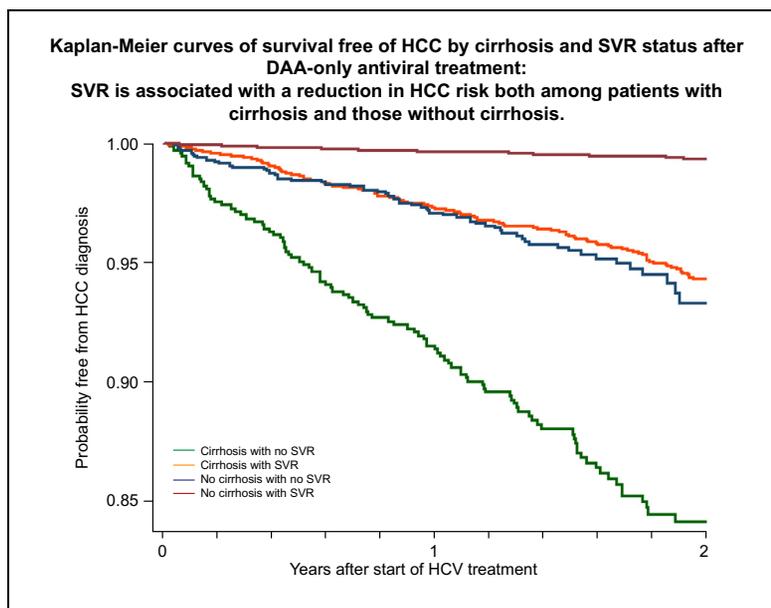


# HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma

## Graphical abstract



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## Lay summary

It was unclear whether direct-acting antiviral treatment-induced sustained virologic response reduces the risk of liver cancer in patients with HCV infection. We demonstrated that eradication of HCV infection with direct-acting antiviral agents reduces the risk of liver cancer by 71%.

## Highlights

- DAA-induced SVR is associated with a 71% reduction in HCC risk.
- SVR is associated with a similar reduction in HCC risk no matter what regimen is used to achieve it.
- Treatment with DAAs is not associated with increased HCC risk compared with interferon.



# HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma

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**Background & Aims:** It is unclear whether direct-acting antiviral (DAA) treatment-induced sustained virologic response (SVR) reduces the risk of hepatocellular carcinoma (HCC) in patients with HCV infection. Therefore, in the current study, our aim was to determine the impact of DAA-induced SVR on HCC risk.

**Methods:** We identified 62,354 patients who initiated antiviral treatment in the Veterans Affairs (VA) national healthcare system from 1 January 1999 to 31 December 2015, including 35,871 (58%) interferon (IFN)-only regimens, 4,535 (7.2%) DAA + IFN regimens, and 21,948 (35%) DAA-only regimens. We retrospectively followed patients until 15 June 2017 to identify incident cases of HCC. We used Cox proportional hazards regression to determine the association between SVR and HCC risk or between type of antiviral regimen (DAA-only vs. DAA + IFN vs. IFN-only) and HCC risk.

**Results:** We identified 3,271 incident cases of HCC diagnosed at least 180 days after initiation of antiviral treatment during a mean follow-up of 6.1 years. The incidence of HCC was highest in patients with cirrhosis and treatment failure (3.25 per 100 patient-years), followed by cirrhosis and SVR (1.97), no cirrhosis and treatment failure (0.87), and no cirrhosis and SVR (0.24). SVR was associated with a significantly decreased risk of HCC in multivariable models irrespective of whether the antiviral treatment was DAA-only (adjusted hazard ratio [AHR] 0.29; 95% CI 0.23–0.37), DAA + IFN (AHR 0.48; 95% CI 0.32–0.73) or IFN-only (AHR 0.32; 95% CI 0.28–0.37). Receipt of a DAA-only or DAA + IFN regimen was not associated with increased HCC risk compared with receipt of an IFN-only regimen.

**Conclusions:** DAA-induced SVR is associated with a 71% reduction in HCC risk. Treatment with DAAs is not associated with increased HCC risk compared with treatment with IFN.

**Lay summary:** It was unclear whether direct-acting antiviral treatment-induced sustained virologic response reduces the risk of liver cancer in patients with HCV infection. We demonstrated that eradication of HCV infection with direct-acting antiviral agents reduces the risk of liver cancer by 71%.

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## Introduction

Eradication of HCV might be expected to reduce the risk of hepatocellular carcinoma (HCC) by preventing the future development of cirrhosis or by reversing early cirrhosis, a major risk factor for HCC. In addition, HCV might itself promote carcinogenesis,<sup>1</sup> such that its eradication directly decreases HCC risk. Indeed, a meta-analysis of 18 studies of interferon (IFN)-based antiviral treatments for HCV suggested that sustained virologic response (SVR) was associated with reduced risk of HCC (relative risk 0.24; 95% CI 0.18–0.31).<sup>2</sup> IFN-based treatments have now been replaced by direct-acting antiviral agents (DAAs). It is unclear whether the impact of SVR on HCC risk is different depending on whether SVR is achieved with either IFN-based regimens or DAAs. Surprisingly, recent studies suggested little or no impact of DAA-based antiviral treatment on HCC risk and even reported that DAAs might increase the risk of HCC recurrence.<sup>3–8</sup> However, these studies were grossly underpowered, had limited follow-up time, mostly studied HCC recurrence rather than incidence, and did not compare those who achieved SVR because of DAAs to those who did not with respect to HCC risk.

In the current study, our aim was to determine the extent to which eradication of HCV with DAA-based treatments was associated with reduction in the risk of HCC, and whether this association was different for SVRs achieved by DAA vs. IFN-based regimens. We also aimed to determine whether receipt of DAA-based treatment compared with IFN-based treatment was associated with HCC risk.

## Methods

### Data source

The Veterans Affairs (VA) healthcare system is the largest integrated healthcare provider of HCV antiviral treatment in the USA. In 2014, 5,857,690 veterans received care in 154 medical centres and 875 ambulatory care and community-based outpatient clinics that comprise the VA healthcare system nationally,<sup>9</sup> including 174,302 patients with known HCV infection (*i.e.* positive serum HCV viral load test).<sup>10</sup>

The VA uses a single, nationwide, comprehensive electronic healthcare information network (known as the Veterans Information Systems and Technology Architecture or VistA), which comprises nearly 180 applications of clinical, financial, administrative, and infrastructure needs integrated into a single, common database of all veterans' health information. We derived electronic data on all patients who initiated antiviral treatment

Keywords: Liver cancer; HCV treatment; Interferon; DAA; Prediction models.  
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in the VA system using the VA Corporate Data Warehouse (CDW), a national, continually updated repository of data from VistA developed specifically to facilitate research.<sup>11</sup> Data extracted included all patient pharmacy prescriptions, demographics, inpatient and outpatient visits, problem lists, procedures, vital signs, diagnostic tests, and laboratory tests.

The study was approved by the Institutional Review Board of the Veterans Affairs Puget Sound Healthcare System.

**Study population**

We identified all HCV antiviral regimens (N = 105,310 regimens in 78,890 patients) initiated in the VA during 17 calendar years from 1 January 1999 to 31 December 2015. We excluded 1,140 patients who had had a diagnosis of HCC (ICD-9 code 155.0 or ICD-10 code C22.0; the VA switched to ICD-10 codes on 1 October 2015) recorded before their first HCV antiviral treatment; 1,100 who died within 180 days from the start date of antiviral treatment or had fewer than 180 days of available follow-up; and 277 patients who were found to have HCC within 180 days from the start date of their antiviral treatment (including 119 who had achieved SVR and 158 who had not), because these cases were unlikely to be incident (new) cases. We excluded 8,855 patients with missing SVR data (SVR results were extracted in 2016 and had not been performed yet in some patients treated in late 2015) and 5,164 with missing genotype data, leaving 62,354 patients in the current analysis, including 3,271 who developed HCC more than 180 days after the treatment start date. These excluded patients were similar to those included in the analysis in terms of their baseline characteristics (Table S1).

**Antiviral treatment regimens**

The antiviral treatment regimens (Table 1) were divided into the following groups:

- a. 'IFN-only' regimens: included pegylated IFN (PegIFN) and regular IFN with or without ribavirin, but without any DAAs.
- b. 'DAA + IFN' regimens: included any DAA (NS3/4, NS5A, or NS5B inhibitors) with concomitant PegIFN (±ribavirin).
- c. 'DAA-ONLY' regimens: included only IFN-free, DAA regimens (±ribavirin).

**Table 1. Types of HCV antiviral treatment regimen included in our study of VA patients from 1999 to 2015.**

Regimen details <sup>a</sup>	First regimen n (%)	All regimens n (%)
IFN only		
IFN	2,629 (4.2)	4,256 (5.1)
PegIFN	33,242 (53.3)	41,786 (50.1)
DAA + IFN		
Boceprevir + PegIFN	3,090 (5.0)	4,815 (5.8)
Telaprevir + PegIFN	479 (0.8)	967 (1.2)
Simeprevir + PegIFN	14 (0.0)	23 (0.0)
Sofosbuvir + PegIFN	952 (1.5)	1,664 (2.0)
DAA only		
Sofosbuvir (±daclatasvir)	2,786 (4.5)	3,727 (4.5)
Sofosbuvir + simeprevir	1,993 (3.2)	3,219 (3.9)
Ledipasvir/sofosbuvir	12,763 (20.5)	17,369 (20.8)
Paritaprevir/ritonavir/ombitasvir/dasabuvir	4,406 (7.1)	5,595 (6.7)

IFN, interferon; DAA, direct-acting antiviral.

<sup>a</sup> Regimens with or without ribavirin were combined.

All VA pharmacy data are included in the CDW; dispensed drugs (rather than just prescribed drugs) were used to define antiviral treatment regimens, as previously published.<sup>12–19</sup>

**Baseline patient characteristics**

For each HCV treatment regimen, we collected baseline data, including age, sex, body mass index (BMI), HCV genotype, HCV viral load, and receipt of prior antiviral treatment. We extracted relevant laboratory tests before treatment and recorded the value of each test closest to the treatment start date within the preceding six months (except serum alpha-fetoprotein [AFP], which was recorded within one year prior to treatment). We contemplated using laboratory test measurements performed after the end of treatment but decided against doing so because many laboratory tests, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), haemoglobin, and creatinine, can change acutely because of treatment and likely reflect underlying fibrosis or HCC risk less accurately compared with their levels before treatment. We defined HBV co-infection based on a positive HBV surface antigen test or viral load. We also determined the presence of cirrhosis, manifestations of decompensated cirrhosis (*i.e.* ascites, encephalopathy, gastro-oesophageal varices, and hepatorenal syndrome), type 2 diabetes mellitus, alcohol-use disorders, substance-use disorders, HIV infection, and liver transplantation based on appropriate ICD-9 or ICD-10 codes recorded at least twice before treatment initiation in any inpatient or outpatient encounter (these codes are shown in Table S2). These ICD-based definitions of HCC<sup>16,20–27</sup> as well as the definitions of cirrhosis and other co-morbidities<sup>23,25,28–32</sup> have been widely used and validated in studies using VA medical records.

**SVR**

We defined a sustained virologic response (SVR) as a serum HCV RNA viral load test below the lower limit of detection performed at least 12 weeks after the end of HCV treatment.<sup>33</sup>

**Incident HCC**

We identified incident cases of HCC diagnosed for the first time at least 180 days after the initiation of antiviral treatment based on ICD-9 code 155.0 or ICD-10 code C22.0 documented at least twice. The ICD-9 code-based definition of HCC using VA records has been shown to have a positive predictive value of 84–94% compared with chart extraction.<sup>21,31,34</sup>

**Statistical analysis**

*Association between SVR and HCC risk*

We used Cox proportional hazards regression with or without adjusting for potential confounders to compare the risk of developing HCC in patients who achieved SVR with those who did not. We calculated the follow-up time starting from 180 days after the initiation of antiviral treatment because cancers diagnosed within 180 days of the treatment start date could not have been prevented by antiviral treatment and were likely present but undiagnosed at the time of antiviral treatment initiation (*i.e.* not truly 'incident' cancers). Follow-up for HCC incidence extended until 15 June 2017, so that even patients treated during late 2015 (*i.e.* the most recent in our cohort) would have substantial follow-up. Patients without incident HCC were censored at either the time of death or last follow-up in the VA.

We considered using the date that treatment ended or the date at which SVR was ascertained as the starting time for the time-to-event analysis. However, we decided against this because of the long and variable duration of the treatment and the interval from treatment end date to ascertainment of SVR, both of which are related to SVR and, therefore, would have introduced significant bias.

In our primary analyses, we analysed the association of SVR with HCC risk following each patient's first antiviral treatment regimen. A significant proportion (42.7%) of patients received more than one antiviral treatment during the study period. This posed an analytical problem because patients who failed the first regimen might have achieved SVR during a subsequent treatment. This would tend to slightly underestimate the magnitude of the association between 'no SVR' and HCC risk, if one truly exists, by classifying some patients in the 'no SVR' group who then later achieved SVR. We performed two secondary analyses to further address this potential problem. First, we performed analyses using the first treatment for patients who never achieved SVR and the last treatment for patients who ever achieved SVR (*i.e.* this included all patients who ever achieved SVR in the SVR category). This tended to slightly overestimate the magnitude of the association between 'no SVR' and HCC risk because almost all patients in the 'no SVR' group who were retreated and finally achieved SVR would not have been expected to develop HCC, otherwise they would not have been retreated. Second, we analysed all treatments that each patient received clustered by patient. The intragroup correlation induced by clustering was accounted for by using robust variance estimation.

We also performed secondary analyses limited to only two years of follow-up because most SVRs were achieved only during the DAA era and had short follow-up, whereas most failures of SVR occurred during the IFN era and had much longer follow-up.

To determine whether SVR was independently associated with HCC risk, our multivariable proportional hazards models were adjusted for the following characteristics that might be associated with both SVR and HCC risk, ascertained at the time of treatment initiation: cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, BMI, HCV genotype, HCV viral load, HIV co-infection, HBV co-infection, type 2 diabetes mellitus, alcohol-use disorders, substance-use disorders, liver transplantation, platelet count, serum bilirubin, serum creatinine, serum albumin, serum AST/ALT ratio, blood international normalised ratio (INR), and blood haemoglobin levels. Continuous variables were categorised and modelled as dummy categorical variables. Survival analyses were stratified by the VA facility at which the antiviral treatment was administered.

#### *Association between type of antiviral treatment regimen and HCC risk*

We performed Cox proportional hazards regression analyses as described above except that the exposure of interest was the type of antiviral regimen (DAA-only vs. DAA + IFN vs. IFN-only) rather than the SVR. The outcome was the same as in the analyses above (incident HCC occurring at least 180 days after initiation of antiviral treatment) and the same potential confounders were adjusted for in the multivariable models. We performed analyses limited to antiviral regimens initiated in years 2009–2015 to capture only the most recent IFN-only regimens (*i.e.* from 2009 to 2011) before the introduction of the first protease inhibitors in 2011, given that HCC incidence appears to be increasing with time [25].

For further details regarding the materials used, please refer to the [CTAT table](#) and [supplementary information](#).

## **Results**

### **Characteristics of study population**

Among the 62,354 patients who initiated their first antiviral regimen from 1 January 1999 to 31 December 2015, 34,660 (55.6%) achieved SVR. The antiviral treatments included 35,871 (58%) IFN-only regimens, 4,535 (7.3%) DAA + IFN regimens, and 21,948 (35%) DAA-only regimens. The distribution of different DAA regimens is shown ([Table 1](#)).

SVR rates were highest in the DAA-only regimens (90.7%), followed by the DAA + IFN regimens (60.9%), and lowest in the IFN-only regimens (33.4%). Patients were mostly male (96.6%) and the majority were White (55.6%), although there was a significant representation of other racial/ethnic groups. Mean age was 55.8 years and 16.8% had cirrhosis, 4.7% decompensated cirrhosis, and 1.1% had undergone liver transplantation. Genotype 1 HCV infection predominated (77.4%) followed by genotypes 2 (13.5%), 3 (8.3%), and 4 (0.8%).

Among those on an 'IFN-only' regimen, patients who achieved SVR were more likely to have genotype 2 or 3 HCV and less likely to have diabetes, cirrhosis, or markers of advanced fibrosis and/or cirrhosis (*e.g.* low platelet count or low albumin level) compared with patients who did not achieve SVR ([Table 2](#)). Among those on a DAA-only regimen, patients who achieved SVR were more likely to have genotype 1 infection and also less likely to have diabetes, cirrhosis, or markers of advanced fibrosis and/or cirrhosis compared with patients who did not achieve SVR.

Compared with patients who received IFN-only regimens, those patients who received DAA-only or DAA + IFN regimens were older, more likely to be Black, less likely to have genotype 2 or 3 HCV, and more likely to have advanced fibrosis or cirrhosis ([Table 2](#)). Also, compared with patients who received IFN-only regimens, those patients who received DAA-only or DAA + IFN regimens had lower mean serum platelet count and albumin level.

### **Association between SVR and HCC risk**

Out of the 62,354 patients in our study, we identified 3,271 incident cases of HCC diagnosed more than 180 days after initiation of the first antiviral regimen during a mean follow-up of 6.1 years. HCC incidence was lower in the patients who achieved SVR (0.43 per 100 patient-years) than in treatment failures (1.14 per 100 patient-years) ([Table 3](#)).

Patients who achieved SVR had a lower incidence of HCC compared with those who did not achieve SVR among both patients with cirrhosis (1.97 vs. 3.25 per 100 patient-years) and those without (0.24 vs. 0.87 per 100 patient-years), also illustrated by the Kaplan-Meier curves ([Fig. 1](#)). The incidence of HCC was highest in patients with cirrhosis and treatment failure (3.25), followed by cirrhosis and SVR (1.97), and no cirrhosis and treatment failure (0.87), and was lowest in patients with no cirrhosis and SVR (0.24) ([Table 3](#) and [Fig. 1A](#)). The same pattern was observed among all patients ([Fig. 1A](#)), as well as among the subgroups treated with IFN-only ([Fig. 1B](#)), DAA + IFN ([Fig. 1C](#)) and DAA-only ([Fig. 1D](#)).

Among all patients, SVR was associated with a 61% reduction in the risk of HCC (adjusted hazard ratio [AHR] 0.39; 95% CI 0.35–0.43) in multivariable analyses adjusting for baseline con-

**Table 2. Baseline characteristics of patients with HCV who received their first antiviral treatment between 1999 and 2015 and who did or did not achieve a sustained virologic response.**

Characteristic	All patients (N = 62,354)	IFN-only		DAA + IFN		DAA-only	
		No SVR (n = 23,883)	SVR (n = 11,988)	No SVR (n = 1,772)	SVR (n = 2,763)	No SVR (n = 2,039)	SVR (n = 19,909)
Age, yr [mean (SD)]	55.8 (7.6)	52.4 (6.2)	52.4 (6.8)	57.7 (5.8)	57.3 (6.7)	60.7 (6.3)	61.0 (6.7)
BMI, kg/m <sup>2</sup> [mean (SD)]	28.2 (5.3)	28.4 (5.2)	28.2 (5.2)	28.7 (5.3)	28.3 (5.0)	28.6 (5.9)	27.9 (5.4)
Male (%)	96.6	97	95.7	95.5	96.4	98.3	96.6
Race/Ethnicity (%)							
White, non-Hispanic	55.6	52.2	67.5	50.3	60.8	52	52.7
Black, non-Hispanic	26.3	26.7	12.5	36.2	24.9	31.9	32.8
Hispanic	6.0	7.0	6.1	6.0	4.5	6.7	5.0
Other	1.6	1.6	1.7	1.4	1.4	1.8	1.6
Declined to answer/missing	10.5	12.6	12.2	6.0	8.4	7.6	7.9
Genotype (%)							
Genotype 1	77.4	80.2	51.2	99.2	96.6	73.6	85.7
Genotype 2	13.5	10.4	31.3	0.1	0.8	13.5	9.3
Genotype 3	8.3	8.5	16.6	0.6	2.2	12	4.2
Genotype 4	0.8	0.9	0.9	0.2	0.4	0.9	0.8
HCV RNA viral load >6 million IU/ml (%)	16.7	14.9	15.2	24.1	21.4	19.6	17.9
HIV co-infection	3.4	3.6	1.8	1.9	1.4	4.0	4.4
HBV co-infection	1.0	0.6	1.0	1.8	1.7	1.0	1.2
Cirrhosis (%)	16.8	13.5	7.8	27.9	20.4	36	22.6
Decompensated cirrhosis (%)	4.7	4.1	2.3	6.5	3.8	12.7	5.9
Liver transplantation (%)	1.1	1.1	0.9	0.1	0.3	0.9	1.5
Diabetes (%)	22	19.9	14.3	25.4	20.1	34.2	27.9
Alcohol-use disorder (%)	39.3	36.0	36.2	41.1	40.8	48	43.7
Substance-use disorder (%)	31.8	28.0	28.2	33.9	32.8	39.3	37.5
Laboratory results [mean (SD)]							
Alpha-fetoprotein, ng/ml	5.8 (4.1)	6.1 (4.2)	4.6 (3.2)	7.9 (4.8)	5.9 (4.0)	7.0 (4.6)	6.0 (4.2)
Haemoglobin, g/dl	14.9 (1.5)	15.0 (1.5)	15.2 (1.4)	14.9 (1.4)	15.0 (1.4)	14.3 (1.7)	14.5 (1.6)
Platelet count, k/ $\mu$ l	192.9 (71.3)	197.0 (71.9)	212.0 (68.6)	174.2 (64.4)	188.9 (63.4)	160.2 (74.6)	182.1 (70.1)
Creatinine, mg/dl	1.0 (0.6)	1.0 (0.7)	1.0 (0.4)	1.0 (0.8)	0.9 (0.3)	1.0 (0.5)	1.0 (0.5)
Bilirubin, g/dl	0.7 (0.5)	0.7 (0.5)	0.6 (0.5)	0.7 (0.4)	0.6 (0.4)	0.8 (0.7)	0.7 (0.5)
Albumin g/dl	4.0 (0.5)	4.0 (0.4)	4.1 (0.4)	3.9 (0.5)	4.0 (0.4)	3.7 (0.6)	3.9 (0.5)
INR	1.1 (1.0)	1.1 (0.9)	1.1 (1.0)	1.2 (1.3)	1.2 (1.1)	1.2 (1.0)	1.2 (0.9)
AST/ALT	0.9 (0.4)	0.9 (0.4)	0.8 (0.3)	1.0 (0.3)	0.8 (0.3)	1.0 (0.4)	1.0 (0.4)

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; INR, international normalised ratio; SVR, sustained virologic response.

**Table 3. Association between SVR and HCC risk among all patients and among subgroups defined by cirrhosis and antiviral regimen.<sup>a</sup>**

Regimen	SVR	No. of patients (%)	Patient-years	No. of patients who developed HCC (%)	HCC per 100 patient-years	Crude hazard ratio (95% CI)	Adjusted <sup>b</sup> hazard ratio (95% CI)
All regimens	No SVR	27,694 (44.4)	230,186	2,629 (9.5)	1.14	1	1
	SVR	34,660 (55.6)	147,988	642 (1.9)	0.43	0.36 (0.33–0.40)	0.39 (0.35–0.43)
All regimens + cirrhosis	No SVR	4,463 (42.6)	26,221	851 (19.1)	3.25	1	1
	SVR	6,005 (57.4)	16,511	326 (5.4)	1.97	0.57 (0.49–0.65)	0.50 (0.43–0.59)
All regimens, no cirrhosis	No SVR	23,231 (44.8)	203,965	1,778 (7.7)	0.87	1	1
	SVR	28,655 (55.2)	131,478	316 (1.1)	0.24	0.29 (0.26–0.33)	0.32 (0.28–0.37)
IFN-only regimens	No SVR	23,883 (66.6)	220,315	2,348 (9.8)	1.07	1	1
	SVR	11,988 (33.4)	107,725	303 (2.5)	0.28	0.25 (0.22–0.29)	0.32 (0.28–0.37)
DAA + IFN regimens	No SVR	1,772 (39.1)	6,690	116 (6.5)	1.73	1	1
	SVR	2,763 (60.9)	9,829	59 (2.1)	0.6	0.34 (0.24–0.46)	0.48 (0.32–0.73)
DAA-only regimens	No SVR	2,039 (9.3)	3,181	165 (8.1)	5.19	1	1
	SVR	19,909 (90.7)	30,434	280 (1.4)	0.92	0.18 (0.14–0.22)	0.29 (0.23–0.37)

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; INR, international normalised ratio; SVR, sustained virologic response.

<sup>a</sup> Intent-to-treat analysis using first treatment.

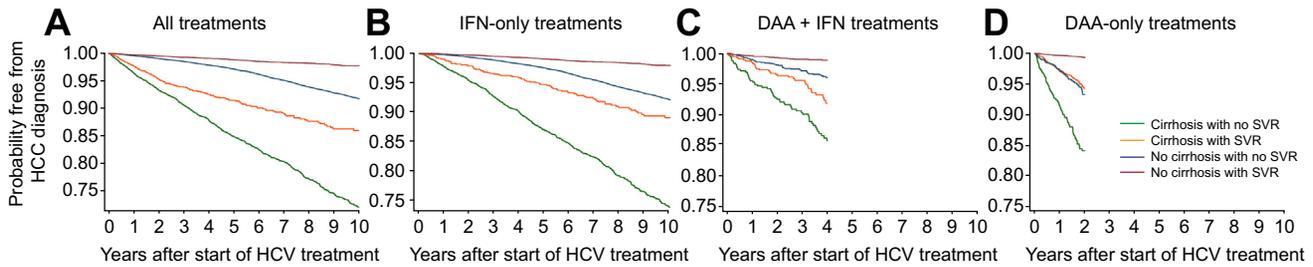
<sup>b</sup> Adjusted by Cox proportional hazards regression for cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HCV genotype, HCV viral load, HIV co-infection, HBV co-infection, type 2 diabetes mellitus, alcohol-use disorders, substance-use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, serum AST/ALT ratio, blood INR, and blood haemoglobin levels. The laboratory tests were categorised into quartiles and modelled as dummy categorical variables.

founders (Table 3). SVR was associated with a decrease in HCC risk among both patients with cirrhosis (AHR 0.50; 95% CI 0.43–0.59) and patients without cirrhosis (AHR 0.32; 95% CI 0.28–0.37).

SVR was associated with a similar and significantly decreased risk of HCC in multivariable models irrespective of

whether the antiviral treatment was IFN-only (AHR 0.32; 95% CI 0.28–0.37), DAA + IFN (AHR 0.48; 95% CI 0.32–0.73) or DAA-only (AHR 0.29; 95% CI 0.23–0.37) (Table 3).

In secondary analyses limited to only two years of follow-up, performed because mean follow-up was inevitably shorter in the DAA-only group (1.53 years) and DAA + IFN group (3.6



**Fig. 1.** Kaplan–Meier curves showing the development of hepatocellular carcinoma (HCC) after antiviral treatment for HCV, by cirrhosis and sustained virologic response (SVR) status. (A) All treatments. (B) Interferon (IFN)-only treatments. (C) Direct-acting antiviral (DAA) + IFN treatments. (D) DAA-only treatments.

years) than in the IFN-only group (9.1 years), SVR was still associated with a significantly reduced risk of HCC irrespective of whether the antiviral treatment was IFN-only (AHR 0.56; 95% CI 0.38–0.81), DAA + IFN (AHR 0.49; 95% CI 0.27–0.86), or DAA-only (AHR 0.28; 95% CI 0.22–0.35) (Table S3).

Also, in secondary analyses in which we looked at the regimen that achieved SVR or a clustered analysis of all antiviral regimens, instead of the first antiviral regimen, SVR was similarly associated with a reduction in HCC risk (Table S4).

#### Association between type of antiviral treatment regimen and HCC risk

Although HCC incidence was higher after DAA-only treatment (1.32 per 100 patient-years) than after DAA + IFN (1.06 per 100 patient-years) or IFN-only (0.81 per 100 patient-years) treatment, there was no significant association between treatment regimen and HCC risk after adjusting for important confounders (Table 4). This was because of the higher prevalence in the DAA-only group of risk factors for HCC, such as cirrhosis, advanced age, diabetes, low platelet count, and low serum albumin level. When analysing separately patients with or without cirrhosis during the period 2009–2015, there was little difference in HCC incidence by antiviral treatment group and no association between antiviral treatment group and HCC risk. Also, when limiting follow-up to two years, there was no association between antiviral treatment group and HCC risk (Table 4).

#### Discussion

Most patients with HCV in the USA will undergo DAA-based antiviral treatment in the next few years and the majority of them will achieve SVR. Our results suggest that DAA-induced SVR is associated with a 71% reduction in HCC risk (AHR 0.29; 95% CI 0.23–0.37) compared with treatment failure. The reduction in HCC risk associated with SVR was similar irrespective of whether SVR was achieved by DAA-only, DAA + IFN, or IFN-only regimens. This suggests that eradication of HCV reduces HCC risk independently of how it is achieved. In contrast to prior reports that suggested an increased HCC risk in patients treated with DAAs,<sup>3,7</sup> we found that receipt of DAA-only antiviral treatment was not associated with increased risk of HCC compared with receipt of IFN-only antiviral treatment.

It is still unclear whether DAA-induced SVR is associated with a reduction in HCC risk. It might seem reasonable to expect that HCV eradication would reduce HCC risk by preventing or reversing cirrhosis, or by eliminating any direct carcinogenic effect of HCV. However, recent studies have demonstrated little

or no impact of DAA-based antiviral treatment on HCC risk and even suggest that DAAs increase the risk of HCC recurrence.<sup>3–8</sup> A recent retrospective Spanish study reported an unexpectedly high rate of HCC recurrence (27.6% after a median follow-up of 5.7 months) following HCV antiviral treatment with DAAs in 58 patients with HCC who had achieved complete response before antiviral treatment,<sup>3</sup> raising concerns that DAAs somehow promote HCC recurrence. However, a French prospective cohort study found a similar risk of HCC recurrence when comparing 189 patients who received DAAs (24/189 or 12.7% with recurrence, incidence 0.73 per 100 patient-months) to 78 who did not receive DAAs (16/78 or 20.5% with recurrence, incidence 0.66/100 patient-months).<sup>4</sup> Finally, an Italian study reported that, after DAA therapy, 9 out of 285 patients with cirrhosis without prior HCC developed new HCC during a 24-week follow-up, whereas 17 out of 59 patients with prior HCC had recurrence; the authors concluded that ‘DAA-induced resolution of HCV infection does not seem to reduce the occurrence of HCC’.<sup>5</sup> However, these studies were underpowered, had limited follow-up time, studied mostly HCC recurrence rather than incidence, and did not compare those who achieved SVR resulting from DAAs with those who did not with respect to HCC risk.

In contrast to these studies, we found that DAA-induced SVR was associated with a 71% reduction in the risk of HCC and that an approximately similar reduction in HCC risk was associated with SVR induced by DAA-only (AHR 0.29; 95% CI 0.23–0.37), DAA + IFN (AHR 0.48; 95% CI 0.32–0.73) or IFN-only (AHR 0.32; 95% CI 0.28–0.37) regimens. This suggests that eradication of HCV reduces the risk of HCC irrespective of the antiviral regimen used to achieve it. However, our study was designed to address the impact of SVR on HCC incidence, not HCC recurrence. Hence, patients with a history of HCC before antiviral treatment were excluded and our study offers no insight into the impact of antiviral treatment on HCC recurrence.

We observed a lower relative reduction in HCC risk associated with SVR in patients with cirrhosis (AHR 0.50; 95% CI 0.43–0.59) than in patients without cirrhosis (AHR 0.32; 95% CI 0.28–0.37). However, the absolute reduction in HCC risk was greater in patients with cirrhosis (from 3.25 to 1.97 per 100 patient-years) than in patients without (from 0.73 to 0.18 per 100 patient-years), as would be expected given the higher baseline HCC risk of patients with cirrhosis. It is generally believed that HCC risk in patients with HCV increases dramatically once they develop cirrhosis, but a lower HCC risk is still present in pre-cirrhotic liver disease, especially in advanced fibrosis. The risk of HCC in patients with HCV but without cirrhosis might be explained by the presence of occult cirrhosis at least in parts of the liver, progression from advanced fibrosis

**Table 4. Association between type of antiviral treatment regimen (DAA-only vs. DAA + IFN vs. IFN-only) and HCC risk.**

Regimen	No. of patients (%)	Patient-years	No. of patients who developed HCC (%)	HCC per 100 patient-years	Crude hazard ratio (95% CI)	Adjusted <sup>a</sup> hazard ratio (95% CI)
<i>All patients</i>						
IFN-only	35,871 (57.5)	328,040	2,651 (7.4)	0.81	1.00	1.00
DAA + IFN	4,535 (7.3)	16,518	175 (3.9)	1.06	1.84 (1.56–2.17)	1.04 (0.87–1.26)
DAA-only	21,948 (35.2)	33,615	445 (2.0)	1.32	2.81 (2.44–3.23)	1.12 (0.95–1.32)
<i>All patients from 2009 to 2015<sup>b</sup></i>						
IFN-only	9,292 (22.8)	51,942	509 (5.5)	0.98	1.00	1.00
DAA + IFN	5,996 (14.7)	22,198	244 (4.1)	1.10	1.22 (1.04–1.44)	0.89 (0.73–1.08)
DAA-only	25,424 (62.4)	39,309	557 (2.2)	1.42	1.78 (1.51–2.09)	0.92 (0.77–1.10)
<i>All patients from 2009 to 2015 (limited to 2 years follow-up)</i>						
IFN-only	9,292 (22.8)	18,188	135 (1.5)	0.74	1.00	1.00
DAA + IFN	5,996 (14.7)	11,665	130 (2.2)	1.11	1.51 (1.19–1.93)	1.16 (0.87–1.54)
DAA-only	25,424 (62.4)	38,204	535 (2.1)	1.40	1.94 (1.60–2.35)	1.04 (0.83–1.30)
<i>All patients from 2009 to 2015 with cirrhosis</i>						
IFN-only	1,491 (15.3)	7,404	223 (15.0)	3.01	1.00	1.00
DAA + IFN	1,617 (16.6)	5,657	147 (9.1)	2.60	0.86 (0.69–1.07)	0.95 (0.74–1.22)
DAA-only	6,626 (68.1)	10,916	395 (6.0)	3.62	1.23 (1.01–1.51)	0.97 (0.77–1.22)
<i>All patients from 2009- to 2015 without cirrhosis</i>						
IFN-only	7,801 (25.2)	44,538	286 (3.7)	0.64	1.00	1.00
DAA + IFN	4,379 (14.1)	16,541	97 (2.2)	0.59	1.11 (0.86–1.42)	0.90 (0.67–1.22)
DAA-only	18,798 (60.7)	28,393	162 (0.9)	0.57	1.33 (1.02–1.72)	0.98 (0.73–1.32)

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; INR, international normalised ratio; SVR, sustained virologic response.

<sup>a</sup> Adjusted by Cox proportional hazards regression for cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HCV genotype, HCV viral load, HIV co-infection, HBV co-infection, type 2 diabetes mellitus, alcohol-use disorders, substance-use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, serum AST/ALT ratio, blood INR, and blood haemoglobin levels. The laboratory tests were categorised into quartiles and modelled as dummy categorical variables.

<sup>b</sup> There were more patients listed under "DAA-only" or "DAA + IFN" regimens in 2009–2015 than in 1999–2015 because some of these patients were listed under "IFN-only" in the 1999–2015 period if their first regimen was "IFN-only".

to cirrhosis during follow-up, or the development of HCC in pre-cirrhotic advanced fibrosis. It is likely that in both patients with and without cirrhosis, SVR reduces HCC risk at least in part by reversing hepatic fibrosis.

The best way to determine whether treatment with DAAs affects HCC risk is to randomise patients to treatment with DAAs vs. no treatment and then follow them up for a long period of time. Such a study design would be unethical. Another possibility would be to compare patients who received DAAs as part of their routine clinical care to those who were untreated with respect to HCC risk. However, this approach is subject to considerable ascertainment bias (the untreated patients are less likely to be found to have HCC in a given time frame than the treated patients because of less screening and less contact with hepatologists and other medical providers) and selection bias (the reasons why certain patients are not treated with DAAs despite their excellent SVR rate might be difficult to determine and accurately adjust for), and confounding by indication (the indication for offering antiviral treatment might be associated with both treatment and outcome). Instead, we compared patients treated with DAAs in the 'current era' to patients treated with IFN in the IFN era to avoid as much as possible these sources of bias. However, this comparison could still be biased by the fact that patients with more advanced liver disease are now candidates for DAAs who were not candidates for IFN and these patients have significantly higher HCC risk. We believe that our adjustment for baseline characteristics adequately accounted for this potential confounding. In addition, the incidence of HCC has been increasing over time<sup>25</sup> and was lower during the IFN era than during the DAA era. We minimised this source of bias

by limiting analyses to regimens initiated from 2009 to 2015, as well as by adjusting for baseline characteristics that are at least partly responsible for the increasing HCC incidence over time. Any residual bias would be in favour of showing increased HCC risk in the patients treated with DAA only; therefore, it is reassuring that no such association was found.

Our study was limited by the relatively short follow-up in the DAA-only group, although we extended follow-up for HCC incidence to a time as close as possible to the time of manuscript preparation (June 2017) to maximise follow-up time. This yielded a substantial mean follow-up time of 1.53 years even in the DAA-only group (with follow-up time starting 180 days after antiviral treatment initiation). It was reassuring that similar associations between SVR and HCC risk were observed among the DAA + IFN and the IFN-only groups, which had much longer follow-up than the DAA-only group. The association between SVR and HCC risk might not be causative: it is theoretically possible that unknown factors that lead to treatment failure might also lead to the future development of HCC, other than the 21 baseline characteristics that we carefully adjusted for that included known markers of advanced fibrosis and/or cirrhosis and risk factors for HCC. It is also possible that HCC was present but undiagnosed at the time of antiviral treatment, also leading to reduced SVR. However, we excluded all HCCs that presented within 180 days of antiviral treatment initiation; in addition, the HCC cumulative incidence curves in the SVR and treatment failure groups continued to diverge for many years after treatment (Fig. 1). A final limitation of the study is that the ICD-10 code for HCC (C22.0) that replaced the ICD-9 code for HCC (155.0) in October 2015 is not yet validated using VA data. However, given that a single ICD-10 code directly replaced

a single ICD-9 code, it is reasonable to expect a similarly high positive predictive value.

The substantial strengths of the study include the large sample size, large number of incident HCCs, and long follow-up time. Baseline characteristics necessary for multivariable analyses to adjust for potential confounding were available. All patients were derived from a single, national healthcare system with fairly uniform antiviral treatment practices and guidelines across its facilities.

In conclusion, DAA-induced SVR is associated with a 71% reduction in HCC risk compared with treatment failure. Eradication of HCV is associated with a similar reduction in HCC risk irrespective of the regimen that is used to achieve the eradication. We found no evidence that treatment with DAAs was associated with increased risk of HCC compared with treatment with IFN.

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### Conflict of interest

The authors declare that they have no conflict of interest related to this manuscript.

Please refer to the accompanying [ICMJE disclosure](#) forms for further details.

### Authors' contributions

All authors approved the final version of the manuscript. G.I. is the guarantor of this paper and was responsible for the study concept and design; acquisition of data; statistical analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript; and obtaining funding; PG was responsible for the acquisition and analysis of data, and study design; and KB was responsible for the study design, analysis of data, and critical revision of the manuscript.

### Disclaimer

The contents of this manuscript do not represent the views of the US Department of Veterans Affairs or the US Government.

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jhep.2017.08.030>.

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