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Hepatitis C Diagnosis and Treatment, Impact on Engagement and Behaviour of People Who Inject Drugs, the Hooked C project

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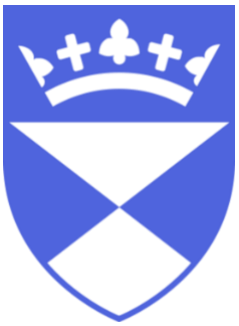
Madeleine Caven



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Signed Declarations

I, Madeleine Caven, hereby certify that I am the author of this thesis, that the work of which it is a record of has been conducted by me, that all references cited have been consulted by me, and that it has not previously been accepted for a Higher Degree.

13/05/20

Signature of Candidate *Date*

I hereby certify that the candidate has fulfilled the Conditions of Ordinance and regulation for the degree of Master of Science (by Research) in the University of Dundee.

13/05/20

Signature of Supervisor *Date*

Contributions

Madeleine Caven, Amy Malaguti, Emma Robinson, Emma Fletcher, Ann Eriksen, and John Dillon contributed to the research reported in this thesis. Madeleine Caven undertook and contributed to all aspects and stages of the research. Amy Malaguti and Emma Robinson participated in the quality assessment stage of the systematic review. Ann Eriksen provided feedback on drafted publications. John Dillon conceived the idea of the Hooked C project. Emma Fletcher and John Dillon provided supervision, assistance and feedback throughout the project.

Abstract

Hepatitis C (HCV) virus affects around 71 million people globally, with people who inject drugs (PWID) the most at-risk population for acquisition of the virus. There is emerging evidence that HCV treatment engagement is associated with change in drug behaviours and reduced risk of mortality among PWID. A systematic review was conducted to determine the impact of HCV treatment on injecting risk behaviours in PWID. Following this, a series of retrospective case control studies investigated whether HCV diagnosis and treatment engagement reduces risk of all-cause mortality and drug related death among PWID, and whether any effect is dependent on treatment regimen and intensity of engagement with staff.

Comparison and synthesis of results of the systematic review was challenging due to heterogeneity between studies. However, results suggested that it is likely that engaging in HCV treatment has a positive impact upon patients' injecting drug use and injection equipment sharing behaviour. Through the case control studies, it was found that HCV diagnosis does not impact upon mortality outcomes of PWID. However, HCV treatment engagement is significantly protective against all-cause mortality and drug related death, with this effect independent of treatment regimen and intensity of engagement with staff.

These findings provide strong evidence of the importance of universal HCV testing and treatment accessibility for PWID, reducing their risk of mortality beyond liver related outcomes. It is vital that efforts are made to actively minimise barriers and stigma relating to treatment access for PWID to facilitate HCV diagnosis and linkage to care. Future research should focus upon understanding the key barriers and facilitators

to engagement to aid the development of interventions that increase the reach, accessibility and effectiveness of HCV care, improving treatment pathways in pursuit of the WHO goal of HCV elimination.

Abbreviations

DAA	Direct acting antiviral
CCT	Controlled clinical trial
CHI	Community Health Index
CINAHL	Centers of Disease Control and Prevention (United States)
EMBASE	Excerpta Medica dataBASE
HCV	Hepatitis C
IFN	Interferon
INHSU	International Network on Hepatitis in Substance Users
MCN	Multidisciplinary managed care network
NHS	National Health Service (United Kingdom)
NE	Non-engagement
OR	Odds ratio
OST	Opioid substitution therapy
PCR	Polymerase chain reaction
PICOS	Population, intervention, comparison, outcome, study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PWID	People who inject drugs
RBV	Ribavirin

RNA	Ribonucleic acid
RCT	Randomised control study
SVR	Sustained virological response
TasP	Treatment as prevention

1. Introduction

Introduction to Hepatitis C virus infection

Chronic Hepatitis C (HCV) infection is a blood borne virus which affects around 71 million people globally (World Health Organisation, 2017; Blach et al., 2017). Prevalence of the virus dramatically varies by country, ranging from less than 1% in certain Western countries, to over 10% in some African and Middle Eastern nations (Hajarizadeh, Grebely, & Dore, 2013). The most common method of transmission is through injecting drug use behaviour, such as the sharing of needles, syringes and other ancillary injecting equipment. Other less common methods of transmission include transfusion of infected blood products, sexual transmission and vertical transmission from HCV positive mothers to babies. In the case of transfusion of infected blood products, this method of transmission was previously more relevant before mandatory blood screening tests became practice, and in less developed healthcare systems, where needle reuse is common. People who inject drugs (PWID) are the most at- risk population for acquisition of the virus, with an estimated 39.2% of PWID currently living with HCV infection worldwide (Grebely et al., 2019). HCV infection is a major cause of morbidity and mortality among this population, through the development of both hepatic diseases, e.g. liver cirrhosis and hepatocellular carcinoma, and extra-hepatic diseases (Stanaway et al., 2016). Extra- hepatic manifestations of HCV can affect the kidneys, immune system, eyes, thyroid, and the nervous system, and are reported in nearly 75% of patients (Cacoub, Gragnani, Comarmond, & Zignego, 2014). Therefore, HCV infection can be described as a multifaceted systematic disease, with complex health consequences. HCV has a long clinical course, with around 20- 30% of patients developing cirrhosis within 20 years of initial diagnosis (Westbrook, & Dusheiko, 2014).

History of Hepatitis C treatment

The objective of Hepatitis C treatment is full eradication of the virus, which is paramount for the prevention of disease progression, and onward viral transmission. Crucially, the primary goal of treatment is for a patient to achieve a sustained virological response (SVR), defined as undetectable HCV RNA either 12 or 24 weeks post treatment completion (European Association for the Study of the Liver, 2018). Initial treatment options beginning in the 1990s were based upon interferon alpha based therapies, injected subcutaneously, with treatment regimens involving 24 or 48 week courses, depending on the genotype of the virus (Powell et al., 1997). Cure rates using interferon alpha based therapy were very poor, with fewer than 10% of patients successfully clearing their virus (Carithers, & Emerson, 1997). However, the addition of ribavirin (RBV) to treatment regimens significantly improved treatment outcomes, with SVR rates rising to around 30% (McHutchison et al., 1998).

Interferon based treatment again progressed with the development of pegylated forms of interferon alpha, eliciting higher SVR rates, and in combination with RBV, was the standard of care for patients until around 2011 (Foster, 2010). Despite improved outcomes, many patients were not eligible for treatment due to numerous contraindications. For example, due to the neuropsychiatric effects of interferon, treatment was not appropriate for patients with unstable psychiatric conditions. Moreover, interferon based treatment regimens evoked multiple arduous side effects, such as flu- like symptoms, fatigue, lethargy, changes in mood, skin reactions, and sleep disturbance, resulting in inadequate tolerability, and poor treatment adherence and completion rates (Fried, 2002). Consequently, many patients declined therapy due to fear of experiencing these side effects.

HCV treatment was greatly advanced by the revolutionary development of multiple direct acting antivirals (DAAs), which target distinct stages within the life cycle of the HCV virus (Dore, 2012). Originally offered in conjunction with interferon alpha and RBV, interferon free regimens quickly became available for the treatment of HCV. DAA based therapies provide simplified treatment regimens, are oral based, of short duration (around 8- 16 weeks), with SVR rates in excess of 95% (Falade- Nwulia et al., 2017). In contrast to interferon based treatment, DAA based therapies have minimal side effects, with vast improvements in tolerability. This has facilitated the treatment of an extensive group patients who were previously ineligible for therapy (Younossi et al., 2015).

The efficacy of pan-genotypic DAAs provides an excellent opportunity to scale up HCV diagnosis and treatment, with the ultimate aim of achieving the World Health Organisation target of global HCV elimination by 2030 (Asselah, Marcellin, & Schinazi, 2018; World Health Organisation, 2016). Research has supported the treatment of Hepatitis C in people who inject drugs , demonstrating successful adherence to treatment and favourable SVR rates (Hajarizadeh et al., 2018; Schulkind et al., 2019). This highlights the feasibility and effectiveness of scaling up treatment services to reduce the prevalence of the disease, using “treatment as prevention” (TasP) models of elimination (Aspinall et al., 2013; Fraser et al., 2018). TasP models of elimination focus on treating PWID for HCV as they are the most at-risk population for acquiring the virus. Therefore, HCV elimination could be achieved by treating those at risk of continuous HCV transmission (Hellard, Doyle, Sacks- Davis, Thompson, & McBryde, 2014; Hellard et al., 2015; Hutchinson et al., 2015).

Barriers and stigma relating to treatment access

Despite the incidence of HCV related liver disease being on the rise, and research supporting the treatment of people who inject drugs; testing, diagnosis, and treatment rates of HCV infection among PWID have found to be inadequate in some settings (Socías et al., 2019; Thrift, El-Serag, & Kanwal, 2017; Wiessing et al., 2014). Barriers to testing and treatment are complex, and operate at various levels. For instance, at a systemic level, modelling of HCV testing and treatment cascades have shown inadequate diagnosis rates, and linkage to care (Ramers, Liu, & Frenette, 2019). Other systemic barriers may include geographic limitations to HCV specialists, lack of consensus around testing and treatment guidelines, lack of knowledge and awareness about HCV among practitioners, disease severity restrictions, and in the case of countries such as the USA, lack of insurance coverage and sobriety restrictions (Grebely, Oser, Taylor, & Dore, 2013).

At a treatment provider level, reluctance and concern around the treatment of people who are actively injecting drugs are considerable barriers to treatment accessibility for this population. For instance, a survey of over one hundred HCV treatment prescribing clinicians at the Liver Meeting in 2014 found that only 15% would be willing to treat active injectors with DAA based therapy (Asher et al., 2016). Concerns around treating people who inject drugs for HCV include: ongoing risk behaviour, such as ongoing drug use and the sharing of injecting paraphernalia; risk of reinfection; and poor treatment adherence (Grebely & Tyndall, 2011). Moreover, the perception that HCV treatment prescribing is restricted to specialist physicians remains prevalent in the DAA era, with many failing to recognise the success of implementing primary care and outreach based treatment pathways of care (Johnson, Aluzaite, Taat, & Schultz, 2019; Tait et al., 2017; Radley, Tait, & Dillon, 2017).

Lastly, various barriers to HCV care are faced by those living with the infection in relation to patients' own perceptions of treatment. Studies have shown that poor knowledge and awareness of HCV is associated with lower likelihood of treatment uptake and willingness to engage with treatment services (Treloar, Hull, Dore, & Grebely, 2012). For example, the absence of noticeable symptoms of HCV results in lack of motivation of individuals to undergo treatment, due to inaccurate perceptions around disease progression and prognosis (Lin et al., 2017). Furthermore, patients' reluctance to undergo treatment may stem from their lack of knowledge around the side effect free nature and high cure rates associated with DAA based treatment, in comparison to the old interferon based regimens (Valerio et al., 2018; Jost et al., 2019). Various sociodemographic factors such as unstable housing, unemployment, mental health problems, ongoing drug use, stigma, and incarceration all affect a patient's ability to access HCV care (Grebely, & Tyndall, 2011; Falade- Nwulia et al., 2019).

HCV diagnosis and injecting behaviours

In spite of these barriers to treatment, there is a suggestion that the benefits of engaging with HCV care stretch beyond liver morbidity outcomes. Studies report the positive impact of HCV status notification on reduction in drug use among PWID. For instance, Aspinall et al. (2014) observed that receiving a HCV diagnosis was associated with a slight reduction in injecting frequency, but not injecting equipment borrowing, in a cohort of Australian PWID. Bruneau et al. (2014) found a sustained trend in reduction of injecting drug use among PWID who had been notified of their HCV positive status. Conversely, PWID who were seronegative, and notified of their status, after testing displayed no change in such behaviour over time. However, subsequent research has contested these findings, with a study using data from multiple countries, by Spelman et al. (2015) finding no difference in post notification injecting behaviours when comparing PWID who received a positive test result to those who tested HCV

negative, highlighting the need for greater communication by healthcare professionals of the importance of reducing injecting risk behaviours.

Healthcare utilisation of people who inject drugs

Research has highlighted the poor health outcomes and increased mortality rates of people who inject drugs in comparison to the general population, including high rates of drug related deaths, HIV related deaths, increased risk of cancers, and various cardiovascular, liver and respiratory conditions (Mathers et al., 2013; Alridge et al., 2018; Degenhardt et al., 2011). Yet, studies have also identified diversified barriers to PWID utilising healthcare services. As discussed previously, healthcare professionals may harbour prejudiced attitudes towards treating PWID, believing them to be drug seeking, and exhibiting problematic behaviour during interactions (Van Boekel, Brouwers, Van Weeghel, & Garretsen, 2013). As a result of these perceptions, patients report delays in seeking treatment due to fear of stigmatisation, and apprehension around insufficient opioid substitution therapy and pain control when hospitalised (Summers, Hellman, MacLean, Rees, & Wilkes, 2018). Consequently, this may lead to postponement of symptom presentation. This is evidenced by a recent meta-analysis investigating frequency of healthcare utilisation reported in observational studies of PWID, which found that PWID attended accident and emergency departments and are admitted to hospital on average 4.8 and 7.1 times more often, respectively, than the general population (Lewer et al., 2019).

Drug related deaths crisis

The dominant causes of mortality among people who inject drugs are all strongly associated with active drug use behaviour, such as trauma and suicide, with the most common cause of mortality being accidental overdose (Degenhardt et al., 2011). The Global Burden of Disease 2016 study reported that 144,000 deaths globally in 2016 were caused by drug use disorders; a rise of 15% when compared to figures in 2006 (Naghavi et al., 2017). Scotland is in the midst of a drug related deaths crisis, and has observed a two fold increase in drug related deaths between 2008 (n= 574) and 2018 (n= 1187), with Tayside experiencing the highest number of drug related deaths ever recorded in the region in 2018 (National Records of Scotland, 2019). Scotland has the highest number of drug related deaths per capita out of any EU country, and the rate is approximately three times higher than the rate of England and Wales (National Records of Scotland, 2019; Office for National Statistics, 2019). Males account for the majority of drug related deaths, with 72% of casualties in Scotland in 2018 being male (National Records of Scotland, 2019). However, Scotland has experienced a 289% increase in drug related deaths in women between 2008 (n= 113) and 2018 (n= 327). Blood borne viruses are associated with higher risk of drug related death, with HCV diagnosis marking PWID with double the risk of mortality (Merrall, Bird, & Hutchinson, 2012).

The Scottish Government is committed to addressing this worrying public health concern, launching its new national drug and alcohol strategy in November 2018 to support evidence based approaches to reduce harms associated with problem drug use, with a particular focus on drug related deaths (Population Health Directorate, Scottish Government, 2018). As part of this strategy, in July 2019, the Drug Deaths Taskforce was convened to coordinate and prompt action to improve the health and wellbeing of people who use drugs, for example, by examining the evidence around

drug deaths prevention, publishing good practice guidelines to reduce drug use related harms, and identifying barriers in the delivery of addiction services. The strategy's key elements focus on: treating people and their complex needs; reducing stigma and discrimination towards people who use drugs; tackling inequalities; providing rapid access to opioid substitution therapy and increasing retention rates; focusing upon early prevention including combating early childhood trauma that can increase future risk of using drugs and associated harms; and utilising a public health approach to reduce the number of vulnerable persons in the justice system. It is hoped that together, these strategic actions will curb the trend in drug related harms, and support individuals and their families on their road to recovery.

Opioid Substitution Therapy (OST) is considered a protective factor against both natural and overdose related deaths, and low threshold prescribing services are strongly related to lower risk of death and increased retention rates (Degenhardt et al., 2011). PWID who are not engaged with treatment services are considered to have a higher mortality risk than those in treatment, and retention in treatment is also considered protective against all-cause mortality and drug related death (Sordo et al., 2017).

Justification for study

The development of multidisciplinary managed care networks (MCN) in HCV care has transformed HCV testing and treatment services, transitioning from standard secondary care outpatient treatment services, to the introduction of numerous specialised nurse led outreach care pathways. A cohort study was conducted to investigate the effectiveness of these specialised HCV care pathways in Tayside, Scotland by evaluating clinical outcomes of HCV antibody positive individuals who

belonged to four subgroups based upon date of first antibody positive test, representing different pathways of care (Tait et al., 2017). The results of this study found that the introduction of multidisciplinary managed care networks in HCV treatment improved HCV testing, diagnosis, treatment, and SVR rates within the region by increasing access to testing and treatment services. Strikingly, the study found that the improvement in access into care for patients led to a significant reduction in risk of death. Individuals in the final subgroup, representing care pathways with increased outreach clinics and DAA treatment regimens, had a 40% reduction in risk of all-cause mortality, in comparison to individuals in the first subgroup, representing early care pathways with limited access to treatment, no specialist nurse input, and interferon based treatment regimens. Crucially, multivariate analysis showed that this increased odds of survival was sustained after SVR, HIV status and age were controlled for. The authors of the study posited that 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 use behaviour.

However, this study was an observational cohort study, with limitations in power to infer associations between interventions and outcomes. Therefore, based on the current limited literature, and the scarcity of strong evidence around the impact of HCV diagnosis and treatment on injecting risk behaviours amongst PWID, there is clearly a place for a review of all the available evidence directly investigating the impact of HCV treatment on injecting drug use behaviour in PWID. This investigation will take the form of a systematic review in Chapter 2.

Additionally, at a time when Scotland, and particularly Tayside, is in the midst of a drug related deaths crisis, investigating the impact of HCV diagnosis and treatment on mortality outcomes of PWID is of great significance and has meaningful implications for the development of specialised HCV treatment pathways. Moreover, 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%) (Falade- Nwulia et al., 2017). 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 people's drug use behaviour, and lower risk of mortality. Therefore, the current project aims to investigate the impact of HCV diagnosis and treatment on mortality outcomes of PWID through a series of case control studies, presented in Chapter 3.

Research questions and hypotheses

The current project aims to answer, through a series of case control studies, three research questions:

- Does HCV diagnosis reduce a) all-cause mortality, b) drug related death among PWID?
- Does engagement in HCV treatment services reduce a) all-cause mortality, b) drug related death among PWID?
- Does any change observed in risk of a) all-cause mortality, b) drug related death depend on if the treatment is interferon based or DAA based, and intensity of engagement with staff?

The following hypotheses are proposed:

- HCV diagnosis will reduce risk of all-cause mortality and drug related death among PWID.

- Engagement in HCV treatment services will reduce risk of all-cause mortality and drug related death among PWID.

- Engagement with interferon based treatment regimens will result in a greater reduction in risk of all-cause mortality and drug related death than engagement with DAA based treatment regimens.

2. Impact of Hepatitis C treatment on behavioural change in relation to drug use in people who inject drugs: a systematic review

This systematic review has been published in the International Journal of Drug Policy in October 2019. A copy of the publication can be found in Appendix A.

Reference: Caven, M., Malaguti, A., Robinson, E., Fletcher, E., & Dillon, J. F. (2019). Impact of Hepatitis C treatment on behavioural change in relation to drug use in people who inject drugs: A systematic review. *International Journal of Drug Policy*, *72*, 169-176. https://doi.org/10.1016/j.drugpo.2019.05.011

Abstract

Background: A systematic review was conducted to determine the impact of HCV treatment on injecting drug use behaviour in people who inject drugs (PWID).

Methods: A search for peer reviewed journal articles from 1991 to present day was conducted using the following databases: PubMed, EMBASE, CINAHL and PsycINFO. Studies were appraised against the following inclusion criteria: recruitment of PWID for HCV treatment (either interferon alpha or direct acting antivirals based); measurement of behavioural change in relation to drug use; studies published in English.

Results: Five studies investigating the impact of HCV treatment on behavioural change in relation to drug use amongst PWID were identified. Studies investigated the impact of HCV treatment on past month injecting drug use (four studies), injecting frequency (two studies), needle and syringe borrowing (two studies) and injecting

equipment sharing (three studies). Three of the four studies assessing impact of treatment on past month injecting frequency found treatment significantly reduced the odds of participants reporting past month injecting at follow up. One study found that there was significant reduction in weekly injecting frequency between enrolment, treatment and follow up. No association was found between treatment engagement and needle and syringe borrowing. Two out of three studies reported a significant decrease in injecting equipment sharing between enrolment, treatment and follow up.

Conclusions: Comparison and synthesis of results was challenging due to heterogeneity between studies. Moreover, four out of the five selected studies were conducted during the interferon era of treatment, possibly limiting the generalisability of the current review's results to the new DAA treatment era. However, it is likely that engaging in treatment has a positive impact upon clients' injecting drug use and injection equipment sharing behaviour. This raises the possibility that this may be an opportune time for further harm reduction measures.

Objectives

To examine the literature investigating how, if at all, the behaviour of PWID changes in relation to injecting drug use when undergoing HCV treatment and during follow up, including changes in injecting behaviour, injecting frequency, needle and/or syringe borrowing, and injecting equipment sharing.

Methodology

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The study was registered in PROSPERO (CRD42018116625).

In response to the stated objectives, a detailed research question was framed following the PICOS (population, intervention, comparison, outcome, study design) approach (Higgins & Green, 2011). The PICOS criteria were also combined with additional exclusion criteria. Inclusion and exclusion criteria can be found in Tables 1 and 2.

Population

The study population of interest was PWID of any gender and age. Studies focusing on non- injecting patients were excluded as we were specifically interested in impact of HCV treatment on behaviour change in relation to injecting drug use. PWID who were treated for other blood borne viruses were also excluded. Studies investigating impact of HCV treatment in prison populations were excluded as measuring behaviour change in relation to drug use in these populations is challenging. This is because people who are incarcerated do not have access to injecting equipment, or harm reduction services, and therefore cannot freely change their behaviour.

Intervention

The intervention of interest is Hepatitis C treatment. Treatment can either be interferon alpha or directing acting antivirals based. Studies only focusing on HCV diagnosis or status notification were excluded.

Comparison

Comparison groups included PWID who did not receive treatment; or PWID who chose to not engage in treatment post HCV diagnosis. Studies which did not utilise comparison groups, but compared participants' behaviour before and after treatment, were also included.

Outcomes

The primary outcome of interest was behavioural change in relation to drug use e.g. injecting behaviour, needle and syringe borrowing, sharing of ancillary equipment. Studies focusing on reinfection rates after treatment were excluded.

Table 1. *Inclusion Criteria*

Inclusion Criteria
• *Population*: people who inject drugs (PWID). • *Intervention*: Hepatitis C treatment (either interferon alpha or direct acting antivirals based). • *Comparison*: participants themselves i.e. behaviour measured before and after treatment; or PWID who did not receive treatment; or PWID who chose to not engage in treatment post HCV diagnosis. • *Primary outcome*: behavioural change in relation to drug use e.g. injecting behaviour, needle and syringe borrowing, sharing of ancillary equipment. • Studies published in English, utilising a quantitative or mixed- methods study design. • Studies conducted between 1991 and 2018.

Table 2. *Exclusion Criteria*

Exclusion Criteria
• Studies utilising a purely qualitative study design; individual case studies. • Studies that are entirely theoretical. • Participants who are non- injecting patients, or PWID who were treated for other blood borne viruses. • Studies investigating the impact of Hepatitis C treatment in prison populations. • Studies focusing on the impact of knowledge of HCV status, and not HCV treatment, on behavioural change in relation to drug use. • Studies focusing on reinfection rates after treatment.

Study Designs

Studies utilising quantitative or mixed methods study designs such as randomised control studies (RCTs), non-randomised controlled clinical trials (CCTs), and prospective and retrospective cohort studies were included. Studies utilising a purely qualitative study design or individual case studies were excluded.

Search strategy

The International Prospective Register of Systematic Reviews (PROSPERO) was searched to confirm no similar review had already been conducted. A search for peer reviewed journal articles was conducted using PubMed, EMBASE, CINAHL and PsycINFO, on 9th November 2018. A grey literature search of the International Network on Hepatitis in Substance Users (INHSU) conference abstracts was also conducted. This symposium was specifically targeted as it is dedicated to research focusing on Hepatitis C in the cohort of interest, namely PWID. A time parameter was implemented for studies conducted from 1991 to 2018, as 1991 was the year interferon became commercially available for treatment of Hepatitis C. An inclusive list of search terms in line with each search topic was generated to develop an effective search strategy. Both keywords and indexed subject headings (MeSH and EMTREE terms) were included in the formulation of search strings for each database search. Search topics included "Hepatitis C treatment", "behaviour change" and "drug use". Table 3 includes a full list of search terms utilised in the search strategy, grouped by search topic. Manual searches of reference lists of selected studies were also conducted. Searches were limited to studies published in English.

Table 3. *Keyword search terms utilised in search strategy, grouped by search topic*

Hepatitis C treatment	Behaviour change	Drug use
Hepatitis C treatment/therapy^	Behavi* change	Drug abuse
Interferon-alpha/ therapeutic use^	Behavi* benefit	Drug misuse
	Drug use change*	Drug use
	Inject behavi*	Drug disorder
	Risk behavi*	Drug addict*
	Inject* frequency	Drug dependen*
		Drug intravenous*

^MeSH/EMTREE terms

Study selection

Fig. 1 shows a PRISMA flowchart of the selection process. Screening of the search strategy results was conducted by two reviewers. The first phase involved importing all citations into EndNote X8 and removing duplicate records. Titles were screened, and irrelevant records removed. Abstracts were then assessed using the inclusion and exclusion criteria. All remaining records were then subjected to a full text evaluation for eligibility. Discrepancies in judgements were resolved by discussion within the whole research team until consensus was met.

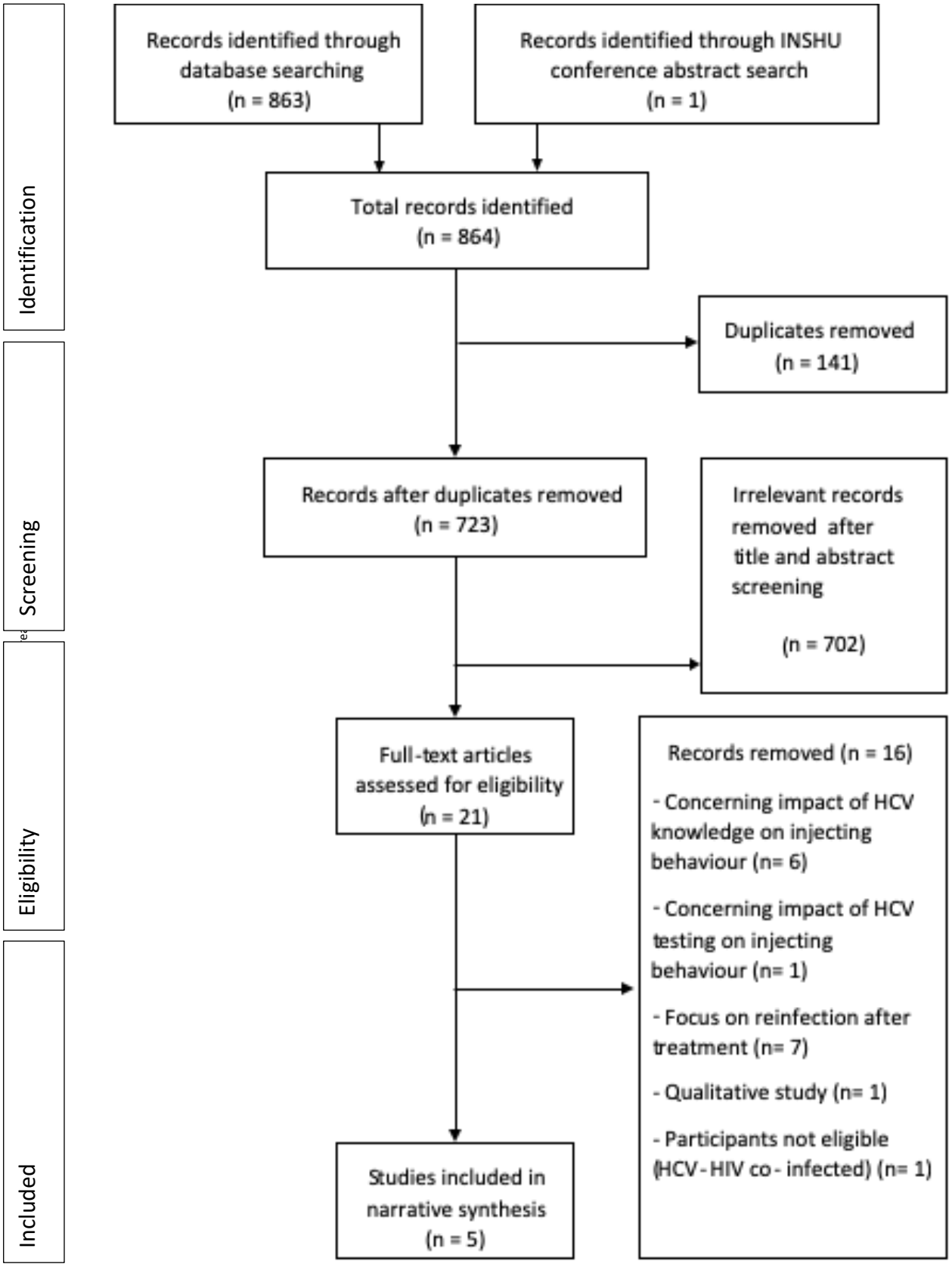

Figure 1. Search Strategy

Data extraction and synthesis

Data from selected studies was extracted using a piloted data extraction form by one reviewer (MC). The following variables were collected: first author, title, publication year, full paper or abstract, primary aim, study design, location, setting, total study duration, follow up period, sample characteristics, sample size, intervention, outcome/ measure of behaviour change, main results, conclusions. The authors of Malaguti et al. (2019) were contacted for clarification regarding follow up period in their study. The authors of Artenie et al. (2019) were contacted to obtain updated data, and they kindly provided an unpublished manuscript relating to their INHSU conference abstract. The data synthesis used an Economic and Social Research Council (ESRC) style quantitative narrative synthesis (Popay et al., 2006). Heterogeneity between studies was manually assessed by reviewers. This was used as there was too much heterogeneity between selected studies for meta- analysis.

Quality appraisal

Risk of bias in individual studies was assessed using the Quality Appraisal Checklist for quantitative intervention studies by NICE public health guidance (National Institute for Health and Care Excellence, 2012). The checklist enables both the evaluation of the study's internal and external validity, addressing aspects of study design such as participant characteristics, definition of and allocation to intervention/control conditions, and methods of analyses. Each study was awarded separate overall quality ratings for internal and external validity, with ratings ranging from 1 to 3. Quality appraisal for four studies was independently conducted by two reviewers (MC and AM), with discrepancies in ratings resolved by discussion until consensus was met. A Cohen's kappa coefficient (κ) was calculated to assess inter-rater agreement, $\kappa = .61$, p

< .001. This kappa (κ) value represents a substantial agreement (Landis & Koch, 1977). A third reviewer (ER), along with the first reviewer (MC), conducted a quality appraisal for the fifth study. This was necessary to reduce bias as the second reviewer (AM) was an author of the study. A Cohen's kappa coefficient (κ) was calculated to assess inter-rater agreement, $\kappa = .68$, $p < .001$, representing a substantial agreement (Landis & Koch, 1977).

Results

Search results

Overall, 864 records were identified through database and conference abstract searching, 723 of which remained after duplicates were removed. After assessment of titles and abstracts, 21 records remained. Sixteen records were removed based on full-text assessment, with the most common reasons being that studies focused on impact of HCV knowledge on injecting behaviour (n= 6) or studies focused on reinfection after treatment (n= 7). Five studies were included in the final narrative synthesis (see Fig. 1).

Characteristics of selected studies

Characteristics and findings of selected studies are summarised in Table 4. Studies evaluated impact of treatment on injecting drug use by recruiting participants from a number of settings including tertiary hospitals; GP and primary care clinics; community clinics; drug and alcohol treatment clinics; private medical practices; and injecting equipment provision services. There were four prospective cohort studies and one retrospective cohort study. Two studies included comparison groups in their study

design. Alavi et al. (2015) utilised PWID that did not receive treatment as their comparison group. Artenie et al. (2017) utilised three comparisons groups, namely PWID who did not engage in treatment post- diagnosis; PWID who did not engage in treatment due to spontaneous clearance of the virus; and HCV positive PWID who were not eligible for treatment due to contra-indications.

Four studies investigated past month injecting drug use; two studies investigated injecting frequency; two studies investigated needle and syringe borrowing; and three studies investigated ancillary injecting equipment sharing. Of the five studies selected, four studies involved treatment with pegylated interferon alpha and/or ribavirin, with only one study involving treatment with direct acting antivirals (DAAs). Follow up periods ranged from 24 weeks to 2 years. In the sampled studies, the majority of participants were Caucasian males, with a mean age ranging from 32- 47 years old, who had injected drugs in the last 6 months prior to study enrolment. Two of the five selected studies solely recruited participants with acute HCV infection (Alavi et al., 2015; Artenie et al., 2017). Recruiting patients for treatment with acute HCV infection is not reflective of standard clinical practice, as these patients have a 20-30% of spontaneous clearance during the acute phase of the infection, making treatment uneconomical at this stage (Aisyah, Shallcross, Hully, O'Brien & Hayward, 2018). However, effect on injecting behaviour may still be relevant.

Table 4. *Summary of Study Characteristics*

Study *Country*	Measure of behaviour change	Design (comparison group(s)) *Follow up period*	Setting	Participant characteristics- age, gender, past month injecting drug use, on OST, HCV status	Treatment	Main Findings
Alavi et al. (2015) *Australia*	Past month Injecting drug use, used needle and syringe borrowing and ancillary injecting equipment sharing at baseline, throughout and after treatment	Prospective cohort study (PWID that did not receive treatment) *24 weeks*	Tertiary hospitals and GP/primary care clinics	124 participants, Mean age= 32 years (25- 39 years), 69% male, past month injecting drug use= 45%, on OST= 18%, recent HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Injecting drug use during follow up was not associated with treatment. Needle and syringe borrowing during follow up was not associated with treatment. Treatment associated with a reduction in ancillary injecting equipment sharing during follow up.
Artenie et al. (2017) *Canada*	Past month injection drug use assessed dichotomously at 12 month treatment follow up	Prospective cohort study (PWID who did not engage in treatment post-diagnosis; did not engage due to spontaneous	Community and hospital based clinics	87 participants, Mean age= 35.6 years, 78% male, past month injecting drug use= 87.4%, on OST= 37.9%, acute HCV	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Participants who received treatment were significantly less likely to report injection drug use at one-year

		clearance; not eligible for treatment due to contra-indications) *1 year*		infection.		follow-up compared to comparison groups.
Artenie et al. (2019) *Australia, Canada, New Zealand, Norway, Switzerland, France, UK and USA*	Past month injection drug use, needle/ syringe sharing, hazardous alcohol use during and following treatment	Prospective cohort study (none) *2 years*	Drug treatment clinics, hospital clinics, private practice, community clinics	190 participants, Mean age= 47 years, 74% male, past month injecting drug use= 62%, on OST= 61%, active HCV infection.	Direct acting antivirals (12 weeks)	Overall decrease in opioid injecting during and following treatment. No changes found in hazardous alcohol consumption observed. Decrease in needle and syringe sharing during and following treatment.
Malaguti et al. (2019) *United Kingdom*	Injecting frequency at baseline, throughout and after treatment	Retrospective cohort study (none) *6 months*	Injecting Equipment Provision (IEP) Service	84 participants (18 to 70 years), 69% male, past month injecting drug use= 100%, on OST= 71.4%, active HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Significant reduction in injecting frequency between baseline and subsequent future time points. Largest reduction between week 1 (baseline) and

						week 8.
Midgard et al. (2017) *Australia, Canada, Switzerland, Belgium, Germany, Norway and the UK*	Past month injection frequency, use of non-sterile needles, needle and syringe borrowing or lending, and injecting paraphernalia during and following treatment	Prospective cohort study (none) *24 weeks*	Hospital clinics, drug and alcohol clinics, office based practices and community clinics	93 participants, Median age= 41 years (35- 50 years), 83% male, past month injecting drug use= 59%, on OST= 71%, chronic HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Injecting drug use decreased during treatment and follow-up. No significant changes were found in >daily injecting, use of non-sterile needles, sharing of injecting paraphernalia, or non-injecting drug use.

Risk of bias in individual studies

Table 5 provides detailed quality appraisal scores for each included study. The results of the scoring process suggests that Artenie et al. (2017) was the methodologically most robust study. Overall, the selected studies scored very highly on external validity. However, several issues of internal validity can be discussed. For instance, the occurrence of losses to follow up may have caused selection bias in several studies, with sizeable differences in socio-demographic characteristics between participants who remained, versus lost to follow up. For example, Midgard et al. (2017) found that participants who remained in 12 weeks follow up were more likely to be employed, have higher education levels, had less history of incarceration, and had injected more often in the last month, in comparison to those lost to follow up. Therefore, it is possible that those remaining in follow up were more likely, for instance, to have greater access to social support, impacting on their ability to engage in treatment and facilitate behavioural changes in relation to their drug use. Another issue of internal validity is the lack of comparison groups in some studies, e.g. Artenie et al. (2019) and Midgard et al. (2017), making it challenging to attribute behavioural changes to the intervention, i.e. HCV treatment. A final point to note is the quality assessment tool's appraisal of the outcome variable's reliability. According to the Quality Appraisal Checklist's guidelines, outcome variables that are measured subjectively, e.g. self-report, are to be scored poorly and could introduce information bias (National Institute for Health and Care Excellence, 2012). As all selected studies utilised a self-reported measure of injecting risk behaviours, they were all poorly scored for this part of the appraisal process. However, research has demonstrated that self-reported drug use among PWID is reliable and valid (Darke, 1998). Therefore, it is the opinion of the authors that the selected studies rate more highly for study design appraisal.

Table 5. *Quality appraisal ratings for each included study*

	Alavi et al. (2015)	Artenie et al. (2017)	Malaguti et al. (2019)	Midgard et al. (2017)	Artenie et al. (2019)
1.1 Description of source population	3	3	3	3	1
1.2 Representativeness of eligible population	3	3	3	3	2
1.3 Representativeness of selected participants	2	3	2	2	2
2.1 Allocation to intervention or comparison	NA	NA	NA	NA	NA
2.2 Description of intervention and comparison	3	3	2	3	2
2.3 Concealment of allocation	NA	NA	NA	NA	NA
2.4 Blinding to exposure/comparison	NA	NA	NA	NA	NA
2.5 Adequacy of exposure to intervention/comparison	NA	NA	NA	NA	NA
2.6 Contamination	NA	NA	NA	NA	NA
2.7 Similarity of other interventions to groups	3	3	NA	NA	NA
2.8 Lost to follow up	1	2	2	2	1
2.9 Setting reflects usual UK practice	2	2	3	3	2
2.10 Intervention reflects usual UK practice	2	2	3	3	2
3.1 Reliability of outcome measures	1	1	1	1	1
3.2 Completion of outcome measures	3	3	3	3	3

3.3 Assessment of important outcomes	NA	NA	NA	NA	NA
3.4 Relevance of outcomes	3	3	3	3	3
3.5 Similarity of follow up times across groups	NA	NA	NA	NA	NA
3.6 Meaningfulness of follow up times	3	3	3	3	3
4.1 Similarity of groups at baseline	3	3	NA	NA	NA
4.2 Intention to treat (ITT) analysis	NA	NA	NA	NA	NA
4.3 Study's power to detect an intervention effect	2	2	2	2	2
4.4 Estimates of effect size	3	3	3	3	3
4.5 Appropriateness of analytical methods	3	3	3	3	2
4.6 Precision of intervention effects	3	3	3	3	3
5.1 Internal validity	2	3	2	2	2
5.2 External validity	3	3	3	3	3

Results of individual studies

Impact of treatment on past month injecting drug use

Four studies investigated the impact of treatment on past month injecting drug use at various time points during treatment and follow up, assessed dichotomously (Alavi et al., 2015; Artenie et al., 2017; Artenie et al., 2019; Midgard et al., 2017). Alavi et al. (2015) reported no association between HCV treatment and past month injecting drug use during 24 weeks follow up, when comparing PWID who did and did not receive treatment (aOR 1.06, 95% CI 0.93- 1.21, n= 124). However, this study did not differentiate between participants based on their reasons for not engaging in treatment after study enrolment, possibly explaining the non-significant results of the study as untreated participants are arguably a more heterogeneous cohort. A second study by Artenie et al. (2017) did make this distinction, evaluating the impact of treatment on injecting drug use at one year follow up when comparing people who received treatment, and three comparison groups: people who spontaneously cleared the virus and did not require treatment; people who were not eligible for treatment due to contra-indications to therapy; and people who voluntarily chose not to engage in HCV care. Results showed that the received treatment group were less likely to report injecting drug use at follow up in comparison to the voluntary non- engagement group (aOR 0.18, 95% CI 0.04- 0.76, n=87). The odds of reporting injecting drug use at follow up amongst the spontaneous clearance (aOR 0.34, 95% CI 0.08–1.40, n=87) and contra- indications to therapy groups (aOR 0.24, 95% CI 0.05– 1.22, n= 87), were not significantly lower in comparison to the voluntary non- engagement group. This finding is supported by Midgard et al. (2017) who found that there was a significant reduction in any past month injecting drug use during treatment and 12 week follow up (OR 0.89, 95% CI 0.83– 0.95, n= 93), with the likelihood of injecting halved at treatment completion compared to study enrolment. A fourth study evaluated the impact of DAA

based treatment on past month injecting drug use and found that there was an overall significant reduction in opioid injecting (OR: 0.95, 95% CI 0.92- 0.99, n= 190) between treatment initiation and 2 year follow up (Artenie et al., 2019). However, no reduction in stimulant (cocaine and amphetamine) injecting was reported (OR 0.98, 95% CI 0.94-1.02, n=190).

Impact of treatment on injecting frequency

Two studies investigated the impact of treatment on injecting frequency. Midgard et al. (2017) measured ≥ daily injecting as a proxy for past month injecting frequency, and found that the proportion of participants who reported ≥ daily injecting did not significantly change during treatment and follow up (OR 0.98, 95% Cl 0.89-1.07, n= 93). It is notable that injection risk behaviours amongst participants in this study were low at baseline, with only 28% of participants who achieved 12 weeks follow up reporting ≥ daily injecting at enrolment. Moreover, the authors mention a lack of statistical power due to the relatively small sample size, providing a second explanation of lack of significant findings. A second study by Malaguti et al. (2019) investigated changes in weekly injecting frequency between enrolment, during treatment and at 6 months follow up. Results showed a significant decrease in injecting frequency between enrolment and future time points (χ^2 (7) = 36.44, p< .001, n= 32), with the largest reduction in injecting reported between enrolment and week 8 of treatment, maintained through to 6 months follow up. A criticism of this study may be the high degree of incomplete data, with only 38% of participants providing data for all time points.

Impact of treatment on needle and syringe borrowing

The impact of treatment on needle and syringe borrowing was investigated by two studies. One such study by Alavi et al. (2015) found that treatment was not associated with a reduction in needle and syringe borrowing during follow up, when comparing PWID who did and did not receive treatment (aOR 0.99, 95% CI 0.89, 1.07, n= 124). A second study found that treatment receipt did not significantly facilitate a reduction in use of non-sterile needles (OR 0.94; 95% CI 0.79–1.12, n= 93) (Midgard et al., 2017).

Impact of treatment on injecting equipment sharing

Facilitation of a reduction in injecting equipment sharing by treatment was explored in three studies. One study reported a significant decrease in injecting equipment sharing, including mixing container, filter and water, during treatment and 24 weeks follow up (aOR 0.85, 95% CI 0.74- 0.99, n=124), with a reduction in the number of participants reporting sharing from 54% at baseline to 17% at follow up (Alavi et al., 2015). In contrast Midgard et al. (2017) reported no association between treatment and injecting equipment sharing, including spoons, mixing containers, drug solution, water and filter, during treatment and 12 week follow up (OR 0.87, 95% CI 0.70–1.07, n= 93). One study investigating the impact of DAA based treatment on behavioural outcomes reported a significant reduction in the number of participants reporting needle and syringe sharing during treatment and 2 year follow up (OR 0.87, 95% CI 0.80- 0.94, n= 190) (Artenie et al., 2019). However, it must be noted that although a reduction in needle and syringe sharing during and after treatment was noted, the baseline prevalence of this risk behaviour was low at only 16% of the 62% of participants who reported past month injecting.

Discussion

Summary of evidence

In spite of the concerns around diagnosing and treating PWID for Hepatitis C, there is a dearth of research on the impact of engaging in treatment on behavioural change in relation to drug use in this population. The current review only identified five studies which directly measured behavioural change outcomes in PWID engaged in treatment. As a consequence of the limited number of studies identified, and variations in follow up times, behavioural outcomes, and treatment interventions, drawing conclusions around whether treatment engagement is effective in reducing injecting drug use and injecting risk behaviours is problematic.

The most common outcome measure of behaviour change in relation to drug use in the selected studies was past month injecting drug use. Three of the four studies assessing this outcome found treatment significantly reduced the odds of participants reporting past month injecting at follow up (Artenie et al., 2017; Artenie et al., 2019; Midgard et al., 2017). However, due to variations in study design, comparing the findings of these separate studies is challenging. Accordingly, combining the data on these results to conduct a meta- analysis was deemed inappropriate. Additionally, it can be argued that dichotomously measuring past month injecting drug use is limiting in regards to providing insight into the impact of treatment on injecting behaviours. Combined with infrequent measurements of injecting drug use, it could be suggested that the results of these studies simply reflect natural fluctuations in injecting frequency among PWID, and do not accurately reflect a reduction in injecting drug use. However, taken together, these findings suggest that engaging in treatment may result in a possible reduction in injecting. This challenges critics who believe that treating

PWID for Hepatitis C is not feasible due to concerns around treatment causing an increase in injecting risk behaviours (Schaefer, Sarker, & Diez- Quevedo, 2013). Moreover, these findings support the notion that treatment engagement may lower the risk of HCV transmission within the PWID population, providing support for accessibility to treatment.

In regards to impact of treatment on other behavioural changes related to drug use, findings are more inconsistent. For instance, of the two studies which investigated the impact of treatment on injecting frequency, only one study observed a significant decline in injecting frequency between enrolment, treatment, and follow up (Malaguti et al., 2019). Nonetheless, comparing the findings of these studies is not suitable due to the contrasting measurements of injecting frequency; namely weekly injecting, measured as a continuous variable (Malaguti et al., 2019), and ≥ daily injecting, measured as a binary variable (Midgard et al., 2017).

Both studies investigating change in needle and syringe borrowing found no association between treatment engagement and reduction in these risk behaviours (Alavi et al., 2015; Midgard et al., 2017). Although no significant decline was observed in either study, the fact that such risk behaviours remain stable throughout treatment and follow up has meaningful implications for risk of reinfection and onward transmission. It should also be considered that the availability of other services, for example, needle syringe programs and opioid substitution therapy, across countries where the studies were conducted may impact drug use behaviour. For instance, in countries where injecting equipment provision is low, patients may have less opportunity to change their injecting risk behaviours due to lack of availability of sterile equipment. Additionally, self-stigma may impact patients' willingness to report sharing behaviour, especially in the context of settings where self-reporting of ongoing risk behaviours may occlude access to treatment. The minimisation of injecting risk

behaviours after treatment is critical to optimise patients' chances of achieving sustained viral responses and to reduce HCV prevalence at a population level (Hickman, De Angelis, Vickerman, Hutchinson, & Martin, 2015). Of the three studies investigating the impact of treatment on injecting equipment sharing, two studies reported significant decreases in such behaviour between enrolment, treatment and follow up. However, of these two studies, one study by Artenie et al. (2019) was conducted during the DAA era of treatment, making the findings of this study incomparable to the other studies investigating this behaviour change.

Limitations of review

The predominant limitation of the current review was the number of studies that met the inclusion criteria and the lack of comparability between studies. As a consequence, a meta- analysis of findings was not possible. Therefore, future reviews may seek to employ a more broadly inclusive eligibility criterion, including, for example, the inclusion of purely qualitative studies. Including studies of this design may provide a more nuanced and informed insight into patients' treatment experiences and impact on their drug use behaviour. However, disadvantages of qualitative research include clients' reporting biases due to researcher presence, and issues of anonymity and confidentiality. Secondly, inclusion of bio-behavioural observational studies, such as the Needle Exchange Surveillance Initiative (NESI), may be advantageous in order to measure and monitor patients' injecting risk behaviours over time. Therefore, it could be argued that the strict search strategy was a limitation of the review. However, the inclusion of grey literature, such as conference abstracts, is a strength.

It is clear that future research should focus on the reasons why engaging in treatment facilitates a possible behavioural change in relation to drug use. A major

limitation of the review was that four of the five selected studies were conducted during the interferon era of treatment. In particular, the characteristics of people undergoing interferon treatment may potentially be different to those undergoing DAA treatment. For example, those treated using interferon based therapy may have experienced more adverse treatment consequences, such as associated psychiatric conditions, in comparison to those treated using the DAA based therapy.

Moreover, the reasons why engaging in treatment facilitates a positive behaviour change in relation to injecting drug use may be disparate between the aforementioned treatment groups. Consequently, the results of the current review may not give insight into the impact of treatment on injecting risk behaviours in the new DAA based treatment era, with future research clearly needed to clarify this issue. Also, the review was hindered by the inclusion of studies with selection bias of participants. All five studies involved clinical trial participants, who were arguably more willing to engage in treatment than the source PWID population. This was characterised by relatively low lost to follow up rates in some studies. Thus, the results of the included studies may not be representative of the wider population of PWID engaging in treatment. A final limitation of the review was that all included studies had sampling issues related to power, for instance as a result of small sample sizes and loss to follow up, and may explain lack of significant findings in some studies. Reasons for losses to follow up are complex, but may include, for instance, sociodemographic characteristics of study participants and issues around treatment adherence.

Conclusions

Five studies investigating the impact of HCV treatment on behavioural change in relation to drug use amongst PWID were identified. The most common measure of

behaviour change in relation to drug use was past month injecting drug use, with three out of four studies reporting treatment significantly reduced the odds of participants reporting past month injecting at follow up. Studies also reported significant reductions in injection equipment sharing between enrolment, treatment and follow up; no significant changes in needle and syringe borrowing; and varying results in regards to impact of treatment on injecting frequency. Comparison and synthesis of results was challenging due to heterogeneity of follow up times, treatment interventions, and measures of behavioural outcomes. For future research, it would be optimal for the research community to report injecting risk behaviour in a standardised manner to enable comparison and strengthen conclusions of published literature. Four out of the five selected studies were conducted during the interferon era of treatment, possibly limiting the generalisability of the current review's results to the new DAA treatment era. However, results suggest the benefits of engaging in HCV care stretch beyond liver morbidity outcomes, with treatment positively impacting on patients' injecting drug use and injection equipment sharing behaviour. These findings have relevance to the "treatment as prevention" model of Hepatitis C care, risk of reinfection and onward HCV transmission (Schulkind et al., 2018; Fraser et al., 2018).

3. Hepatitis C Diagnosis and Treatment, Impact on Engagement and Behaviour of People Who Inject Drugs, a service evaluation, the Hooked C project

This study has been published in Journal of Viral Hepatitis in January 2020. A copy of the publication can be found in Appendix B.

Reference: Caven, M., Robinson, E. M., Eriksen, A. J., Fletcher, E. H., & Dillon, J. F. (2020). Hepatitis C Diagnosis and Treatment, Impact on Engagement and Behaviour of People Who Inject Drugs, a service evaluation, the Hooked C project. *Journal of Viral Hepatitis*, *27*(6), 576-584. https://doi.org/10.1111/jvh.13269

Abstract

Introduction: There is emerging evidence that HCV treatment engagement is associated with change in drug use behaviours and reduced drug related death rates amongst 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.

Methods: 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 non-engagers; and patients who received interferon vs DAA based treatment.

Results: 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 non-engaging persons compared to treatment engaging cases (aOR 12.15, 95% CI 7.03- 20.99, $p < 0.001$). The odds of a drug related death was 5.5 times higher in non-engaging persons compared to treatment engaging cases (aOR 5.52, 95% CI 2.67- 11.44, $p < 0.001$). No differences in risk of all-cause mortality or drug related death between interferon treated cases and DAA treated controls were detected.

Conclusions: 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.

Objectives

The current project aims to answer, through a series of case control studies, three research questions:

- Does HCV diagnosis reduce a) all-cause mortality, b) drug related death among PWID?
- Does engagement in HCV treatment services reduce a) all-cause mortality, b) drug related death among PWID?

- Does any change observed in risk of a) all-cause mortality, b) drug related death depend on if the treatment is interferon based or DAA based, and intensity of engagement with staff?

Three case control studies will be carried out, comparing:

- PWID with active HCV infection (PCR Positive) vs PWID who were HCV infected but cured spontaneously (PCR Negative) to elucidate whether HCV diagnosis impacts risk of mortality
- PCR Positive patients who engaged vs did not engage with treatment services to assess if outcomes are dependent on engagement
- Pegylated interferon alpha treated patients vs Direct acting antiviral patients to explore the effect of intensity of HCV therapy provider interaction on outcomes

The following hypotheses are proposed:

- HCV diagnosis will reduce risk of all-cause mortality and drug related death among PWID.
- Engagement in HCV treatment services will reduce risk of all-cause mortality and drug related death among PWID.
- Engagement with interferon based treatment regimens will result in a greater reduction in risk of all-cause mortality and drug related death than engagement with DAA based treatment regimens.

Methodology

Approvals

Approval for access to relevant data from all data sources was obtained from the Caldicott Guardian of NHS Tayside Information Governance Team (issued November 2018, Ref Caldicott/IGTCAL5540). This approval is attached in Appendix C.

Study design

We employed a retrospective case control study design, matching participants by age and sex.

Data sources and data linkage

The main data source utilised was the Tayside Hepatitis C Clinical Database. This database is kept for clinical purposes to record 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 the 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.

Identification of selected cohort

Inclusion and exclusion criteria are presented in Table 6. From the Tayside clinical database, a cohort of individuals was identified whose risk factor for HCV was injecting 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. Although there may be variation in the cohort regarding recent/active drug use, it was decided that it was appropriate to include "former" PWID, i.e. those who may have ceased injecting, as a proportion of HCV infections are found in this group. It could be argued that the inclusion of former PWID in the cohort could lead to biases due to differences in injecting behaviours and therefore risk of mortality, when compared to current PWID. However, we only included individuals who were tested/treated from 2008 onwards, which reduces the likelihood that we have included a significant number of former PWID. Moreover, given the relapsing nature of drug dependence, determining a cut off to define current/recent vs former PWID is problematic and leads to biases. Therefore, the definition that would least likely bias the study was chosen, by being inclusive. 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 e.g. HIV or Hepatitis B, 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.

Table 6. *Inclusion/Exclusion Criteria*

Inclusion Criteria
• Risk factor for HCV: injecting drug use • Postcode within Tayside • Tested/initiated treatment between January 2008 and November 2017
Exclusion Criteria
• Risk factor for HCV: high prevalence country, blood products, maternal transmission, renal dialysis • Postcode out with Tayside • Co-infected with other blood borne viruses e.g. Hepatitis B, HIV • Tested/initiated treatment before January 2008 • Tested/initiated treatment after November 2017

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.

Outcome variables

All-cause mortality and drug related death

The definition of a drug related death is a death where the underlying cause is: drug abuse or drug dependence; or drug poisoning (intentional or accidental) that involves any substance controlled under the Misuse of Drugs Act 1971 (National Records of Scotland, 2019). 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.

Predictor variables

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, e.g. if a sustained viral response (SVR) was achieved. Correspondingly, patients who did not commence treatment were classified as "treatment non-engagers".

Opioid substitution therapy (OST)

Data was 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 Non-Engagers), data was 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 was collected on whether individuals were on OST at the time of treatment commencement, +/- 6 months.

Cirrhosis

Data was 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 (Castéra et al., 2005).

SVR

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

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 22. For analysis 1 (PCR Negative vs PCR Positive) and analysis 2 (Treatment Engagers vs Non-Engagers), 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). Baseline characteristics were summarised using descriptive statistics. Inter-correlations between predictor variables were summarised using Pearson's correlational analyses. Point-biserial correlations were carried out to assess the association between categorical and continuous variables.

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.

Assumptions for binary logistic regressions

Prior to running the binary logistic regressions, the assumptions underlying this method of statistical analysis were evaluated.

Firstly, binary logistic regression requires the dependent variable to be categorical, and both dependent variables (all-cause mortality and drug related death) met this assumption.

Secondly, for all analyses, the assumption of multicollinearity was met after inspection of the correlation matrices revealed no evidence of strong correlations between predictor variables.

Thirdly, for all analyses, the assumption of independence of errors was met after it was determined that the error terms were independent.

Lastly, the assumption of linearity was met, with non-significant Hosmer and Lemenshow tests for all analyses (p = 0.10- 0.71).

Coding of categorical predictors

Dummy variables were calculated for all categorical predictors: sex, SVR, OST, cirrhosis, PCR status, Treatment Engagement, and Treatment Regimen. For sex, males were used as a baseline, with which females were compared (Male vs Female). For SVR, not achieving SVR was used as a baseline, with which achieving SVR was compared (No vs Yes). For OST, not on OST was used as a baseline, with which on OST was compared (No vs Yes). For cirrhosis, non-cirrhotic patients were used as a baseline, with which cirrhotic patients were compared (No vs Yes). For PCR status, PCR Negative controls were used as a baseline, with which PCR Positive cases were compared (Negative vs Positive). For Treatment Engagement, Treatment Engaging cases were used as a baseline, with which Treatment Non-Engaging controls were compared

(Engagers vs Non-Engagers). Lastly, for Treatment Regimen, DAA treated controls were used as a baseline with which interferon treated cases were compared (DAA vs IFN).

Results

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 2), 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 7. 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, $\chi^2(2) = .425$, $p = .515$ (see Figure 3). 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 8).

For drug related deaths, the survival distributions for the two groups were not significantly different, $\chi^2(2) = .291$, $p = .590$ (see Figure 4). 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 9).

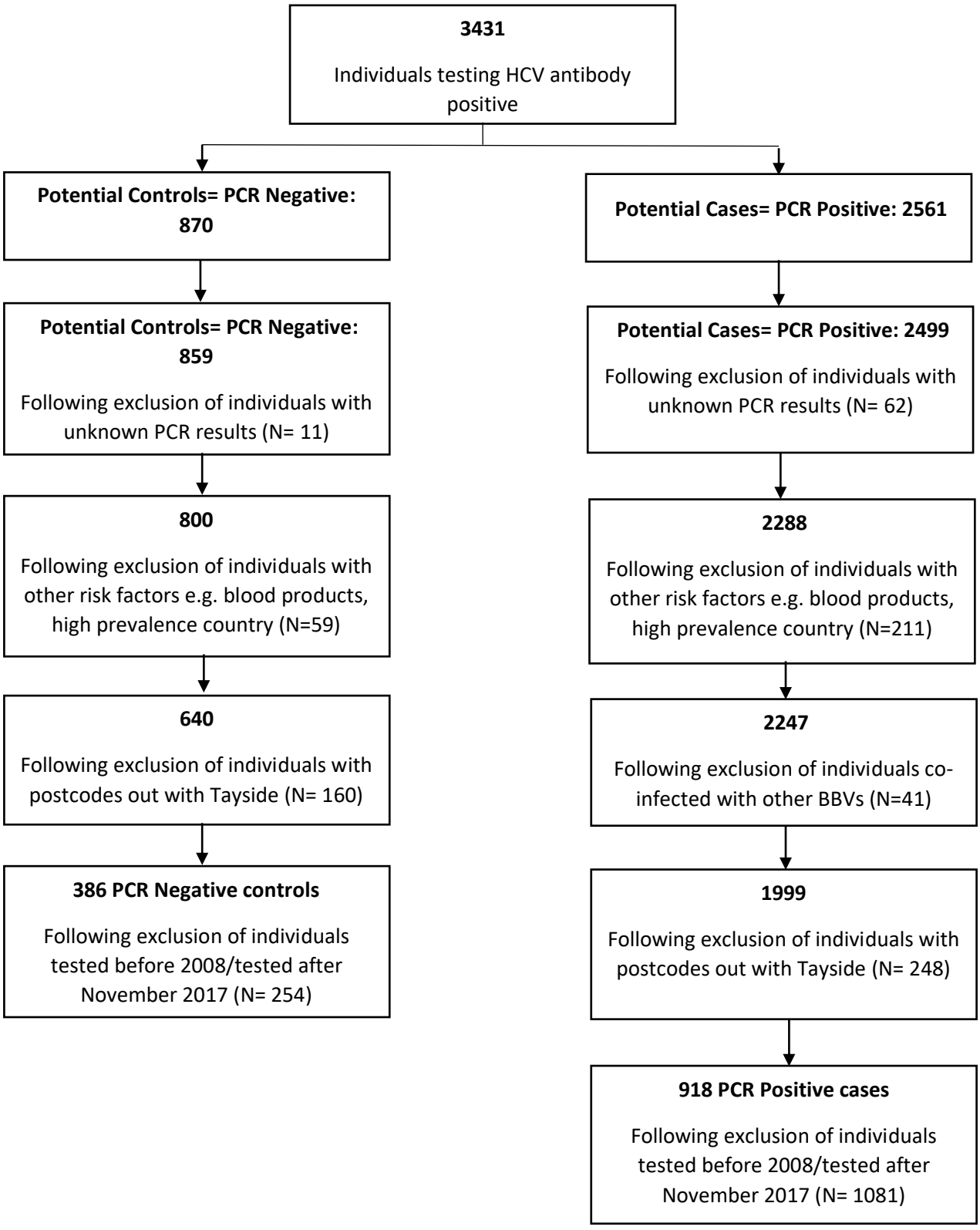

Figure 2. Selection of PCR Positive cases and PCR Negative controls based on inclusion/ exclusion criteria.

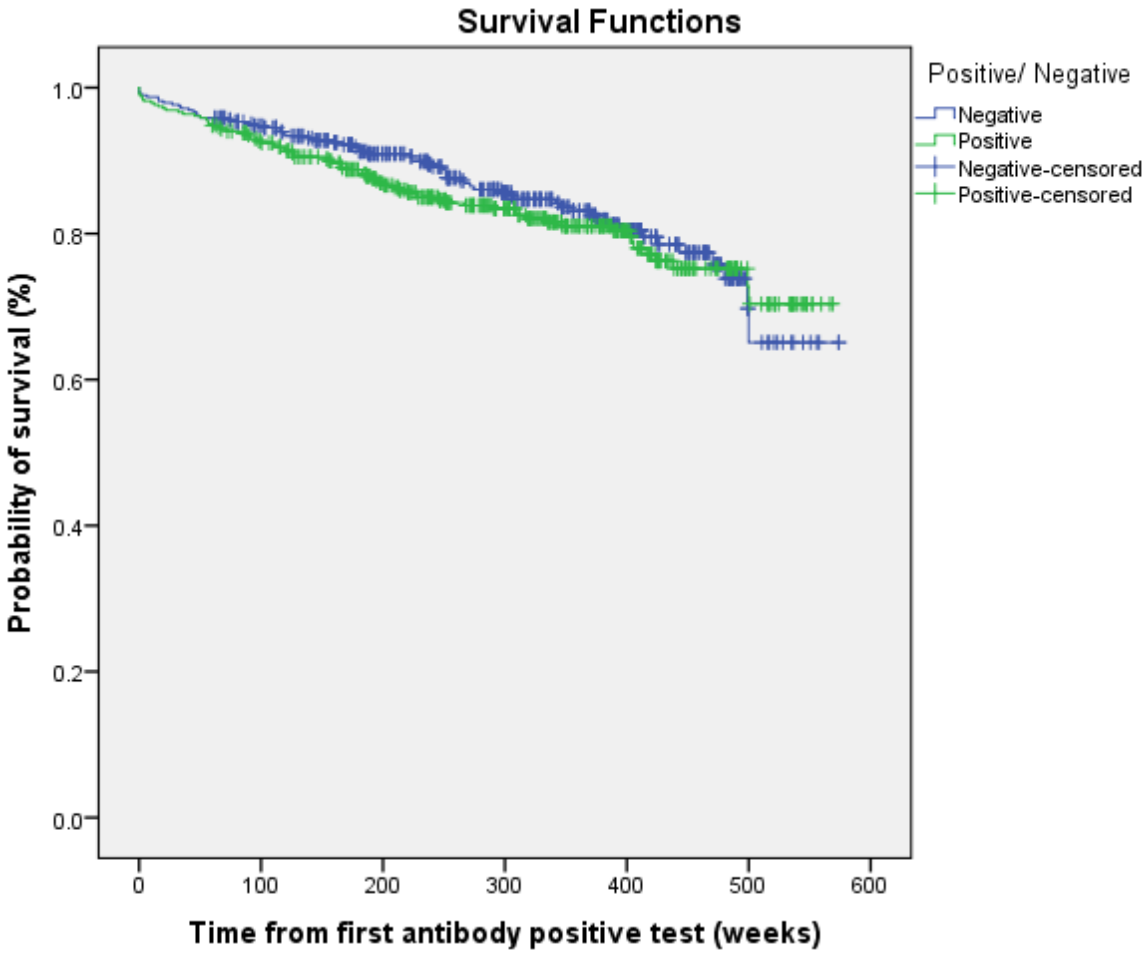

Figure 3. Kaplan Meier survival curve for time from first antibody positive test to all-cause mortality comparing PCR Positive cases and PCR Negative controls

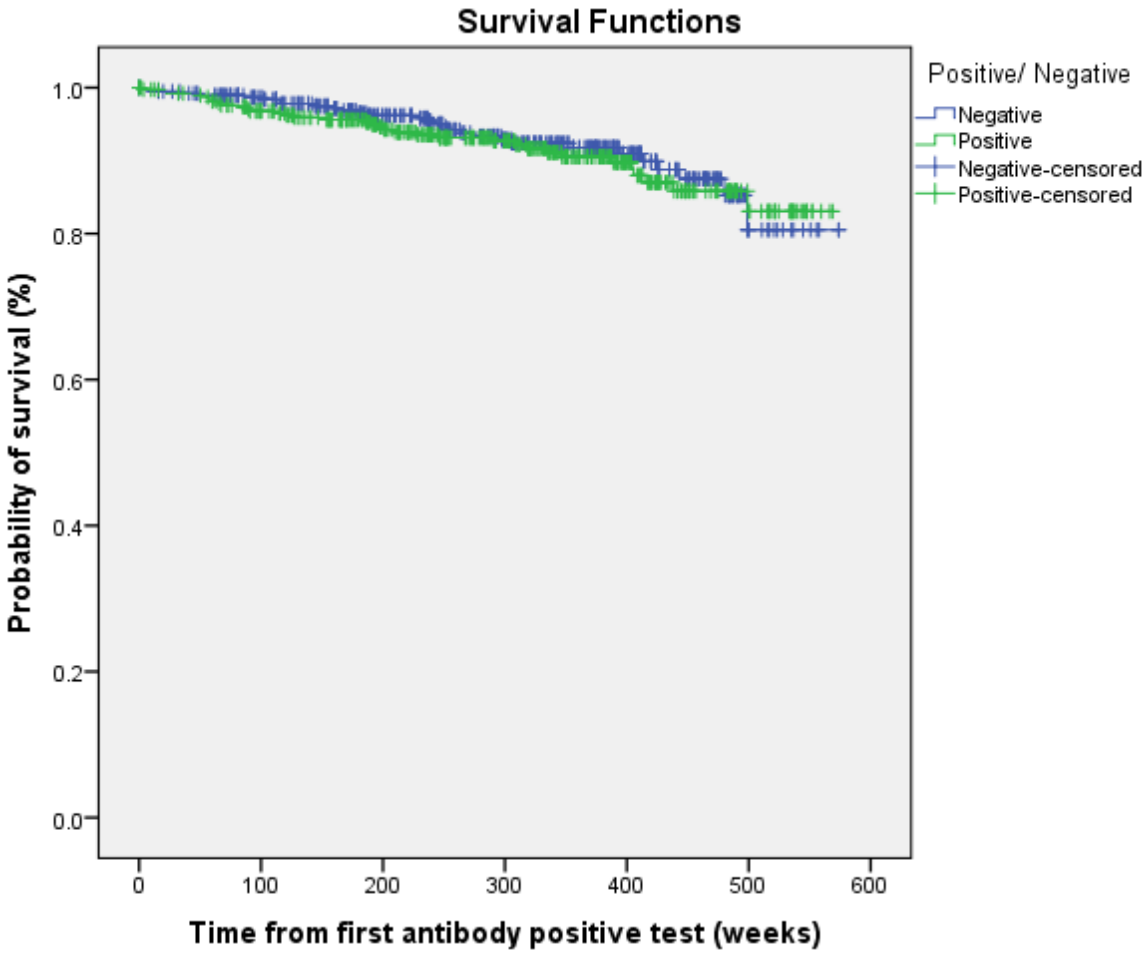

Figure 4. Kaplan Meier survival curve for time from first antibody positive test to drug related death comparing PCR Positive cases and PCR Negative controls

Table 7. 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%)

Table 8. 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)	-.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)= .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 Non Engagers)	-2.50* (0.28)	7.03	12.15	20.99
R^2 (Cox & Snell)= .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)= .04				

Note: *$p < 0.05$.

Table 9. 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)= .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 Non Engagers)	-1.71* (0.37)	2.67	5.52	11.44
R^2 (Cox & Snell)= .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)= .03				

Note: *$p < 0.05$

Analysis 2- PCR Positive treatment engagers vs PCR Positive treatment non- engagers

A total of 2499 individuals who tested HCV PCR Positive were identified. Of these, 267 treatment non- engaging controls and 650 treatment engaging cases met the inclusion criteria (see Figure 5), and were randomly matched by age group and sex, leading to 263 treatment non- engaging 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 7. 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 non- engaging 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 non-engaging controls at a significantly higher risk of all-cause mortality, $\chi^2(2) = 91.395$, $p = <.001$ (see Figure 6). The odds of all-cause mortality was 12.2 times higher amongst treatment non- engaging controls, (aOR 12.15, 95% CI 7.03- 20.99, $p < .001$) compared to treatment engaging cases, after adjustment for age, sex and OST (see Table 8).

For drug related deaths, the survival distributions for the two groups were significantly different, with non-engaging controls at a significantly higher risk of drug related death, χ^2 (2) = 32.364, *p* = <.001 (see Figure 7). The odds of a drug related death was 5.5 times higher amongst treatment non- engaging controls, (aOR 5.52, 95% CI 2.67- 11.44, p < 0.001) compared to treatment engaging cases, after adjustment for age, sex and OST (see Table 9).

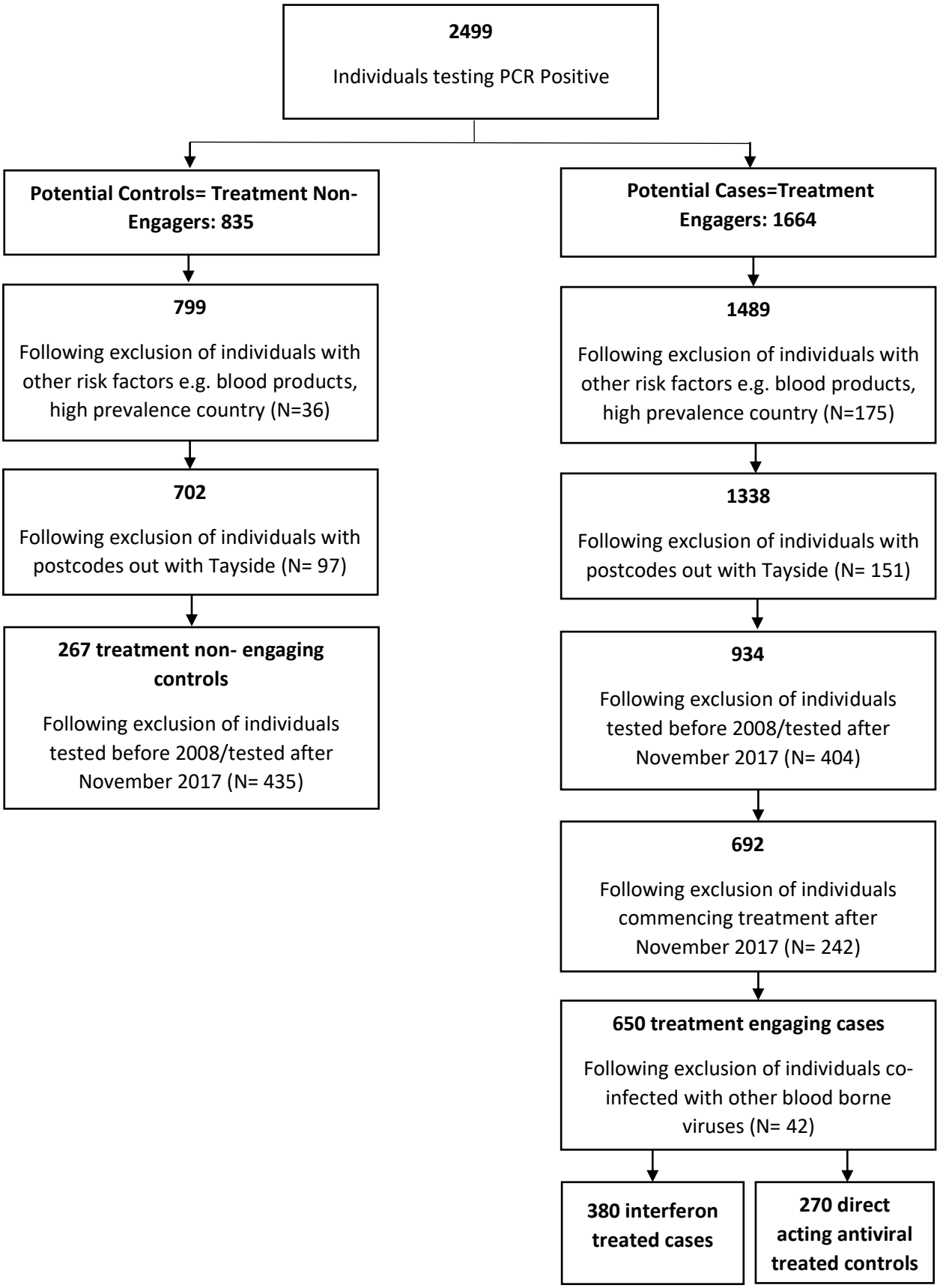

Figure 5. Selection of treatment engaging/interferon treated cases and treatment non- engaging/direct acting antiviral treated controls based on inclusion/exclusion criteria.

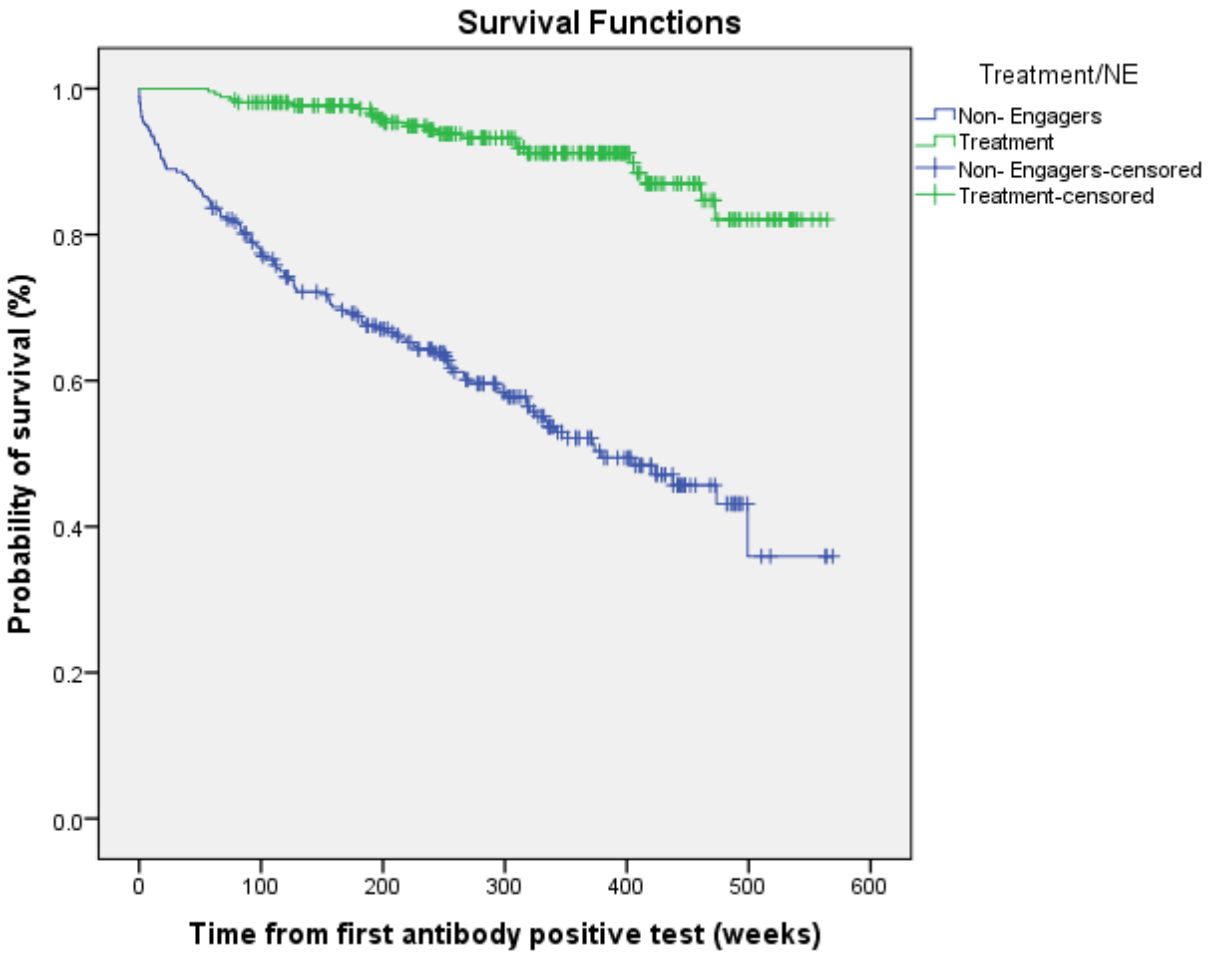

Figure 6. Kaplan Meier survival curve for time from first antibody positive test to all-cause mortality comparing treatment engaging cases and treatment non-engaging controls

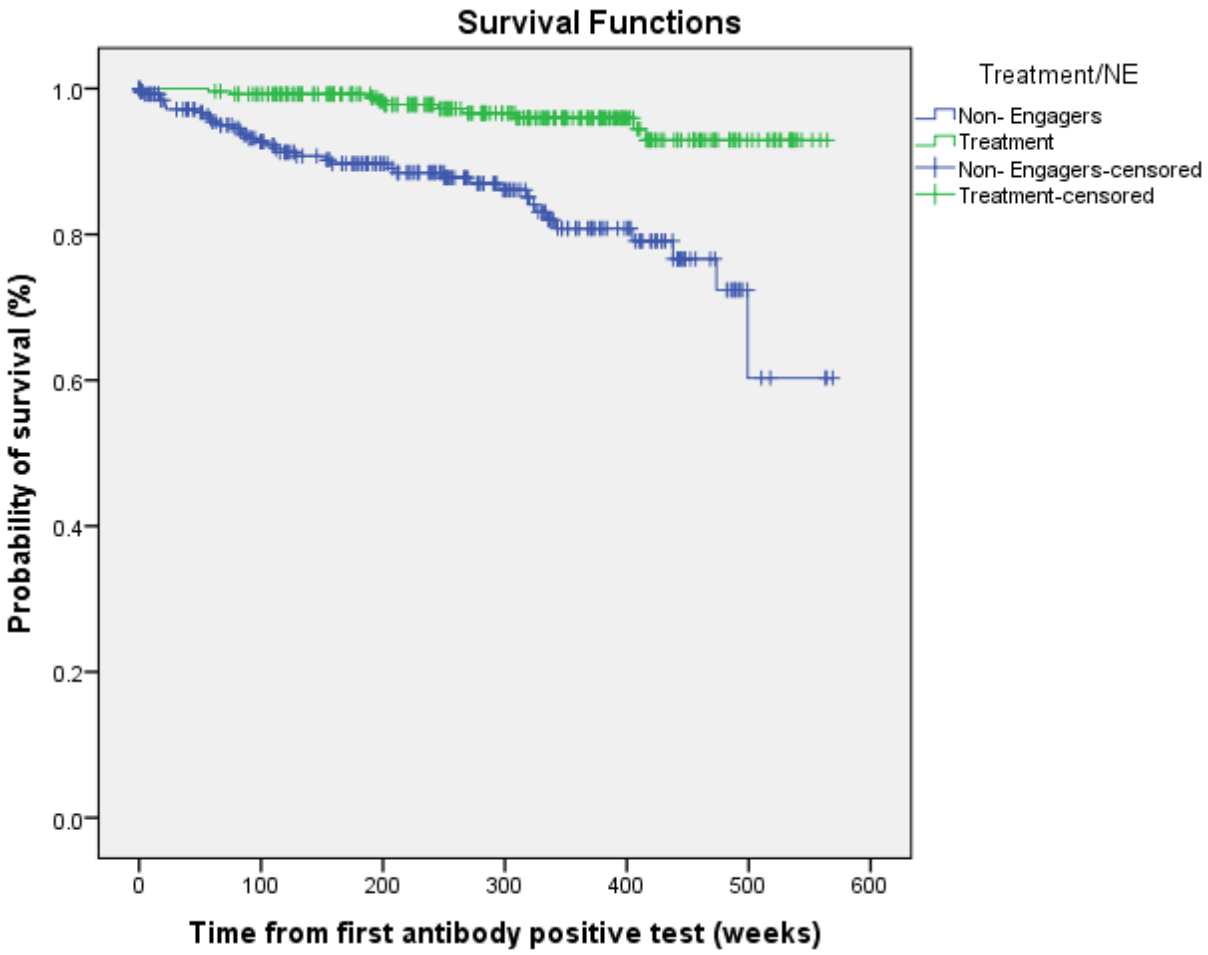

Figure 7. Kaplan Meier survival curve for time from first antibody positive test to drug related death comparing treatment engaging cases and treatment non-engaging controls

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 direct acting antiviral treated controls met the inclusion criteria (see Figure 5), and were randomly matched by age group and sex, leading to 266 interferon treated cases and 266 direct 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 7. 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 7 (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, 9 of the 35 deaths, and 3 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, $\chi^2(2) = .071$, $p = .789$ (see Figure 8). 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 8). Note, 28 individuals were omitted from the regression analysis due to missing data on cirrhosis; 8 controls and 20 cases.

For drug related deaths, the survival distributions for the two groups were not significantly different, $\chi^2(2) = .281$, $p = .596$ (see Figure 9). 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 9).

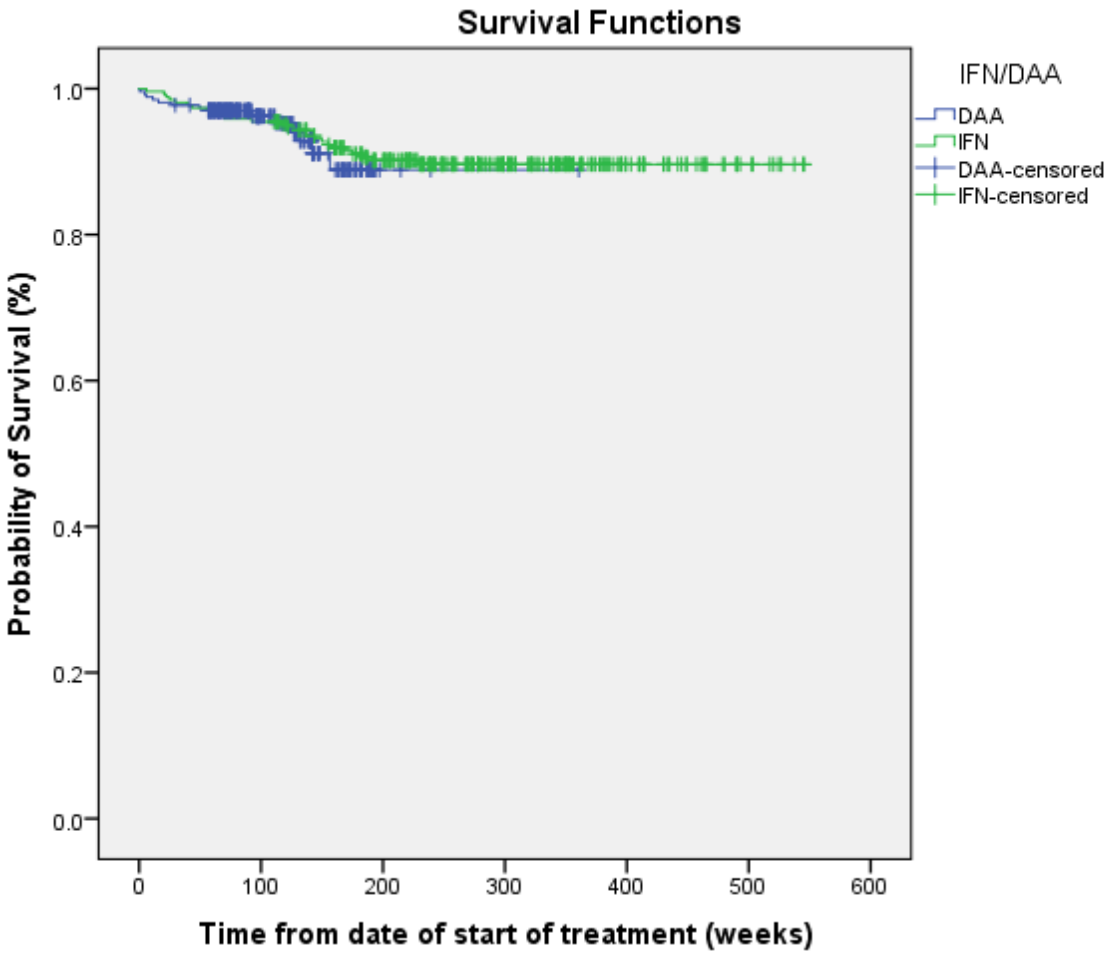

Figure 8. Kaplan Meier survival curve for time from treatment commencement to all-cause mortality comparing interferon treated cases and direct acting antiviral agent treated controls

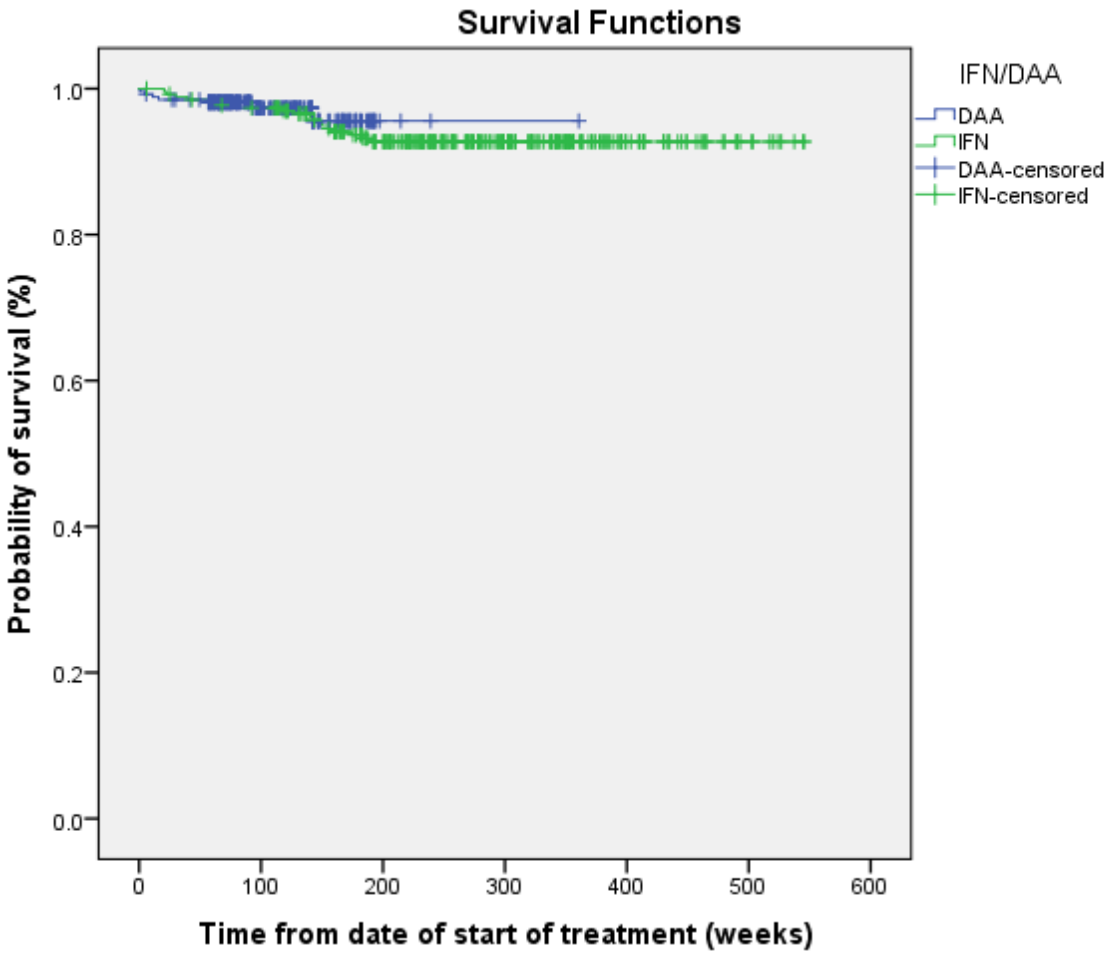

Figure 9. Kaplan Meier survival curve for time from treatment commencement to drug related death comparing interferon treated cases and direct acting antiviral agent treated controls

Discussion

The aim of the project was to investigate whether HCV diagnosis and engagement with treatment services reduces all-cause 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 to answer three main research questions.

The first case control study compared PWID with active HCV infection (PCR Positive) vs PWID who had been HCV infected but cured spontaneously (PCR Negative) to answer the research question does HCV diagnosis reduce risk of mortality among PWID. We hypothesised that HCV diagnosis will reduce mortality outcomes among PWID. 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. Contrary to our hypothesis, our results suggest that awareness of HCV positive infection status makes no difference to mortality, either all cause or drug related. This finding is line with Spelman et al. (2015) who found no difference in post notification injecting behaviours when comparing PWID who received a positive test result to those who tested HCV negative. This highlights the need for greater communication by healthcare professionals to patients diagnosed of HCV of the importance of reducing injecting risk behaviours.

The second case control study compared PCR Positive patients who engaged vs did not engage with treatment services to answer the research question does engagement with HCV treatment services impact mortality outcomes of PWID. We hypothesised that engagement with HCV treatment services would reduce both risk of all-cause mortality and drug related death. Consistent with this hypothesis, our findings

provide evidence that HCV treatment engagement is a significant protective factor against both all-cause mortality and drug related death amongst PWID, with non-engaging 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 (Tait et al., 2017). It could be argued that embarking on the HCV treatment process enables a "teachable moment" (TM) for patients; a concept first theorised by Hochbaum (1958) which describes health events which motivate individuals to adopt risk reducing health behaviours, with TMs already suggested in relation to sexual behaviours and HIV prevention (Fabiano, 1993). It is also possible that the event of achieving SVR may also be a teachable moment. It is important to note that our cohort was selected from a population that has high testing, diagnosis, and treatment rates, nearly reaching WHO 2030 targets. Therefore, there is minimal selection bias in our cohorts.

The final case control study endeavoured to explore further if there was any effect of treatment engagement by comparing the mortality outcomes of intensive interaction with health care in interferon treated patients vs DAA treated patients, who have much shorter and less intense engagement. We hypothesised that engagement with interferon based treatment regimens would result in a greater reduction in risk of all-cause mortality and drug related death than engagement with DAA based treatment regimens. 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. The comparability of these two treatment groups must be scrutinised due to, for example, considerable differences in treatment experiences and the availability of illicit drugs during the respective periods when these patients were treated. However, eligibility for inclusion in the study cohort began from 2008, as the introduction of the MCN for HCV care took place in 2008. Thus, the care pathways for these two treatment groups were adequately similar.

Nonetheless, other factors such as changes in the type of illicit drugs available, naloxone programmes, austerity, the increasing age of PWID in Tayside, and poly drug use behaviours may also contribute to DRD rates over the study period of 2008 to 2017. These unmeasured potential confounding variables could contribute to the association between treatment engagement and risk of mortality amongst the study cohort.

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. Furthermore, it could be proposed that people are engaging with treatment at a time of declining risk due to experiencing greater stability when compared to treatment non-engagers. It is not clear if non-engaging behaviour is amenable to change or improved prognosis.

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. 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. Future research is needed to elucidate whether intensive staff contact is protective against other important outcomes, such as reinfection, and injecting equipment sharing behaviour.

Congruent with prior research, the current study found that achieving SVR is a protective factor against all-cause mortality and drug related death (Innes et al., 2015; Cacoub, Desbois, Comarmond, Saadoun, 2018; Backus, Belperio, Shahoumian, & Mole, 2018; Ioannou & Feld, 2019). It has been posited that achieving SVR is a psychologically positive experience for patients due to the subjective feeling of achievement this brings, providing motivation to reduce injecting risk behaviours. Hence, it is interesting that in our study, patients treated with DAA therapies do not have better outcomes than those treated with interferon based therapies, simply as a result of higher SVR rates.

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 was not available. For instance, OST data was 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 non-fatal overdoses would also have been advantageous, as previous research has demonstrated that non-fatal overdose is classified as a risk factor for ensuing fatal overdose in PWID (Caudarella et al., 2016). 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, such as homelessness and mental health problems, 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 non-engagement.

Another limitation to the current study is the lack of differentiation of individuals in analysis 2 (Treatment Engagers vs Non-Engagers). Specifically, engagers were not differentiated by a more specific measurement of treatment engagement e.g. how many weeks of treatment they completed and/or whether they completed their full course of treatment. Equivalently, non-engagers were not differentiated by the reason for their non-engagement. 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 to 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. Likewise, in analysis 3 (Interferon vs DAA patients), we did not differentiate between treatment experienced and treatment naïve patients. Such differentiation may provide understanding as to whether previous treatment experience, and specifically treatment with interferon based regimens, has an impact on patients' willingness to engage with future treatment.

Strengths

Although our study has several limitations, a range of strengths can be identified mainly regarding the location of the study. Specifically, Tayside is uniquely placed to perform this type of study as all HCV testing in Tayside is carried out by the National Health Service (NHS) laboratory in Tayside, with all positive results entered into the

local clinical database. All services work through central laboratories which perform all HCV related testing and relay these results to the Hepatitis Specialist Service who record them in the clinical database. Moreover, NHS Tayside has a HCV testing and treatment service with a decentralised, person focussed approach which has led to over 90% of the prevalent population being diagnosed and over 80% of those diagnosed treated. Coupled with the aforementioned unique data capture, we believe that these strengths minimise biases that could impact on conclusions and have allowed us to address questions that are vital to the design of HCV treatment pathways.

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 non- engaging PCR Positive individuals 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. 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 amongst PWID, reducing their risk of mortality, beyond liver related outcomes.

4. General Discussion

The current project aimed to investigate the impact of HCV treatment on injecting risk behaviours and mortality outcomes of PWID. Our systematic review focused upon reviewing all available literature on the impact of HCV treatment on behavioural change in relation to drug use, including injecting behaviour and injecting equipment sharing. This review revealed a lack of published literature in this important research area, with varying study designs and interventions. Consequently, drawing conclusions around whether treatment engagement beneficially changes patients' injecting risk behaviours is challenging. Moreover, it is clear that additional research is required to explore this research question in the new DAA era of HCV treatment. However, after examination of the available research, results of our review suggest that treatment engagement positively impacts clients' injecting drug use and injection equipment sharing behaviour.

These findings, coupled with previous work conducted by our group, which suggested that improved access to HCV care leads to greater engagement with healthcare services and substantially reduced risk of all-cause mortality, provided a sound basis to conduct several case control studies, investigating the impact of HCV treatment on mortality outcomes of PWID. Specifically, we aimed to investigate whether HCV diagnosis and treatment reduce risk of all-cause mortality and drug related death among PWID, and whether any change is dependent on treatment regimen and intensity of engagement with staff. Results showed that HCV diagnosis did not impact mortality outcomes. However, it was found that HCV treatment engagement is significantly protective against both all-cause mortality and drug related death, independent of treatment regimen and intensity of engagement with staff.

Overall, the current project provides strong evidence of the importance of universal HCV testing and treatment accessibility, with widening access to treatment instrumental in lowering patients' risk of mortality. It is crucial that every effort is made by service providers to encourage HCV positive individuals to initiate treatment, emphasising the importance of ongoing engagement during their treatment process and the prioritisation of reducing injecting risk behaviours. At a systemic level, it is vital that an aggressive and sustained effort is made to minimise barriers and stigma relating to treatment access for PWID to facilitate HCV diagnosis and linkage to care. Treatment providers should be encouraged to ensure patients feel supported and respected, rather than stigmatised, and be active agents in their healthcare. With Tayside demonstrating high testing, diagnosis and treatment rates, it is imperative that a person- focussed approach to HCV care is continued in order to reach individuals who have not yet successfully engaged with treatment services, with the possibility of the creation of individualised pathways of care in order to engage "hard to reach" patients.

Directions for future research

While the current project highlights that engagement in HCV treatment is significantly protective against drug related death and all-cause mortality among PWID, further investigation is required to evaluate the underlying mechanisms of this engagement effect and how HCV treatment engagement facilitates behaviour change. Future qualitative research could be used to explore psychosocial differences in HCV treatment engagers and non-engagers to understand the factors that prevent people living with HCV engaging in testing and treatment. For example, it would be beneficial to examine the differing attitudes and emotional responses to HCV infection, health status and interpretation of illness between those who engage and those who are reluctant to engage, and whether an individual's peer network has an influence on this. Greater understanding of the key barriers and facilitators to engagement would aid the

development of a co-designed intervention that increases the reach, accessibility, and effectiveness of HCV care, improving treatment pathways in pursuit of the WHO goal of elimination. This would require multifaceted input from people living with HCV, referring staff and service providers to adapt current testing and treatment pathways to incorporate stakeholder preferences. Furthermore, 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.

Other directions for future research may be to investigate whether patients who engage with different specialised treatment pathways (e.g. hospital outpatient clinic, drug treatment outreach clinic, community pharmacy outreach) have differing mortality risk, again allowing for greater insight into the complex mechanisms underlying this engagement effect, and how treatment pathways can be improved to promote engagement. Future research may also seek to further investigate the engagement effect by employing varying measurements of engagement such as attendance of appointments during the treatment process. By measuring engagement in such a way, this could act as a proxy for intensity of staff contact, and allow for additional investigation into whether the engagement effect is dependent on intensity of staff interaction.

Lastly, future research may seek to investigate whether sense of achievement through achieving SVR has an impact on behaviour change in relation to patients' injecting behaviours. This could be prospectively accomplished by measuring patients' subjective sense of achievement at time of SVR, along with measurements of injecting risk behaviours before and after. Alternatively, mortality outcomes of DAA treated patients who completed their course of treatment could be analysed by comparing those who received SVR blood results, and those who were lost to follow up after treatment completion.

Implementation

Pressingly, there is 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. Services should be encouraged to implement a person centred, public health approach in their delivery of care. This is in line with the Scottish Government's National Drug and Alcohol Strategy which encourages the addressing of patients' complex needs, such as treating both their HCV infection and their problematic drug use (Population Health Directorate, Scottish Government, 2018). 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 psychosocial interventions to reduce injecting behaviours and promote further harm reduction measures.

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Impact of Hepatitis C treatment on behavioural change in relation to drug use in people who inject drugs: A systematic review

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ABSTRACT

Background: A systematic review was conducted to determine the impact of Hepatitis C (HCV) treatment on substance use behaviour in people who inject drugs (PWID).

Methods: A search for peer reviewed journal articles from 1991 to present day was conducted using the following databases: PubMed, EMBASE, CINAHL and PsycINFO. Studies were appraised against the following inclusion criteria: recruitment of PWID for HCV treatment (either interferon alpha or direct acting antivirals based); measurement of behavioural change in relation to drug use; studies published in English.

Results: Five studies investigating the impact of HCV treatment on behavioural change in relation to drug use amongst PWID were identified. Studies investigated the impact of HCV treatment on past month injecting drug use (four studies), injecting frequency (two studies), needle and syringe borrowing (two studies) and injecting equipment sharing (three studies). Three of the four studies assessing impact of treatment on past month injecting frequency found treatment significantly reduced the odds of participants reporting past month injecting at follow up. One study found that there was significant reduction in weekly injecting frequency between enrolment, treatment and follow up. No association was found between treatment engagement and needle and syringe borrowing. Two out of three studies reported a significant decrease in injecting equipment sharing between enrolment, treatment and follow up.

Conclusions: Comparison and synthesis of results was challenging due to heterogeneity between studies. Moreover, four out of the five selected studies were conducted during the interferon era of treatment, possibly limiting the generalisability of the current review's results to the new DAA treatment era. However, it is likely that engaging in treatment has a positive impact upon patients' injecting drug use and injection equipment sharing behaviour. This raises the possibility that this may be an opportune time for further harm reduction measures.

Introduction

Hepatitis C (HCV) is a blood borne virus which affects around 71 million people globally (Blach et al., 2017; World Health Organisation, 2017). It is estimated that 39.2% of PWID are currently living with HCV infection worldwide (Grebely et al., 2019). HCV infection is a major contributor to morbidity and mortality among this population (Stanaway et al., 2016). Research has supported the treatment of active drug users for Hepatitis C, demonstrating successful adherence to treatment and favourable sustained viral response rates (Hajarizadeh et al., 2018). This highlights the feasibility and effectiveness of scaling up treatment services to reduce the prevalence of the disease, using "treatment as prevention" (TasP) models of elimination (E. J. Aspinall et al., 2013; Fraser et al., 2018). TasP models of elimination focus on treating PWID for HCV as they are the most at- risk population for acquiring the virus. Therefore, HCV elimination can be achieved by treating those at risk of continuous HCV transmission (Hellard, Doyle, Sacks-Davis, Thompson, & McBryde, 2014; Hellard et al., 2015; Hutchinson et al., 2015). However, testing, diagnosis and treatment rates of HCV infection among PWID have found to be inadequate in some settings, despite evidence that the incidence of HCV- related liver disease is on the rise (Socías et al., 2019; Thrift, El-Serag, & Kanwal,

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2017; Wiessing et al., 2014). Barriers to testing and treatment are complex, but include concerns among providers around ongoing risk behaviour, such as ongoing substance misuse, and the sharing of injecting paraphernalia; risk of reinfection; the worsening of psychiatric comorbidities; and poor treatment adherence (Grebely & Tyndall, 2011).

In spite of these barriers to treatment, there is a suggestion that the benefits of engaging with HCV care stretch beyond liver morbidity outcomes. Studies report the positive impact of HCV status notification on reduction in drug use among PWID (E. Aspinall et al., 2014; Bruneau et al., 2013). PWID accessing HCV treatment have the opportunity to develop a therapeutic relationship with healthcare professionals involved in their care, which may facilitate behavioural change (Spelman et al., 2015).

Understanding the influence of treatment receipt on behaviour in relation to drug use in PWID may have an effect on treatment accessibility for this population, and may facilitate the development of supplementary support services to be offered with treatment. The objective of this review was to examine the literature investigating how, if at all, the behaviour of PWID changes in relation to drug use when undergoing HCV treatment and during follow up, including changes in injecting behaviour, injecting frequency, needle and/or syringe borrowing, and injecting equipment sharing.

Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The study was registered in PROSPERO (CRD42018116625).

Search strategy

The International Prospective Register of Systematic Reviews (PROSPERO) was searched to confirm no similar review had already been conducted. A search for peer reviewed journal articles was conducted using PubMed, EMBASE, CINAHL and PsycINFO, on 9th November 2018. A grey literature search of the International Network on Hepatitis in Substance Users (INHSU) conference abstracts was also conducted. This symposium was specifically targeted as it is dedicated to research focusing on Hepatitis C in the cohort of interest, namely PWID. A time parameter was implemented for studies conducted from 1991 to 2018, as 1991 was the year interferon became commercially available for treatment of Hepatitis C. An inclusive list of search terms in line with each search topic was generated to develop an effective search strategy. Both keywords and indexed subject headings (MeSH and EMTREE terms) were included in the formulation of search strings for each database search. Search topics included “Hepatitis C treatment”, “behaviour change” and “drug use”. Table 1 includes a full list of search terms utilised in the search strategy, grouped by search topic. Manual searches of reference lists of selected studies were also conducted. Searches were limited to studies published in English.

Table 1
Keyword search terms utilised in search strategy, grouped by search topic.

Hepatitis C treatment	Behaviour change	Drug use
Hepatitis C treatment/therapy[a]	Behavi* change	Drug abuse
Interferon-alpha/ therapeutic use[a]	Behavi* benefit	Drug misuse
	Drug use change*	Drug use
	Inject behavi*	Drug disorder
	Risk behavi*	Drug addict*
	Inject* frequency	Drug dependen*
		Drug intravenous*

[a] MeSH/EMTREE terms.

Study selection

Fig. 1 shows a PRISMA flowchart of the selection process. Screening of the search strategy results was conducted by two reviewers. The first phase involved importing all citations into EndNote X8 and removing duplicate records. Titles were screened, and irrelevant records removed. Abstracts were then assessed using the inclusion and exclusion criteria (see Table 2). All remaining records were then subjected to a full text evaluation for eligibility.

Data extraction and synthesis

Data from selected studies was extracted using a piloted data extraction form by one reviewer (MC). The following variables were collected: first author, title, publication year, full paper or abstract, primary aim, study design, location, setting, total study duration, follow up period, sample characteristics, sample size, intervention, outcome/measure of behaviour change, main results, conclusions. The authors of Malaguti et al. (2019) were contacted for clarification regarding follow up period in their study. The authors of Artenie et al. (2019) were contacted to obtain updated data, and they kindly provided an unpublished manuscript relating to their INHSU conference abstract. The data synthesis used a ESRC style quantitative narrative synthesis (Popay et al., 2006). This was used as there was too much heterogeneity between selected studies for meta- analysis.

Quality appraisal

Risk of bias in individual studies was assessed using the Quality Appraisal Checklist for quantitative intervention studies by NICE public health guidance (National Institute for Health & Care Excellence, 2012). The checklist enables both the evaluation of the study’s internal and external validity, addressing aspects of study design such as participant characteristics, definition of and allocation to intervention/control conditions, and methods of analyses. Each study was awarded separate overall quality ratings for internal and external validity, with ratings ranging from 1 to 3. Quality appraisal for four studies was independently conducted by two reviewers (MC and AM), with discrepancies in ratings resolved by discussion until consensus was met. A Cohen’s kappa coefficient (κ) was calculated to assess inter-rater agreement, $\kappa = .61$, $p < .001$. This kappa (κ) value represents a substantial agreement (Landis & Koch, 1977). A third reviewer (ER), along with the first reviewer (MC), conducted a quality appraisal for the fifth study. This was necessary to reduce bias as the second reviewer (AM) was an author of the study. A Cohen’s kappa coefficient (κ) was calculated to assess inter-rater agreement, $\kappa = .68$, $p < .001$, representing a substantial agreement (Landis & Koch, 1977).

Results

Search results

The database search produced a total number of 863 records. After removing duplicates (n = 141), a further 702 were removed after title and abstract screening. Twenty- one full text articles were assessed for eligibility, 16 were removed with reasons, leading to the final inclusion of 5 studies (see Fig. 1).

Characteristics of selected studies

Characteristics and findings of selected studies are summarised in Table 3. Studies evaluated impact of treatment on drug use by recruiting participants from a number of settings including tertiary hospitals; GP and primary care clinics; community clinics; drug and alcohol treatment clinics; private medical practices; and injecting equipment provision services. There were four prospective cohort studies and one

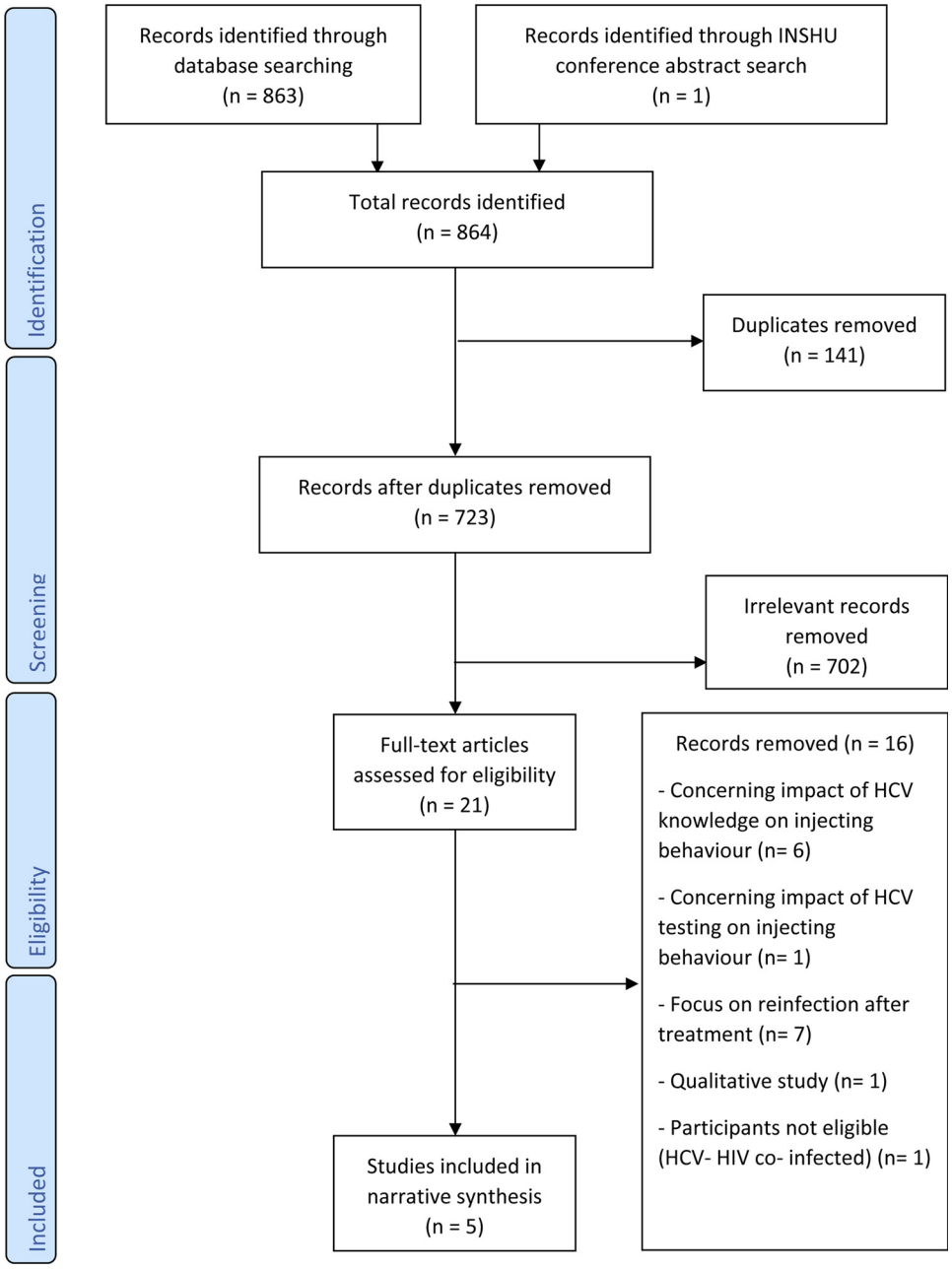

Fig. 1. Search Strategy.

retrospective cohort study. Two studies included comparison groups in their study design. Alavi et al. (2015) utilised PWID that did not receive treatment as their comparison group. Artenie et al. (2017) utilised three comparisons groups, namely PWID who did not engage in treatment post- diagnosis; PWID who did not engage in treatment due to spontaneous clearance of the virus; and HCV positive PWID who were not eligible for treatment due to contra-indications.

Four studies investigated past month injecting drug use; two studies investigated injecting frequency; two studies investigated needle and syringe borrowing; and three studies investigated ancillary injecting equipment sharing. Of the five studies selected, four studies involved treatment with pegylated interferon alpha and/or ribavirin, with only one study involving treatment with direct acting antivirals (DAAs). Follow up periods ranged from 24 weeks to 2 years. In the sampled studies, the majority of participants were Caucasian males, with a mean age ranging from 32 to 47 years old, who had injected drugs in the last 6 months prior to study enrolment. Two of the five selected studies solely recruited participants with acute HCV infection (Alavi et al., 2015; Artenie et al., 2017). Recruiting patients for treatment with acute HCV infection is not reflective of standard clinical practice, as these patients have a 20–30% of spontaneous clearance during the acute phase of the infection, making treatment uneconomical at this stage (Aisyah, Shallcross, Hully, O'Brien, & Hayward, 2018). However, effect on injecting behaviour may still be relevant.

Risk of bias in individual studies

Table 4 provides detailed quality appraisal scores for each included study. The results of the scoring process suggests that Artenie et al. (2017) was the methodologically most robust study. Overall, the selected studies scored very highly on external validity. However, several issues of internal validity can be discussed. For instance, the occurrence of losses to follow up may have caused selection bias in several studies, with sizeable differences in socio-demographic characteristics between

Table 2
Inclusion/Exclusion Criteria.

Inclusion Criteria
Participants: people who inject drugs (PWID).
Study intervention: Hepatitis C diagnosis and treatment (either interferon alpha or direct acting antivirals based).
Comparators: participants themselves i.e. behaviour measured before and after treatment; or PWID who did not receive treatment; or PWID who chose to not engage in treatment post HCV diagnosis.
Primary outcome: behavioural change in relation to drug use e.g. injecting behaviour, needle and syringe borrowing, sharing of ancillary equipment.
Studies published in English, utilising a quantitative or mixed- methods study design.
Exclusion Criteria
Studies utilising a purely qualitative study design; individual case studies.
Studies that are entirely theoretical.
Participants who are non- injecting patients, or PWID who were treated for other blood borne viruses.
Studies investigating the impact of Hepatitis C treatment in prison populations.
Studies focusing on the impact of knowledge of HCV status, and not HCV treatment, on behavioural change in relation to drug use.
Studies focusing on reinfection rates after treatment.

participants who remained, versus lost to follow up. For example, Midgard et al. (2017) found that participants who remained in 12 weeks follow up were more likely to be employed, have higher education levels, had less history of incarceration, and had injected more often in the last month, in comparison to those lost to follow up. Therefore, it is possible that those remaining in follow up were more likely, for instance, to have greater access to social support, impacting on their ability to engage in treatment and facilitate behavioural changes in relation to their drug use. Another issue of internal validity is the lack of comparison groups in some studies, e.g. Artenie et al. (2019) and Midgard et al. (2017), making it challenging to attribute behavioural changes to the intervention, i.e. HCV treatment. A final point to note is the quality assessment tool's appraisal of the outcome variable's reliability. According to the Quality Appraisal Checklist's guidelines, outcome variables that are measured subjectively, e.g. self report, are to be scored poorly and could introduce information bias (National Institute for Health & Care Excellence, 2012). As all selected studies utilised a self-reported measure of injecting risk behaviours, they were all poorly scored for this part of the appraisal process. However, research has demonstrated that self-reported drug use among PWID is reliable and valid (Darke, 1998). Therefore, it is the opinion of the authors that the selected studies rate more highly for study design appraisal.

Results of individual studies

Impact of treatment on past month injecting drug use

Four studies investigated the impact of treatment on past month injecting drug use at various time points during treatment and follow up, assessed dichotomously (Alavi et al., 2015; Artenie et al., 2017; Artenie et al., 2019; Midgard et al., 2017). Alavi et al. (2015) reported no association between HCV treatment and past month drug use during 24 weeks follow up, when comparing PWID who did and did not receive treatment (aOR 1.06, 95% CI 0.93–1.21, n = 124). However, this study did not differentiate between participants based on their reasons for not engaging in treatment after study enrolment, possibly explaining the non-significant results of the study as untreated participants are arguably a more heterogeneous cohort. A second study by Artenie et al. (2017) did make this distinction, evaluating the impact of treatment on injecting drug use at one year follow up when comparing people who received treatment, and three comparison groups: people who spontaneously cleared the virus and did not require treatment; people who were not eligible for treatment due to contra-indications to therapy; and people who voluntarily chose not to engage in HCV care. Results showed that the received treatment group were less likely to report drug use at follow up in comparison to the voluntary non- engagement group (aOR 0.18, 95% CI 0.04- 0.76, n = 87). The odds of reporting drug use at follow up amongst the spontaneous clearance (aOR 0.34, 95% CI 0.08–1.40, n = 87) and contra- indications to therapy groups (aOR 0.24, 95% CI 0.05–1.22, n = 87), were not significantly lower in comparison to the voluntary non- engagement group. This finding is supported by Midgard et al. (2017) who found that there was a significant reduction in any past month injecting drug use during treatment and 12 week follow up (OR 0.89, 95% CI 0.83– 0.95, n = 93), with the likelihood of injecting halved at treatment completion compared to study enrolment. A fourth study evaluated the impact of DAA based treatment on past month injecting drug use and found that there was an overall significant reduction in opioid injecting (OR: 0.95, 95% CI 0.92- 0.99, n = 190) between treatment initiation and 2 year follow up (Artenie et al., 2019). However, no reduction in stimulant (cocaine and amphetamine) injecting was reported (OR 0.98, 95% CI 0.94–1.02, n = 190).

Impact of treatment on injecting frequency

Two studies investigated the impact of treatment on injecting frequency. Midgard et al. (2017) measured ≥ daily injecting as a proxy for past month injecting frequency, and found that the proportion of participants who reported ≥ daily injecting did not significantly change during treatment and follow up (OR 0.98, 95% Cl 0.89–1.07, n = 93). It is notable that injection risk behaviours amongst participants in this study were low at baseline, with only 28% of participants who achieved 12 weeks follow up reporting ≥ daily injecting at enrolment. Moreover, the authors mention a lack of statistical power due to the relatively small sample size, providing a second explanation of lack of significant findings. A second study by Malaguti et al. (2019) investigated changes in weekly injecting frequency between enrolment, during treatment and at 6 months follow up. Results showed a significant decrease in injecting frequency between enrolment and future time points (χ^2 (7) = 36.44, p < .001, n = 32), with the largest reduction in injecting reported between enrolment and week 8 of treatment, maintained through to 6 months follow up. A criticism of this study may be the high degree of incomplete data, with only 38% of participants providing data for all time points.

Impact of treatment on needle and syringe borrowing

The impact of treatment on needle and syringe borrowing was investigated by two studies. One such study by Alavi et al. (2015) found that treatment was not associated with a reduction in needle and syringe borrowing during follow up, when comparing PWID who did and did not receive treatment (aOR 0.99, 95% CI 0.89, 1.07, n = 124). A second study found that treatment receipt did not significantly facilitate a reduction in use of non-sterile needles (OR 0.94; 95% CI 0.79–1.12, n = 93) (Midgard et al., 2017).

Impact of treatment on injecting equipment sharing

Facilitation of a reduction in injecting equipment sharing by treatment was explored in three studies. One study reported a significant decrease in injecting equipment sharing, including mixing container, filter and water, during treatment and 24 weeks follow up (aOR 0.85, 95% CI 0.74- 0.99, n = 124), with a reduction in the number of participants reporting sharing from 54% at baseline to 17% at follow up (Alavi et al., 2015). In contrast Midgard et al. (2017) reported no association between treatment and injecting equipment sharing, including spoons, mixing containers, drug solution, water and filter, during treatment and 12 week follow up (OR 0.87, 95% CI 0.70–1.07, n = 93). One study investigating the impact of DAA based treatment on behavioural outcomes reported a significant reduction in the number of participants reporting needle and syringe sharing during treatment and 2 year follow up (OR 0.87, 95% CI 0.80- 0.94, n = 190) (Artenie et al., 2019). However, it must be noted that although a reduction in needle and syringe sharing during and after treatment was noted, the baseline

Table 3
Summary of Study Characteristics.

Study *Country*	Measure of behaviour change	Design (comparison group(s)) *Follow up period*	Setting	Participant characteristics- age, gender, past month injecting drug use, on OST, HCV status	Treatment	Main Findings
Alavi et al. (2015) *Australia*	Past month Injecting drug use, used needle and syringe borrowing and ancillary injecting equipment sharing at baseline, throughout and after treatment	Prospective cohort study (PWID that did not receive treatment) *24 weeks*	Tertiary hospitals and GP/primary care clinics	124 participants, Mean age = 32 years (25- 39 years), 69% male, past month injecting drug use = 45%, on OST = 18%, recent HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Injecting drug use during follow up was not associated with treatment. Needle and syringe borrowing during follow up was not associated with treatment. Treatment associated with a reduction in ancillary injecting equipment sharing during follow up.
Artenie et al. (2017) *Canada*	Past month injection drug use assessed dichotomously at 12 month treatment follow up	Prospective cohort study (PWID who did not engage in treatment post-diagnosis; did not engage due to spontaneous clearance; not eligible for treatment due to contra-indications) *1 year*	Community and hospital based clinics	87 participants, Mean age = 35.6 years, 78% male, past month injecting drug use = 87.4%, on OST = 37.9%, acute HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Participants who received treatment were significantly less likely to report injection drug use at one-year follow-up compared to comparison groups.
Artenie et al. (2019) *Australia, Canada, New Zealand, Norway, Switzerland, France, UK and USA*	Past month injection drug use, needle/ syringe sharing, hazardous alcohol use during and following treatment	Prospective cohort study (none) *2 years*	Drug treatment clinics, hospital clinics, private practice, community clinics	190 participants, Mean age = 47 years, 74% male, past month injecting drug use = 62%, on OST = 61%, active HCV infection.	Direct acting antivirals (12 weeks)	Overall decrease in opioid injecting during and following treatment. No changes found in hazardous alcohol consumption observed. Decrease in needle and syringe sharing during and following treatment.
Malaguti et al. (2019) *United Kingdom*	Injecting frequency at baseline, throughout and after treatment	Retrospective cohort study (none) *6 months*	Injecting Equipment Provision (IEP) Service	84 participants (18 to 70 years), 69% male, past month injecting drug use = 100%, on OST = 71.4%, active HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Significant reduction in injecting frequency between baseline and subsequent future time points. Largest reduction between week 1 (baseline) and week 8.
Midgard et al. (2017) *Australia, Canada, Switzerland, Belgium, Germany, Norway and the UK*	Past month injection frequency, use of non-sterile needles, needle and syringe borrowing or lending, and injecting paraphernalia during and following treatment	Prospective cohort study (none) *24 weeks*	Hospital clinics, drug and alcohol clinics, office based practices and community clinics	93 participants, Median age = 41 years (35- 50 years), 83% male, past month injecting drug use = 59%, on OST = 71%, chronic HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Injecting drug use decreased during treatment and follow-up. No significant changes were found in > daily injecting, use of non-sterile needles, sharing of injecting paraphernalia, or non-injecting drug use.

Table 4
Quality appraisal ratings for each included study.

	Alavi et al. (2015)	Artenie et al. (2017)	Malaguti et al. (2019)	Midgard et al. (2017)	Artenie et al. (2019)
1.1 Description of source population	3	3	3	3	1
1.2 Representativeness of eligible population	3	3	3	3	2
1.3 Representativeness of selected participants	2	3	2	2	2
2.1 Allocation to intervention or comparison	NA	NA	NA	NA	NA
2.2 Description of intervention and comparison	3	3	2	3	2
2.3 Concealment of allocation	NA	NA	NA	NA	NA
2.4 Blinding to exposure/comparison	NA	NA	NA	NA	NA
2.5 Adequacy of exposure to intervention/comparison	NA	NA	NA	NA	NA
2.6 Contamination	NA	NA	NA	NA	NA
2.7 Similarity of other interventions to groups	3	3	NA	NA	NA
2.8 Lost to follow up	1	2	2	2	1
2.9 Setting reflects usual UK practice	2	2	3	3	2
2.10 Intervention reflects usual UK practice	2	2	3	3	2
3.1 Reliability of outcome measures	1	1	1	1	1
3.2 Completion of outcome measures	3	3	3	3	3
3.3 Assessment of important outcomes	NA	NA	NA	NA	NA
3.4 Relevance of outcomes	3	3	3	3	3
3.5 Similarity of follow up times across groups	NA	NA	NA	NA	NA
3.6 Meaningfulness of follow up times	3	3	3	3	3
4.1 Similarity of groups at baseline	3	3	NA	NA	NA
4.2 Intention to treat (ITT) analysis	NA	NA	NA	NA	NA
4.3 Study's power to detect an intervention effect	2	2	2	2	2
4.4 Estimates of effect size	3	3	3	3	3
4.5 Appropriateness of analytical methods	3	3	3	3	2
4.6 Precision of intervention effects	3	3	3	3	3
5.1 Internal validity	2	3	2	2	2
5.2 External validity	3	3	3	3	3

prevalence of this risk behaviour was low at only 16% of the 62% of participants who reported past month injecting.

Discussion

Summary of evidence

In spite of the concerns around diagnosing and treating PWID for Hepatitis C, there is a dearth of research on the impact of engaging in treatment on behavioural change in relation to drug use in this population. The current review only identified five studies which directly measured behavioural change outcomes in PWID engaged in treatment. As a consequence of the limited number of studies identified, and variations in follow up times, behavioural outcomes, and treatment interventions, drawing conclusions around whether treatment engagement is effective in reducing drug use and injecting risk behaviours is problematic.

The most common outcome measure of behaviour change in relation to drug use in the selected studies was past month injecting drug use. Three of the four studies assessing this outcome found treatment significantly reduced the odds of participants reporting past month injecting at follow up (Artenie et al., 2017; Artenie et al., 2019; Midgard et al., 2017). However, due to variations in study design, comparing the findings of these separate studies is challenging. Accordingly, combining the data on these results to conduct a meta- analysis was deemed inappropriate. Additionally, it can be argued that dichotomously measuring past month injecting drug use is limiting in regards to providing insight into the impact of treatment on injecting behaviours. Combined with infrequent measurements of drug use, it could be suggested that the results of these studies simply reflect natural fluctuations in injecting frequency among PWID, and do not accurately reflect a reduction in drug use. However, taken together, these findings suggest that engaging in treatment may result in a possible reduction in injecting. This challenges critics who believe that treating PWID for Hepatitis C is not feasible due to concerns around treatment causing an increase in injecting risk behaviours (Schaefer, Sarkar, & Diez-Quevedo, 2013). Moreover, these findings support the notion that treatment engagement may lower the risk of HCV transmission within the PWID population, providing support for accessibility to treatment.

In regards to impact of treatment on other behavioural changes related to drug use, findings are more inconsistent. For instance, of the two studies which investigated the impact of treatment on injecting frequency, only one study observed a significant decline in injecting frequency between enrolment, treatment, and follow up (Malaguti et al., 2019). Nonetheless, comparing the findings of these studies is not suitable due to the contrasting measurements of injecting frequency; namely weekly injecting, measured as a continuous variable (Malaguti et al., 2019), and ≥ daily injecting, measured as a binary variable (Midgard et al., 2017).

Both studies investigating change in needle and syringe borrowing found no association between treatment engagement and reduction in these risk behaviours (Alavi et al., 2015; Midgard et al., 2017). Although no significant decline was observed in either study, the fact that such risk behaviours remain stable throughout treatment and follow up has meaningful implications for risk of reinfection and onward transmission. The minimisation of injecting risk behaviours after treatment is critical to optimise patients' chances of achieving sustained viral responses and to reduce HCV prevalence at a population level (Hickman, De Angelis, Vickerman, Hutchinson, & Martin, 2015). Of the three studies investigating the impact of treatment on injecting equipment sharing, two studies reported significant decreases in such behaviour between enrolment, treatment and follow up. However, of these two studies, one study by Artenie et al. (2019) was conducted during the DAA era of treatment, making the findings of this study incomparable to the other studies investigating this behaviour change.

Limitations of review

The predominant limitation of the current review was the number of studies that met the inclusion criteria and the lack of comparability between studies. As a consequence, a meta- analysis of findings was not possible. Therefore, future reviews may seek to employ a more broadly inclusive eligibility criterion, including, for example, the inclusion of purely qualitative studies. Moreover, it is clear that future research should focus on the reasons why engaging in treatment facilitates a possible behavioural change in relation to drug use. A major limitation

of the review was that four of the five selected studies were conducted during the interferon era of treatment. In particular, the characteristics of people undergoing interferon treatment may potentially be different to those undergoing DAA treatment. For example, those treated using interferon based therapy may have experienced more adverse treatment consequences, such as associated psychiatric conditions, in comparison to those treated using the DAA based therapy. Moreover, the reasons why engaging in treatment facilitates a positive behaviour change in relation to drug may be disparate between the aforementioned treatment groups. Consequently, the results of the current review may not give insight into the impact of treatment on injecting risk behaviours in the new DAA based treatment era, with future research clearly needed to clarify this issue. Also, the review was hindered by the inclusion of studies with selection bias of participants. All five studies involved clinical trial participants, who were arguably more willing to engage in treatment than the source PWID population. This was characterised by relatively low lost to follow rates in some studies. Thus, the results of the included studies may not be representative of the wider population of PWID engaging in treatment.

Conclusions

Five studies investigating the impact of HCV treatment on behavioural change in relation to drug use amongst PWID were identified. The most common measure of behaviour change in relation to drug use was past month injecting drug use, with three out of four studies reporting treatment significantly reduced the odds of participants reporting past month injecting at follow up. Studies also reported significant reductions in injection equipment sharing between enrolment, treatment and follow up; no significant changes in needle and syringe borrowing; and varying results in regards to impact of treatment on injecting frequency. Comparison and synthesis of results was challenging due to heterogeneity of follow up times, treatment interventions, and measures of behavioural outcomes. For future research, it would be optimal for the research community to report injecting risk behaviour in a standardised manner to enable comparison and strengthen conclusions of published literature. Four out of the five selected studies were conducted during the interferon era of treatment, possibly limiting the generalisability of the current review's results to the new DAA treatment era. However, results suggest the benefits of engaging in HCV care stretch beyond liver morbidity outcomes, with treatment positively impacting on patients' injecting drug use and injection equipment sharing behaviour. These findings have relevance to the "treatment as prevention" model of Hepatitis C care, risk of reinfection and onward HCV transmission (Fraser et al., 2018; Schulkind et al., 2018).

Credit author statement

MC carried out the literature search, selected and reviewed the studies identified by the search, extracted and synthesised the data and wrote the manuscript. AM and ER reviewed the studies identified by search as secondary reviewers. EF, JFD, AM, and ER reviewed the draft manuscript and provided critical feedback. All authors read and approved the final manuscript.

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Conflict of interest statement

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ORIGINAL ARTICLE

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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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).

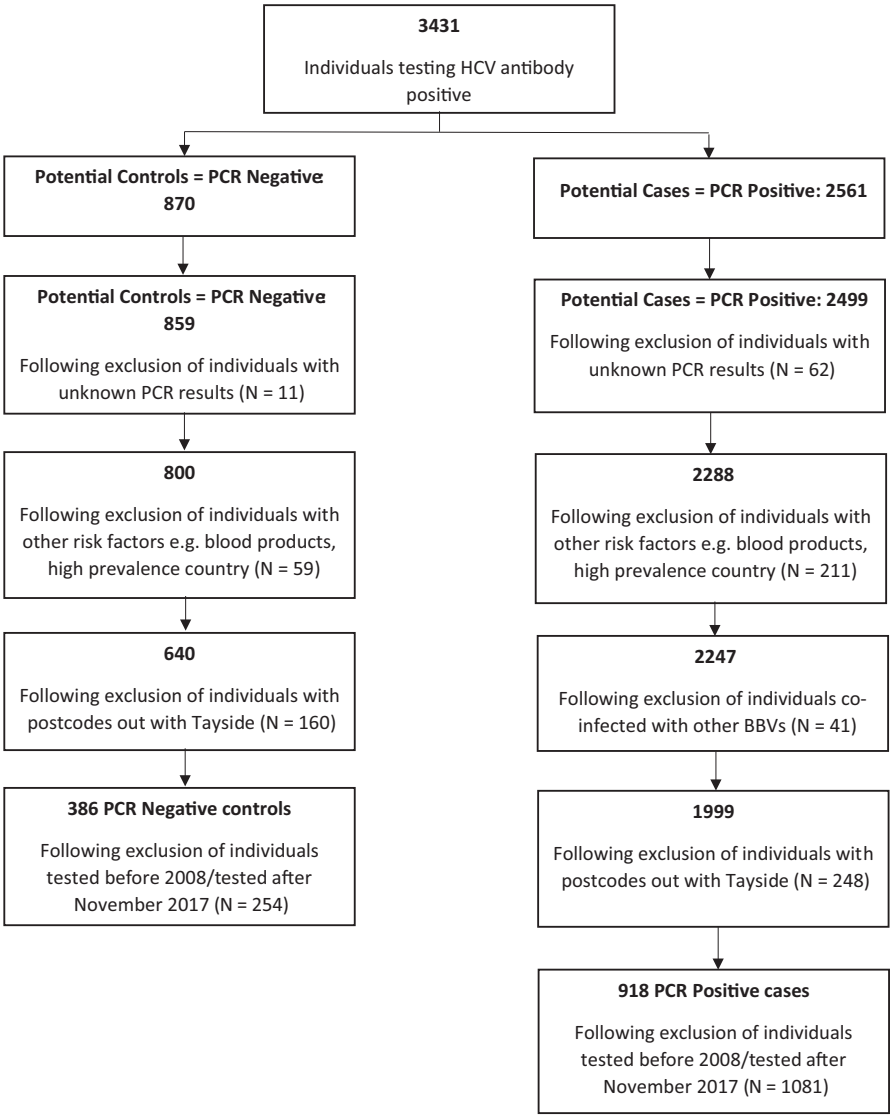

FIGURE 1 Selection of PCR-positive cases and PCR-negative controls based on inclusion/exclusion criteria

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

	B (SE)	95% CI for odds ratio		
		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

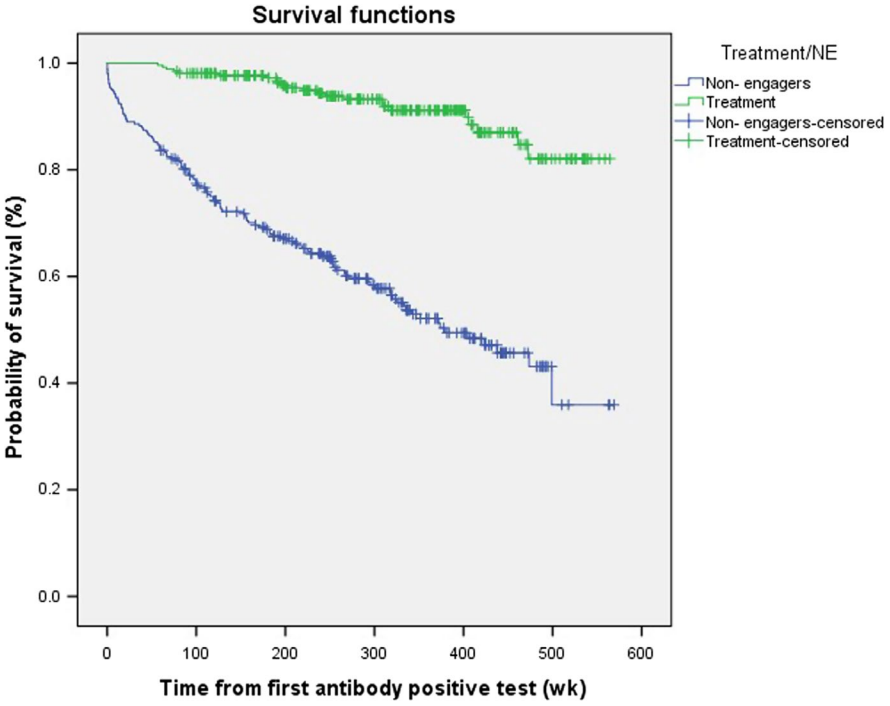

FIGURE 2 Kaplan-Meier survival curve for time from first antibody positive test to all-cause mortality comparing treatment engaging cases and treatment nonengaging controls

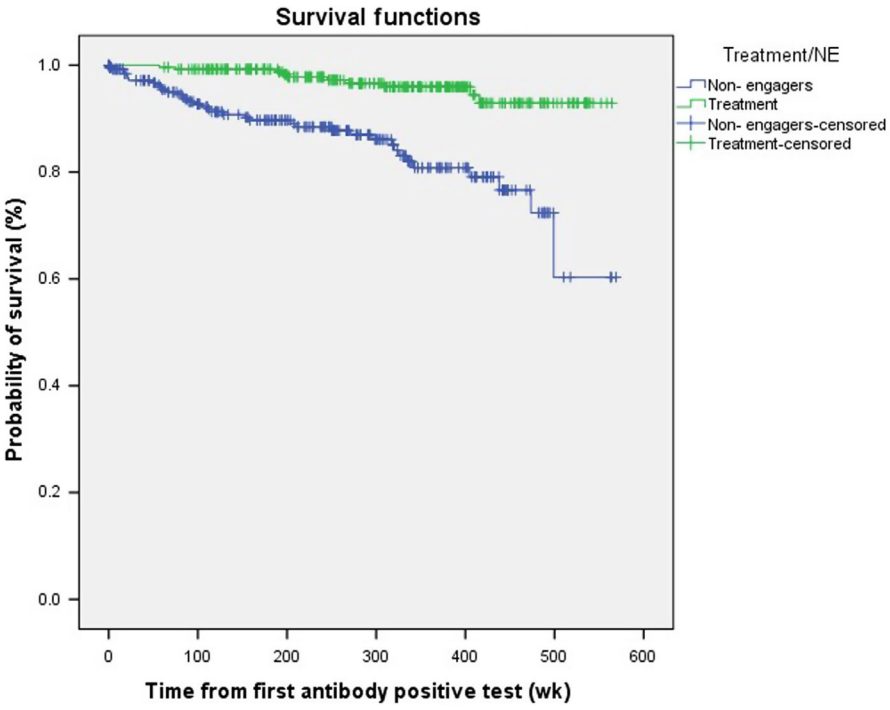

FIGURE 3 Kaplan-Meier survival curve for time from first antibody positive test to drug-related death comparing treatment engaging cases and treatment nonengaging controls

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

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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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Date 15 November2018
Your Ref
Our Ref IGTCAL5540
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Dear Madeleine

CALDICOTT APPROVAL – HCV diagnosis and treatment, impact of knowledge of HCV status on behaviour of people who inject drugs, a service evaluation, The Hooked C project.

Proposal Sponsor: Prof. John Dillon, Consultant Gastroenterologist & Hepatologist, NHS Tayside

Data User(s): Madeleine Caven, Data Co-ordinator and Analyst, Medicine & Cardiovascular, NHS Tayside
Dr Emma Fletcher, Consultant in Public Health Medicine, NHS Tayside

Caldicott approval is given for you to access relevant and proportionate personal data in the Tayside portion of the National Hepatitis C service NHS database, for people who inject drugs (PWID) with active HCV infection, and PWID whose HCV infection was spontaneously cured. This dataset will also contain PWID who received either Interferon, or direct-acting antiviral (DAA) based treatment. Authorisation is also given to link this data to relevant and proportionate data from the Tayside Drugs Death Database, in order to carry out retrospective case control studies, in order to identify any differences in drug-related deaths, all-cause mortality, and change in drug use behaviour, when comparing those who received vs did not require treatment, those who received Interferon vs DAA based treatment, and PCR positive patients who engaged vs did not engage with treatment, as described in your application and supporting information.

It is noted that all data will be anonymised prior to exporting from the NHS database.

Thank you for your co-operation in providing us with the information requested by us in this process.
Please contact me should any queries arise from the application of this approval.

Everyone has the best care experience possible
Headquarters: Ninewells Hospital & Medical School, Dundee, DD1 9SY (for mail) DD2 1UB (for Sat Nav)

Chairman, John Brown CBE
Chief Executive, Malcolm Wright

Yours sincerely

Joseph Donnelly

Joseph Donnelly
Data Protection Officer

Copy to: Prof. John Dillon, Consultant Gastroenterologist & Hepatologist, NHS Tayside
Dr Emma Fletcher, Consultant in Public Health Medicine, NHS Tayside