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Untreated alcohol use disorder in people who inject drugs (PWID) in France: a major barrier to HCV treatment uptake (the ANRS-FANTASIO study)

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ABSTRACT

Background and Aims Although people who inject drugs (PWID) are the core at-risk population in the hepatitis C virus (HCV) epidemic in industrialized countries, few initiate treatment. Alcohol use disorder (AUD), common within this population, has been identified as a barrier to HCV treatment uptake in the general population. We investigated whether the arrival of new and well-tolerated HCV treatments (direct-acting antivirals: DAA) has improved HCV treatment uptake in French PWID compared with former treatments (pegylated interferon-based treatments: Peg-IFN). **Design** Using discrete-time Cox proportional hazards models based on exhaustive care delivery data, we tested for associations between AUD (defined by AUD-related long-term illness status, diagnosis coding during hospitalization and/or AUD pharmacological treatment) and first HCV treatment delivery, after adjusting for gender, age, complementary universal health cover, liver disease severity and type of opioid agonist therapy (OAT) received. Separate analyses were performed for 2012–13 (Peg-IFN era) and 2014–16 (DAA era). **Setting** France. **Participants** All French people chronically HCV-infected who received OAT at least once during 2012–16 and were covered by the national health insurance (n = 24 831). **Measurements** Incidence rate of HCV treatment uptake, hazard ratios associated with AUD and other covariates. **Findings** Incidence rate (IR) of HCV treatment uptake per 100 person-years was 6.56, confidence interval (CI) = 6.30–6.84; and IR = 5.70, 95% CI = 5.51–5.89 for Peg-IFN-based treatment (2012–13) and DAA (2014–16), respectively. After multiple adjustment, people with AUD not receiving related medication had 30 and 14% lower Peg-IFN-based treatment and DAA uptake, respectively, than those without AUD [hazard ratio (HR) = 0.70, 95% CI = 0.62–0.80 and HR = 0.86, 95% CI = 0.78–0.94]. No difference was observed between those treated for AUD and those without AUD. **Conclusions** Despite the benefits of direct-acting antiviral treatment, untreated alcohol use disorder appears to remain a major barrier to hepatitis C virus treatment access for people who inject drugs in France.

Keywords Alcohol use disorder, AUD treatment, direct-acting antivirals, France, hepatitis C virus treatment, people who inject drugs.

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INTRODUCTION

A major cause of death and disability, hepatitis C virus (HCV) remains a serious concern world-wide [1,2]. It has recently been estimated that 52% of people who inject drugs (PWID) globally are HCV-antibody positive [3]. In Europe, as in most industrialized countries, injecting drug use (IDU) is the main route of HCV transmission. Drug injection accounted for 78% of newly diagnosed cases with a known route of transmission in Europe in 2014 [4]. In

western Europe, the prevalence of viraemic infection among people with recent IDU is 40% (48% in France). Representing 17% of the total HCV-infected population (20% in France) [5], this subgroup therefore constitutes a key target for HCV elimination [6].

The most recent results for France indicate that almost one-third of HCV-infected PWID are unaware of their status [7]. In addition, a majority of PWID remain untreated even after diagnosis. European and French data (published in 2000–12) showed treatment uptake levels of approximately 30% or less in HCV-positive PWID [8]. The main barriers to HCV treatment uptake in PWID include patient-related factors, health-care provider-related factors and system-related/institutional factors [9]. In the past, IDU constituted a barrier to accessing HCV treatment for two reasons: first, interferon and pegylated interferon (Peg-IFN)-based treatments were associated with psychiatric side effects [10], which are very prevalent in PWID [11]; and secondly, some caregivers had concerns about patient adherence and the risk of re-infection [10]. In recent years however, the advent of new highly effective and safer HCV treatments called 'direct-acting antivirals' (DAA) has changed the situation. In France, the first DAA was approved in 2014. Given that DAA are effective even in difficult-to-treat populations, PWID are now included in international guidelines as a target population for treatment, with an emphasis on risk-reduction strategies to minimize post-HCV cure re-infection rates [12,13]. In addition, modelling studies have highlighted the potential of HCV 'treatment as prevention', with a view to cost-effective reduction of HCV prevalence among PWID [14].

DAA are as effective in people receiving opioid agonist therapy (OAT) as they are in other HCV-infected patients [15], with HCV cure rates exceeding 90%. However, it is still unknown whether specific comorbidities may delay DAA initiation in PWID. Alcohol use disorder (AUD) is a common comorbidity among PWID, with a prevalence of approximately 30% among people treated with OAT [16]. It has been a major barrier to HCV care for many years [17–19]. Alcohol misuse accelerates liver disease progression in people with HCV infection [20–22]. In France, it has been estimated that AUD contributes to more than two-thirds of the burden of liver-related complications, liver transplantations and liver-related mortality in young and middle-aged adults with chronic HCV infection [23]. Furthermore, in the European Union (EU), fewer than 10% of those with AUD receive appropriate treatment [24]. In France, more than half of those with AUD have never received treatment [25]. In the era of Peg-IFN, the poorer response to HCV treatment in those with AUD was seemingly mainly mediated by lower patient adherence [26]. However, this result was not found for HIV-HCV coinfected individuals [27].

Sustained virological response (SVR) to IFN-based treatments have been reported for heavy alcohol drinkers (despite continued consumption in some cases), with SVR rates comparable to those of people with no history of unhealthy alcohol use [28]. In the DAA era, SVR does not appear to be influenced by alcohol misuse [29]. Accordingly, new national [30] and international [31] guidelines for HCV treatment include people with AUD, and highlight their specific needs.

The FANTASIO [*Facteurs d'Accès aux Nouveaux Traitements Antiviraux chez les Sujets Infectés par l'hépatite C recevant des traitements de substitution aux Opioïdes* (Factors in accessing new antiviral medications among HCV-infected individuals on OAT)] project aims to longitudinally explore HCV treatment uptake among PWID with chronic HCV infection, using the exhaustive French insurance claims database [National Social Insurance System database (SNIIRAM)], which covers virtually the entire national population. Given that approximately 80% of French PWID receive OAT [32], prescriptions for OAT were used in FANTASIO to identify the PWID population.

Data from FANTASIO provided us with the opportunity to estimate, using a longitudinal multivariable analysis, the relationship between the presence of AUD and AUD treatment and HCV treatment uptake rates before and after the introduction of DAA to France.

MATERIALS AND METHODS

Data source

The analysis plan for this study was not pre-registered, and the findings should be considered exploratory. Analyses were based on individual data from the SNIIRAM, the main health-care reimbursement database in France [33]. The SNIIRAM covers 98.8% [33] of the country's resident population. It collects exhaustive anonymized data from all health cover schemes (primarily data on all health-care reimbursements), as well as data from public and private hospitals through the programme for the medicalization of information systems (PMSI) [34]. SNIIRAM data include demographic characteristics (dates of birth and death, gender, etc.), complementary universal health cover status, long-term illness (ALD) status and health-care expenditure reimbursement data (drugs, clinical tests and procedures, hospitalizations) [33,34]. Complementary universal health cover is an administrative measure targeted at low-income individuals. The French health-care system provides 100% reimbursement for those with complementary universal health cover and those classified with ALD (for the latter, only expenditures directly related to the long-term disease in question are considered).

The use of SNIIRAM data was approved by the National Institute of Health Data (IDS no. 176 issued on 2 March

2016) and the CNIL (no. 1 946 535 issued on 4 August 2016).

Data selection and study outcome

We used individual SNIIRAM data collected during two periods where different HCV treatments were available: 2012–13 (Peg-IFN-based treatment era) and 2014–16 (DAA era). Our database included all individuals with OAT (buprenorphine or methadone) delivery on at least one occasion between 2012 and 2016. In France, methadone and high-dose buprenorphine are only prescribed for opioid dependence. OAT delivery was used as a proxy for IDU status.

Chronically HCV-infected patients were identified using the International Classification of Diseases (ICD)-10 (B18.2 code for chronic HCV infection). Patients who had an HCV-related ALD classification or an HCV-related hospitalization during 2012–16 were considered to have chronic HCV infection. Consequently, patients who received HCV treatment between 2012 and 2016 without HCV-related ALD or HCV-related hospitalization were excluded from the analyses.

For this study, we had access to aggregated annual data for all covariates, recorded as categorical variables, which summarized an individual's status for each given year. For instance, in the case of AUD, all patients diagnosed with AUD during the course of year *x* were coded as having AUD for year *x*. Consequently, the time unit chosen for all variables in the analyses was the year, not the date.

Two separate analyses were performed. The first analysis covered the 2012–13 period (pre-DAA era), while the second covered the 2014–16 period (DAA era). Given the specificities of the SNIIRAM database (no information concerning history of treatments or virological response), all individuals identified as chronically HCV-infected between 2012 and 2013 were included in the pre-DAA era analysis, and all individuals identified as chronically HCV-infected between 2014 and 2016, with no previous HCV treatment between 2012 and 2013, were included in the DAA-era analysis.

The study outcome was first Peg-IFN-based HCV treatment delivery in the pre-DAA era analysis and the first DAA-based HCV treatment delivery in the DAA-era analysis. Peg-IFN-based treatments included Peg-IFN/ribavirin with or without boceprevir or telaprevir. DAA included sofosbuvir, daclatasvir, dasabuvir, simeprevir, ombitasvir, paritaprevir and ritonavir with or without ribavirin.

For each analysis, the follow-up period for each individual was defined as the period between chronic HCV infection identification and the outcome date or the censoring date (2013 and 2016 for the pre-DAA era and DAA-era analysis, respectively) or death, whichever came first. In the DAA era analysis, data for individuals receiving Peg-IFN-based treatment after 2014 were censored at the date of treatment.

AUD and AUD treatment

AUD (past or current) was defined as meeting at least one of the following criteria: AUD-related ALD (ICD-10 code F10), AUD diagnosis during hospitalization for any cause (ICD-10 code F10) and/or delivery of disulfiram, acamprosate, naltrexone or nalmefene, which were the only drugs approved for AUD treatment in France during the study period. The term 'AUD treatment' hereafter only refers to these four drugs, and excludes non-pharmacological treatments for which data were not available.

Other covariates

Gender and age were tested as covariates in the analyses. Liver disease severity was also tested for, as it was a criterion for HCV treatment initiation until 2016 in France. Severity of liver disease was characterized by the presence or absence of cirrhosis (ICD-10 codes K74.3 to K74.6) or liver cancer (ICD-10 codes C22.0 to C22.4, C22.7 and C22.9) using a three-category variable (no cirrhosis and no liver cancer, cirrhosis without liver cancer, liver cancer). Other medical comorbidities were not considered as possible covariates, as corresponding data were unavailable. Complementary universal health cover was included in the analysis as a marker of low income. OAT was coded as 'not yet received', 'methadone only', 'buprenorphine only' or 'buprenorphine and methadone' when both treatments had been delivered during the same year. We included the type of OAT as a possible confounder in the analysis because, in France, buprenorphine and methadone may be delivered to people with opioid dependence who have different profiles.

Statistical analyses

The incidence rate of treatment uptake was computed, in each of the two analyses, as the number of treatment uptakes occurring during the corresponding period divided by the number of person-years (computed as the sum of the number of years of follow-up for all individuals included in the corresponding analysis).

In each of the two analyses, discrete-time Cox proportional hazard models based on Efron's method were used to estimate the relationship between AUD status and HCV treatment uptake, after adjustment for gender, age, complementary universal health cover, liver disease severity and type of OAT received. As the database included data aggregated by year for many variables, the year was chosen as the time unit in both models. All covariates except age and gender were time-varying. As excessive alcohol

consumption fosters liver disease, we tested for the interaction between AUD and liver disease severity in both multivariable models.

We performed a sensitivity analysis based on the DAA era model (2014–16), but including Peg-IFN-based treatment uptake. The outcome was therefore 'first delivery of HCV treatment (regardless of the type of treatment)'.

Analyses were performed with Stata software version 14.2 (StataCorp LP, College Station, TX, USA).

RESULTS

Characteristics of the study population by AUD status

In the pre-DAA analysis, cirrhosis or liver cancer was less frequent in AUD-treated patients (8.3%) than in AUD-untreated patients (15.2%), but more frequent when compared with non-AUD patients (4.2%, $P < 0.001$). Similarly, in the DAA era analysis, 10.1, 16.4 and 5.40% of AUD-treated, AUD-untreated and non-AUD cases, respectively, had cirrhosis or liver cancer ($P < 0.001$) (data not shown).

Incidence rate of HCV treatment uptake

A total of 19 700 and 22 545 patients were included in the pre-DAA era (2012–13) and DAA era (2014–16) analysis, respectively. The incidence rates (IR) of HCV treatment uptake per 100 person-years [95% confidence interval (CI)] were IR = 0.56, 95% CI = 6.30–6.84 and IR = 5.70, 95% CI = 5.51–5.89 for Peg-IFN-based treatment (2012–13) and DAA (2014–16), respectively.

Pre-DAA analysis (2012–13)

In the pre-DAA era analysis, gender, age, liver disease severity and AUD were significantly associated with Peg-IFN-based treatment uptake in both univariable and multivariable analyses (Table 1).

In the multivariable model, individuals with untreated AUD had a 30% lower Peg-IFN-based treatment uptake rate [hazard ratio (HR) = 0.70, 95% confidence interval (CI) = 0.62–0.80, $P < 0.001$] (Table 1) than those with no AUD. Furthermore, they had a 24% lower Peg-IFN-based treatment uptake rate (HR = 0.76, 95% CI = 0.63–

Table 1 Pre-DAA analysis: factors associated with pegylated interferon (Peg-IFN) treatment uptake between 2012 and 2013 in French PWID receiving OAT (ANRS FANTASIO project: data from the French national health-care system database; discrete-time Cox proportional hazards models).

		Univariable analysis		*Multivariable analysis*	
		n = 19 700 *2286 individuals (11.6%) with delivery of Peg-IFN based treatment*			
Covariates	*Frequency (%) or median [IQR]*[a]	*HR [95% CI]*	*P-value*	*HR [95% CI]*	*P-value*
Gender					
Male	15 609 (79.2)	1		1	
Female	4091 (20.8)	0.65 [0.58–0.73]	< 0.001	0.64 [0.57–0.72]	< 0.001
Age (years)	46 [42–50]	0.99 [0.99–0.99]	0.019	0.99 [0.98–0.99]	< 0.001
Complementary universal health cover					
No	14 390 (73.1)	1		1	
Yes	5310 (27.0)	1.05 [0.95–1.15]	0.343	1.07 [0.97–1.17]	0.168
Liver disease severity					
No cirrhosis	18 442 (93.6)	1		1	
Cirrhosis	1051 (5.3)	2.21 [1.91–2.56]	< 0.001	2.50 [2.15–2.91]	< 0.001
Liver cancer	207 (1.1)	1.31 [0.86–1.99]	0.215	1.49 [0.98–2.28]	0.063
Current or past alcohol use disorder (AUD)					
No AUD	14 755 (74.9)	1		1	
Untreated AUD	3205 (16.3)	0.80 [0.70–0.91]	< 0.001	0.70 [0.62–0.80]	< 0.001
Treated AUD	1740 (8.8)	1.00 [0.85–1.17]	0.972	0.93 [0.80–1.09]	0.385
Type of OAT received					
OAT not yet received	3029 (15.4)	1		1	
Methadone only	5556 (28.2)	1.10 [0.96–1.26]	0.167	1.13 [0.98–1.29]	0.089
Buprenorphine only	10 702 (54.3)	1.03 [0.91–1.17]	0.625	1.05 [0.92–1.20]	0.444
Methadone and Buprenorphine	413 (2.1)	0.91 [0.67–1.23]	0.522	0.91 [0.67–1.24]	0.552

[a]Characteristics described for last year of follow-up. DAA = direct-acting antivirals; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; PWID = people who inject drugs; OAT = opioid agonist therapy.

0.93, $P = 0.003$; data not shown) than those treated for AUD. No difference was observed between those treated for AUD and those with no AUD (Table 1). Female gender and older age were both associated with a lower Peg-IFN-based treatment uptake rate (HR = 0.64, 95% CI = 0.57–0.72 and HR =0.99, 95% CI = 0.98–0.99) per 1-year increase, respectively, $P < 0.001$), while cirrhosis was associated with a higher treatment uptake rate (HR = 2.50, 95% CI = 2.15–2.91, $P < 0.001$) (Table 1).

DAA era analysis (2014–16)

In the DAA era analysis, gender, age, complementary universal health cover, liver disease severity and type of OAT were all significantly associated with DAA treatment uptake in both univariable and multivariable analyses (Table 2). AUD was significantly associated with treatment uptake only in the multivariable analysis.

In the multivariable analysis, individuals with untreated AUD had a lower DAA treatment uptake rate than both those with no AUD (HR = 0.86, 95% CI = 0.78–0.94, $P < 0.001$) (Table 2) and those with treated AUD (HR = 0.83, 95% CI = 0.74–0.94, $P = 0.006$) (data not shown), while no difference was found between treated AUD and no AUD individuals (Table 2). Female gender and complementary universal health cover were associated with a lower DAA uptake rate (HR = 0.83, 95% CI = 0.76–0.90, $P < 0.001$ and HR =0.90, 95% CI = 0.83–0.98, $P = 0.014$, respectively), while older age, cirrhosis and liver cancer were associated with a higher DAA uptake rate (HR =1.03, 95% CI = 1.02–1.03, $P < 0.001$ per 1-year increase, HR = 3.74, 95% CI = 3.38–4.13 and HR = 2.92, 2.34–3.64, $P < 0.001$, respectively).

In both analyses, interaction between AUD and liver disease severity was tested for, but the results remained unchanged (data not shown). Consequently, this interaction was not included in the final multivariable models.

Sensitivity analysis

Including Peg-IFN-based treatments alongside DAA-based treatments during the DAA era in the model did not change the main results (data not shown). Compared with the DAA era analysis, all previously statistically significant associations remained significant, with HR of similar magnitude. The only exception was the association between complementary universal health cover and treatment uptake, which was no longer significant ($P = 0.064$).

Table 2 DAA era analysis: factors associated with DAA treatment uptake between 2014 and 2016 in French PWID receiving OAT (ANRS FANTASIO project: data from the French national health-care system database; discrete-time Cox proportional hazards models).

		Univariable analysis		*Multivariable analysis*	
		n = 22 545 *3332 individuals (14.8%) with delivery of DAA*			
Covariates	*Frequency (%) or median [IQR]*[a]	*HR [95% CI]*	*P-value*	*HR [95% CI]*	*P-value*
Gender					
Male	17 621 (78.2)	1		1	
Female	4924 (21.8)	0.79 [0.73–0.87]	< 0.001	0.83 [0.76–0.90]	< 0.001
Age (years)	49 [44–53]	1.04 [1.03–1.04]	< 0.001	1.03 [1.02–1.03]	< 0.001
Complementary universal health cover					
No	16 060 (71.2)	1		1	
Yes	6485 (28.8)	0.81 [0.75–0.88]	< 0.001	0.90 [0.83–0.98]	0.014
Liver disease severity					
No cirrhosis	20 617 (91.5)	1		1	
Cirrhosis	1560 (6.9)	3.88 [3.53–4.27]	< 0.001	3.74 [3.38–4.13]	< 0.001
Liver cancer	368 (1.6)	3.42 [2.76–4.25]	< 0.001	2.92 [2.34–3.64]	< 0.001
Current or past alcohol use disorder (AUD)					
No AUD	14 349 (63.7)	1		1	
Untreated AUD	5176 (23.0)	1.03 [0.94–1.12]	0.553	0.86 [0.78–0.94]	< 0.001
Treated AUD	3020 (13.4)	1.04 [0.94–1.16]	0.437	0.99 [0.89–1.1]	0.852
Type of OAT received					
OAT not yet received	5194 (23.0)	1		1	
Methadone only	6214 (27.6)	1.32 [1.19–1.46]	< 0.001	1.39 [1.25–1.55]	< 0.001
Buprenorphine only	10 770 (47.8)	1.32 [1.20–1.45]	< 0.001	1.34 [1.22–1.48]	< 0.001
Methadone and Buprenorphine	367 (1.6)	1.04 [0.77–1.4]	0.813	1.25 [0.93–1.7]	0.143

[a]Characteristics described for last year of follow-up. DAA = direct-acting antivirals; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; PWID = people who inject drugs; OAT = opioid agonist therapy.

DISCUSSION

This study used the French National Social Insurance System database (SNIIRAM) to longitudinally assess the relationship between AUD diagnosis/treatment and HCV treatment uptake among PWID. Individuals with at least one delivery of OAT between 2012 and 2016 were included. Peg-IFN-based treatment uptake (i.e. in the pre-DAA era) in individuals with untreated AUD was lower than in patients with no AUD or with treated AUD. Similarly, DAA uptake in untreated AUD was lower than in patients with no AUD or with treated AUD.

Several barriers to HCV treatment in PWID were previously identified in a systematic review performed in 12 European countries [8]. Barriers at the patient level included unwillingness to be treated, lack of knowledge, low priority given to HCV, lack of financial resources [35] and fear of side effects. Depression was also considered to potentially strengthen perceived barriers [36]. Barriers at the provider level included poor patient–provider relationship, reluctance by physicians to treat PWID because of concerns regarding treatment adherence, re-infection, comorbidities and stigmatization [36]. PWID with HCV face a double stigmatization and the impact of this has been associated with various health outcomes, including psychiatric disorders [37]. At the system level, barriers include highly structured care settings, the risk of PWID being lost to follow-up when they are transferred and a high probability of missing appointments [36,38]. Previous results from a sample of HCV-infected patients never treated for HCV in a French hospital also highlighted that opioid-dependent patients have poorer access to HCV treatment [39]; that study also showed higher levels of alcohol consumption in that subgroup.

Our finding of a negative influence of comorbid AUD on HCV treatment uptake contrasts with findings by Agostini *et al.* on a sample of HCV treatment-naive patients recruited through French general practitioners [18]. They found that being on OAT was independently associated with lower antiviral HCV treatment uptake, but that excessive alcohol intake was not. This discrepancy may be explained by methodological differences. Their recruitment protocol through general practitioners led to a smaller proportion of people with drinking problems than in our study. In addition, they identified alcohol problems as 'excessive alcohol intake', a variable seemingly based on self-reported consumption. Dever *et al.*, in the United States, found an association between AUD and non-engagement in care among high-risk hepatitis C veteran patients on DAA [17].

There may be several reasons why PWID with AUD are less likely to receive HCV care in France than PWID without AUD, including stigmatization [40], affective disorders [41], a sense of guilt [42], depression [43] and impaired social cognition [44]. The increased HCV treatment uptake which we observed for AUD-treated patients was to be expected, given that AUD treatment is supposed to counteract these factors. Similarly, the smaller proportion of cirrhosis among AUD-treated than in AUD-untreated individuals is most probably a consequence of reduced alcohol consumption in the former group. Moreover, access to AUD treatment may be associated with better general access to care and/or willingness to take charge of one's own health.

Community-based approaches may help to improve HCV treatment uptake for PWID. In France, the ANRS-AERLI programme, implemented in harm reduction centres, efficiently reduced HCV at-risk practices and increased HCV testing [45]. Similar programmes could be further enhanced by integrating other elements to improve the entire cascade of HCV care, such as adapted community-based point-of-care testing [46,47], same-day anti-HCV and HCV RNA tests [48], nurse-led services that facilitate linkage to care [49] and integration of HCV care in the drug and alcohol setting [50], especially for individuals with comorbid AUD. Community-based 'test-and-treat' approaches have also proved effective in local contexts, and may inspire future programmes targeting PWID [51]. In France, entry points in care for PWID consist of specialized care centres for addiction (CSAPA, CAARUD) and general medical practice, and there is still a strong need for better HCV care integration. Given that alcohol is responsible for approximately half of global liver cirrhosis disability-adjusted life-years [52], tackling the issue of excessive alcohol consumption is crucial when considering liver disease in the broader context. Alcohol control policies (e.g. tax policy interventions or minimum unit pricing) have been shown to be robust levers to lower alcohol consumption and alcohol-related harms [53–55].

DAA have less severe side effects and higher efficacy than Peg-IFN-based treatments [56–58], and are therefore likely to attenuate both patients' and providers' reluctance to treatment initiation. Brouard *et al.*, who also used the SNIIRAM database, found that authorities' approval of DAA prescription was followed by a marked increase in HCV treatment uptake in France [59]. Until 2016, only patients with severe fibrosis or comorbidities were entitled to 100% reimbursement for DAA-related health expenditures in the country [59]. In June 2016, this was extended to cover people with F2 fibrosis and PWID sharing syringes [60]. In 2017, following the French National Authority for Health's recommendations, DAA became fully reimbursable for all HCV chronic patients [30]. It is expected that DAA delivery will continue to increase in the coming years in France.

The relationship we found between both cirrhosis (in the two analyses) and liver cancer (DAA era analysis) and HCV treatment uptake reflects: (i) the urgency for medical treatment; (ii) the fact that until mid-2016, the use of DAA was restricted to patients with severe liver

fibrosis or comorbidities [59]; and (iii) the fact that patients with decompensated cirrhosis could not undergo an IFN-based regimen while DAA proved their effectiveness in such cases [61]. These stringent initial criteria for DAA prescription probably explain the lower absolute incidence rate of treatment uptake we found in the DAA era than in the Peg-IFN era. In addition, in our database, while a substantial proportion of individuals are recorded as having started HCV treatment at the beginning of 2012, it is probable that some of them had in fact initiated treatment in 2011. This may have led to a slight overestimation of incidence for the period 2012–13. However, we have no data for this. The association between older age and better DAA uptake is probably related to the fact that the older the patient, the greater the chance of previous treatment failure with Peg-IFN (although treatment failure was not measured in our study), and the greater the risk of worse liver disease severity due to longer HCV infection exposure.

The arrival of DAA led to a decrease in the large gender inequity previously observed in terms of HCV treatment. Further research is needed to determine whether this was more attributable to system-based or individual barriers. The poorer uptake of DAA associated with those with complementary universal health cover could be mediated by restricted access to care and fewer frequent medical visits, which are consequences of lower medical density (especially regarding specialists) in socially disadvantaged areas [62]. Previously reported poor coordination of care [63], to which patients from low-income households may be more vulnerable, may also hamper referral to hepatologists or to hospital pharmacies delivering HCV treatment. HCV linkage to care could be facilitated for complementary universal health cover beneficiaries through HCV bridge counsellors or patient navigators, as has been tested elsewhere [64].

The main strength of the present study is that it was based on the SNIIRAM database, which encompasses almost all the French population's health-care consumption. Some people not covered by the health insurance system because of incomplete administrative requirements—most probably marginalized populations—were absent from our database. Nevertheless, given that anyone with stable residency for at least 3 months in France can benefit from universal medical coverage, we expect this number to be small. The SNIIRAM database provides reliable data on hospitalizations, ALD and drug delivery which, together with the good statistical power of the study—thanks to the large study sample—guaranteed robustness in our results.

Although we assumed that data regarding individuals receiving at least one OAT delivery covered a high proportion of France's PWID population, it is likely that PWID not included in this data set have poorer access to HCV treatment than those included, as they have even less contact with the health-care system. Accordingly, our study may not be representative of all PWID in France. In particular, the findings may not apply to PWID who did not receive OAT during the study period. In addition, the proportion of people with AUD may have been underestimated, given that we only considered AUD in the context of hospitalization and long-term illness (i.e. probably the most severe cases) and that screening for AUD by general practitioners is low in France [65]. However, our results are in line with figures generally found for people on OAT [66–68]. Moreover, if individuals with undetected AUD were indeed erroneously categorized as non-AUD, this would have only reduced the difference observed, and would certainly not have generated false differences between AUD and non-AUD PWID. Individuals classified by us as having chronic HCV infection (either because they had official long-term disease status or were hospitalized for a HCV-related cause) may not be representative of all HCV-chronic individuals. However, given the exhaustiveness of the SNIIRAM database for health-care reimbursement data, this population should account for a large proportion of patients diagnosed with HCV and in care.

The lack of data before 2012 may be a limitation for our study. Indeed, we cannot completely rule out the possible 'warehousing' of patients in the period immediately preceding the arrival of DAA, leading to delays in HCV treatment uptake for some patients and, in turn, to lower HCV treatment uptake during this period. However, global descriptive data concerning the implementation of HCV treatment in France show that the annual number of patients initiating treatment first decreased from 2007 to 2010, then increased in 2012 with the introduction of first-wave protease inhibitors, before decreasing again in 2013, and finally increasing in 2014 with the arrival of second-wave DAA [59]. Our 2012–16 study period may thus be large enough to reflect the main changes in HCV treatment uptake in France before and after the introduction of DAA. The analyses would have benefited from the addition of covariates such as HIV or hepatitis B infections, exact fibrosis stage and psychiatric comorbidities other than AUD, but the relevant data were not available. Finally, the limitation of identifying AUD treatment through pharmacological treatment prevents us from being able to draw a conclusion about the benefits of pharmacological treatment alone, as interactions with stays in addiction centres or psychosocial interventions are to be expected. However, the magnitude and statistical significance of our results still suggest a net benefit from these drugs regarding access to HCV treatment. These results need to be confirmed in future studies.

To conclude, in 2016, AUD diagnosis not coupled with AUD medication uptake continued to impair HCV treatment uptake for PWID in France. Despite the great potential of DAA, efforts are still needed to improve HCV

treatment uptake. Systematic AUD screening during OAT may help AUD care and lead to indirect benefits in terms of HCV care.

Declaration of interests

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