Editorial

Hepatitis C treatment in patients with substance use disorder: the faster the better

Antonio Saviano[1,2,3], Lucile Heroin[2,3], Pierre Mayer[2,3], Thomas F. Baumert[1,2,3,4]

[1]Institut de Recherche sur les Maladies et Hépatiques (IVH), Inserm U1110, Strasbourg, France; [2]Institut Hospitalo-Universitaire, Service d'hépato-gastroentérologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [3]University of Strasbourg, Strasbourg, France; [4]Institut Universitaire de France (IUF), Paris, France

Correspondence to: Prof. Thomas F. Baumert, MD. Université de Strasbourg, 3 Rue Koeberlé, F-67000 Strasbourg, France.
Email: thomas.baumert@unistra.fr.

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Hepatitis C virus (HCV) infection is a major cause of liver disease and hepatocellular carcinoma worldwide (1). HCV is a blood-borne infection and prevalence is particularly high in patients with a history of injective drug use or unsafe health care or sexual practices. Substance use disorder (SUD), and especially opioid misuse is a growing problem worldwide (2). This is particularly relevant in the United States (US) where opioid misuse has raised sharply in the last years (3,4), termed also opioid epidemic. SUD is associated with an increase incidence of HCV infections and reinfections and associated liver disease (2,4). Moreover, alcohol use disorder is frequent in patients with SUD (5), representing another major risk factor for chronic liver disease in this population. Patients with SUD often experience poor access to health care resulting in higher mortality (5,6). Finally, SUD is associated with psychiatric conditions and social problems such as housing instability, unemployment, and reduced access to medical care (7) which could result in a reduced access and compliance to HCV treatment.

HCV cure by treatment with direct antiviral agents (DAA) reduces liver disease progression and hepatocellular carcinoma (HCC) occurrence and overall liver-related deaths (8). DAA are all-oral regimens highly effective in obtaining viral cure (>95%) with only minor side effects (9). Little is known regarding the long-term outcomes of HCV treatment on liver disease in patients with SUD. Social vulnerability, concomitant alcohol and opioid abuse and HCV reinfection could, in theory, reduce the benefit of HCV treatment in terms of liver-related outcomes.

In the article by Park *et al.* recently published in *Hepatology* (10), the authors conducted a retrospective analysis on two large databases of patients from US to assess liver-related outcomes associated with DAA treatment in chronic HCV patients with and without SUD. Disease identification and patient selection were performed using the International Classification of Diseases (ICD) codes. Included patients had a newly diagnosed chronic HCV infection, untreated or treated with DAA, and had no recent history (1-year before the HCV diagnosis) of liver decompensation or HCC. The primary endpoint was the incidence of HCC and liver decompensation according to SUD and cirrhosis status.

Patients with SUD were younger at time of HCV diagnosis and more likely to have alcoholic liver disease (ALD). HCV treatment initiation rate was significantly lower in SUD patients (24% in SUD *vs.* 34% in non-SUD patients). Patients with SUD had also a more aggressive disease. Non-cirrhotic SUD patients had a 2-fold increased risk of liver decompensation while cirrhotic SUD patients had >1.5-fold increased risk of both HCC and liver decompensation.

Overall, DAA treatment markedly reduced HCC and liver decompensation incidence rates in patients with and without SUD. Among patients without cirrhosis, DAA reduced liver decompensation incidence by more

Table 1 Adjusted hazard ratio of DAA treatment effect stratified by the presence of SUD and cirrhosis in the study by Park *et al.* (10)

Outcomes	Without cirrhosis		Cirrhosis	
	SUD	Non-SUD	SUD	Non-SUD
Liver decompensation	0.13 (0.06–0.30)*	0.11 (0.07–0.18)*	0.64 (0.37–1.13)	0.27 (0.18–0.41)*
Hepatocellular carcinoma	0.91 (0.33–2.48)	0.31 (0.18–0.53)*	0.33 (0.13–0.88)*	0.40 (0.25–0.65)*

*, statistically significant. DAA, direct antiviral agents; SUD, substance use disorder.

than 85% in SUD and non-SUD patients, and HCC risk by almost 70% in non-SUD patients. Among patients with cirrhosis, DAA reduced liver decompensation and HCC incidence in patients without SUD by more than 60%. SUD patients treated with DAA also experienced a reduction of HCC incidence by more than 60% while the benefit on liver decompensation occurrence was more limited (36% of reduction, non-statically significant). These data, summarized in *Table 1*, highlight the importance of universal treatment of HCV. Both SUD and non-SUD patients, independently from liver cirrhosis, greatly benefit from DAA treatment in terms of reduction of liver disease complications.

The results from the stratified analysis according to the SUD and cirrhosis status have shown no benefit in HCC prevention in SUD patients without cirrhosis while non-SUD patients had a 69% reduction risk. This difference between SUD and non-SUD patients should not induce an underestimation of the HCV treatment benefit in non-cirrhotic SUD patients. The lack of effect on HCC incidence in non-cirrhotic SUD patients is probably due to the smaller cohort including more younger patients with an overall short follow-up (5 years). Indeed, the crude incidence of HCC in SUD HCV untreated patients was low, 3 per 1,000 person-years, and the impact of any preventive therapy would be difficult to evaluate on a short term and small population.

How can we explain the differences in liver decompensation incidence in cirrhotic patients with and without SUD? The SUD group had higher prevalence of patients with alcohol abuse which is a major risk factor for liver decompensation and therefore, may have reduced the benefit of HCV treatment (11).

Interestingly, chronic kidney disease (CKD) has been found to be an independent risk factor for HCC or liver decompensation in both SUD and non-SUD patients, together with other well-known risk factors such as cirrhosis and diabetes. CKD incidence is constantly increasing among patients with chronic liver disease and cirrhosis (12), in line with the increased incidence of metabolic diseases and risk factor for CKD such as diabetes and hypertension. CKD has been reported to be associated with negative kidney and liver outcomes and associated with worse liver function (13). Whether CKD is an independent risk factor for HCC is still unclear because CKD is strongly associated with major HCC risk factors such as diabetes, obesity, decompensated cirrhosis.

It is important to note that HCV treatment was offered to only a minority (around 30%) of patients in both SUD and non-SUD patients. There might be several social or economic reasons behind this limited treatment of eligible patients. This may be due to insurance restrictions, uncertainty regarding patient compliance or treatment outcomes. Collectively, these data should rise awareness for intensifying both medical, economic, and social initiatives and policies enabling offer HCV treatment to all infected patients.

The study was conducted using ICD codes and medical databases. This methodology probably underestimates the prevalence of SUD and overestimate the HCV treatment rates, making the overall results more alarming. Other limitations of the study are the short follow-up, the absence of data of HCV reinfections and of former SUD.

In conclusion, the study of Park *et al.* confirms that HCV treatment should be universally offered to all eligible patients. SUD is a risk factor for more aggressive liver disease and should not be a limiting factor for treatment, conversely, should result in intensified HCV management and care. Finally, HCV treatment rates are still too low, with only 1 patient out of 3 who received DAA. It is urgent then to implement social and medical policies to increase HCV screening, expand access to HCV drugs and improve treatment rates.

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Footnote

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