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Prevalence and risk factors for Hepatitis C viral infection amongst a cohort of Irish drug users attending a drug treatment centre for Agonist Opioid Treatment (AOT)

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Summary

Background: Injecting drug use (IDU) is a major driver of the European hepatitis C virus (HCV) epidemic. National data on prevalence of HCV amongst Irish drug users remains confined to certain treatment sites and prison settings. **Aim:** To examine the prevalence of HCV infection and risk factors associated with infection among the 228 patients attending agonist opioid treatment (AOT) in a clinic in Dublin. **Methods:** A retrospective cross-sectional study was conducted using data collected from Health Research Board (HRB) forms and standardised written and electronic assessment forms routinely completed on treatment initiation. **Results:** The prevalence of HCV infection was 63.6 % (n= 145) with no significant gender difference (p=0.717). Patients who were infected with HCV were older than those uninfected (41.1 ± 7.5 years versus 37.5 ± 8.5 years; p = 0.001), with prevalence significantly lower in younger adults (p=0.002). Multivariate analysis identified age of first drug use (p=0.002) and first injection (p=0.001), type of first drug used; cannabis (p=0.015), heroin (p=0.014) and cocaine (p=0.018) and early age of AOT entry (p=0.001) as the most significant risk factors for HCV infection in this cohort. Those with no IDU had decreased odds of being HCV positive by 91.1%. **Conclusion:** Data for this Irish sample indicates high prevalence of HCV infection, and the need to consider age of first drug onset and injecting use, particular drug types and earlier commencement of AOT to inform targeted HCV treatment and prevention interventions in Ireland.

Key Words: Hepatitis C; HCV; Agonist Opioid Treatment; Blood Borne Virus

1. Introduction

Worldwide one hundred and eighty five million people are estimated to have acquired the hepatitis C virus (HCV) [38]. In the World Health Organization (WHO) European Region, fifteen million adults are estimated to have active HCV infection as defined by the presence of HCV-RNA [22, 28]. HCV antibody prevalence levels in the European general population range from 0.1% to 22%, with prevalence lower in northwestern European countries and higher in the countries of the south and southeast [19]. This translates into a regional adult prevalence rate of 2.0% [22]. Chronic disease outcomes occur in 55-85% of untreated HCV cases, with long term and chronic consequences including liver cirrhosis, liver failure and hepatocellular carcinoma. HCV is associated with impaired quality of life [51], with rates of advanced liver disease, related healthcare costs, and liver related mortality and morbidity rising [20].

HCV epidemics are driven by transmission in the smoking or inhaling of heroin, cocaine or crack [43], injecting of drugs [14, 50, 52] and from hetero-sexual and homo-sexual contact [49]. Injecting drug use (IDU) is a major driver of the European HCV epidemic [28]. HCV is primarily transmitted through unsafe injection practices, including sharing of needles, cookers, cottons, rinse water, and the practice of

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backloading [42]. 2010/11 data across 18 European countries has indicated that IDU accounts for 58% of HCV diagnosis [10]. Two million of the WHO European Region's 15 million adults with HCV-RNA are people who inject drugs (PWID) [22]. Hahne et al. [19] in their systematic review estimate HCV antibody prevalence among PWID in 29 European countries ranging from 5% to 90%. In eight of the 12 countries with HCV antibody data in the 2013 European Drug Report, prevalence exceeded 40% in national samples of PWID. Recent increases in HCV infection rates in PWID are observed in some European countries, despite enhanced coverage of effective prevention strategies [29]. Elsewhere, median prevalence among PWID in the United States (US) is estimated to be 65% [17, 39].

Continued risk of new HCV outbreaks and clusters are evident globally. In recent years, clusters of acute HCV infection amongst those misusing prescription opioids and transitioning to IDU are reported in the United States [25]. Outbreaks amongst other at risk populations include new injectors originating from the prescription opioid epidemic [5]; men who have sex with men (MSM) particularly among those infected with HIV [18], and injectors of new synthetic psycho-actives [13]. Difficulties also centre on high prevalence of HCV in an aging PWID population, with many undiagnosed and not accessing HCV prevention, care and treatment [14] and with low HCV treatment uptake reported among PWID in many settings [23, 28, 52]. PWID whilst being at greatest risk of HCV viral infection, are often denied immediate treatment due to concerns around on-going risk behaviour [50]. HCV treatment outcomes in PWID however are comparable to patients with no history of drug use [3]. Treatment also eliminates potential for further transmission [35]. The advocated 'HCV cascade of care' consists of enhanced diagnosis, linking of individuals into HCV care, increasing treatment uptake and enhancing viral cure, and requires an integrated evaluation model addressing multiple points along the cascade [30]. Combined harm reduction, agonist opioid treatment (AOT) and needle and syringe exchange programmes (NSP) and provision of AOT alone can reduce HCV incidence [15]. The continued development of HCV treatment has created opportunities to offer HCV treatment in conjunction with addiction treatment in a holistic manner, particularly to the aging patient with history of IDU [36].

In Ireland, up until 2004, HCV was not a notifiable disease, although cases could be notified as 'viral hepatitis type unspecified' [7]. The National Hepatitis C Strategy in 2011-2014 observes the limited information available on distribution of HCV infection, and outlines a series of action plans to reduce HCV transmission and improve patient care in Ireland. Little has been published in Ireland on the prevalence of co-infection of HCV with HIV and/or hepatitis B [33]. More than 10 000 people were HCV infected in 1989–2004, with the numbers peaking in 2000 [4]. There were 9, 282 cases of HCV notified in Ireland between 2004 and 2010 (surveillance data has been implemented since 2007). It is estimated now that between 20 000-50 000 people in Ireland are chronically infected with HCV (prevalence of 0.5–1.2%), and is similar to other Northern European countries. Of the six HCV genotypes, Genotype 1 and 3 are most common in Ireland [6, 26]. Risk factors for HCV status in Ireland are similar to extant literature elsewhere and centre on injecting drug use, length of time injecting, frequency of injecting, needle sharing and having a prison history [1, 4, 44, 48]. It is estimated that 70% of patients in drug treatment are HCV infected [33]. Most recent data indicates prevalence of HCV in the Irish PWID population ranges from 62%-81% [21]. Localised prevalence estimates within the PWID population attending community drug services range from 54% [45] to 84% [44]. Irish prison inmates and entrants are 81% [1] and 72% [31] respectively. Smyth et al. [47] in a later study reported on incidence of HCV among PWID attending treatment in Dublin was 66 per 100 person years. Grogan et al. [16] reported an incidence of 24.5 per 100 person years among a sample (n=358) of Irish opiate users (including some non-injectors) attending treatment. Recent studies in Irish prisons of patients on methadone indicated the need for more extensive screening of HCV and other blood borne virus infections [9, 12]. Addiction services in Ireland provide routine screening for HCV infection with follow-up PCR testing and referral to the acute hospital specialist services when recommended [7]. However, low uptake of screening and follow up assessments are reported amongst Irish drug users [37, 40] and prisoners [32]. Other concerns centre on continued HCV risk behaviours amongst Irish drug users despite presence of harm reduction interventions [46]. The aims of the study were primarily to estimate the prevalence of HCV infection among patients attending the Thompson Centre, a drug treatment clinic providing AOT and operated by the HSE in Dublin, Ireland, and secondly to estimate risk factors associated with HCV infection among this particular patient cohort.

2. Methods

2.1. Setting

The HSE is the national executive responsible for the provision of AOT in Ireland. Methadone treatment services are provided via specialist addiction treatment centres, community-based clinics) and general practitioners (GPs). This study was conducted in a satellite clinic in Dublin's North Inner City. The clinic's viral screening policy is to offer all patients a complete viral drug screen within a one month period of starting AOT. This screen includes testing for Hepatitis A, B, and C and HIV infection. Each patient is reviewed annually to assess if further risk behaviour has occurred and is retested where appropriate. Testing for HCV antibodies (anti-HCV) is carried out using a third generation enzyme-linked Immunoabsorbent Assay (ELISA). Alternatively, if a patient reports that a viral screen has been taken recently at another location, following the getting of the patients' written consent the test results are verified in writing by the National Virus Reference Laboratory (NVRL). These results are kept in the patients' clinical records.

Ethical approval for the study was granted by the School of Health Sciences Ethics Committee, School of Medicine, Trinity College Dublin, Ireland.

2.2. Sample

The study sample (n=273) was the number of patients registered on the Central Treatment List (a national register for all patients in receipt of AOT) and attending the Thompson Centre for AOT on 31 January 2015. A Patient Information Letter (PIL) was given to each patient. The letter explained the purpose of the study and the requirements for involvement. The gatekeeper explained the study in detail and answered any questions or concerns which arose in this regard. Seven days after the date of distribution of the letter, author one (DK) met each patient at their next clinic appointment and a consent form was read to each patient. The patient then indicated, in writing, his/her consent or refusal to allow the researcher access to their medical records for the purposes of the study. Out of 273 suitable patients, 45 were excluded for the reasons outlined in Figure 1, with 228 patients remaining.

2.3. Data collection

The data was extracted from historical records obtained from the medical charts (written and computerized) held on each patient at the study site. Prior to initiation onto AOT, the clinic nurse completes a standardised initial assessment and Health Research Board (HRB) form on each patent. These forms collect a range of demographic and clinical details on each patient, including patient date of birth (DOB); sex; age of first drug use, type of first drug used, age of first injection, date of first episode of AOT, history of IDU and HCV status. The data submitter extracted all available data from completed written assessment and HRB forms. In instances where data was missing from the written records, the data controller reviewed electronic records and extracted the relevant missing

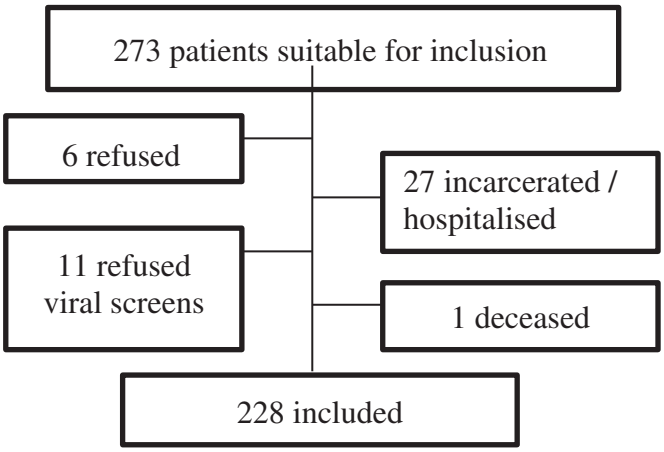

Figure 1. Recruitment and exclusion of patients

Table 1. Demographic characteristics, drug use behaviour and HCV status of patients

	Total (n=228)	HCV Antibody Negative(n=83)	HCV Antibody Positive(n=145)	P-Value**
Age (yrs) *	39.7 ± 8.0	37.5 ± 8.5	41.1 ± 7.5	0.001
Female n (%)	60(26.3)	23(27.7)	37(25.5)	0.717
Age first drug use (yrs) *	15.4 ± 5.1	16.8 ± 6.9	14.6 ± 3.5	0.002
Type of first drug n (%)				
Alcohol	7 (3.1)	3(3.6)	4(2.8)	0.719
Benzodiazepine Hypnotic	15(6.6)	2(2.4)	13(9)	0.055
Cannabis	150 (65.8)	63(75.9)	87(60)	0.015
Cocaine	1(0.4)	1(1.2)	1(0.4)	0.018
Ecstasy	3(1.3)	2(2.4)	1(0.7)	0.273
Hallucinogens-Lysergic	6(2.6)	1(1.2)	5(3.4)	0.309
Heroin	19(8.3)	2(2.4)	17(11.7)	0.014
Opioid tablet	2(0.9)	1(1.2)	1(0.7)	0.688
Opioids	12(5.3)	6(7.2)	6(4.1)	0.315
Solvents	3(1.3)	0	3(2.1)	0.187
Stimulants	8(3.5)	1(1.2)	7(4.8)	0.153
Benzodiazepine	2(0.9)	1(1.2)	1(0.7)	0.688
Age first IDU (yrs) *	21.7±7.2	26.5 ± 8.6	20.1 ± 6.0	<0.001
Age first AOT (yrs) *	24.9 ± 7.7	27.3 ± 8.2	23.5± 7.1	<0.001

Mean & SD=Standard Deviation; **P assessed by independent T-test or chi-squared analysis where applicable. P-value ≤ (0.05) set for levels of significance.

data and provided it to the data submitter.

At the initial phase of data entry onto Excel, patients' initials were used and only the data submitter had access to the records, which were held on a password protected computer at the study location. Once the data entry was complete, each patient's record was anonymised by removing the patient's initials and replacing them with a numerical identifier. An audit of the data set was conducted on patients with HCV antibody positive results in order to verify that the data submitter's HCV status recording matched the HCV status on the patient's records thus giving an accurate representation of HCV prevalence.

2.4. Data analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (Version 21.0; SPSS UK Ltd; Chersey, UK). Data was assessed for normality by means of a Kolmogorov-Smirnov test and Q-Q plots, and the data was log-transformed for normalization purposes. Data are expressed as means and Standard Deviations (SD) and where appropriate, an independent sample T-test was applied to determine statistical significance ($p \leq 0.05$). Categorical variables were assessed by chi-square analysis. A multinomial logistic regression analysis was performed to determine the predictors of HCV positive results.

3. Results

3.1. Patient demographics and HCV infection

Of the 228 study participants, 168 (73.7%) were male and 60 (26.3%) were female. In total, 145 of the 228 patients tested positive for HCV antibodies giving an overall prevalence in this cohort of 63.6%. There was no significant difference between gender and HCV status. Approximately, 57 (25%) were aged between 21-34 years, termed 'younger adults' and 171 (75%) were aged between 35 and 65 years, termed 'older adults'. The mean age of the study participants at cohort entry was 39.7 years (SD 8.0) with an age range of 21 to 65 years. Age was found to be statistically significant in HCV status; patients who were infected with HCV were older than those who were uninfected (41.1 ± 7.5 years versus 37.5 ± 8.5 years; $p = 0.001$). The prevalence of a HCV positive result was significantly lower in younger adults compared to older adults ($p=0.002$).

3.2. Drug related risk factors

Analysis of the type of first drug used showed that the vast majority of the sample used cannabis (70%) followed by heroin (8.3%) and benzodiazepines (6.6%). The use of cannabis ($p= 0.05$) co-

Table 2. All Cases

Variable	Test	β-Value	Odds ratio	95% Confidence Interval	*p* Value
Age (yrs)	-	+ 0.105	1.111	1.051 – 1.175	<0.001
Age First time Drug use (yrs)	-	-0.077	0.926	0.850 – 1.009	0.079
Age First time AOT (yrs)	-	- 0.114	0.892	0.843 – 0.944	<0.001
Reference Category					
Male	Female	+ 0.233	1.262	0.571 – 2.792	0.565
IDU Yes	IDU No	- 2.491	0.089	0.040 – 0.198	<0.001
Reference category is HCV Negative (Multinomial logistic regression)					

Table 3. All cases IDU only

Variable	Test	β-Value	Odds ratio	95% Confidence Interval	*P* Value
Age (yrs)	-	+ 0.138	1.148	1.071 – 1.231	<0.001
Age 1st Drug use (yrs)	-	-0.045	0.956	0.870 – 1.049	0.342
Age 1st AOT T (yrs)	-	- 0.062	0.940	0.870 – 1.016	0.121
Age 1st IDU (yrs)	-	- 0.114	0.892	0.040 – 0.198	0.008
Reference Category					
Male	Female	+ 0.463	1.589	0.575 – 4.392	0.372
Reference category is HCV Negative (Multinomial logistic regression)					

caine (p=0.015) and heroin (p=0.014) as a first drug was significantly associated with HCV infection. Other substances such as the use of opioid tablets (p= 0.315), stimulants (p=0.153), alcohol (p=0.719) and benzodiazepines (p=0.69) as a first time drugs used were not significantly associated with HCV infection. The patients infected with HCV were statistically significantly younger at first drug use (p=0.002), first IDU (p< 0.001) and first AOT (p<0.001). Table 1.

3.3. Multivariate analysis: All Cases

A multiple logistic regression analysis was conducted on factors significantly associated with HCV status in the univariate analyses: age, age of first drug use, age of first IDU and age of first AOT. Analyses investigated the effects of patient age, sex, age of first drug use, age of first IDU and age of first AOT on a HCV positive result, in order to calculate increased or decreased risks of infection. Table 2.

In the regression analysis of all cases using HCV negative as the reference category, with increasing age the odds of being in the HCV positive group increased by 11.1%, while with each unit increase in age of first AOT, the odds of being in the HCV positive group decreased by 10.8%. Those with no history of IDU had decreased odds of being HCV positive by 91.1%. In a regression analysis of all cases IDU only using HCV negative as the reference category, with each unit increase in age, the odds of being in the HCV positive group increased by 14.8% while with each unit increase in age of first IDU, the odds of being in the HCV positive group decreased by 10.8%. Table 3.

3.4. Multivariate analysis: Females

In a regression analysis of females only using HCV as the reference category, it was observed that with each unit increase in age of first AOT, the odds of being in the HCV positive group decreased by 12.6%. Females with no IDU had decreased odds of being HCV positive by 93.5%. (Table 4 and 5).

3.5. Multivariate analysis: Males

In a regression analysis of males only using HCV negative as the reference, with increasing age, the odds of being in the HCV positive group increased by 13.6%, while with each unit increase in age of first time drug use, the odds of being in the HCV positive group decreased by 14.9%. With each unit increase in age of first AOT, the odds of being in the HCV positive group decreased by 10.9%. Patients with no IDU had decreased odds of being HCV positive by 91.1%. Males with no IDU had decreased odds of being HCV

Table 4. Females only

Variable	Test	β-Value	Odds ratio	95% Confidence Interval	P Value
Age (yrs)	-	+ 0.045	1.046	0.931 – 1.174	0.448
Age 1st Drug use (yrs)	-	+ 0.094	1.098	0.924 – 1.306	0.289
Age 1st AOT (yrs)	-	- 0.135	0.874	0.766 – 0.996	0.044
Reference Category					
IDU Yes	IV use No	- 2.739	0.065	0.013 – 0.325	0.065
Reference category is Hep C Negative (Multinomial logistic regression)					

Table 5. Females IDU only

Variable	Test	β-Value	Odds ratio	95% Confidence Interval	P Value
Age (yrs)	-	+ 0.041	1.041	0.893 – 1.214	0.604
Age 1st Drug use (yrs)	-	+ 0.093	1.097	0.885 – 1.360	0.398
Age 1st AOT (yrs)	-	- 0.008	0.992	0.774 – 1.272	0.951
Age 1st IDU (yrs)	-	- 0.072	0.931	0.743 – 1.165	0.531
Reference category is Hep C Negative (Multinomial logistic regression					

Table 6. Males only

Variable	Test	β-Value	Odds ratio	95% Confidence Interval	P Value
Age (yrs)	-	+ 0.127	1.136	1.062 – 1.214	<0.001
Age 1st Drug use (yrs)	-	- 0.162	0.851	0.743 – 0.974	0.019
Age 1st AOT (yrs)	-	- 0.116	0.891	0.835 – 0.950	<0.001
Reference Category					
IDU Yes	IV use No	- 2.362	0.094	0.035 – 0.251	<0.001
Reference category is Hep C Negative (Multinomial logistic regression)					

Table 7. Males IDU only

Variable	Test	β-Value	Odds ratio	95% Confidence Interval	P Value
Age (yrs)	-	+ 0.172	1.188	1.088 – 1.297	<0.001
Age 1st Drug use (yrs)	-	- 0.137	0.872	0.731 – 1.041	0.129
Age 1st AOT (yrs)	-	- 0.081	0.922	0.842 – 1.009	0.078
Age 1st IDU (yrs)	-	- 0.139	0.870	0.784 – 0.966	0.009
Reference category is Hep C Negative (Multinomial logistic regression)					

positive by 90.6%. In a regression analysis of males IV use only using HCV negative as the reference category, with increasing age, the odds of being in the HCV positive group increased by 18.8%, while with each unit increase in age first IDU, the odds of being in the HCV positive group decreased by 13.0%. (Table 6 and 7).

4. Discussion

PWID constitute a high-risk and high-prevalence population for HCV infection [28, 41]. This Irish study presents prevalence data of HCV infection in a North Dublin clinic providing patients with AOT. The 3:1 male to female ratio is a consistent ratio for patients on AOT and in the general opioid using population. The prevalence rate of 63.6% among this cohort falls within the range reported in the available Irish literature [21, 33, 43, 45], in Europe [19] and the US [17, 39]. The systematic approach to viral screening and risk assessment with repeat testing at the centre enhances reliability of this estimate, along with the high follow-up rate (84%). We speculate given the high retention rate of AOT patients (>95%) in the

clinic, and the mix of patients attending, that the prevalence rate is generalizable to the wider problematic drug using population in the Dublin area. The high prevalence rate of HCV infection is a cause for concern and underscores the need for renewed efforts in primary prevention (including vaccine development), as well as new approaches to secondary and tertiary prevention in order to reduce the burden of chronic liver disease and to improve survival for these drug users having signs of liver disease.

This study has identified particular risk factors for HCV infection which can inform and target prevention strategies. Risks identified are similar to other studies by identifying IDU as risk factor and age, with HCV prevalence increasing particularly among those reporting injecting behaviours. No gender difference was reported. Of note was that patients with no injecting history had decreased odds of being HCV positive by 91.1%. Our study supports the need for enhanced focus on interventions reaching out to non-injectors to deter injecting, interventions likely to reduce injecting or stimulate reverse route transitioning, as well as promoting safe injecting tactics [34]. Other indicators centred on age of first-time drug use and first injecting drug use, and types of first drugs used. Age of first IDU in this study was found to be associated with an increased risk of HCV infection. Larney et al. [27] have underscored the need to gain a greater understanding of those who have 'ever' injected drugs, including those who did so for a short duration or infrequently, in order to understand and characterize HCV infection among PWID. The transmission of HCV is complex among PWID, with many transmission events occurring between infected older and younger injectors, and phylogenetic clustering associated with younger age and HIV [24]. Of note is that some PWID despite long injection histories remained uninfected [11].

Barriers to effective HCV management amongst Irish injecting drug users centre on negative experiences at diagnosis, investigations and treatment and are similar to structural barriers reported elsewhere [8, 53]. The report by Long in 2006 [33] on blood borne viral infections among PWID in Ireland indicated a decentralised approach to HCV treatment with the initial assessment being done in general practice and treatment provided at local drug treatment centre achieved higher uptake and compliance rates than the hospital based centralised approach. Artenie et al. [2] have reported that for PWID attending harm reduction services, visiting a primary care provider was related to lower risk of HCV infection, despite only a minority of participants visiting primary care. This study highlighted the need to intensify efforts to engage PWID with GPs, particularly in combination with harm reduction. AOT can underpin successful HCV prevention interventions by treating non injectors, preventing their transitioning to injecting, and as a platform to engage HCV infected PWID in the HCV cascade of care continuum [41]. However, for patients attending AOT in primary care settings routine testing and vigilance is required. Revised international recommendations for the management of HCV infection among PWID stipulate how high coverage of combined AOT and NSP programs can reduce HCV incidence, as well as AOT on own in reducing HCV transmissions and injecting risk behaviours [15]. Engaging opiate drug users in AOT at earlier stages in their drug using trajectories warrants consideration in further planning for preventative HCV interventions in Ireland. Of interest was the finding that with each unit increase in age of first AOT, the odds of being in the HCV positive group decreased by 10.8% indicating that the younger the first of age of AOT the more likely the patient was to be HCV infected. This finding was unexpected and was the reverse to what might have been predicted, and may reflect earlier starting age for drug use and/or IDU, and increased severity of drug use amongst these younger AOT patients. Further research on younger drug users, and on patients infected with HCV with no history of injecting is warranted to explore specific risk factors, and informed targeted HCV prevention strategies. Additionally, data around co-infection in Ireland needs surveillance.

Limitations

Limitations of the study centre on the convenience nature of the sample and the availability of medical records. It was also beyond the scope of the current study to examine the relationship between HCV infection and other factors such as injecting practices (frequency of injecting and engaging in risk behaviours such as back-loading and sharing needles, location of injecting) and socio-demographic characteristics (education and employment history, time spent in prison etc.).

5. Conclusions

Irish studies have indicated success with opt-out blood borne viral screening at different clinical settings [40]. However, marginalised subgroups of

PWID are less likely to access health care due to stigma, discrimination, and health care professional misunderstanding of their needs and their lifestyles. A comprehensive and scaled up HCV treatment and prevention approach to address HCV transmission rates among PWID situated in medical infrastructures designed for drug user health (e.g. community health centres, AOT clinics, primary care), with specialist support, elements of harm reduction and access to health care interventions such as screening, testing and treatment, and peer supports is recommended [36]. Addiction care doctors and infectious disease/ internal medicine specialist liver doctors are advised to collaborate and work together in addressing the health needs of patients with history of IDU and dependence [36]. Equally further efforts to understand and target non injectors, former injectors and current injectors is important to inform HCV prevention and treatment.

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All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

Conflict of interest

All authors declare no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Ethical approval for the study was granted by the School of Health Sciences Ethics Committee, School of Medicine, Trinity College Dublin, Ireland.

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