Effectiveness of direct-acting antivirals for chronic hepatitis C treatment in migrant and non-migrant populations in France

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TITLE

- Effectiveness of direct-acting antivirals for chronic hepatitis C treatment in migrant and non-migrant populations in France (ANRS CO22 HEPATHER)

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LIST OF ABBREVIATIONS

DAA	Direct-acting antivirals
HCV	Hepatitis C virus
ANRS	French National Agency for HIV and viral hepatitis research
CO22- HEPATHER	Therapeutic option for hepatitis B and C: a French cohort
HCV-RNA	Hepatitis C Virus - Ribonucleic Acid
aIRR	Adjusted incidence rate ratio
INSEE	French National Institute for Statistical and Economic Studies
CHC	Chronic hepatitis C
HBV	Hepatitis B virus
MSM	Men who have sex with men
WHO	World health organization
SVR	Sustained virological response
HIV	Human immunodeficiency virus
CPP	French personal protection agency
ANSM	French Regulatory Authority
PCR	Polymerase Chain Reaction
PWUD	People who use drugs
OAT	Opioid agonist therapy
AU	Alcohol units
IQR	Interquartile range

CONFLICT OF INTEREST DECLARATION FOR ALL AUTHORS

The authors declare that they have no competing interests.

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ABSTRACT

Background & aims

Although the efficacy of direct-acting antivirals (DAA) treatment against hepatitis C virus (HCV) infection has been widely proven, data on their effectiveness in the most socially vulnerable groups are lacking. Despite universal health coverage in France, migrants face specific socioeconomic barriers that increase the likelihood of a suboptimal cascade of care for chronic HCV infection and impaired treatment effectiveness in this sub-population. Using data from the prospective multicenter ANRS CO22 HEPATHER cohort, we tested whether treatment failure rates differed between HCV-infected migrants and non-migrants receiving DAA in France.

Methods

We selected data collected from 2012 to 2018 in the ANRS CO22 HEPATHER prospective cohort study for chronic HCV participants with available data on treatment failure (defined as the presence of a detectable HCV-RNA load 12 weeks after their first DAA treatment ended). We performed multivariable Poisson regression models to assess whether treatment failure rates significantly differed between migrants and non-migrants (cross-sectional analysis), while taking into account the former's world region of birth and other potential social vulnerability factors (drug use, unhealthy alcohol use, living in poverty, and for men, having has sex with men).

Results

Among the study population's 7,879 patients, 5,829 (74%) were non-migrants, and 2,050 (26 %) migrants. Median [interquartile range] age was 57 [51-65] years, 4433 (56%) were men, and 369 (5%) of the entire study population had treatment failure. After multivariable adjustment, migrants from Central Asia were the only migrant subgroup at higher risk of treatment failure than non-migrants (aIRR=2.83; 95% CI [1.72, 4.65]).

Conclusions

Results from this large-scale study performed in France suggest a higher risk of DAA treatment failure in migrants from Central Asia than in non-migrants. They also provide real-world evidence confirming the overall low treatment failure rate in chronic HCV patients treated with DAA (whether migrants or not) in France. Simplified models of care taking into account language and cultural barriers are needed to improve DAA effectiveness in migrants from Central Asia. These findings can help stakeholders advocate for improved screening and access to treatment for HCV-infected migrants, especially those most vulnerable.

KEYWORDS

Hepatitis C; vulnerable population; migrant; direct-acting antivirals; sustained virological response; Central Asia

LAY SUMMARY

In this study, we tested whether the effectiveness of direct-acting antivirals differed between migrants - a socially vulnerable population - and non-migrants in France. Our results showed a higher risk of treatment failure in migrants from Central Asia than in non-migrants. This suggests the need for tailor-made treatment and care strategies for this population.

INTRODUCTION

According to data from the French National Institute for Statistical and Economic Studies (INSEE), 6.7 million migrants were living in France in 2019 (i.e., 9.9% of the country's total population). Of these, 2.5 million had acquired French nationality (1). A further 700,000 residents were born in France but had another nationality. With regard to migrants, 33.3% were European, 46.5% African, 14.7% Asian, and 5.4% American or Oceanian (2). Chronic hepatitis C (CHC) prevalence in migrants was estimated at 1.8% to 3.1% in the PRECAVIR and Comede surveys (data collected between 2007 and 2016 by French care centers for migrants and hospital-based medico-social care units for comprehensive access to healthcare and social support (called PASS in France))(3,4). This contrasts with the 2016 Barotest survey's estimated 0.3% in the French general population (5). CHC prevalence in migrants already infected with hepatitis C virus (HCV) before their arrival in France largely depends on how endemic hepatitis C is in their country of birth (6). Available epidemiological data in countries from Central Asia and Eastern Europe underline the heavy burden of HCV infection in these regions (7). Moreover, data from the social rights association COMEDE (French committee for the health of exiles) show that among individuals provided with a medical consultation in their premises between 2007 and 2016, people from Central Asia were more likely to have HCV (8).

Since 2016, irrespective of liver disease stage, direct-acting antiviral (DAA) treatments have been prescribed free of charge to all CHC patients in France. These include people from the most vulnerable groups, who are often isolated from the healthcare system and for whom the HCV cascade of care is not yet optimized (9–12) as follows: regular and irregular migrants infected with HCV, people who use drugs (PWUD), prisoners, HCV-HIV (human immunodeficiency virus) co-infected patients, and men who have sex with men (MSM) (13). All these groups are priority targets for screening, risk reduction and antiviral treatment. Migrants in particular face delayed HCV screening and entry into HCV care in France (14–18). Moreover, having migrant status - especially for individuals coming from low-resource countries - is associated with multiple socioeconomic difficulties, including problems finding accommodation, employment and care (17,19–21).

The 2016 French guidelines for managing HCV infection represent a major step toward the country's goal of HCV elimination by 2025 and are aligned with the World Health Organization's (WHO) target for worldwide elimination of the virus by 2030 (22).

Although the effectiveness of DAA in HCV-infected individuals has been demonstrated in several clinical trials (23–28), 'real-world' data, especially for the most vulnerable groups described above, are lacking. Migrants face multiple difficulties, including a precarious administrative status (29) and discrimination, both of which may preclude their access to the healthcare system and impact the care they receive (30,31).

Given the results mentioned above regarding Asian migrants in France, we used data for HCV-infected individuals participating in the prospective multicenter ANRS CO22 HEPATHER cohort (full title: 'French National Agency for HIV and viral hepatitis research-Therapeutic option for hepatitis B and C: a French cohort') to test whether treatment failure rates differed between migrants from central Asia, migrants from other world regions, and non-migrants receiving DAA, while taking into account the presence of additional socio-behavioral vulnerabilities, and other potential predictors of sustained virological response (SVR).

METHODS

Study design

ANRS CO22 HEPATHER (ClinicalTrials.gov number NCT01953458) is an ongoing French nationwide multicenter observational prospective cohort study, characterized by the longitudinal collection of both clinical/biological and socio-behavioral data.

Its primary aim is to assess the benefits and risks associated with existing treatment modalities for patients diagnosed with HCV and/or HBV infection (chronic, acute or cured), and to identify the virological, environmental, and social factors predicting the clinical evolution of patients with CHC infection after receiving DAA (32).

Patients were enrolled from August 2012 to September 2014 in 34 hepatology expert centers throughout France. They are being followed for 10 years.

Exclusion criteria in the cohort were HIV co-infection, ongoing HCV treatment, having discontinued HCV treatment for less than three months, life expectancy of less than one year, being aged under 18, current incarceration, and for women, being pregnant. CHC was defined as testing positive for anti-HCV antibodies for at least six months and a positive HCV-RNA test. The design of ANRS CO22 HEPATHER is detailed in full elsewhere (33,34).

Sociodemographic, behavioral, clinical, and biological data were collected at cohort enrolment using a dedicated electronic case-report form and biological samples. Historical patient data were imported from existing medical files in each center. Data were updated both during clinical follow-up visits scheduled once a year, and through spontaneous reports on dedicated forms for particular events (such as clinical events or therapy initiation).

In the present study, we used data collected in ANRS CO22 HEPATHER until 2018.

Our study population included cohort participants with CHC, whether HCV treatment-naive or not at enrolment, who received DAA treatment during follow-up and who had available data on treatment

failure, defined as the presence of detectable HCV-RNA 12 weeks after ending their first DAA treatment.

Ethical considerations

Written informed consent was obtained from each patient before enrolment. The protocol was developed 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) in 2012.

Variables

Study outcome

The study outcome was treatment failure, defined as the lack of SVR - measured by Polymerase Chain Reaction (PCR) - 12 weeks after the end of patients' first DAA treatment.

Variables for migrant status and additional social vulnerabilities

Migrants were defined as individuals not born in France who reported having at least one parent of non-French origin. We created different variables for migrant status to take into account two components. First, patients' world country and region of birth (distinguishing between endemic regions e.g., Sub-Saharan Africa, North Africa, and Asian countries). Countries of birth were defined using the World Bank definition, with a distinction made between certain regions according to HCV prevalence (for instance, Europe was not grouped with Central Asia). The following countries of birth were categorized into the Central Asia region: Armenia; Azerbaijan; Georgia; Kazakhstan; Kirghiziztan; Mongolia; and Uzbekistan. Second, the presence of the following additional social vulnerabilities, as defined by the French guidelines for the management of HCV infection (12): drug use, unhealthy alcohol use, living in poverty, and being an MSM. Data on social vulnerabilities were collected at enrolment.

With regard to drug use, people who use drugs (PWUD) included individuals who reported that they had been infected with HCV through drug injection, crack cocaine users, and individuals who reported having injected or snorted drugs at least once in their lives and/or who were receiving opioid agonist therapy (OAT), including methadone, buprenorphine, morphine sulfate or any other opioid prescribed as an OAT. When the mode of drug administration was not reported, only heroin or cocaine users were considered as PWUD.

Unhealthy alcohol use was defined as reporting alcohol consumption > 2(3) alcohol units (AU)/day for women (men).

Living in poverty was defined as reporting a monthly household income below 1,015 euros per adult equivalent, which corresponds to the relative poverty line for France in 2015, as defined by the French National Institute for Statistical and Economic Studies (INSEE) (35).

MSM were identified by asking men whether they had had a sexual relationship with another man at least once in their lifetime.

Other variables considered

The following variables were also tested as potential correlates of treatment failure:

i. Sociodemographic characteristics: age at treatment initiation, sex, living with a main partner, educational level, employment status, having primary health insurance (through France's universal healthcare system).
ii. Environmental factors: family history of liver disease (HCV, HBV, decompensated cirrhosis, hepatocellular carcinoma (HCC)).
iii. Clinical data: time between diagnosis and treatment initiation, HCV genotype, HBV-HCV co-infection at inclusion, METAVIR score at enrolment (measured by invasive and non-invasive tests), Child-Pugh score at inclusion, decompensated cirrhosis at inclusion, hepatocellular carcinoma at treatment initiation.
iv. Calendar year at the end of treatment: this variable provided information about the different 'generations' of patients in terms of both levels of disease severity (decreasing over time) and generation of DAA, with more recent antivirals presumed to be more effective than older ones.

Age was considered as a fixed variable, measured at treatment initiation date. All other variables in 'i.' and 'ii.' were measured at cohort enrolment.

Statistical analysis

First, we performed a descriptive analysis of the sociodemographic, behavioral and clinical characteristics of the study population.

Poisson regression models then helped us assess the relationship between 'migrant status' and treatment failure. Categorical variables with a p-value <0.20 for at least one category in the univariable analysis were considered eligible to enter the multivariable model. The variable 'migrant status' was systematically included in the multivariable model, independently of its p-value. We performed a backward selection of all the other variables to maintain only significant variables (p-value <0.05 for at least one category of each variable) and confounders (variables modifying the association between migrant status and treatment failure) in the multivariable model.

The stability of the results obtained was then checked in a sensitivity analysis which was restricted to patients who were HCV treatment-naive at enrolment in ANRS CO22 HEPATHER (n=3401).

All analyses were performed with STATA/SE 14.2 software for Windows (StataCorp, Lakeway Drive, College Station, USA).

RESULTS

Sociodemographic and clinical characteristics of the study population

For the 9,212 patients who received DAA treatment during their follow-up in the ANRS CO22 HEPATHER cohort, we selected SVR data collected for the first DAA treatment received and excluded patients that did not meet the present study's criteria (i.e., HCV-treated with DAA before cohort inclusion *or* having no data on SVR *or* having missing data on geographical world region of origin *or* having missing data on migrant status) (Figure 1). Accordingly, 7,879 individuals were included (i.e., study population), 5,829 (74%) being classified as non-migrants, and 2,050 (26 %) as migrants. Median [interquartile range (IQR)] age was 57[51-65] years, 4433 (56 %) were male, 4503 (57%) were living with a main partner, 3474 (45%) had an educational level higher than high-school diploma, 3276 (42%) were employed, and all 7,879 (100%) had primary health insurance (through France's universal healthcare system) (Table 1).

Some sociodemographic characteristics differed significantly between migrants and non-migrants. Migrants were more likely than non-migrants to be living with a main partner and to have an educational level higher than high-school diploma (N=1260 (62 %) *versus* N=3243(56%), $p<10^{-3}$ and N=952 (47 %) *versus* N=2522 (44%) p= 0.013), respectively. However, they were less likely to be employed (N=728 (36%) than non-migrants (N=2548 (44%), $p<10^{-3}$) (Table 1).

When focusing on clinical characteristics, overall median [IQR] time between HCV diagnosis and treatment was 15 [8-21] years. Only 59 (1%) of the participants were coinfected with hepatitis B virus (HBV) and 3401 (43%) were classified as HCV treatment-naive at cohort enrolment. The treatment failure rate was 5% (N=369). Most participants (N=6042 (81%)) received sofosbuvir-based DAA treatment. Few patients were classified with decompensated cirrhosis (N=715 (9%)) and with HCC (N=175 (2%)). However, many (N=2757 (39%)) had a fibrosis-METAVIR score of F3/F4 or F4, 2132 (29%) had a recorded Child-Pugh score value (A, B or C), and 1550 (20%) had a family history of liver disease (Table 1).

No significant difference was observed between both groups regarding treatment failure. Neither was the type of treatment prescribed significantly different between migrants and non-migrants. However, migrants were more likely to have shorter delays between diagnosis and treatment than non-migrants. They were also more likely to be HBV coinfected and to have a family history of liver disease (Table 1).

Analysis of factors associated with treatment failure

In the univariable analyses, being a migrant from Central Asia, not having primary health insurance, being an MSM, shorter time between diagnosis and treatment, and calendar year of the end of treatment, were all significantly associated with treatment failure ($p< 0.05$) (Table 2). The other variables eligible for the multivariable analysis ($p< 0.20$) were employment, living in poverty, accumulation of social vulnerabilities, and being HCV treatment naive (Table 2).

In the multivariable model, which was adjusted for calendar year of treatment (the only other significant variable in the final multivariable model), migrants from Central Asia were the only migrant subgroup at higher risk of experiencing treatment failure than non-migrants (aIRR=2.83, 95% CI [1.72, 4.65]) (Figure 2). Furthermore, the treatment failure rate decreased between 2014 and 2017-2018 (with a 59%, 64% and 78% reduction in 2015, 2016 and 2017-2018, respectively, in comparison with 2014) ($p<10^{-3}$).

These results were confirmed in a sensitivity analysis (n=3401), with an aIRR [95% CI] =3.15 [1.80 – 5.50] for migrants from Central Asia (compared with non-migrants) after adjustment for calendar year of treatment, which, just as in the main analysis, was the only adjustment variable significantly associated with treatment failure in the multivariable model.

Among the 105 migrants from Central Asia, 25 (24%) were born in Armenia, 16 (15%) Azerbaijan, 45 (43%) Georgia, 6 (6%) Kazakhstan, 5 (5%) Kirghiziztan, 7 (7%) Mongolia, and 1 (1%) Uzbekistan.

Migrants from Central Asia (94%) were more likely to face an accumulation of social vulnerabilities than other migrants (63%) and non-migrants (18%). They were also more affected by poverty (90%) than other migrants (52%) and non-migrants (26%). However, non-migrants were more likely to be PWUD (41%) and MSM (2%) than were migrants from Central Asia (37% and 0%) and other migrants (19% and 1%). Unhealthy alcohol use rates were similar for non-migrants (5%), migrants from Central Asia (5%) and other migrants (2%) (Figure 3).

Migrants from Central Asia were more likely to be infected only by HCV genotypes 1, 2 and 3 while non-migrants and other migrants were more likely to have HCV genotypes 1 to 5. Time between HCV diagnosis and treatment was shorter (5 years in median, [interquartile range]: [2-10]) in Central Asia migrants than in non-migrants (16[9-21] years) and other migrants (12[6-18] years). However, treatment failure was higher in the former group (13% *versus* 5% in both non-migrants and other

migrants). Calendar year, METAVIR score, Child-Pugh score, decompensated cirrhosis and HCC were not significantly different between the three groups (Table 3 in supplementary materials).

DISCUSSION

This is the first study in France to compare DAA treatment failure rates between migrants and non-migrants in a real-world setting, in a large sample of chronically HCV-infected patients treated with DAA. Using data on the first DAA treatment received, overall, we found a very low treatment failure rate over the study period (2012-2018). This result reflects findings from the only other recent study on DAA effectiveness in migrant populations in France - the PRECAVIR study - which showed the effectiveness of a coordinated HCV care network organized for a migrant population (36).

However, despite being low globally, the treatment failure rate in our study was significantly higher in migrants from Central Asia than in non-migrants. Available data on the HCV cascade of care in the Central Asia region show great disparities between countries (7). For instance, Georgia, which is the country of birth most represented among Central Asian migrants in our study, has significantly scaled up HCV treatment since the establishment of its national HCV program in 2015 (37). Indeed, the country is now well on the way to eliminating the disease (38). By contrast, there is still a lack of epidemiological data for Azerbaijan, another of the Central Asia countries strongly represented in our study (39).

Unlike our study, several studies on migrant populations in Europe have found good rates of HCV treatment effectiveness, with no association between treatment effectiveness and geographic world region of origin (36,40).

The higher risk of treatment failure observed among migrants from Central Asia in our study could have been related to differences with other migrants and non-migrants concerning type of DAA received, HCV genotype, calendar year of treatment ("generational" effect), and liver disease stage.

However, post-hoc comparisons of characteristics between migrants from Central Asia, other migrants and non-migrants (Table 3 in supplementary material) showed no significant differences in the type of DAA treatment received between these three groups.

In addition, sofosbuvir-based treatments - which were the most frequent DAA in our cohort - have been proven to be over 90% effective in CHC patients with HCV genotypes 1 to 3 (41–46). Considering that migrants from Central Asia in our study were only infected by these same genotypes, and that the association between this sub-population and treatment failure persisted even after adjustment for genotype, we therefore also presume that this association is not attributable to genotype.

Moreover, we found no significant difference in the calendar year of the end of treatment between migrants from Central Asia, non-migrants and other migrants and liver disease status (measured at cohort enrolment) of migrants from Central Asia was not significantly different from that of the other subgroups of patients (Table 3 in supplementary materials).

We found that migrants from Central Asia reported drug use and very poor social conditions more frequently than the other patient subgroups (Figure 3). However, in the univariable analyses, drug use and living in poverty were not significantly associated with SVR.

Given all the points above, the question therefore arises as to what were the probable reasons for the higher risk of treatment failure we observed in migrants from Central Asia. We hypothesize that other possible social vulnerabilities, not measured in our study (e.g., literacy, language barriers, discrimination), may partially explain this finding.

Nevertheless, the treatment failure rate was relatively low among migrants from Central Asia (13%) and could probably be reduced further with adequate interventions focused on improving adherence and retention in care. To this end, there is a need to implement care strategies which take into account language and cultural barriers specific to migrants from Central Asia. Feedback from field-based experience, including feedback from the non-governmental organization Médecins du Monde's centers of care and orientation (CASO) (47), can be of great help in designing such strategies. Proposing HCV screening during immigration medical check-up (15) and implementing test-and-treat strategies could also potentially improve the HCV cascade of care for migrant populations.

SVR rates increased significantly according to the calendar year of the end of treatment in our study. This may be the result of increased effectiveness of newer generations of DAA which foster better adherence and fewer treatment interruptions (36,40,48)(49)(50)(49)(47)(45)(44)(43)(42)(41)(40). However, we did not have data to determine whether individuals with detectable HCV-RNA load had not been fully adherent to treatment, whether they were non-responders to treatment or whether they were re-infected (although this was unlikely to occur in patients in HEPATHER as they were not exposed to classic reinfection risk factors (injecting drug use, chemsex, etc.)). Although there is a dearth of studies on DAA treatment adherence in migrant populations, studies on the general population in various countries have shown good adherence (50,51). Another hypothesis for the increase in SVR rates according to the calendar year of the end of treatment, was that patients treated with DAA in the first years of the advent of these new treatments had the most complex liver conditions. However, this hypothesis was rejected, as the proportion of those with advanced liver disease did not change according to the calendar year of the end of treatment.

Our study found that migrants from Central Asia and other migrants had shorter delays between diagnosis and treatment initiation than non-migrants, which may suggest delayed diagnosis for the former two groups, although this cannot be verified, as data on fibrosis at diagnosis were not available. Another reason for shorter delays could be a family history of liver disease - a classic social vulnerability factor -, which tended to be higher in migrants than non-migrants-, and which, in clinical practice, is positively associated with treatment acceptability and demand.

Our finding that migrants from Central Asia had significantly higher treatment failure rates than non-migrants and other migrants suggests the need for specific care and treatment strategies for this sub-population. Previous studies in France highlighted that, in general, migrants are under-screened and under-treated (3). Other studies on vulnerable populations, including migrants, have shown that the latter are less likely to access DAA treatment, and more likely to have delayed treatment than non-vulnerable populations (19, 20).

Strengths and limitations:

The main strength of our study is its statistical power, which is crucial to minimize beta error. However, this can also be considered a limitation, as negligible differences in size can become significant due to the statistical power. Accordingly, results need to be interpreted with caution. Some self-reported items (e.g., alcohol use) may have been underestimated in our study. This may have reduced estimates of incidence rate ratios to more conservative values. Furthermore, exposure to non-DAA treatments for some individuals in the study sample may have influenced treatment failure rates. However, we found a very low rate of treatment failure. Furthermore, the results of the sensitivity analysis on a population of naive patients at enrolment and receiving a single DAA treatment showed similar results.

CONCLUSIONS

This is the first large real-world study in France to explore differences in SVR rates following DAA treatment between HCV-infected migrants and non-migrants. Despite an overall low treatment failure rate, migrants from Central Asia presented a higher risk of treatment failure than non-migrants. Simplified models of care taking into account language and cultural barriers are needed to improve effectiveness of DAA for this sub-population. Findings from this study can help stakeholders advocate for improved screening and access to treatment for HCV-infected migrants, especially those who are most vulnerable, not only in France but worldwide.

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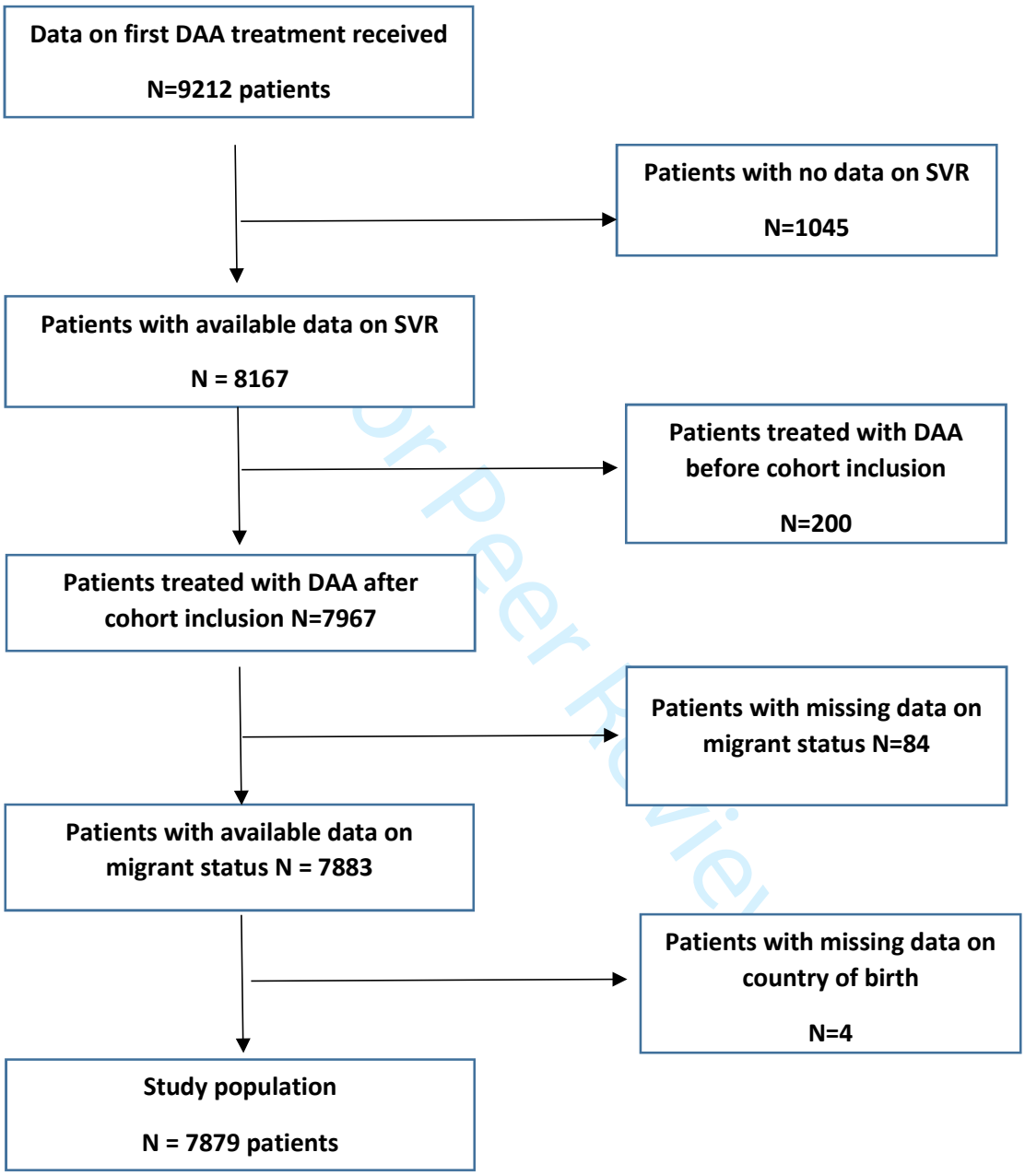
Tables and figures

Figure 1: Selection of the study population



Abbreviations: DAA = direct-acting antivirals; SVR = sustained virological response

Table 1: Comparisons of sociodemographic and clinical characteristics between migrants and non-migrants (ANRS CO22 HEPATHER cohort, n=7879)

Variables	Total n=7879	Non-migrants n (%) 5829(74 %)	Migrants n (%) 2050(26 %)	p-value
Age at treatment initiation (Median[IQR] years)	57[51-65]	56[51-65]	58[50-66]	0.117
Male sex	4433(56)	3292(56)	1141(56)	0.521
Living with a main partner	4503(57)	3243(56)	1260(62)	$<10^{-3}$
Educational level ≥ high-school diploma	3474(45)	2522(44)	952(47)	0.013
Employment	3276(42)	2548(44)	728(36)	$<10^{-3}$
Having primary health insurance (through France's Universal Insurance Scheme)	7838(100)	5806(100)	2032(99)	$<10^{-3}$
Time between diagnosis and treatment (in years)	15[8-21]	16[9-21]	12[6-17]	$<10^{-3}$
HCV treatment-naive	3401(43)	2531(44)	870(43)	0.449
Calendar year at the end of treatment				
2014	1890(24)	1405(24)	485(24)	
2015	3206(41)	2366(41)	840(41)	0.479
2016	1407(18)	1058(18)	349(17)	
2017-2018	1376(17)	1000(17)	376(18)	
Treatment failure	369(5)	265(5)	104(5)	0.331
Family history of liver disease (viral infection, decompensated cirrhosis, HCC)	1550(20)	1090(19)	460(23)	$<10^{-3}$
METAVIR score				
F0 - F3	4354(61)	3265(62)	1089(59)	
F3/F4 – F4	2757(39)	2015(38)	742(41)	0.074
Child-Pugh score				
A/B/C	2132(29)	1550(29)	582(31)	
No suspicion of cirrhosis	5135(71)	3818(71)	1317(69)	0.145
Decompensated cirrhosis	715(9)	521(9)	194(10)	0.451
Hepatocellular carcinoma (HCC)	175(2)	137(2)	38(2)	0.190
HCV genotype				
1	5006(65)	3886(68)	1120(56)	
2	505(7)	327(6)	178(9)	$<10^{-3}$
3	1001(13)	823(14)	178(9)	
4	1028(13)	537(9)	491(24)	
5/6/7	154(2)	114(2)	40(2)	
Type of HCV treatment				
Ombitasvir/Paritaprevir/Ritonavir-based	748(10)	561(10)	187(10)	
Glecaprevir/Pibrentasvir or Grazoprevir/Elbasvir	413(6)	295(5)	118(6)	
Sofosbuvir-based	6042(81)	4475(81)	1567(81)	
Other	247(3)	177(3)	70(4)	0.475
Chronic active HBV coinfection	59(1)	28(1)	31(2)	$<10^{-3}$

The total for some variables may differ from the number of individuals in the study population because of missing data.
Missing data in variables: Age at treatment initiation=10(0%); Living with a main partner=41(1%); Educational level=123(2 %); Employment=62(1 %); Having primary health insurance=83(0 %); Time between diagnosis and treatment=229(3%); HCV treatment-naive=47(1%); Family history of liver disease=105(1%); METAVIR score=768(10%); Child-Pugh score=612(8%); Decompensated cirrhosis=85(1); Hepatocellular carcinoma=2(0%); HCV genotype=185(2%); Type of HCV treatment=429(5%); Chronic active HBV coinfection=1753(22%)
Abbreviations: IQR= interquartile range; HCV=hepatitis C; HCC= hepatocellular carcinoma
Statistical tests used: Chi-square test and Wilcoxon-Mann-Whitney test for categorical and continuous variables, respectively.

Table 2: Association between migrant status and DAA treatment failure in patients with chronic HCV infection (Poisson regression models, univariable, ANRS CO22 HEPATHER cohort, n=7879)

Variables	Total	Univariable analyses			Multivariable analysis		
	N (%)	IRR	[95% CI]	p-value	IRR	[95% CI]	p-value
Migrant status							
Non-migrant	5829(74)	1			1		
Migrant from Central Asia[1]	105(1)	2.93	[1.78 ; 4.84]	$<10^{-3}$	2.83	[1.82 ; 4.65]	$<10^{-3}$
Other migrant	1945(25)	1.02	[0.81 ; 1.29]	0.882	1.02	[0.82 ; 1.30]	0.808
Age at treatment initiation (in years)	57[51-65]	1.00	[0.99 ; 1.00]	0.372			
Sex							
Male	4433(56)	1					
Female	3446(44)	1.05	[0.86 ; 1.28]	0.653			
Living with a main partner							
Yes	4503(57)	1					
No	3335(43)	1.10	[0.90 ; 1.35]	0.339			
Educational level ≥ high-school diploma							
<high-school diploma	4282(55)	1					
≥ high-school diploma	3474(45)	1.01	[0.83 ; 1.24]	0.909			
Employment							
Yes	4541(58)	1					
No	3276(42)	0.85	[0.70 ; 1.05]	0.135			
Primary health insurance (through France's Universal Insurance Scheme)							
Yes	7838(100)	1					
No	19(0)	3.39	[1.19 ; 9.62]	0.022			
Drug use							
No	5087(65)	1					
Yes	2792(35)	0.90	[0.73 ; 1.11]	0.330			
Unhealthy alcohol use							
No	7483(96)	1					
Yes	335(4)	0.69	[0.38 ; 1.24]	0.215			
Living in poverty							
No	5106(67)	1					
Yes	2514(33)	1.22	[0.99 ; 1.50]	0.063			
MSM							
No	7761(98)	1					
Yes	118(2)	1.83	[1.00 ; 3.34]	0.049			
Accumulation of vulnerability factors							
0-1	5315(70)	1					
2-4	2276(30)	1.20	[0.97 ; 1.48]	0.08			
Time between diagnosis and treatment (in years)	15[8-21]	0.98	[0.97 ; 1.00]	0.016			
HCV treatment naive							
No	4431(57)	1					
Yes	3401(43)	1.14	[0.93 ; 1.40]	0.196			
Family history of liver disease (viral infection, cirrhosis, HCC)							
No	6224(80)	1					
Yes	1551(20)	0.86	[0.66 ; 1.12]	0.275			
METAVIR score							
F0-F3		1					
F3/F4-F4		1.02	[0.83 ; 1.27]	0.817			
Child-Pugh score							
No suspicion of cirrhosis	5135(71)	1					
A/B/C	2132(29)	1.09	[0.43 ; 0.87]	0.79			
Decompensated cirrhosis							
No	7079(91)	1					
Yes	715(9)	1.18	[0.85 ; 1.63]	0.313			
Hepatocellular carcinoma							
No	7702(98)	1					
Yes	175(2)	1.22	[0.51 ; 0.67]	0.65			
Calendar year at the end of treatment							
2014	1890(24)	1			1		
2015	3206(41)	0.40	[0.32 ; 0.51]	$<10^{-3}$	0.41	[0.32 ; 0.51]	$<10^{-3}$
2016	1407(18)	0.37	[0.27 ; 0.51]	$<10^{-3}$	0.63	[0.27 ; 0.50]	$<10^{-3}$
2017-2018	1376(17)	0.22	[0.15 ; 0.33]	$<10^{-3}$	0.22	[0.15 ; 0.33]	$<10^{-3}$

HCV genotype								
	1	5006(65)	1					
	2	505(7)	0.84	[0.53 ; 1.31]	0.431			
	3	1001(13)	0.98	[0.73 ; 1.33]	0.914			
	4	1028(13)	0.83	[0.60 ; 1.15]	0.265			
	5/6/7	154(2)	0.81	[0.37 ; 1.79]	0.604			
Chronic active HBV coinfection								
	No	6067(99)	1					
	Yes	59(1)	1.45	[0.45 ; 0.56]	0.446			

[1] The following countries of birth were categorized as belonging to the Central Asia region: Armenia; Azerbaijan; Georgia; Kazakhstan; Kirghiziztan; Mongolia; and Uzbekistan.

Missing data in variables: Migrant status with/without vulnerability=181(2%); Age at treatment initiation=10(0%); Living with a main partner=41(1%); Educational level=123(2 %); Employment=62(1 %); Primary health insurance=83(0 %); Unhealthy alcohol use=61(01%); Living in poverty=259(3%); Accumulation of vulnerability factors =292(4%), Time between diagnosis and treatment=229(3%); HCV treatment naive patient =47(1%); Family history of liver disease=105(1%); METAVIR score=768(10%); Child-Pugh score=612(8%); Decompensated cirrhosis=85(1); Hepatocellular carcinoma=2(0%); HCV genotype=185(2%); Chronic active HBV coinfection=1753(22%)

Definition of variables:

Treatment failure = the lack of sustainable virological response (SVR), measured by Polymerase Chain Reaction (PCR), 12 weeks after the end of first DAA treatment.

Migrants = individuals not born in France who reported having at least one parent of non-French origin.

People who use drugs (PWUD) = individuals who reported that they had been infected with HCV through drug injection, crack users, and individuals who reported having injected or snorted drugs at least once in their lives and/or who were receiving opioid agonist therapy (OAT), including methadone, buprenorphine, morphine sulfate or any other opioid prescribed as an OAT. When the mode of drug consumption was not reported, only heroin and cocaine users were considered PWUD.

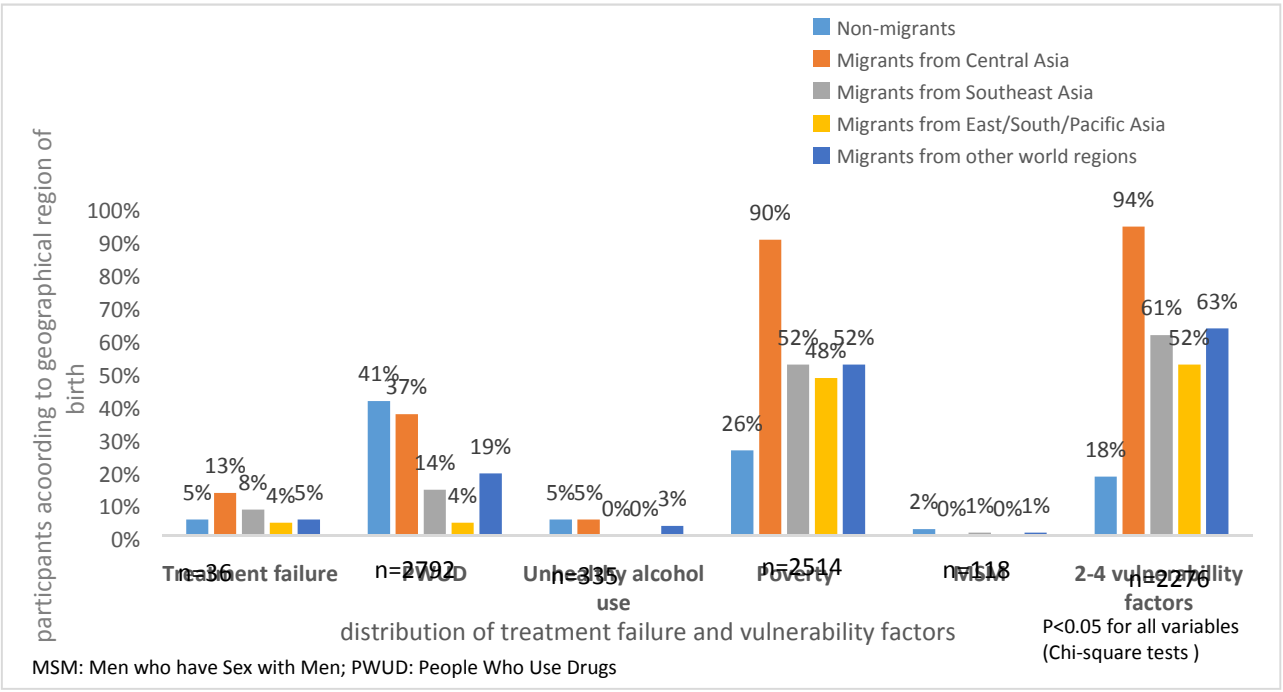
Unhealthy alcohol use = alcohol consumption > 2(3) alcohol units (AU)/day for women (men).

Living in poverty = a monthly household income below 1,015 euros per adult equivalent, which corresponds to the relative poverty line for France in 2015, as defined by the French national institute for statistical and economic studies (INSEE).

Men who have sex with men (abbreviation MSM) = men who reported having sexual relationships with male partners at least once in their life

Abbreviations: IQR= interquartile range; HCV=hepatitis C; HCC= hepatocellular carcinoma; MSM = men who have sex with men

Figure 2: Distribution of DAA treatment failure and vulnerability factors according to migrant status and world region of birth in patients with chronic HCV infection (ANRS CO22 HEPATHER cohort, n=7,879)



MSM: Men who have Sex with Men; PWUD: People Who Use Drugs

Migrants from Central Asia[1]

Migrants from Southeast Asia

Migrants from East/South/Pacific Asia

Migrants from other world regions

[1] The following countries of birth were categorized as belonging to Central Asia: Armenia; Azerbaijan; Georgia; Kazakhstan; Kirghiziztan; Mongolia; and Uzbekistan

Missing data in variables:

Unhealthy alcohol use = 61(01%); Living in poverty=259(3%); Accumulation of vulnerability factors=292(4%)

Definition of variables:

Treatment failure = the lack of sustained virological response (SVR), measured by Polymerase Chain Reaction (PCR), 12 weeks after the end of first DAA treatment.

Migrants = individuals not born in France who reported having at least one parent of non-French origin.

People who use drugs (PWUD) = individuals who reported that they had been infected with HCV through drug injection, crack cocaine users, and individuals who reported having injected or snorted drugs at least once in their lives and/or who were receiving opioid agonist therapy (OAT), including methadone, buprenorphine, morphine sulfate or any other opioid prescribed as an OAT. When the mode of drug consumption was not reported, only heroin or cocaine users were considered PWUD.

Unhealthy alcohol use = alcohol consumption > 2(3) alcohol units (AU)/day for women (men).

Living in poverty = a monthly household income below 1,015 euros per adult equivalent, which corresponds to the relative poverty line for France in 2015, as defined by the French National Institute for Statistical and Economic Studies (INSEE).

Men who have sex with men (MSM) = men who reported having sexual relationships with male partners at least once in their life.