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Hepatitis C diagnosis and treatment, impact on engagement and behaviour of people who inject drugs, a service evaluation, the hooked C project

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NHS Tayside Sexual Health & Blood Borne Virus Managed Care Network (MCN)

Abstract

There is emerging evidence that Hepatitis C (HCV) treatment engagement is associated with change in drug behaviours and reduced drug-related death rates among people who inject drugs (PWID). The project aims to investigate whether HCV diagnosis and treatment engagement reduces all-cause mortality and drug-related death, and whether any effect is dependent on treatment regimen and intensity of engagement with staff. Case-control studies comparing: PWID with active HCV infection (PCR positive) to PWID HCV infected but spontaneously resolved (PCR negative); PCR-positive patients who engaged with treatment services to nonengagers; and patients who received interferon vs direct-acting antiviral (DAA) based treatment. No differences in risk of all-cause mortality or drug-related death between PCR-negative controls and PCR-positive cases were detected. The odds of all-cause mortality was 12.2 times higher in nonengaging persons compared to treatment engaging cases (aOR 12.15, 95% CI 7.03-20.99, $P < .001$). The odds of a drug-related death were 5.5 times higher in nonengaging persons compared with treatment engaging cases (aOR 5.52, 95% CI 2.67- 11.44, $P < .001$). No differences in risk of all-cause mortality or drug-related death between interferon-treated cases and DAA-treated controls were detected. HCV treatment engagement is significantly protective against all-cause mortality and drug-related death. This engagement effect is independent of treatment regimen, with the introduction of DAA therapies not increasing risk of drug-related death, suggesting intensity of HCV therapy provider interaction is not an important factor.

KEYWORDS

case-control studies, drug-related death, hepatitis C, injecting behaviour, people who inject drugs

Abbreviations: CHI, community health index; DAA, direct-acting antiviral; HCV, hepatitis C; IFN, interferon; MCN, multidisciplinary managed care network; NE, non-engagement; OR, odds ratio; OST, opioid substitution therapy; PCR, polymerase chain reaction; PWID, people who inject drugs; RNA, ribonucleic acid; SVR, sustained virological response.

1 | INTRODUCTION

Hepatitis C (HCV) is a blood-borne virus and affects up to 1% of the Scottish Population.[1] Around 90% of those infected with HCV acquire the virus through injecting drug use behaviour.[2] HCV related liver disease is a primary contributor to morbidity and mortality among people who inject drugs (PWID).[3] HCV is preventable, treatable and curable, with research supporting the treatment of active injecting drug users for Hepatitis C.[4] The efficacy of pan-genotypic direct-acting antivirals (DAA) provides an excellent opportunity to scale up HCV diagnosis and treatment, ultimately achieving the WHO target of HCV elimination by 2030.[5,6]

There is evidence that HCV care engagement is associated with change in behaviours among PWID. Studies have demonstrated the positive impact of HCV status notification on reduction in injecting behaviour among PWID.[7,8] Furthermore, a systematic review highlighted the positive impact of HCV treatment on patients' injecting and sharing behaviour.[9]

The causes of death among PWID are strongly associated with active drug use.[10] Scotland has observed a twofold increase in drug-related deaths between 2008 and 2018, with Tayside experiencing the highest number of drug deaths ever recorded in the region in 2018.[11,12] It is vital that informed action is urgently undertaken to reverse this trend.

The introduction of Multidisciplinary Managed Care Networks (MCN) in HCV treatment has increased access to services and reduced all-cause mortality.[13] The associated improvement in access into care and HCV treatment may have led to a greater degree of engagement with health services and may have had a stabilizing effect on drug using behaviour. However, there is concern around the potential impact of reduction in intensity of staff contact when transitioning from the interferon era to the DAA era of treatment. Interferon based treatment required a greater intensity of staff to patient engagement due to adverse side effects and long treatment duration. Contrastingly, DAA based treatment has minimal side effects and higher cure rates (in excess of 95%).[14] Thus, treatment pathways are streamlined and arguably provide less opportunity for patients to develop a therapeutic relationship with healthcare professionals involved in their care, and therefore reduced opportunities to facilitate change in patients' drug use behaviour, and lower risk of mortality.

The aims were to investigate whether HCV diagnosis and engagement in treatment services reduced all-cause mortality and drug-related death, and whether any effect was dependent on treatment regimen or intensity of engagement with staff. A series of retrospective case-control studies were carried out. Initially, comparing PWID with active HCV infection (PCR positive) vs PWID who were HCV infected but cured spontaneously (PCR negative), to elucidate whether knowledge of HCV infection status impacted risk of mortality. Secondly, comparing PCR-positive patients who engaged vs did not engage with treatment services to assess if outcomes were dependent on engagement. Finally, comparing interferon treated patients vs DAA-treated patients, exploring the effect of intensity of HCV therapy provider interaction on outcomes.

2 | METHODS

2.1 | Data sources and data linkage

The main data source utilised was the Tayside Hepatitis C Clinical Database which records patients tested for Hepatitis C, awaiting treatment, on treatment, cured and re-infected in Tayside, Scotland. Data collected from this database included demographic information, risk factors, laboratory tests, follow-up and treatment outcomes. Patients identified from this database and forming our cohort were electronically linked with electronic medical records and the Tayside Drug Deaths Database, using patients' Community Health Index (CHI) numbers (unique identification numbers given to every patient registered with a GP in Scotland). Information on patients' mortality status was obtained via electronic medical records. Information regarding confirmed drug-related deaths in Tayside was sourced from the Tayside Drug Deaths Database which records data on all drug-related deaths in Tayside and feeds into national reporting mechanisms through NHS Information Services Division and also informs the work of the Tayside Drug Death Review Group.

2.2 | Identification of selected cohort

From the Tayside clinical database, a cohort of individuals was identified whose risk factor for HCV was intravenous drug use. Therefore, the definition of PWID in our study is people who have "ever injected" drugs, with no differentiation between recent/active and former PWID. Individuals with other risk factors, such as transfusion of blood products or maternal transmission were excluded as we were specifically investigating the impact of HCV treatment on the behaviour of PWID. Individuals with non-Tayside postcodes were excluded as drug-related death outcomes would not be registered for non-Tayside individuals on the Tayside Drug Deaths Database. Individuals co-infected with other blood-borne viruses were excluded from the selected cohort as these individuals would have differing mortality rates and treatment experiences to those only infected with HCV. Individuals who were tested or initiated on treatment before January 2008 were excluded as the MCN for HCV care in Tayside was introduced in 2008 and this substantially changed the care pathways. Lastly, individuals who were tested or initiated treatment after November 2017 were excluded to allow for a minimum of one year of follow-up.

For each analysis, cases and controls were defined differently, although derived from the same cohort previously described. For analysis 1, all individuals who tested HCV antibody positive were identified. Cases were defined as PWID with active HCV infection (PCR positive), and controls were defined as PWID who were HCV

infected but cured spontaneously (PCR negative). For analysis 2, all individuals who tested HCV PCR positive were identified. Cases were defined as PCR-positive patients who engaged with treatment services, and controls were defined as PCR-positive patients who did not engage with treatment services. For analysis 3, all individuals who were PCR positive and engaged with treatment were identified. Cases were defined as pegylated interferon alpha treated patients, and controls were defined as DAA-treated patients. For all analyses, each case was matched with one control by age group (20-35, 36-51, 52-67, 68-83, 84+) and sex. Controls from the respective categories were randomly selected using an online random number generator.

2.3 | Definition of drug-related death

The definition of a drug-related death is a death where the underlying cause is as follows: drug abuse or drug dependence; or drug poisoning (intentional or accidental) that involves any substance controlled under the Misuse of Drugs Act 1971.[11] The National Records of Scotland uses the ICD 10 classification system to identify cases of drug-related death once a death certificate has been issued.

2.4 | Definitions of predictor variables

2.4.1 | Treatment engagement

"Treatment engagement" was defined as engaging with healthcare professionals and commencing treatment. All patients who commenced treatment were classified as "treatment engagers", irrespective of how many days/weeks of treatment they completed, whether they completed their entire course of treatment or not, and the outcome of their treatment, for example if a sustained viral response (SVR) was achieved. Correspondingly, patients who did not commence treatment were classified as "treatment non-engagers".

2.4.2 | Opioid substitution therapy (OST)

Data were collected on individuals' OST status around the time of testing or treatment. Specifically, for analysis 1 (PCR negative vs PCR positive) and analysis 2, (treatment engagers vs nonengagers), data were collected on whether individuals were on OST at the time of HCV RNA PCR testing, ±6 months. For analysis 3 (interferon vs DAA-treated patients), data were collected on whether individuals were on OST at the time of treatment commencement, ±6 months.

2.4.3 | Cirrhosis

Data were collected on individuals' cirrhosis status. Individuals were classified as being cirrhotic if their liver stiffness (FibroScan) score was 12.5 kPa or above, or their FIB-4 score was 3.25 or above.[15]

2.4.4 | SVR

Data were collected on individuals' sustained virologic response (SVR) status. SVR was defined as absence of detectable HCV RNA at 24 weeks after cessation of treatment.

2.5 | Statistical analysis

For analysis 1 (PCR negative vs PCR positive) and analysis 2 (treatment engagers vs nonengagers), follow-up began from first antibody positive test. For analysis 3 (interferon vs DAA-treated patients), follow-up began from date of treatment commencement. For all analyses, survival time was exactly observed or censored at the last follow-up date (31st December 2018). All statistical analyses were performed using IBM SPSS Statistics 22. Baseline characteristics were summarised using descriptive statistics. Inter-correlations between predictor variables were summarised using Pearson's correlational analyses.

Kaplan-Meier survival analysis was performed to investigate differences in the rates of all-cause mortality and drug-related deaths between cases and controls. Comparison of survival curves was performed using log-rank tests. Binary logistic regressions were used to compare the odds of all-cause mortality and dying of a drug-related death among cases with those among controls. We estimated odds ratios (ORs) and 95% confidence intervals for all comparisons and adjusted all models for the matching variables; age and sex. A number of other covariates were also included in certain models; SVR, OST and cirrhosis.

3 | RESULTS

3.1 | Analysis 1 - PCR positive vs negative

A total of 3431 individuals who tested HCV antibody positive were identified. Of these, 386 PCR-negative controls and 918 PCR-positive cases met the inclusion criteria (see Figure 1) and were randomly matched by age group and sex, leading to 386 PCR-negative controls and 386 PCR-positive cases included in the study.

Baseline characteristics of cases and controls are presented in Table 1. The majority of cases (96.4%) and controls (96.1%) were under the age of 65 years, and male (57.0%).

During the study's follow-up period, there were 135 deaths out of 722 individuals who were antibody positive; 72 (53.3%) deaths were in PCR-positive cases, and 63 (46.7%) were in PCR-negative controls. Of 135 deaths, 63 were classified as drug-related deaths; 34 (54.0%) were in cases, and 29 (46.0%) were in controls.

For all-cause mortality, the survival distributions for the two groups were not significantly different, χ^2 (2) = 0.425, P =.515. No difference in risk of all-cause mortality between PCR-negative controls and PCR-positive cases was detected (aOR 1.18, 95% CI 0.80-1.73, P = .40), after adjustment for age and sex (see Table 2).

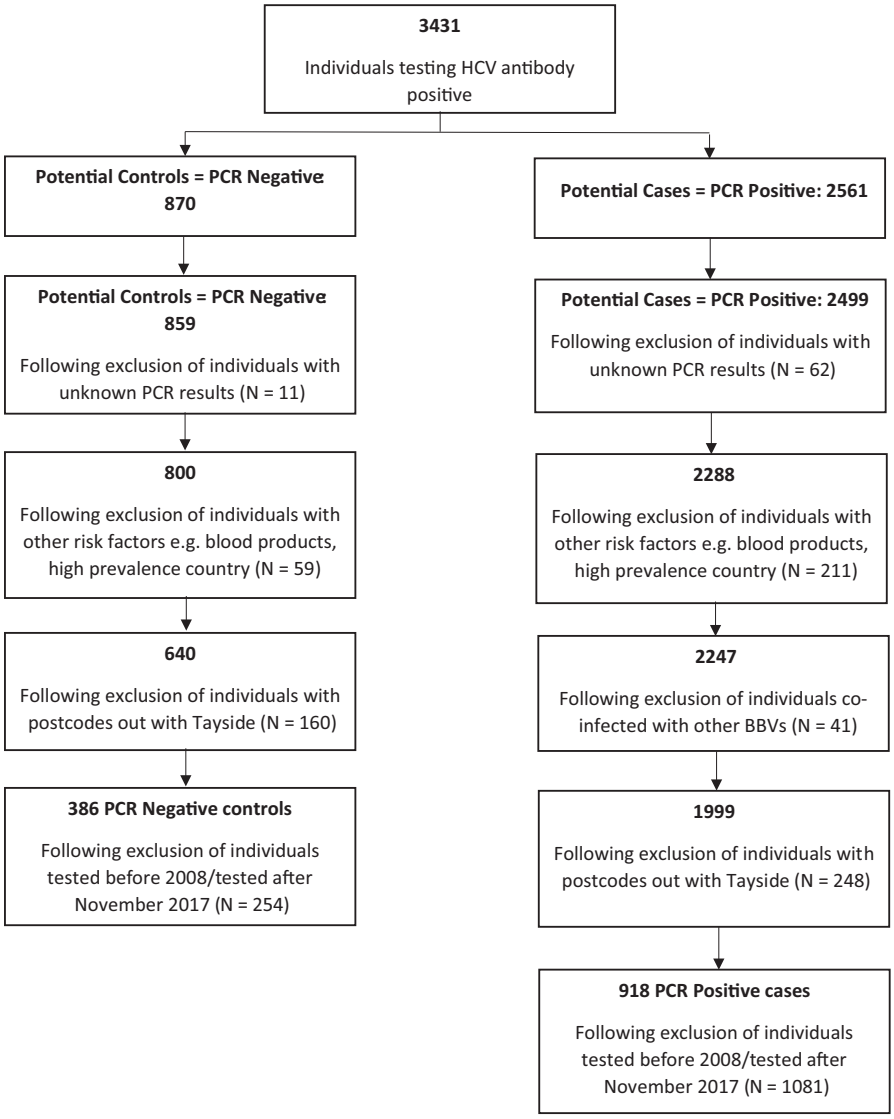

FIGURE 1 Selection of PCR-positive cases and PCR-negative controls based on inclusion/exclusion criteria

TABLE 1 Baseline characteristics of PCR-positive cases and PCR-negative controls (Analysis 1); Treatment Engaging cases and Treatment Non-Engaging controls (Analysis 2); and Interferon-treated cases and DAA-treated controls (Analysis 3)

	Analysis 1		Analysis 2		Analysis 3	
	Cases (N = 386)	Controls (N = 386)	Cases (N = 263)	Controls (N = 263)	Cases (N = 266)	Controls (N = 266)
Age, years (mean ± SD)	41.77 ± 10.9	41.56 ± 10.92	42.86 ± 10.64	42.98 ± 11.17	43.20 ± 9.20	43.80 ± 9.09
Age ≥ 65 years	14 (3.6%)	15 (3.9%)	9 (3.4%)	7 (2.7%)	3 (1.1%)	6 (2.3%)
Male	220 (57.0%)	220 (57.0%)	177 (67.3%)	177 (67.3%)	201 (75.6%)	201 (75.6%)
SVR			187 (71.1%)	122 (46.4%)	234 (88.0%)	211 (79.3%)
OST					197 (74.1%)	184 (69.2%)
Cirrhosis					34 (13.9%)	40 (15.5%)

For drug-related deaths, the survival distributions for the two groups were not significantly different, χ^2 (2) = 0.291, P =.590. No difference in risk of drug-related death between PCR-negative controls and PCR-positive cases was detected (aOR 1.19, 95% CI 0.71-2.00, P = .512), after adjustment for age and sex (see Table 3).

TABLE 2 Summary of logistic regression analyses for control variables (age, sex, SVR, OST and cirrhosis), PCR status (Analysis 1), Treatment Engagement (Analysis 2) and Treatment Regimen (Analysis 3) predicting all-cause mortality

		95% CI for odds ratio		
	B (SE)	Lower	Odds ratio	Upper
Analysis 1				
Constant	−3.82 (0.42)			
Age	0.05* (0.01)	1.04	1.05	1.07
Sex (Male vs Female)	−0.23 (0.20)	0.53	0.79	1.18
PCR status (Negative vs Positive)	0.16 (0.20)	0.80	1.18	1.73
R^2 (Cox & Snell) = 0.06				
Analysis 2				
Constant	−6.12* (0.71)			
Age	0.08* (0.01)	1.05	1.08	1.11
Sex (Male vs Female)	−0.40 (0.27)	0.40	0.67	1.13
OST (No vs Yes)	0.54* (0.25)	1.05	1.71	2.80
Treatment Engagement (engagers vs nonengagers)	−2.50* (0.28)	7.03	12.15	20.99
R^2 (Cox & Snell) = 0.25				
Analysis 3				
Constant	−3.16* (1.20)			
Age	0.02 (0.02)	0.98	1.02	1.06
Sex (Male vs Female)	−0.85 (0.55)	0.15	0.43	1.27
SVR (No vs Yes)	−1.17* (0.39)	0.15	0.31	0.66
OST (No vs Yes)	0.44 (0.45)	0.64	1.46	3.71
Cirrhosis (No vs Yes)	0.82 (0.44)	0.95	2.26	5.39
Treatment Regimen (DAA vs IFN)	0.37 (0.37)	0.70	1.45	2.98
R^2 (Cox & Snell)= 0.04				

*$P < .05$.

3.2 | Analysis 2 - PCR-positive treatment engagers vs PCR-positive treatment nonengagers

A total of 2499 individuals who tested HCV PCR positive were identified. Of these, 267 treatment nonengaging controls and 650 treatment engaging cases met the inclusion criteria (see Appendix S1) and were randomly matched by age group and sex, leading to 263 treatment nonengaging controls and 263 treatment engaging cases included in the study (successful matching was not possible for four controls).

Baseline characteristics of cases and controls are presented in Table 1. The majority of cases (96.6%) and controls (97.3%) were under the age of 65 years, and male (67.3%).

During the study's follow-up period, there were 141 deaths out of 527 individuals who were PCR positive; 23 (16.3%) deaths were in treatment engaging cases, and 118 (83.7%) were in treatment nonengaging controls. Of 141 deaths, 54 were classified as drug-related deaths; 10 (18.5%) were in cases, and 44 (81.5%) were in controls.

For all-cause mortality, the survival distributions for the two groups were significantly different, with nonengaging controls at a significantly higher risk of all-cause mortality, $\chi^2(2) = 91.395$, $P = <.001$ (see Figure 2). The odds of all-cause mortality were 12.2 times higher among treatment nonengaging controls, (aOR 12.15, 95% CI 7.03-20.99, $P < .001$) compared with treatment engaging cases, after adjustment for age, sex and OST (see Table 2).

For drug-related deaths, the survival distributions for the two groups were significantly different, with nonengaging controls at a significantly higher risk of drug-related death, χ^2 (2) = 32.364, $P = <.001$ (see Figure 3). The odds of a drug-related death were 5.5 times higher among treatment nonengaging controls, (aOR 5.52, 95% CI 2.67-11.44, $P < .001$) compared to treatment engaging cases, after adjustment for age, sex and OST (see Table 3).

3.3 | Analysis 3 - Interferon treated vs DAA treated

A total of 1664 PCR-positive individuals who engaged with treatment were identified. Of these, 380 interferon treated cases and 270 directing acting antiviral-treated controls met the inclusion criteria (see Appendix S1) and were randomly matched by age group

TABLE 3 Summary of logistic regression analyses for control variables (age, sex, SVR, OST, and cirrhosis), PCR status (Analysis 1), Treatment Engagement (Analysis 2) and Treatment Regimen (Analysis 3) predicting drug-related death

		95% CI for odds ratio		
	B (SE)	Lower	Odds ratio	Upper
Analysis 1				
Constant	−2.45 (0.57)			
Age	0.00 (0.01)	0.98	1.00	1.03
Sex (Male vs Female)	−0.36 (0.28)	0.40	0.70	1.20
PCR status (Negative vs Positive)	0.17 (0.26)	0.71	1.19	2.00
R^2 (Cox & Snell)= 0.00				
Analysis 2				
Constant	−3.39* (0.81)			
Age	−0.01 (0.02)	0.97	0.97	1.03
Sex (Male vs Female)	−0.12 (0.33)	0.47	0.89	1.69
OST (No vs Yes)	0.33 (0.32)	0.74	1.39	2.58
Treatment Engagement (engagers vs nonengagers)	−1.71* (0.37)	2.67	5.52	11.44
R^2 (Cox & Snell)= 0.05				
Analysis 3				
Constant	−3.13* (1.57)			
Age	−0.01 (0.03)	0.94	0.99	1.05
Sex (Male vs Female)	−0.70 (0.65)	0.14	0.50	1.77
SVR (No vs Yes)	−1.38* (0.46)	0.10	0.25	0.62
OST (No vs Yes)	1.45 (0.77)	0.94	4.05	19.35
Cirrhosis (No vs Yes)	0.10 (0.69)	0.29	1.12	4.30
Treatment Regimen (DAA vs IFN)	0.72 (0.48)	0.81	2.06	5.23
R^2 (Cox & Snell)= 0.03				

*$P < .05$.

and sex, leading to 266 interferon-treated cases and 266 directing acting antiviral-treated controls included in the study (successful matching was not possible for four controls).

Baseline characteristics of cases and controls are presented in Table 1. The majority of cases (96.6%) and controls (97.3%) were under the age of 65 years, and male (67.3%).

During the study's follow-up period, there were 49 deaths out of 532 PCR-positive individuals who engaged with treatment; 35 (71.4%) deaths were in interferon treated cases, and 14 (28.6%) were in DAA-treated controls. Of 49 deaths, 28 were classified as drug-related deaths; 21 (75%) in cases, and seven (25%) in controls.

Differences in length of follow-up time between cases and controls were controlled for by implementing a limit of a maximum follow-up period of 55 months after treatment commencement. This time parameter was decided upon as the first recorded date of treatment commencement in the DAA control group was 1st June 2014, with a 55 months of follow-up until the final day of follow-up 31st December 2018. Accordingly, any deaths occurring after the established maximum follow-up period in the interferon case group were not included in the subsequent analysis. Consequently, nine of the 35 deaths, and three of the 21 drug-related deaths, occurring in cases were not included in the analysis.

For all-cause mortality, the survival distributions for the two groups were not significantly different, χ^2 (2) = 0.071, P =.789. No difference in risk of all-cause mortality between DAA-treated controls and interferon-treated cases was detected (aOR 1.45, 95% CI 0.70-2.98, P = .37), after adjustment for age, sex, SVR, OST and cirrhosis (see Table 2). Note, 28 individuals were omitted from the regression analysis due to missing data on cirrhosis; eight controls and 20 cases.

For drug-related deaths, the survival distributions for the two groups were not significantly different, χ^2 (2) = 0.281, P =.596. No difference in risk of drug-related death between DAA-treated controls and interferon-treated cases was detected (aOR 2.06, 95% CI 0.80-5.23, P = .13), after adjustment for age, sex, SVR, OST and cirrhosis (see Table 3).

4 | DISCUSSION

The aim of the project was to investigate whether HCV diagnosis and engagement with treatment services reduces all-cause

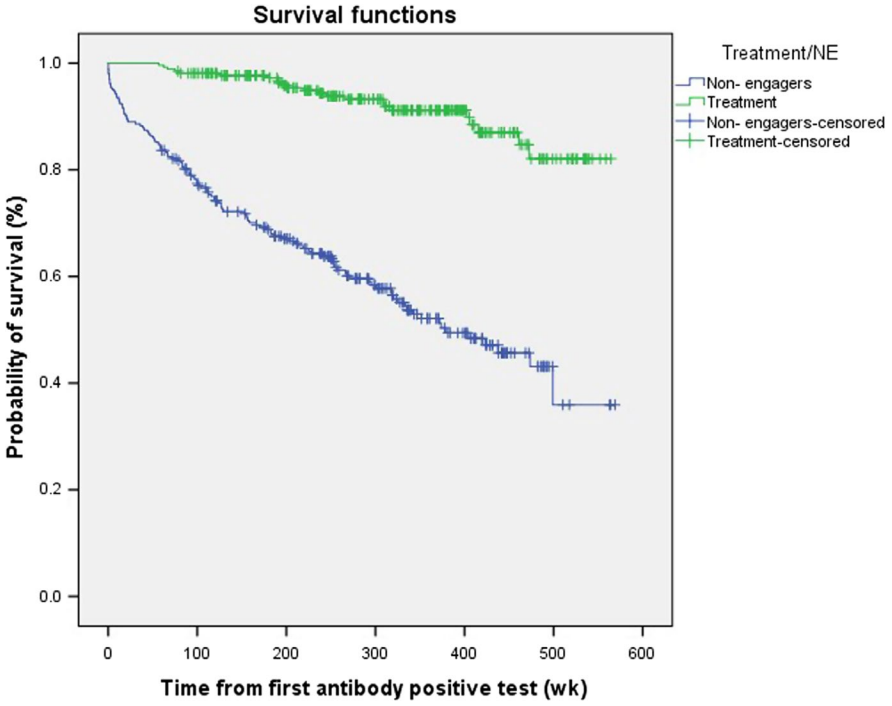

FIGURE 2 Kaplan-Meier survival curve for time from first antibody positive test to all-cause mortality comparing treatment engaging cases and treatment nonengaging controls

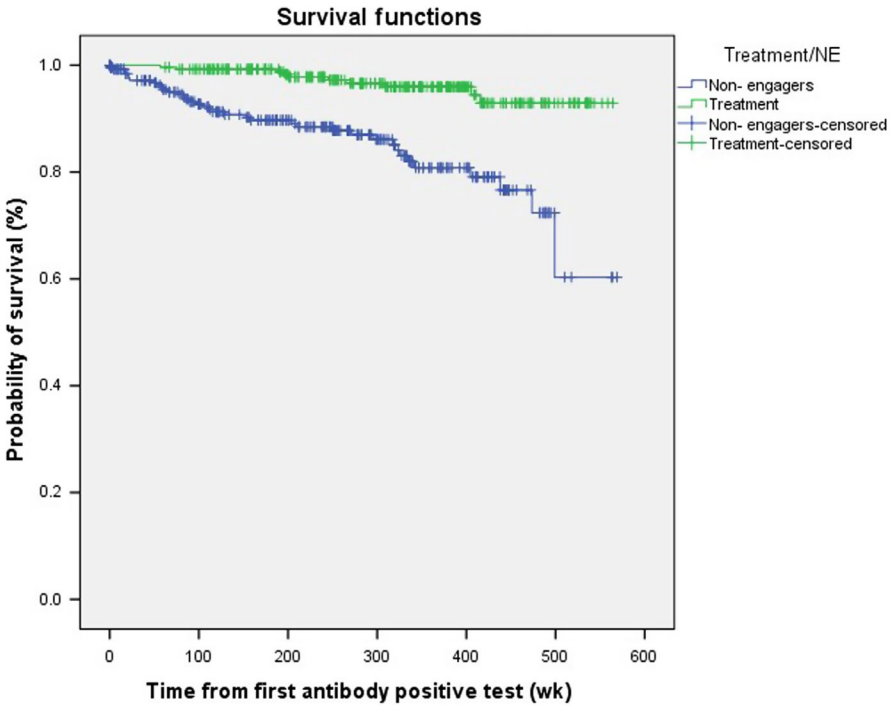

FIGURE 3 Kaplan-Meier survival curve for time from first antibody positive test to drug-related death comparing treatment engaging cases and treatment nonengaging controls

mortality and drug-related death, and whether any effect is dependent on treatment regimen and intensity of engagement with HCV treatment service staff. A series of retrospective case-control studies were performed. The first compared PWID with active HCV infection (PCR positive) vs PWID who had been HCV infected but cured spontaneously (PCR negative) to answer the question does knowledge of HCV infection status change risk of death. The only difference between cases and controls was the random biological event of spontaneous HCV cure; the two cohorts can be presumed to have behaved in the same way up to the point of being told their HCV status. Our results suggest that awareness of HCV infection status makes no difference to mortality, either all cause or drug related.

PWID with a diagnosis of HCV have an increased risk of mortality compared with noninfected PWID.[16] Recent studies have shown that awareness of HCV status can be protective, with a reduction in injecting behaviour seen in those who have been notified of their status.[7,8] It has been posited that this behavioural change may occur as a result of treatment engagement by some patients rather than due to knowledge of HCV status itself.

In the second analysis, we looked at PCR-positive patients who engaged vs did not engage with treatment services to explore whether self-selecting engagement behaviour accounts for the perceived difference in mortality. Our findings provide evidence that HCV treatment engagement is a significant protective factor against both all-cause mortality and drug-related death among PWID, with nonengaging PCR-positive individuals having 12 times higher odds of all-cause mortality and 5 times higher odds of drug-related death, in comparison to PCR-positive treatment engaging persons. These findings confirm previous research that engaging in Hepatitis C treatment leads to a reduction in all-cause mortality.[13] It is important to note that our cohort was selected from a population that has a high testing and diagnosis rate, nearly reaching WHO 2030 targets with a large proportion being treated to date, so there is minimal selection bias in our cohorts. This highlights the need for greater collaboration between specialist substance misuse services and HCV treatment services to operate in an integrated structure to tackle the observed rising trends in drug-related deaths. It is imperative to ensure that all services are equipped with adequate levels of resources and staffing to assess, manage and treat both patients' Hepatitis C and problematic drug use successfully. Furthermore, engagement in HCV care may provide an opportune time to implement targeted interventions to reduce injecting behaviours and promote further harm reduction measures.

The final analysis attempted to explore further if there was any effect of treatment engagement by comparing the outcomes of intensive interaction with health care in interferon treated patients vs DAA-treated patients, who have much shorter and less intense engagement. The result clearly shows no difference, suggesting that the benefits of treatment engagement are associated with the act of engaging with treatment rather than the treatment regime itself. It could be argued that patients engaging with HCV treatment services are self-selecting individuals who are more willing to engage with services in general, and that we have observed a generalised engagement effect, rather than a specific HCV treatment effect. Additionally, it is not clear if nonengaging behaviour is amendable to change or improved prognosis. Future research should focus on promotion of HCV care and engagement strategies, highlighting the psychological, social and physical health benefits of achieving a cure, as well as treatment options.[17] This finding highlights the importance of inclusive accessibility of HCV treatment for PWID.

This finding also has significant implications for addressing ongoing concern around the change in intensity of staff contact when transitioning from the interferon era to the DAA era of treatment. In addition, it is important to consider that DAA-treated patients are arguably more unstable than interferon treated patients as many would have been deemed to be unsuitable for interferon therapy due to associated adverse side effects. Indeed, it has been hypothesised that DAA-treated patients might have worse outcomes than interferon treated patients given the less intensive support during therapy. Thus, the fact that we observed no difference in risk of all-cause mortality or drug-related deaths between the two groups is evidence that intensity of staff engagement is not an important protective factor. Consequently, current treatment practice does not need to implement an increase in intensity of staff contact.

4.1 | Limitations

The predominant limitation of the current study was the retrospective study design, with substantial limitations in quality of available data. Data on a number of meaningful variables were not available. For instance, OST data were not attainable for PCR-negative individuals and therefore could not be included as a predictor variable in the regression model in analysis 1. Moreover, available OST data indicated whether individuals were on OST at the time of diagnosis, but not whether they were on OST at the time of their death, which could have given more insights. Data on history of nonfatal overdoses would also have been advantageous, as previous research has demonstrated that nonfatal overdose is classified as a risk factor for ensuing fatal overdose in PWID.[18] Other unattainable data which could have been beneficial were injecting history, injecting status, change in injecting behaviours and other significant comorbidities.

Furthermore, data on unmeasured potential confounding variables which may explain the association between engagement and decreased risk of mortality is lacking, with further research needed to elucidate the complex reasons that lead to nonengagement.

Another limitation to the current study is the lack of differentiation of individuals in analysis 2 (treatment engagers vs nonengagers). Specifically, engagers were not differentiated by a more specific measurement of treatment engagement, for example how many weeks of treatment they completed and/or whether they completed their full course of treatment. Equivalently, nonengagers were not differentiated by the reason for their nonengagement. For instance, a minority of patients may have not started treatment due to concerns around treatment contra-indications or age. This is particularly relevant for patients treated in the interferon treatment era due to higher incidence of associated adverse side effects compared with DAA based treatment regimens. Arguably such differentiation may provide greater insight into the impact of treatment engagement on subsequent risk of death, and whether, for example, completion of treatment potentiates the engagement effect.

5 | CONCLUSIONS

In conclusion, a series of case-control studies were conducted to investigate the impact of HCV diagnosis and engagement in treatment services on risk of all-cause mortality and drug-related death among PWID. No difference in risk of all-cause mortality or drug-related death was observed between PWID with active HCV infection (PCR positive) and HCV infected but cured spontaneously (PCR negative). HCV treatment engagement is significantly protective against all-cause mortality and drug-related death, with nonengaging PCR-positive individuals 12 times higher odds of all-cause mortality and five times higher odds of

drug-related death, in comparison to PCR-positive treatment engaging persons. This engagement effect is independent of treatment regimen, with no difference in risk of all-cause mortality or drug-related death between interferon treated patients and DAA-treated patients, suggesting intensity of engagement with staff is not an important factor. These findings provide further evidence of the importance of HCV diagnosis and treatment engagement among PWID, reducing their risk of mortality, beyond liver-related outcomes.

ACKNOWLEDGEMENTS

We would like to thank NHS Tayside Sexual Health & Blood Borne Virus Managed Care Network (MCN) for funding this project.

CONFLICT OF INTEREST

No authors declare any conflicts of interest.

ETHICS STATEMENT

This study has been performed according to the Declaration of Helsinki. Ethics approval was not required for this study as it involved retrospective data analysis and did not involve participant recruitment or intervention. Approval for access to relevant data was obtained from the Caldicott Guardian of NHS Tayside Information Governance Team (issued November 2018, Ref Caldicott/IGTCAL5540).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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