acting antivirals targeting viral proteins—eg, NS3/4A protease inhibitors, NS5B polymerase inhibitors, and NS5A replication complex inhibitors—has pan-genotypic efficacy in HCV infection, with a sustained viral response of more than 95% and fair tolerance. Treatment lasts 8–16 weeks depending on baseline factors including stage of fibrosis, genotype, treatment history, and pre-existing resistance-associated variants.[4,5]

Findings of observational studies in patients with HCV infection show reduced risk for hepatocellular carcinoma, complications of liver disease, and mortality in patients treated with interferon or direct-acting antivirals who

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Research in context

Evidence before this study

We searched PubMed for reports published in any language between Jan 1, 2012, and Jan 1, 2018, with the MESH terms ("hepatitis C, chronic/drug therapy" OR "hepatitis C, chronic/therapy") AND ("hepatitis C, chronic/mortality" OR "hepatitis C, chronic/complications"). We searched for evidence of randomised trials or observational studies assessing the risk of mortality, liver cancer, and the complications of liver disease after antiviral treatment with direct-acting antivirals in patients with chronic hepatitis C virus (HCV) infection. We identified a 2017 review of 138 randomised trials assessing the effects of 51 different direct-acting antivirals, indicating that use of these drugs increased the proportion achieving a sustained virological response. However, the review did not reach any conclusions on clinical effects. We only found one additional retrospective cohort study reporting a significant decrease in all-cause mortality in patients receiving either paritaprevir, ritonavir, ombitasvir, and dasabuvir or sofosbuvir and ledipasvir, compared with untreated patients. This study did not report on liver-related mortality or liver-related events (eg, liver cancer or liver decompensation). No existing prospective study has examined the benefits and harms of direct-acting antivirals in chronic HCV infection on liver-related clinical outcomes using time-to-event analyses and by comparison of treated and untreated patients.

Added value of the study

To our knowledge, the ANRS CO22 Hepather cohort study is the first prospective longitudinal study to investigate clinical outcomes associated with direct-acting antiviral treatment in patients with chronic HCV infection, by comparing patients treated with direct-acting antivirals with those untreated with these drugs, irrespective of the status of sustained virological response, with careful control of confounding and indication biases. The adjusted multivariable analyses show that direct-acting antiviral treatment is associated with a rapid decrease in all-cause mortality and the incidence of hepatocellular carcinoma, and that these inverse associations are stronger in patients with cirrhosis.

Implications of all the available evidence

For ethical reasons, a trial with an untreated control arm cannot be undertaken to confirm these findings. We encourage other researchers to do similar comparisons of patients treated with direct-acting antivirals and untreated patients, using existing observational databases. Nevertheless, our results support urgent treatment of patients with advanced liver disease and extension of the follow-up of treated patients with less severe disease to assess the long-term clinical effect of direct-acting antiviral treatment.

achieve a sustained virological response.[6-12] However, very few studies have compared the clinical outcomes of patients treated and not treated with direct-acting antivirals, as would be done in a randomised trial.[13] The findings of a single-centre cohort study showed decreased mortality in patients receiving a combination of paritaprevir, ritonavir, ombitasvir, and dasabuvir, or of sofosbuvir and ledispasvir, compared with untreated patients.[14] However, this study did not report the incidence of liver-related events such as liver decompensation or hepatocellular carcinoma, and this information is important because of controversy surrounding a potential increase in risk for hepatocellular carcinoma with direct-acting antiviral treatment.[15,16]

The aim of this study was to further clarify the benefits or harms of direct-acting antivirals by comparing the incidence of death, hepatocellular carcinoma, and decompensated cirrhosis in patients treated with direct-acting antivirals and untreated, from the prospective French ANRS CO22 Hepather cohort.

Methods

Study design and participants

The ANRS CO22 Hepather cohort is a French national, multicentre, prospective, observational cohort study of patients with active or inactive hepatitis B virus (HBV) or past or present HCV infection, which started in August, 2012.[17] The main objectives of the study are to quantify the clinical efficacy and safety of new hepatitis treatments in real life. The anticipated cohort size is 15 000 patients serum-positive for anti-HCV (>90% with existing chronic HCV infection at entry—ie, serum-positive for HCV-RNA—and <10% with past chronic HCV infection) and 10 000 patients with active or inactive chronic HBV infection, to be followed up for a median of 7 years. Main exclusion criteria are HIV co-infection and ongoing treatment for HCV infection at inclusion. In the current analysis, we selected all patients with chronic HCV infection at entry. Participants were recruited consecutively during a medical visit at one of 32 expert hepatology centres in France.

Written informed consent was obtained from each patient before enrolment. The protocol was undertaken 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).

Procedures

Blood and urine samples were obtained and stored in a centralised biobank (Cell & Co Biorepository, Pont du Château, France). Detailed demographic, clinical (including fibrosis staging and history of past treatment), and biological data were gathered during the inclusion visit using an electronic case-report form. Follow-up included systematic visits once a year and spontaneous reports for particular events, which were recorded on specific data forms (eg, death, hepatocellular carcinoma,

decompensated cirrhosis, onset of treatment). In April, 2014, the follow-up protocol was modified to include local HCV-RNA assessments and visits with the clinician when HCV treatment was started, during treatment, and up to 24 weeks after the last treatment. This study is observational, and decisions about treatment combination, treatment timing, and screening for hepatocellular carcinoma or progression of fibrosis were made by the clinician, but the choices made accorded with French national recommendations, based on European Association for the Study of the Liver (EASL) guidelines.[18]

Exposure to direct-acting antivirals was regarded as a time-dependent covariate, and the first day of the first treatment defined the timepoint to switch exposure from 0 to 1. If a patient received several direct-acting antiviral treatments during follow-up (eg, because of virological failure), she or he was considered to be continuously exposed to direct-acting antivirals from her or his first day of first treatment. The other potential predictors of clinical outcome assessed at entry in the cohort were age, sex, body-mass index, geographical origin, infection route, time since HCV diagnosis, fibrosis score, HCV treatment-naive, HCV genotype, diabetes, arterial hypertension, past and current alcohol consumption, biological variables (albumin, aspartate aminotransferase, alanine aminotransferase, haemoglobin, prothrombin time, platelet count, α-fetoprotein), and model for end-stage liver disease (MELD) score in patients with cirrhosis.

Patients with a platelet count lower than 150 000 platelets per µL or a prothrombin time less than 70% were considered to have cirrhosis unless specified otherwise.[19,20] These criteria were validated in 757 patients who were also assessed for liver fibrosis, including 755 who had been classified with cirrhosis by different techniques. Fibrosis assessment was done closest to the date of inclusion, but less than 1 year before and up to 3 months after inclusion. Fibrosis was assessed either by liver biopsy or another non-invasive method (liver stiffness measurement; Fibroscan, Echosens, Paris, France), Fibrotest (Biopredictive, Paris, France), Fibrometer (Echosens), or the Hepascore.[21] If a recent measurement of fibrosis was not available, or in case of discrepancies between non-invasive fibrosis markers, clinicians were asked to assess the level of fibrosis based on past fibrosis scores and the patient's history of liver-related comorbidities. Mild fibrosis (F0–F2), severe fibrosis (F3), and cirrhosis (F4) were defined by the Metavir score.[22] Cutoffs for severe fibrosis and cirrhosis by non-invasive methods were, respectively, 9·5 kPa and 12·5 kPa with Fibroscan, 0·59 and 0·75 with Fibrotest, 0·62 and 0·98 with Fibrometer, and 0·61 and 0·84 with the Hepascore.

Outcomes

Co-primary study outcomes were all-cause mortality (later classified into liver-related or non-liver-related deaths), incident hepatocellular carcinoma, and incident decompensated cirrhosis. Causes of death were classified by an adjudication committee including two hepatologists (HF, MB) and one methodologist (CD). Adjudication was based on medical records, and investigators filled in a specific case-report form. Data for incident hepatocellular carcinoma included the number of tumours at diagnosis, the largest nodule size, total size, diagnostic imaging procedures, and treatment. Decompensated cirrhosis was defined as the development of ascites, variceal haemorrhage, encephalopathy, jaundice, or a combination of these.[23]

Statistical analysis

A post-hoc calculation was done based on 33% of included patients with cirrhosis at entry, an annual incidence of two per 100 person-years all-cause mortality in the absence of treatment in patients with cirrhosis,[24] and a multivariable-adjusted hazard ratio (HR) for all-cause mortality of 0·43 (95% CI 0·33–0·57) in treated versus untreated patients.[14] This calculation showed that 1500 person-years of follow-up would be needed in

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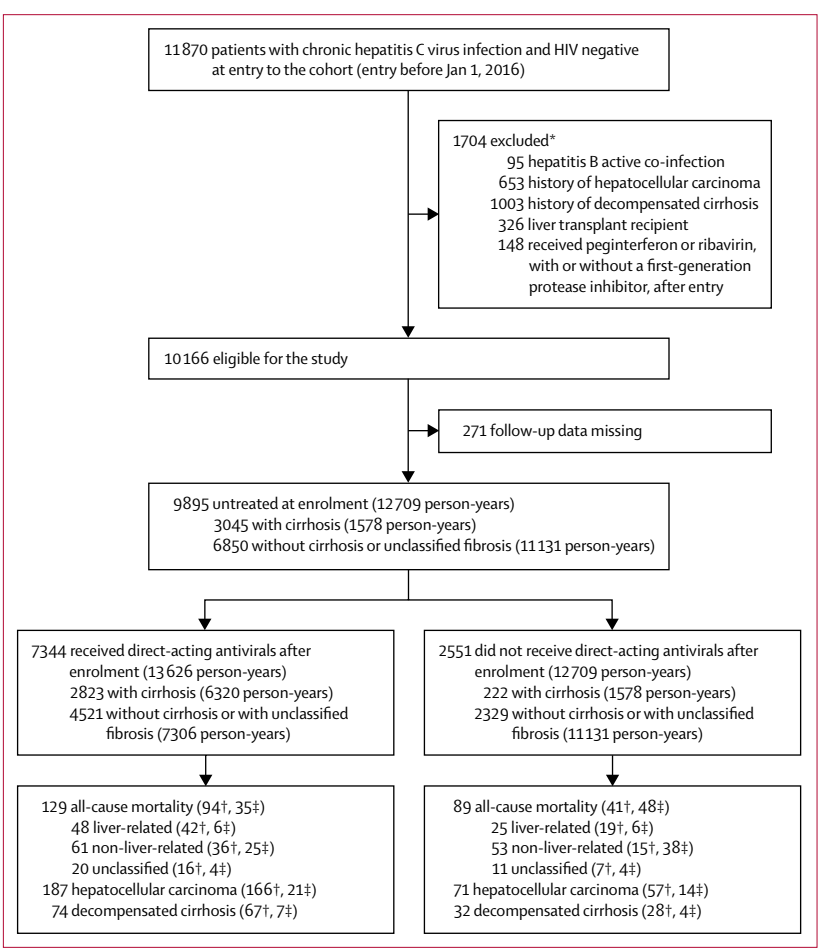

Figure 1: **Flow of participants through the study**
*Patients could meet more than one criterion for exclusion. †Number with cirrhosis. ‡Number without cirrhosis or with unclassified fibrosis.

	Received direct-acting antivirals (n=7344)	Did not receive direct-acting antivirals (n=2551)	p value
Age (years)	57·0 (51·0–65·0)	54·0 (47·0–62·0)	<0·0001
Sex	..	..	<0·0001
Male	4105/7344 (56%)	1174/2551 (46%)	..
Female	3239/7344 (44%)	1377/2551 (54%)	..
Body-mass index (kg/m²)	..	..	<0·0001
<18·5	219/7239 (3%)	82/2457 (3%)	..
18·5 to <25·0	3592/7239 (50%)	1397/2457 (57%)	..
25·0 to <30·0	2434/7239 (34%)	683/2457 (28%)	..
≥30·0	994/7239 (14%)	295/2457 (12%)	..
Geographical origin	..	..	<0·0001
Asia	173/7224 (2%)	76/2491 (3%)	..
Eastern Europe	275/7224 (4%)	85/2491 (3%)	..
France	4555/7224 (63%)	1559/2491 (63%)	..
North Africa	788/7224 (11%)	245/2491 (10%)	..
Sub-Saharan Africa	479/7224 (7%)	258/2491 (10%)	..
Other	954/7224 (13%)	268/2491 (11%)	..
Infection route	..	..	0·056
Injecting drug use	1862/7232 (26%)	608/2434 (25%)	..
Transfusion	2254/7232 (31%)	711/2434 (29%)	..
Other or unknown	3116/7232 (43%)	1115/2434 (46%)	..
Excessive alcohol use at entry in the cohort*	..	..	0·41
No	7104/7344 (97%)	2459/2551 (96%)	..
Yes	240/7344 (3%)	92/2551 (4%)	..
Past excessive alcohol use*	..	..	0·0018
No	5251/7255 (72%)	1868/2471 (76%)	..
Yes	2004/7255 (28%)	603/2471 (24%)	..
Time since HCV diagnosis (years)	15·0 (8·0–21·0)	14·0 (7·0–20·0)	0·0004
Missing data	252	157	..
HCV treatment history	..	..	<0·0001
Treated	4159/7324 (57%)	974/2516 (39%)	..
Treatment-naive	3165/7324 (43%)	1542/2516 (61%)	..
HCV genotype	..	..	<0·0001
1	4818/7227 (67%)	1531/2375 (64%)	..
2	420/7227 (6%)	231/2375 (10%)	..
3	918/7227 (13%)	211/2375 (9%)	..
4	918/7227 (13%)	334/2375 (14%)	..
5, 6, or 7	153/7227 (2%)	68/2375 (3%)	..
Fibrosis scoring	..	..	<0·0001
F0, F1, or F2	2805/6800 (41%)	1865/2223 (84%)	..
F3	1172/6800 (17%)	136/2223 (6%)	..
F4 (cirrhosis)	2823/6800 (42%)	222/2223 (10%)	..
APRI score	1·20 (1·55)	0·62 (0·85)	<0·0001
Missing data	625	449	..
FIB4 score	2·90 (2·96)	1·78 (1·89)	<0·0001
Missing data	633	453	..
MELD score in patients with cirrhosis†	..	..	0·15
<13	2426/2629 (92%)	157/175 (90%)	..
13 to <20	143/2629 (5%)	10/175 (6%)	..
≥20	60/2629 (2%)	8/175 (5%)	..

(Table 1 continues on next page)

patients unexposed to direct-acting antivirals, and 4500 person-years of follow-up in patients exposed to direct-acting antivirals, to achieve a statistical power of 86% to detect an HR lower than 0·5.

Survival time was calculated as the time between entry (unexposed period) or the start of first treatment (exposed period) and the last follow-up visit, the date of an outcome (death, hepatocellular carcinoma, or decompensated cirrhosis) or Jan 1, 2018, whichever occurred first. Baseline characteristics were compared using the Mann-Whitney test for quantitative variables or the Fisher's exact test for categorical variables. Pseudo Kaplan-Meier curves were drawn using a clock reset procedure for patients exposed to direct-acting antiviral treatment during follow-up.[25] Incidence and 95% CIs were estimated with an exact method based on the Poisson distribution. We used a multivariable Cox proportional hazards model with exposure to treatment modelled as a time-varying covariate in our main analysis. This analysis was adjusted for the baseline values of all predictor variables (age, sex, body-mass index, geographical origin, infection route, fibrosis score, HCV treatment-naive, HCV genotype, alcohol consumption, diabetes, arterial hypertension, biological variables, and MELD score in patients with cirrhosis) and used a time-dependent variable for the baseline hazard by a smooth function of the time since August, 2012, using natural cubic splines with four knots. Categorisation of continuous covariates was based on clinically relevant thresholds determined a priori (all biological variables) or quartile limits (age, time since HCV diagnosis). Missing covariate values were handled using indicators for missing data in the multivariable model. To better characterise the potential effect of a sustained virological response in patients exposed to direct-acting antivirals compared with untreated patients, the exposure period was divided into the on-treatment period (from first to last day of direct-acting antiviral treatment, extended by 3 months), and the period with a measurable sustained virological response status (from 3 months after the last day of direct-acting antiviral treatment to the end of follow-up), which were regarded as time-dependent covariates in the Cox model (appendix). Sustained virological response status was assessed after the first direct-acting antiviral treatment and was not updated if a patient received several consecutive treatments. These analyses were repeated both in patients with and without cirrhosis or unknown fibrosis score at entry in the cohort. To deal with potential residual indication bias, time-dependent censoring, and confounding, we also assessed the robustness of our findings using inverse probability of treatment weighting[26] and sequential weighted Cox models.[27] Because the most severely ill patients could be excluded from treatment because of the high risk of complications, an additional sensitivity analysis was done including patients with at least 12 months of follow-up. Robust variance estimates were ascertained for all

analyses to obtain conservative 95% CIs. All analyses were done with SAS version 9.4. We judged a p value less than 0·05 significant.

Role of the funding source

The funder contributed to study design and writing of the report. The funder had no role in data collection, data analysis, or data interpretation. The corresponding author had full access to all data in the study and FC and SP had final responsibility for the decision to submit for publication.

Results

Between Aug 6, 2012, and Dec 31, 2015, 14 389 anti-HCV-positive patients had been recruited to the ANRS CO22 Hepather cohort, including 11 870 with chronic HCV infection at entry (figure 1). 95 patients had active HBV co-infection at entry, 653 had a history of hepatocellular carcinoma, 1003 had decompensated cirrhosis, and 326 had undergone liver transplantation; these patients were excluded from this study. A further 148 patients were excluded who had received peginterferon and ribavirin with or without a first-generation protease inhibitor after entry in the cohort.

10 166 patients were judged eligible for this study (figure 1). Follow-up information was missing for 271 patients, therefore post-entry follow-up information was available for 9895 (97%) patients, who were included in analyses. The appendix presents a comparison of characteristics of eligible patients with missing follow-up information.

Of 9895 patients analysed, 1326 (13%) had a platelet count lower than 150 000 platelets per µL or a prothrombin time less than 70% and were considered to have cirrhosis. In other patients, fibrosis was assessed by liver biopsy for 398 (4%) patients, by Fibroscan for 3188 (32%), by Fibrotest for 1812 (18%), by Fibrometer for 635 (6%), and by the Hepascore for 143 (1%). The clinician assessed the level of fibrosis for 1521 (15%) patients, and the baseline fibrosis score remained unknown in 872 (9%). In total, 3045 (31%) patients had cirrhosis. The median time between assessment of fibrosis and end of follow-up in patients who received direct-acting antivirals was 34·5 months (IQR 25·1–43·0), and for those who were untreated, median time was 32·3 months (IQR 22·7–43·0).

Baseline demographic, clinical, and laboratory characteristics of included patients, according to exposure to direct-acting antivirals during follow-up, are provided in table 1. Median patients' age was 56·0 years (IQR 50·0–64·0) and 5279 (53%) patients were men. 7344 patients began direct-acting antiviral treatment after a median time from entry of 4·3 months (IQR 0·2–17·2). Median follow-up (untreated plus treated periods) in these patients was 33·4 months (IQR 24·0–40·7). At the last follow-up visit, 2551 patients remained untreated, with a median follow-up of 31·2 months (IQR 21·5–41·0). Patients who received direct-acting antivirals were older, more frequently men, had a higher body-mass index, and reported past excessive alcohol use compared with those who remained untreated at the final follow-up visit. Receiving direct-acting antiviral treatment was also strongly associated with the severity of liver disease and other comorbidities (table 1). Compared with untreated patients, those who received direct-acting antivirals had been diagnosed with HCV for a longer time, 2823 (42%) of 6800 patients had cirrhosis (*vs* 222 [10%] of

	Received direct-acting antivirals (n=7344)	Did not receive direct-acting antivirals (n=2551)	p value
(Continued from previous page)			
APRI score in patients with cirrhosis†	1·94 (2·05)	1·68 (2·14)	0·0014
≤2·00	1807/2664 (68%)	133/182 (73%)	0·16
>2·00	857/2664 (32%)	49/182 (27%)	..
FIB4 score in patients with cirrhosis†	4·41 (3·85)	4·39 (4·76)	0·31
<3·25	1330/2662 (50%)	96/182 (53%)	0·49
≥3·25	1332/2662 (50%)	86/182 (47%)	..
Diabetes	..	..	<0·0001
No	6325/7270 (87%)	2277/2475 (92%)	..
Yes	945/7270 (13%)	198/2475 (8%)	..
Arterial hypertension	..	..	<0·0001
No	5105/7266 (70%)	1878/2467 (76%)	..
Yes	2161/7266 (30%)	589/2467 (24%)	..
Anaemia‡	..	..	0·69
No	6303/6879 (92%)	2014/2191 (92%)	..
Yes	576/6879 (8%)	177/2191 (8%)	..
Albumin	..	..	0·042
≥30 g/L	6160/6239 (99%)	1751/1763 (99%)	..
<30 g/L	79/6239 (1%)	12/1763 (1%)	..
Prothrombin time	..	..	<0·0001
>70%	6041/6360 (95%)	1921/1972 (97%)	..
≤70%	319/6360 (5%)	51/1972 (3%)	..
Platelet count	..	..	<0·0001
≥10^5 per µL	6232/6830 (91%)	2106/2156 (98%)	..
<10^5 per µL	598/6830 (9%)	50/2156 (2%)	..
Alanine aminotransferase	..	..	<0·0001
≤5 ULN	6646/7050 (94%)	2247/2286 (98%)	..
>5 ULN	404/7050 (6%)	39/2286 (2%)	..
Aspartate aminotransferase	..	..	<0·0001
≤5 ULN	6701/7013 (96%)	2198/2256 (97%)	..
>5 ULN	312/7013 (4%)	58/2256 (3%)	..
α-fetoprotein	..	..	<0·0001
<5·5 ng/mL	2647/5072 (52%)	1051/1416 (74%)	..
≥5·5 ng/mL	2425/5072 (48%)	365/1416 (26%)	..

Data are median (IQR), mean (SD), n/N (%), or n. Denominators are provided because data are missing for some variables. APRI=aspartate aminotransferase to platelet ratio index. FIB4=fibrosis 4 score. HCV=hepatitis C virus. MELD=model for end-stage liver disease. ULN=upper limit of normal. *Defined as at least 15 alcoholic drinks (150 g) per week for a woman or 22 alcoholic drinks (220 g) per week for a man, or at least six consecutive alcoholic drinks (60 g) on at least one occasion per week. †Cirrhosis was diagnosed in 2823 patients in the group who had received direct-acting antivirals by the last follow-up visit and in 222 patients in the group who had not received direct-acting antivirals by the last follow-up visit. ‡Defined as haemoglobin <12 g/dL in women and <13 g/dL in men.

Table 1: **Characteristics of patients at entry in the cohort in relation to direct-acting antiviral treatment during follow-up**

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	Received direct-acting antivirals (exposed)		Did not receive direct-acting antivirals (not exposed)		Exposed *vs* not exposed	
	n per person-years	Incidence per 100 person-years (95% CI)	n per person-years	Incidence per 100 person-years (95% CI)	Univariable HR (95% CI)	Multivariable adjusted HR (95% CI)
All patients (n=9895)						
All-cause mortality	129/13 626	0·95 (0·79–1·12)	89/12 709	0·70 (0·56–0·86)	1·14 (0·85–1·52)	0·48 (0·33–0·70)
Liver-related	48/13 626	0·35 (0·26–0·47)	25/12 709	0·20 (0·13–0·29)	1·46 (0·89–2·39)	0·39 (0·21–0·71)
Non-liver-related	61/13 626	0·45 (0·34–0·58)	53/12 709	0·42 (0·31–0·55)	0·92 (0·62–1·37)	0·60 (0·36–1·00)
Hepatocellular carcinoma	187/13 375	1·40 (1·20–1·61)	71/12 660	0·56 (0·44–0·71)	2·77 (2·07–3·71)	0·66 (0·46–0·93)
Decompensated cirrhosis	74/13 520	0·55 (0·43–0·69)	32/12 698	0·25 (0·17–0·36)	3·83 (2·29–6·42)	1·14 (0·57–2·27)
Patients with cirrhosis (n=3045)						
All-cause mortality	94/6320	1·49 (1·20–1·82)	41/1578	2·60 (1·86–3·52)	0·35 (0·23–0·53)	0·34 (0·22–0·55)
Liver-related	42/6320	0·66 (0·48–0·90)	19/1578	1·20 (0·72–1·88)	0·32 (0·17–0·59)	0·28 (0·15–0·54)
Non-liver-related	36/6320	0·57 (0·40–0·79)	15/1578	0·95 (0·53–1·57)	0·36 (0·18–0·71)	0·40 (0·19–0·83)
Hepatocellular carcinoma	166/6104	2·72 (2·32–3·17)	57/1539	3·70 (2·80–4·80)	0·63 (0·44–0·90)	0·57 (0·40–0·81)
Decompensated cirrhosis	67/6223	1·08 (0·83–1·37)	28/1567	1·79 (1·19–2·58)	0·67 (0·40–1·11)	0·95 (0·48–1·89)
Patients without cirrhosis (n=5978) or with an unknown fibrosis score (n=872)						
All-cause mortality	35/7307	0·48 (0·33–0·67)	48/11 131	0·43 (0·32–0·57)	0·94 (0·58–1·50)	0·74 (0·43–1·28)
Liver-related	6/7307	0·08 (0·03–0·18)	6/11 131	0·05 (0·02–0·12)	1·33 (0·46–3·84)	ND
Non-liver-related	25/7307	0·34 (0·22–0·51)	38/11 131	0·34 (0·24–0·47)	0·89 (0·51–1·56)	0·75 (0·42–1·35)
Hepatocellular carcinoma	21/7271	0·29 (0·18–0·44)	14/11 120	0·13 (0·07–0·21)	2·49 (1·18–5·27)	1·02 (0·40–2·61)
Decompensated cirrhosis	7/7297	0·10 (0·04–0·20)	4/11 131	0·04 (0·01–0·09)	3·59 (0·66–19·5)	ND

HR=hazard ratio. ND=not done because of insufficient number of events.

***Table 2*: Incidence of and risk for death, hepatocellular carcinoma, and decompensated cirrhosis, according to exposure to direct-acting antiviral treatment during follow-up**

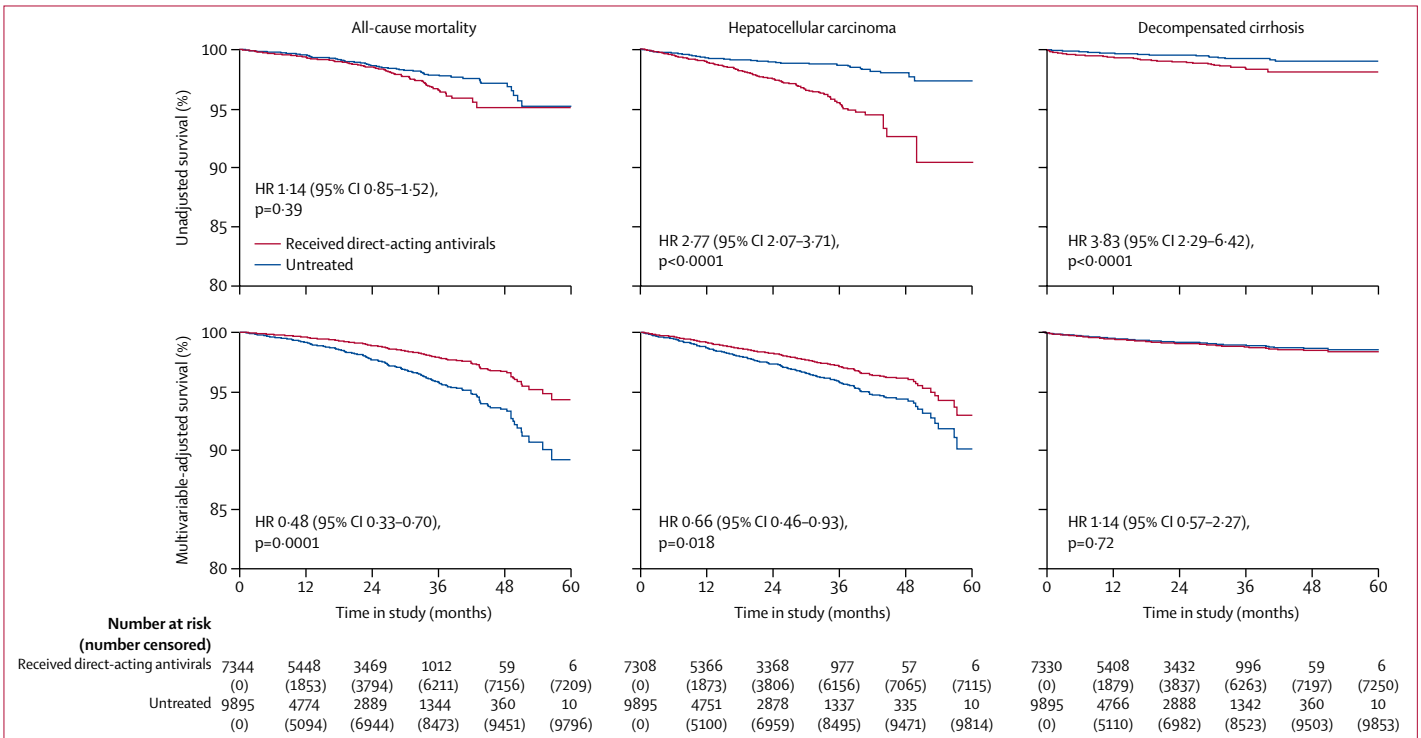

***Figure 2*: Global survival, survival free from hepatocellular carcinoma, and survival free from decompensated cirrhosis, according to exposure to direct-acting antivirals in all patients analysed**
Upper panel shows unadjusted survival curves. Lower panel show multivariable-adjusted survival curves estimated with a time-dependent Cox proportional hazards model. HR=hazard ratio.

2223 untreated patients), 4159 (57%) of 7324 patients had received HCV treatment at entry (*vs* 974 [39%] of 2516 untreated patients), including 49 (1%) of 7324 with past use of interferon-free regimens (*vs* three [<1%] of 2516 untreated patients), 918 (13%) of 7227 patients were infected with HCV genotype 3 (*vs* 211 [9%] of 2375 untreated patients), 945 (13%) of 7270 patients had diabetes (*vs* 198 [8%] of 2475 untreated patients), and 2161 (30%) of 7266 patients had arterial hypertension (*vs* 589 [24%] of 2467 untreated patients). Of note, 1049 (40%) of 2607 patients with past excessive alcohol use had cirrhosis versus 1977 (28%) of 7119 without (p<0·0001), which could be why past excessive alcohol users were more likely to initiate direct-acting antiviral treatment. Combinations of direct-acting antivirals used in the study are listed in the appendix.

218 patients died during the study; 73 were classified as liver-related deaths, 114 as non-liver-related (appendix), and 31 deaths were unclassified. 258 cases of hepatocellular carcinoma and 106 cases of decompensated cirrhosis were reported during follow-up (figure 1). 25 patients also underwent liver transplantation during follow-up. The crude incidence of all-cause mortality, liver-related death, hepatocellular carcinoma, and decompensated cirrhosis was higher in patients exposed to direct-acting antivirals than in unexposed patients (table 2; figure 2). Exposure to direct-acting antivirals was associated with increased risk for hepatocellular carcinoma (HR 2·77, 95% CI 2·07–3·71; p<0·0001) and decompensated cirrhosis (3·83, 2·29–6·42; p<0·0001) in the unadjusted Cox model. After adjustment in the multivariable analysis, exposure to direct-acting antivirals was associated with a decrease in all-cause mortality (HR 0·48, 95% CI 0·33–0·70; p=0·0001), liver-related death (0·39, 0·21–0·71; p=0·0020), non-liver-related death (0·60, 0·36–1·00; p=0·048), and hepatocellular carcinoma (0·66, 0·46–0·93; p=0·018), and was no longer associated with decompensated cirrhosis (1·14, 0·57–2·27; p=0·72). Similar findings were obtained using inverse probability of treatment weighting and weighted sequential Cox models or when analyses were restricted to events that occurred after 12 months of follow-up (appendix). Other predictors independently associated with risk for all-cause mortality, hepatocellular carcinoma, or decompensated cirrhosis are presented in table 3 and include cirrhosis, markers of liver failure, hypertension, anaemia, and serum α-fetoprotein; a description of events by covariate levels is provided in the appendix.

A sustained virological response was achieved by 5615 (76%) of 7344 patients who started direct-acting antivirals, was not achieved by 341 (5%) patients, and was unknown in 709 (10%) patients; sustained virological response status could not be established for 679 (9%) patients because of insufficient follow-up (these patients are classified as on-treatment; appendix). Thus, the proportion of patients achieving a sustained

	All-cause mortality	Hepatocellular carcinoma	Decompensated cirrhosis
Exposed to direct-acting antivirals (yes *vs* no)	0·48 (0·33–0·70)*	0·66 (0·46–0·93)*	1·14 (0·57–2·27)
Age (years)			
<50 (reference)	1·00	1·00	1·00
≥50 to <56	1·37 (0·84–2·26)	1·78 (1·08–2·95)*	1·77 (0·84–3·71)
≥56 to <64	1·41 (0·86–2·30)	2·41 (1·47–3·95)*	2·08 (1·05–4·14)*
≥64	2·02 (1·27–3·23)*	3·47 (2·07–5·81)*	1·60 (0·79–3·24)
Sex (male *vs* female)	1·43 (1·06–1·92)*	2·37 (1·71–3·29)*	1·39 (0·84–2·31)
Body-mass index (kg/m²)			
<18·5	2·57 (1·36–4·85)*	0·23 (0·03–1·75)	2·18 (0·63–7·50)
≥18·5 to <25 (reference)	1·00	1·00	1·00
≥25 to <30	0·90 (0·65–1·25)	0·89 (0·67–1·20)	1·92 (1·16–3·16)*
≥30	1·00 (0·66–1·51)	0·99 (0·69–1·44)	1·68 (0·92–3·08)
Geographical origin (France *vs* other)	1·35 (0·99–1·84)	1·46 (1·11–1·92)*	1·25 (0·80–1·96)
Infection route			
Injecting drug use (reference)	1·00	1·00	1·00
Transfusion	1·62 (1·04–2·53)*	1·36 (0·90–2·07)	1·10 (0·60–2·02)
Other or unknown	1·18 (0·77–1·81)	1·14 (0·79–1·64)	0·73 (0·41–1·33)
Excessive alcohol use†			
At entry in the cohort (yes *vs* no)	1·32 (0·67–2·60)	0·78 (0·39–1·53)	1·01 (0·31–3·37)
Past (yes *vs* no)	1·27 (0·91–1·78)	1·29 (0·95–1·75)	0·83 (0·53–1·29)
Time since HCV diagnosis (years)			
<7 (reference)	1·00	1·00	1·00
≥7 to <15	0·66 (0·43–1·02)	1·08 (0·72–1·64)	1·37 (0·70–2·69)
≥15 to <21	0·82 (0·54–1·25)	1·06 (0·71–1·59)	1·01 (0·49–2·05)
≥21	0·71 (0·46–1·10)	1·06 (0·70–1·60)	1·24 (0·62–2·48)
HCV treatment-naive (yes *vs* no)	0·85 (0·61–1·18)	0·83 (0·60–1·15)	1·32 (0·80–2·18)
HCV genotype			
1 (reference)	1·00	1·00	1·00
2	1·14 (0·64–2·00)	1·07 (0·58–1·99)	1·34 (0·60–2·97)
3	1·46 (0·97–2·20)	2·27 (1·63–3·16)*	1·68 (1·01–2·79)*
4	1·13 (0·71–1·80)	0·70 (0·43–1·15)	0·58 (0·28–1·21)
5, 6, or 7	1·18 (0·51–2·76)	1·93 (1·02–3·64)*	1·36 (0·43–4·34)
Fibrosis scoring			
F0, F1, or F2 (reference)	1·00	1·00	1·00
F3	1·45 (0·79–2·67)	5·03 (2·29–11·0)*	1·41 (0·32–6·24)
F4	3·69 (2·32–5·87)*	15·3 (7·55–30·9)*	9·01 (3·30–24·6)*
Diabetes (yes *vs* no)	1·23 (0·86–1·76)	1·05 (0·76–1·43)	1·23 (0·79–1·90)
Hypertension (yes *vs* no))	1·51 (1·10–2·08)*	1·44 (1·09–1·91)*	1·60 (0·99–2·59)
Anaemia (yes *vs* no)‡	2·45 (1·69–3·55)*	1·28 (0·89–1·84)	2·10 (1·22–3·62)*
Albumin (<30 g/L *vs* ≥30 g/L)	2·03 (0·87–4·74)	2·49 (1·23–5·03)*	1·87 (0·73–4·81)
Prothrombin time (≤70% *vs* >70%)	1·71 (1·07–2·71)*	1·44 (0·97–2·14)	1·72 (1·01–2·94)*
Platelet count (< 10^5 per µL *vs* ≥10^5 per µL)	1·50 (0·97–2·33)	2·24 (1·66–3·01)*	6·05 (3·75–9·77)*
Alanine aminotransferase (>5 ULN *vs* ≤5 ULN)	0·54 (0·24–1·22)	0·79 (0·42–1·48)	0·53 (0·22–1·30)
Aspartate aminotransferase (>5 ULN *vs* ≤5 ULN)	1·31 (0·67–2·57)	0·78 (0·44–1·38)	0·95 (0·37–2·42)
α-fetoprotein (≥5·5 ng/mL *vs* <5·5 ng/mL)	1·03 (0·73–1·44)	2·09 (1·48–2·95)*	0·82 (0·51–1·34)

A time-dependent Cox model was used for the analysis. Dummy variables were used for missing covariate values. The baseline hazard was modelled as a smooth function of time since first patient's inclusion visit. HCV=hepatitis C virus. ULN=per limit of normal. *Significant adjusted analysis associations at the p<0·05 level. †Defined as at least 15 alcoholic drinks (150 g) per week for a woman or 22 alcoholic drinks (220 g) per week for a man, or at least six consecutive alcoholic drinks (60 g) on at least one occasion per week. ‡Defined as haemoglobin <12 g/dL in women and <13 g/dL in men.

Table 3: **Factors associated with all-cause mortality, hepatocellular carcinoma, and decompensated cirrhosis in all patients analysed**

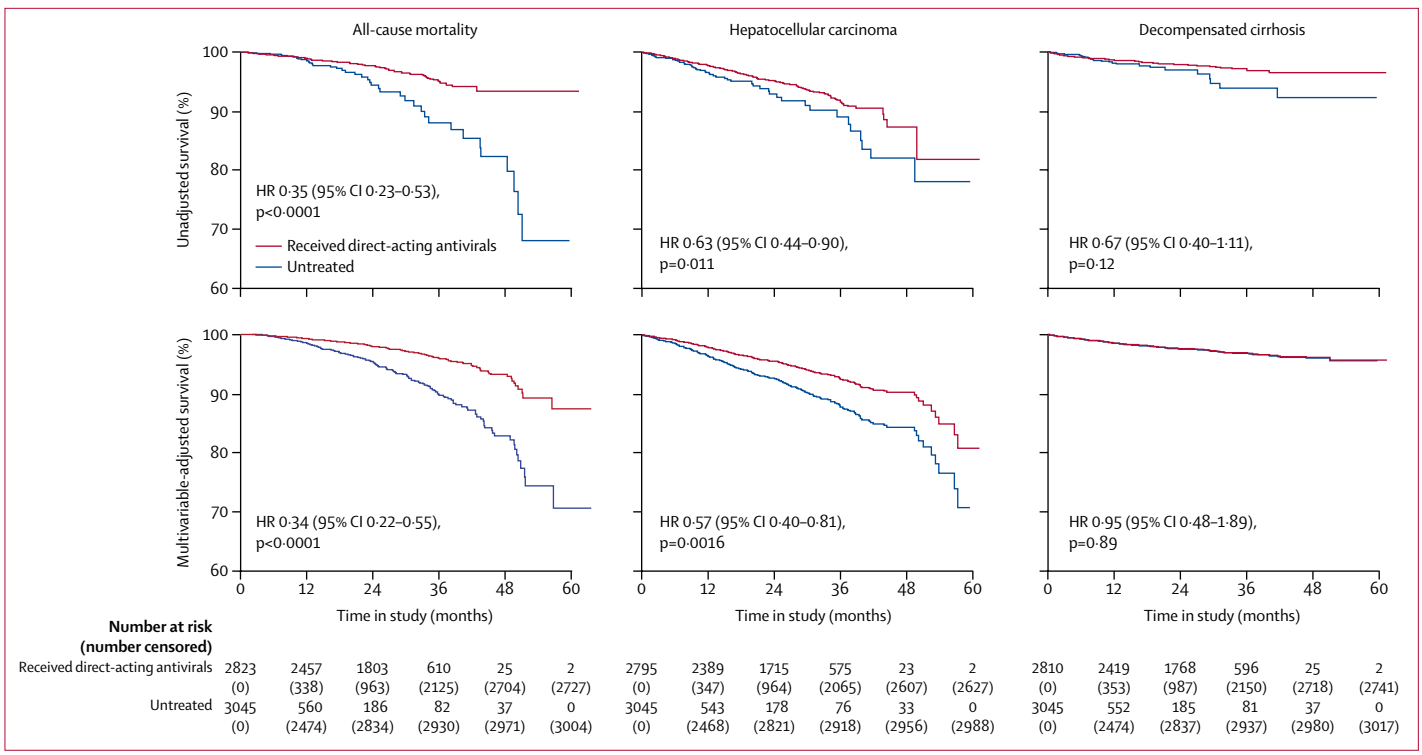

Figure 3: **Global survival, survival free from hepatocellular carcinoma, and survival free from decompensated cirrhosis, according to exposure to direct-acting antivirals in patients with cirrhosis**
Upper panel shows unadjusted survival curves. Lower panel shows multivariable-adjusted survival curves estimated with a time-dependent Cox proportional hazards model. HR=hazard ratio.

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See Online for appendix

virological response was 94% (5615 of 5956 patients who had known status and sufficient follow-up). In the adjusted multivariable analysis, compared with untreated patients, achieving a sustained virological response in patients who received direct-acting antivirals was associated with a decrease in all-cause mortality, liver-related mortality, non-liver-related mortality, and hepatocellular carcinoma, and with a non-significant decrease in decompensated cirrhosis, whereas not achieving a sustained virological response was associated with a significant increase in hepatocellular carcinoma (adjusted HR 2·23, 95% CI 1·37–3·64; p=0·0012; appendix). The median time between assessment of a sustained virological response and diagnosis of hepatocellular carcinoma was 14·0 months (IQR 7·4–21·1) in patients without a sustained virological response and 12·1 months (5·9–20·1) in those with a sustained virological response (p=0·29). No evidence was found of increased risk for hepatocellular carcinoma during the on-treatment period (adjusted HR 0·74, 95% CI 0·49–1·13; p=0·17).

In adjusted multivariable analyses in 3045 patients with baseline cirrhosis, exposure to direct-acting antivirals was strongly associated with a decrease in all-cause mortality (HR 0·34, 95% CI 0·22–0·55; p<0·0001), liver-related mortality (0·28, 0·15–0·54; p=0·0001), non-liver-related mortality (0·40, 0·19–0·83; p=0·015), and hepatocellular carcinoma (0·57, 0·40–0·81; p=0·0016; table 2; figure 3). Predictors of clinical events in patients with cirrhosis were similar to those identified in the entire cohort (appendix). A sustained virological response was achieved by 2329 (83%) of 2823 patients with cirrhosis who initiated direct-acting antivirals, was not achieved by 195 (7%) patients, and was unknown in 179 (6%) patients; 120 (4%) patients were still on-treatment. Thus, the proportion of patients with cirrhosis achieving a sustained virological response was 92% (2329 of 2524 patients who had known status and sufficient follow-up). Multivariable analyses confirmed the association between achieving a sustained virological response and a decrease in all-cause mortality, liver-related mortality, non-liver-related mortality, and hepatocellular carcinoma. The association was also confirmed between not achieving a sustained virological response and increased risk for hepatocellular carcinoma (appendix).

We did not find any association between exposure to direct-acting antivirals and mortality and clinical outcomes in the subset of patients without cirrhosis or with an unknown fibrosis score at entry (table 2). A sustained virological response was achieved by 3286 (73%) of 4521 patients who initiated direct-acting antivirals, was not achieved by 146 (3%), and was unknown in 530 (12%); 559 (12%) patients were still on-treatment. Thus, the proportion of patients without cirrhosis or with an unknown fibrosis score who achieved a sustained virological response was 96% (3286 of 3432 patients who had known status and sufficient follow-up).

Detailed characteristics of hepatocellular carcinoma were obtained for 249 (97%) of 258 patients with incident hepatocellular carcinoma. No difference was found between patients treated with direct-acting antivirals and untreated patients in the delay between the last normal imaging test and diagnosis, macroscopic pattern, number of tumours at diagnosis, total nodule size, largest nodule size, or serum α-fetoprotein (appendix).

Discussion

The findings of this large French cohort study show that direct-acting antiviral treatment is associated with reduced risk for mortality and hepatocellular carcinoma, after adjustment for potential confounding factors. Similar associations were identified in the subgroup of patients with cirrhosis. These inverse associations persisted in the subgroup of patients who achieved a sustained virological response, whereas those who did not achieve a sustained virological response were at higher risk for hepatocellular carcinoma. No signs were seen of increased risk for hepatocellular carcinoma during direct-acting antiviral treatment.

Overall, our results are similar to those reported in the ERCHIVES retrospective cohort.[14] In that study, a significant (57%, 95% CI 43–67) decrease in all-cause mortality was noted in patients receiving direct-acting antivirals compared with propensity-score-matched untreated patients. Moreover, results showed that age, cirrhosis, comorbidities (diabetes and chronic kidney disease), and anaemia were positively correlated with mortality. In our study, we reported a strong independent relation between all-cause mortality and cirrhosis, markers of liver failure, hypertension, and anaemia. Our results also confirm those of studies in which a lower risk of death was noted in patients treated with direct-acting antivirals who achieved a sustained virological response, compared with those who did not achieve a sustained virological response.[10] The incidence of hepatocellular carcinoma in patients with a sustained virological response after treatment with direct-acting antivirals in our study (appendix) overlapped with the incidence reported in another study (1·15 [95% CI 0·93–1·41] per 100 person-years *vs* 0·90 [0·77–1·03] per 100 person-years),[8] whereas incidence in patients without a sustained virological response was significantly higher in our study compared with this other study (7·19 [95% CI 5·16–9·76] per 100 person-years *vs* 3·45 [2·73–4·18] per 100 person-years). This difference could be because patients at highest risk for hepatic morbidity and mortality (eg, those with a history of excessive alcohol use) received direct-acting antivirals in our study.

A striking finding in our study was the lower risk for non-liver-related mortality in patients treated with direct-acting antivirals compared with untreated patients. Although a decrease in long-term non-liver-related mortality has been reported in patients with sustained virological response compared with those without a sustained virological response after interferon-based therapy,[28] reverse causality could be another possibility if patients with the most severe liver disease and the highest risk for death from any cause had a lower probability of starting direct-acting antiviral treatment. However, patients with decompensated cirrhosis or a history of hepatocellular carcinoma were excluded at baseline. We adjusted for many markers of liver insufficiency and comorbidities in our multivariable analyses. Finally, our results were similar when data from the first 12 months of follow-up were excluded. These elements seem to exclude reverse causality.

Our study has several limitations. First, the assessment of fibrosis and cirrhosis was based on patients' records at entry in the cohort, ascertained by different methods, and not updated during follow-up or when patients started direct-acting antiviral treatment. We validated the predictive value of platelet count and prothrombin time for diagnosis of cirrhosis, using other methods for the assessment of fibrosis. The median time between assessment of fibrosis and end of follow-up did not differ between untreated and treated patients. Fibrosis probably worsened in some patients, thus accounting for the development of liver-related complications in patients classified as without cirrhosis at entry in the cohort. However, any difference in the progression of fibrosis between patients untreated and treated with direct-acting antivirals during follow-up would be directly attributable to the effect of treatment on fibrosis. Thus, lack of assessment of fibrosis during follow-up should not be regarded as a bias but rather a plausible explanation for the inverse relation between treatment and risk for liver-related outcomes. Moreover, results in the subgroup of patients with baseline cirrhosis, which should be less biased by the misclassification of fibrosis, were consistent.

A second limitation of our study is that the duration of follow-up was short, making assessment of long-term outcomes associated with direct-acting antivirals impossible. Nevertheless, an inverse relation was noted between treatment with direct-acting antivirals and liver-related mortality or hepatocellular carcinoma in patients with cirrhosis over this short-term follow-up period, and a longer duration of follow-up would probably not change these findings.

Third, because of the observational nature of our study, some patients might have undergone less regular screening for hepatocellular carcinoma than recommended, resulting in potentially missed diagnoses. However, the average number of follow-up visits and ultrasound examinations (weighted by person-years of follow-up) were higher in patients during treatment and the year after treatment than in untreated patients or before treatment (data available on request). Therefore, any screening bias would result in a decrease in detection of hepatocellular carcinoma in patients not treated with direct-acting antivirals, compared with treated patients, and would not affect our conclusions.

A fourth limitation is that no association was seen between direct-acting antivirals and risk for decompensated cirrhosis. However, the analysis according to sustained virological response status (appendix) shows a non-significant inverse association in patients with cirrhosis at baseline (patients treated with direct-acting antivirals who achieved a sustained virological response *vs* untreated patients, HR 0·51, 95% CI 0·23–1·14), and our study probably does not have statistical power for this outcome.

Finally, although many multivariable analyses were done, we cannot exclude either a residual risk of bias from confounding factors associated with unmeasured prognostic factors or another complex time-dependent selection bias. We used different statistical methods to account for these different sources of bias, with similar results.

Because of the observational design of our study, we cannot formally conclude that inverse associations between direct-acting antiviral treatment and mortality or incidence of hepatocellular carcinoma reflect cause and effect relations. However, we can postulate about plausible mechanisms. Direct-acting antivirals induce a sustained virological response, reducing liver damage and inflammation. This effect causes liver regeneration, decreasing risk for progression to liver-related complications or hepatocellular carcinoma. Our results showing strikingly different risks for these liver-related events in patients with and without a sustained virological response support these mechanisms. Researchers have also suggested that not achieving a sustained virological response could be a sign of hepatocellular carcinoma.[29,30] However, the median time between assessment of sustained virological response and diagnosis of hepatocellular carcinoma did not differ between patients with and without a sustained virological response. This finding does not support the presence of pre-existing hepatocellular carcinoma in patients without a sustained virological response.

In summary, the findings of this large prospective cohort study showed a significant decrease in risk for all-cause mortality and hepatocellular carcinoma associated with direct-acting antiviral treatment. Our results also suggest that direct-acting antivirals do not adversely affect the development of hepatocellular carcinoma. The long-term effects of direct-acting antivirals on liver decompensation must still be clarified.

Contributors

FC, CD, HF, MS, and SP contributed to the study idea and design. HF, CD, CH, VdL, DL, J-PB, FZ, TA, PaM, DT, VL, AT, FH, DS, DG, OC, PhM, SM, LA, GR, JG, AA, PC, NG, VL-R, LDA, XC, CG, AM, IR, MG-S, IP, FR, MB, and SP contributed to data acquisition. FC, CD, GH, MB, and SP contributed to data analysis and data interpretation. FC, HF, and SP wrote the report, and all authors reviewed the manuscript for important intellectual content. FC and GH contributed to the statistical analysis. FC, HF, CD, MS, AD, MB, and SP provided administrative, technical, or material support. FC HF, CD, MS, and SP supervised the study.

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Declaration of interests

FC reports grants from INSERM-ANRS, during the conduct of the study; and personal fees from Imaxio, outside the submitted work. HF reports personal fees and invitations for medical meetings from Gilead, AbbVie, Bristol-Myers Squibb, MSD, and Janssen, outside the submitted work. CH reports personal fees from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and MSD, outside the submitted work. VdL reports personal fees from AbbVie, Gilead, Merck, and Bristol-Myers Squibb, outside the submitted work. J-PB reports personal fees from AbbVie, Gilead, MSD, Bristol-Myers Squibb, and Janssen, outside the submitted work. FZ reports personal fees from AbbVie and Gilead, during the conduct of the study. TA reports grants from INSERM-ANRS, outside the submitted work; and personal fees from AbbVie, Gilead, Janssen, and MSD, outside the submitted work. PaM reports grants from AbbVie, Genfit, Gilead, Janssen, and MSD, outside the submitted work. VL reports grants, personal fees, and non-financial support from AbbVie, Bristol-Myers Squibb, and Gilead, outside the submitted work; personal fees and non-financial support from MSD, outside the submitted work; and personal fees from Echosens, outside the submitted work. FH reports an invitation for medical meetings from Gilead and AbbVie, outside the submitted work. DS reports consulting fees from Astellas, Bristol-Myers Squibb, Gilead, LFB, MSD, Novartis, Roche, Biotest, AbbVie, and Intercept, outside the submitted work. DG reports personal fees and non-financial support from Gilead, MSD, and AbbVie; during the conduct of the study; and grants, personal fees, and non-financial support from Janssen, during the conduct of the study. OC reports an invitationfor scientific meetings from AbbVie, outside the submitted work. PhM reports personal fees from MSD, AbbVie, and Gilead, outside the submitted work. LA reports grants and personal fees from MSD and AbbVie, outside the submitted work; personal fees from Gilead, outside the submitted work; and grants from Janssen and Bristol-Myers Squibb, outside the submitted work. JG reports personal fees from Gilead, MSD, and AbbVie, during the conduct of the study; and personal fees from Intercept, outside the submitted work. AA reports grants and personal fees from Gilead, AbbVie, and MSD, outside the submitted work. NG reports grants from Echosens, outside the submitted work; personal fees and non-financial support from Gilead, AbbVie, and Bayer, outside the submitted work; and non-financial support from MSD, outside the submitted work. VL-R reports grants from INSERM-ANRS, during the conduct of the study; and personal fees from AbbVie, Gilead, MSD, and Bristol-Myers Squibb, outside the submitted work. XC reports personal fees from AbbVie, Gilead, and MSD, outside the submitted work. AM reports personal fees and non-financial support from Gilead and Merck, outside the submitted work; and non-financial support from AbbVie, outside the submitted work. FR reports personal fees from Gilead and Abbott, outside the submitted work; and grants and personal fees from MSD, outside the submitted work. MB reports grants and personal fees from AbbVie and Gilead, outside the submitted work; and personal fees from MSD, Janssen, Boehringher Ingelheim, Intercept, and Bristol-Myers Squibb, outside the submitted work. SP received consulting and lecturing fees from Bristol-Myers Squibb, Janssen, Gilead, Roche, Boehringer Ingelheim, MSD, and AbbVie, outside the submitted work; and grants from Bristol-Myers Squibb, Gilead, and MSD, outside the submitted work. CD, MS, AD, DL, GH, DT, AT, SM, GR, PC, LDA, CG, IR, MG-S, and IP declare no competing interests.

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