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The Hepatitis C Awareness Through to Treatment (HepCATT) study: Improving the cascade of care for hepatitis C virus-infected people who inject drugs in England


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Running Head: HepCATT study

Competing Interests

PL, KR, AO, KT, CS, SO are employed by Providers of Specialist Drug Service clinics (Addaction and Change Grow Live). No other relevant competing interests are declared.

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ABSTRACT

Background and Aims: Previous studies have shown low rates of diagnosis and treatment of hepatitis C virus (HCV) infection in people who inject drugs (PWID). Our aims were to test the effect of a complex intervention (“HepCATT”) in drug and alcohol clinics – primarily, on engagement of HCV-positive PWID with therapy, and, secondarily, on testing for HCV, referral to hepatology services, and start of HCV treatment.

Design and setting: A non-randomised pilot study in three specialist addiction clinics in England comparing an intervention year (starting between September 2015 and February 2016) with a baseline year (2014), together with three control clinics.

Participants: Analysis included a total of 5,225 PWID, of whom 1,055 were identified as HCV-positive.

Intervention: A half-time facilitator placed in each clinic undertook various activities, which could include training of key workers, direct interaction with clients, streamlining and support for hepatology appointments, and introduction of dried blood-spot testing.

Measurements: For each clinic and period, we obtained the total number of clients and, as relevant, their status as PWID, tested for HCV, known HCV-positive, engaged with HCV therapy, or treated.

Findings: Compared to baseline, there is strong evidence that engagement with HCV therapy in the intervention year increased (p<0.001) more in the HepCATT centres than controls, up +31 percentage points (95% CI 19 to 43) vs -12 (CI -31 to +6) and odds ratio 9.99 (CI 4.42–22.6) vs 0.35 (CI 0.08–1.56). HepCATT centres also had greater increases in HCV testing (OR 3.06 vs 0.78, p<0.001), referral to hepatology (OR 9.60 vs 0.56, p<0.001) and treatment initiation (OR 9.5 vs 0.74, p<0.001).

Conclusions: Introducing a half-time facilitator into drug and alcohol clinics in England increased engagement of HCV-positive PWID with HCV care pathways, with increased uptake also of testing, referral to hepatology and initiation of treatment.

KEY WORDS:
Hepatitis C; People who inject drugs; Antiviral therapy; engagement with therapy
INTRODUCTION

The UK has recently signed up to the WHO Global Health Sector Strategy (GHSS) on viral hepatitis, which includes commitments to reduce the incidence of and mortality arising from complications of chronic hepatitis C virus (HCV) infection, thereby providing a major public health challenge. The recent availability of safe and effective directly acting antiviral (DAA) agents for the treatment of chronic HCV infection has transformed outcome, with sustained virological response (SVR) rates of over 90%. In the UK, more than 90% of chronic infections are among people who inject drugs (PWID). However, audits of the “cascade of care” (the pathway from diagnosis through to cure) have repeatedly demonstrated considerable drop-out of diagnosed individuals at all stages, especially for PWID diagnosed within specialist community drug services.

The incidence of HCV infection amongst PWID in the UK has changed very little since 2011, if anything showing an increase in more recent years. Thus, to have any realistic prospect of achieving the WHO GHSS targets, there is a need for radical new approaches to engaging HCV-infected PWID. The barriers to treatment of chronic HCV infection in PWID attending specialist services are well known. These include problems of stigma (both from healthcare staff and other PWID), lack of awareness that HCV is a serious disease but that it can be treated effectively, perception and fears about treatment, and competing priorities in relation to management of their drug and other social problems. Potential facilitators to case finding include: peer support, availability of Dried Blood Spot (DBS) testing, training in HCV test discussion for drug clinic and other staff, outreach provision of specialist nurse and treatment clinics, and contingency management. In addition, qualitative studies have suggested that cultural and management changes in drug agencies (such as changing performance targets, database monitoring and priorities for drug workers) could support HCV case finding.

Increasing case finding and treatment is complex and will likely require a range of interventions requiring collaboration and support between local drug treatment agencies, commissioners and drug strategy teams, public health, primary care, diagnostic virology laboratories, and specialist hepatitis services.

A systematic review of strategies to increase hepatitis case finding conducted for the National Institute for Health and Care Excellence (NICE) found very little published evidence. Whilst a number of initiatives have been introduced in different settings around the UK, there is a lack of clear evidence and quantitative data on the success or otherwise of these interventions in relation to the proportion of PWID diagnosed, and their subsequent movement down the cascade of care. The Hepatitis C Awareness Through to Treatment (HepCATT) study aimed to assess the impact of a complex (i.e. multi-faceted) intervention in specialist drug services primarily on the rate of engagement of HCV-infected PWID with an appropriate treatment pathway, and secondarily on the rates of testing for HCV infection in PWID, of referral of diagnosed PWID for specialist assessment, and of attendance at referral clinics.
METHODS

Design

We undertook a non-randomised controlled feasibility study of a complex intervention to improve the HCV cascade of care in specialist drug clinics – specifically to increase HCV case-finding, referral and engagement with HCV treatment services. The intervention was conducted in 3 specialist drug clinics and outcomes compared with controls selected using similar criteria.

Complex intervention.

The intervention comprised the placement of a half-time facilitator at selected specialist drug services for a period of 12 months with the brief to increase diagnosis of HCV infection within clients at those services and the engagement of diagnosed individuals with an appropriate care pathway. The means to achieving those ends were not specified in advance, as the baseline characteristics in terms of capacity to diagnose and treat HCV infection were expected to vary between clinics. However, suggested facilitator activities included:

- training of key workers with direct contact with PWID clients in relation to the natural history of and treatment options for HCV infection, and in how to engage clients in pre- and post-test discussion
- direct interaction with clients attending the service to encourage testing, referral, attendance at appointments and engagement with therapy
- streamlining and simplification of referral pathways, including immediate arrangement of clinic appointments taking into account client preferences for timing and integration of HCV appointments with their commitments to opiate substitution therapy
- establishment of local peer champion and buddy support systems to assist education of clients and attendance at clinic appointments
- introduction of DBS testing
- active management of client referrals with a systematic approach to reminding clients of dates/times using client-specified means of communication, and to retrieving and re-booking clients who fail to attend
- we also encouraged networking and feedback between the 3 facilitators so that ideas of good practice could be shared across sites

Selection of intervention and control sites.

It is recommended that clients attending any specialist drug service in the UK for reasons of addiction should also be offered testing for HCV infection, and that those with positive results should be referred into an appropriate care pathway. An initial review of referrals from local specialist services into clinics connected with the trial team indicated that the implementation of this recommendation varied widely across different sites, dependent upon a variety of factors, most notably the degree to which local initiatives in support of HCV testing and referral had been implemented.

Criteria for selection of intervention sites were therefore set as

(i) having a large enough clientele of PWID such that there were likely to be significant numbers with HCV infection i.e. at least 200 clients with a history of injecting drug use attending annually;
the site had not been subject to multiple interventions aimed at enhancing diagnosis and treatment of chronic HCV infection in the previous 3 years;

agreement/support available from the national and local drug treatment centre management team, the hepatology lead/local NHS Trust, public health and clinical commissioning group, and the diagnostic virology laboratory.

We also purposefully chose sites with differing demographic characteristics i.e. urban and rural settings.

Consultation with Public Health England and the Hepatitis C Trust enabled verification of criteria (i) and (ii) above.

Each intervention site acted as its own control for clinic characteristics, as performance characteristics at each clinic were compared before and during the intervention period.

In order to control for secular effects (i.e. a general change in outcomes over time between the baseline and intervention periods), control sites were sought using criteria (i) and (ii) above, and on the basis of willingness to provide the relevant data by the local NHS Trust hepatology team. However, contact with the drug treatment centre management team was only made at the end of the intervention period, in order to request precise data relating to numbers of clientele attending, and HCV testing and positivity rates.

All the intervention (A-C) and control (1-5) sites provided a wide range of addiction services, including for alcohol and non-injecting drug use. Sites A, 1 and 2 provided services to largely rural areas. Sites B and 5 were located in large inner cities, and Sites C, 3 and 4 were in medium-sized inner cities. All intervention sites and control sites 1–3 provided full data and are included in analysis. Control sites 4 and 5 did not contribute to formal analysis because clinic-collated data (total numbers of clients/PWID and HCV testing) were not available; information was limited to referral, engagement and treatment (taken from secondary referral centre records).

Facilitators.

In sites A and B, the facilitator was a specialist hepatitis nurse employed primarily by the local NHS Trust hepatology department who was therefore seconded to spend half-time in the specialist drug service. In site C, the appointee was a health and well-being nurse employed through the drug service provider. The 12 month intervention period at each site was: Site A Sept 2015 –Aug 2016; Site B Oct 2015 –Sept 2016 and Site C Feb 2016 –Jan 2017.

Endpoints

During the study period, access to all oral DAA therapy for HCV in England was restricted on the basis of fibrosis severity or the presence of life-threatening extra hepatic disease. We therefore selected engagement with a treatment service as the primary study outcome. Successful engagement with treatment services was defined as:

Diagnosed with chronic HCV (documented testing for HCV RNA, genotype and viral load), assessment of stage of liver disease, and consultation with HCV specialist with discussion of treatment options.

Secondary outcomes for HCV-positive PWID were referral to hepatology services for specialist assessment, and initiation of HCV treatment. Another secondary outcome, applying to all PWID, was testing for HCV. We report also “treatment-readiness”, when the hepatologist would have
recommended immediate oral DAA treatment if at the time of the study there had been no restrictions on HCV treatment access.

**Data collection.**

The baseline year was the calendar year 2014. Data were obtained retrospectively from the databases used routinely by the drug service providers. The following definitions were used:

- **HCV positive** = any client who self-declared as having tested positive for HCV
- **HCV negative** = any client who self-declared as having tested negative for HCV, with evidence of a history of HCV testing
- **Status unknown** = any client where there was no self-declaration of having been tested, or no evidence to confirm a negative test.

Data relating to referral/attendance at specialist hepatology services were extracted from local NHS IT systems, whilst engagement and treatment rates were defined by NHS staff by reference to the patient’s clinical notes.

For the intervention year, client numbers and HCV status data were again collected retrospectively at the end of the period from the drug service IT systems. Referral, attendance, engagement and treatment rates were prospectively collected by facilitators.

Referral, attendance, engagement and treatment data for the control sites were derived retrospectively from the local hepatology clinic records and IT systems.

For clients who dropped out of the planned cascade of care, the facilitator at each site provided an assessment, based on their knowledge of each client, for why this happened. These were grouped into:

- **“social/lifestyle/mental health issues”**, which included clients whose drug or alcohol usage, and/or mental health problems and/or homelessness were such that clinic attendance/engagement with therapy/initiation of therapy was precluded.
- **“physical constraints”**, which refers to clients who had moved out of area, left the drug service, been incarcerated, or had been hospitalised for non-HCV-related reasons.
- **“awaiting decision”**, used for those clients who had not yet completed their journey down the pathway but were still regarded as being capable of doing so. In the context of the engaged but not treated, this includes patients who had decided to wait for interferon-free regimens to become available rather than start treatment straight away.

For clients who had engaged with therapy but had not received treatment during the intervention, the attending physician was asked to judge whether, had access to all oral DAA therapy not been precluded by the NHS England “run-rate” (quota) system, he/she would have been treated.

**Governance and ethics.**

Funding was provided by the UK government Department of Health. The study sponsor was the University of Nottingham and research ethics committee approval was provided by the Derby East REC (ref 15/EM/0016).

**Statistical analysis.**

Analysis used aggregate data at clinic level; there was no adjustment for individual characteristics. The outcomes in the pre-intervention and intervention periods were plotted and linked for each of
the centres (intervention and control) on one graph to give a visual representation of change over time, and of variation between centres. We estimated the odds ratio (OR) for the intervention period (compared to pre-intervention) for each centre individually and combined the results by random effects meta-analysis, stratified by intervention group (HepCATT or control); Forest plots then showed the estimated OR (‘effect’) of period in each centre individually and overall in each group. Centre 3 had no engaged patients so, to avoid dropping it from this analysis, we approximated by adding one engaged patient in each period; we approximated ORs for treatment similarly at centres 3 and C. We estimated the overall intervention effect as a difference in difference of OR by including all centres in a logistic regression model with group (HepCATT vs control site), period (intervention vs baseline) and group-period interaction as predictors, and random effects for centre. For descriptive purposes, we estimated and combined risk differences for each outcome in a similar way to ORs. The package Stata v14.2 (StataCorp, College Station, TX) was used throughout.

**Patient involvement.**

Members of the Hepatitis C Trust, a patient-led and patient-run organisation were co-applicants on the grant application, members of the trial Steering Committee, and participated in all aspects of HepCATT. The Trust led the establishment and training of peer support groups at the intervention clinics. HepCATT includes a qualitative study reported elsewhere\(^1\) which recruited patients and drug treatment centre staff to participate in focus groups and one-to-one interviews to assess the impact of the HepCATT intervention from their perspective.
RESULTS

Primary outcome: engagement with therapy

Figure 1(a) shows the change in engagement of HCV-positive PWID at each site; the figures are detailed in Tables 1a and 1b. Combined estimates show an increase in percentage engagement of 31 points (95% CI 19–43) at the three intervention sites, compared with a decrease of 12 points at the three control sites (CI 31 point decrease to 6 point increase). Figure 1(b) shows these changes as ORs. The full logistic regression model gave strong evidence (p<0.001) for an effect of the HepCATT intervention, estimated as an interaction odds ratio of 29.2, but with a wide 95% confidence interval (11.9–71.8). Table 2 gives further evidence of minimal change in outcomes at control sites 4 and 5.

Secondary outcomes: HCV testing, referral and treatment

Detailed data are provided in Table 1. The combined estimates showed an increase in the percentage of PWID tested for HCV of 17 points (CI 7–26) at intervention sites, as against a fall of 2 points at control sites (CI 8-point drop to 4-point increase). The corresponding ORs are shown in figure 2. In logistic regression, an interaction OR of 3.9 (CI 2.7–5.5, p<0.001) gave strong evidence of a positive intervention effect on testing.

Referral of HCV-positive PWID for hepatology investigation increased by an estimated 38 percentage points at intervention sites (CI 12–63), but fell by 12 points at control sites (CI 46-point fall to 21-point rise). Logistic regression showed a significant intervention effect on referral, with OR 16.0 (CI 8.0–32.2, p<0.001).

Despite restrictions on the availability of DAA in the intervention period and small numbers treated in total, there was also evidence of increased treatment initiation (OR 21.4, CI 8.2–56.1, p<0.001), with an increase of 13 percentage points at intervention sites (CI 9–16) and little change at control sites (-1 point, CI -6 to +3).

The cascade of care
Drop-out from the cascade of care was evident at all points in the pathway. Overall, at the intervention sites during the intervention period, 246 clients were referred for specialist assessment, but only 159 (65%) attended their clinic appointment; whilst a high proportion of those (143/159, 90%) fulfilled the study definition of engagement with therapy, within the timeline of this study, only 54 of the engaged patients (38%) were treated, although this is in comparison to only 3 patients in the baseline year.

Reasons for drop-out, as determined by the facilitator, are summarised in Table 3. The majority (n = 55) of the engaged but not treated clients eligible for treatment would, according to their attending physician, have been treated had access to all oral DAAs not been precluded.

**Facilitator activities**

HepCATT was a “complex” (multifaceted) intervention. The baseline infrastructure and clinic organisation differed at each intervention site, and so activities undertaken by the facilitators to improve the cascade of care differed accordingly:

**Site A:** At baseline, testing was well-established. During the intervention, the facilitator encouraged testing by the key workers themselves or by referring clients to the health and well-being nurses. She set up a self-referral pathway, empowering individual clients to enter the care pathway themselves. She made connections with a local General Practice who were then able to refer PWID to her within the drug service; she located PWID clients in the local prison and arrange onward referral for them; she encouraged drug service attenders using the needle and syringe provision service to come forward for testing.

**Site B:** At the beginning of 2014, no testing was performed, but for the period Oct-Dec 2014, funding was obtained to allow oral swab testing, with follow-up DBS testing from swab anti-HCV positive clients. Funding for testing of DBS samples was available at the beginning of the HepCATT intervention. Hepatology clinic appointments were arranged such that by the time a client attended for Fibroscan, all other investigations would have been completed and the treatment discussion would happen at the time of attendance. 100% of attendees were therefore deemed to have engaged.

**Site C:** At baseline, relatively little testing was done, but a change in funding resulted in an increase in the 7 months immediately preceding onset of the intervention, with 66 clients tested for anti-HCV. In the 12 months of the intervention, this increased further to 189 clients.

Each facilitator was asked to provide a list of key tasks undertaken as part of their brief to increase testing and treatment engagement - see Table 4, which also shows the 3 individual most important ones as determined by each facilitator.
DISCUSSION

This pilot study was designed to determine the effect of introducing a part-time facilitator within specialist drug service clinics, with the responsibility of strengthening the HCV care-pathway and supporting PWID, traditionally regarded as a “difficult to reach” patient group, to access HCV diagnosis, onward referral and engagement with local care pathways. For the primary endpoint, engagement increased by 31 percentage points at the intervention sites but fell at control sites; thus the odds of engagement increased 29-fold more at intervention sites than control sites. Secondary endpoints including testing, referral and treatment rates also showed increases of estimated odds ratios of 3.9, 16 and 28-fold. In addition, 55 of 89 of the engaged but not treated PWID were regarded by their physicians as “treatment ready” and would likely have been treated but for the system-level barrier of limited access to DAA drugs.

We selected a non-randomised design because (a) this was a feasibility study and we needed to show that we could introduce the intervention as well as examine whether it could be effective; and (b) there was a considerable amount of time (12 months) in pre-intervention set-up requiring participation from multiple partners (specialist drug agencies, local commissioners, local NHS hepatology services, diagnostic laboratories) requiring the signing, ultimately, of 21 separate contracts/memoranda of understanding to allow multi-agency execution of the research project, which mitigated against then adding a further randomisation step.

It is conceivable that our selection criteria identified sites which were more ready than average sites to respond to the intervention. However, we do not think it is plausible that such a large effect size was due to the unwitting selection by the Hepatitis C Trust of intervention sites where staff and/or clients were extraordinarily susceptible to improvement of their processes. Also, there was heterogeneity in the way the intervention was carried out, one intervention site was recommissioned before our intervention started, and pre-intervention outcomes were similar to our control sites.

We sought to control the data generated at our intervention sites in 2 ways. Firstly, each site acted as its own control in terms of its operational and functional characteristics, as we compared intervention data with baseline data generated at the same site. Secondly, to control for changes over time in general attitudes towards HCV testing and treatment, we chose 5 control, non-interventional sites. Two of those 5 sites were unable/unwilling to provide us with data relating to their total number of PWID attendees and rates of HCV testing and positivity, in the absence of a data sharing agreement, but we were able to use data from their respective secondary care clinics in order to get a picture of the cascade of care at those sites. Our data demonstrate that in fact, the very large effect size was driven mainly by the increased odds of engagement in the intervention period compared to the baseline period within the HepCATT sites (OR 9.99). The comparison with control sites contributed much less (OR 0.35).

The study aim was to identify changes in rates of diagnosis, referral, engagement and treatment arising as a result of our intervention. We did not collect disaggregated data from the specialist drug clinics so could not adjust for individual characteristics – to do so would require a much larger study. However, as our intervention and key outcome operated at the clinic/site level we do not think this is a disadvantage. Data in relation to the intervention period was collected by the facilitators, whereas data relating to the baseline, and for both time points at the control sites, was by reference to the local IT systems. The former will undoubtedly be more accurate, especially in relation to the HCV status of individual clientele, as one task of the facilitators was specifically to target PWID whose HCV status was unknown in order to encourage testing. This facilitator action would have the
effect of increasing the numbers of known infected PWID, but we also observed that a number of instances of self-reported HCV positivity were not, in fact, correct, when confirmatory testing was performed.

In addition to the above limitations related to the study design, we identified a number of practical difficulties which impacted on the conduct of this study and on patient management. Service provision was put out for tender at all sites at various times during the study, with a change in management at site C before our intervention but after the baseline year, not only introducing potential differences in management priorities, but also altering the geographical coverage of the service which complicated the collection of accurate data relating to the clientele size. The ability to execute comprehensive HCV testing of drug service clientele was out of the control of HepCATT, being dependent on funds available to support testing, but we would recommend that consideration be given to introduction of true opt-out testing in drug services. Finally, engagement with therapy, rather than the more direct outcome of initiation of therapy, was chosen as the primary endpoint because access to treatment is governed by the commissioning and reimbursement arrangements for provision of access to DAA drugs. The landscape of therapy changed completely from entirely interferon-based therapy at the study planning stage, through to restricted access to DAA therapy at intervention onset, through to “open” access (but with quota restrictions) by the end of the intervention period. There is no doubt that all oral therapy with much lower adverse effects profiles make the option of therapy much more attractive to patients, many of whom had personal experience or knowledge of the difficulties of interferon-based regimens. However, all of the above issues will have been pertinent at the control sites, so this turbulence does not invalidate our findings of substantial gains in engagement and treatment arising from the intervention.

The challenges of delivering care to populations of PWID has been widely acknowledged, and there have been many previous interventions aimed at optimising the HCV care cascade in these populations, including strategies to enhance HCV testing;\textsuperscript{12-15} the application of technologies for rapid and DBS testing;\textsuperscript{16-20} and interventions to enhance linkage of testing to HCV treatment pathways,\textsuperscript{21-23} including models of integrated care in harm reduction settings in drug and alcohol services and primary care.\textsuperscript{24-30} However, all of the latter studies are observational and descriptive in nature without non-interventional data. The outcome of such interventions has been variable, but many have become established in the cascade of care for ‘hard to reach’ HCV patients. The HepCATT study provides a quantitative aspect of the effect of intervention under study on clinically relevant endpoints, which was comparatively dramatic and this may reflect the value of a complex and flexible intervention which recognises and addresses the diverse barriers to patient engagement in different harm reduction settings.

Meeting the WHO GHSS targets for hepatitis C in the UK has become a major public health challenge; however, HepCATT has provided robust data for health-care planners and commissioners indicating that investment of resource into the complex pathway between diagnosis and cure of HCV infection in PWID can result in substantial improvement of the cascade of care. The HepCATT intervention was purposefully multi-faceted, and baseline characteristics of the 3 intervention sites differed considerably. Thus it is not possible to state which of the many facilitator activities had most impact. We also conducted a qualitative study within HepCATT which is reported in detail elsewhere.\textsuperscript{31} There was still significant drop-out along the care pathway at all points at all sites. The reasons for this are multifarious, ranging from physical constraints through to issues such as continued drug and alcohol use, mental health problems or homelessness. Thus, although the
facilitators had a significant impact, it is unrealistic to expect that all HCV-infected PWIDs attending a drug service facility can be integrated into appropriate care pathways at any one time.

Performance measured against all end-points improved at all 3 intervention sites, but the magnitude of this improvement varied considerably between sites, with the numbers of clients engaged and treated being lowest at site C. This was largely due to the much lower prevalence of HCV infection in PWIDs attending this site (9%) in comparison to the other two (32% and 31%, see Table 1a). Local seroprevalence rates will no doubt impact on the cost-effectiveness of the intervention, something which will be addressed in a separate cost-effectiveness analysis of HepCATT.

Whilst feedback from the facilitators suggests that the key interventions to improve the cascade of care will vary between different clinics, the over-arching lesson to be learnt from this study is that diagnosis and treatment of HCV infection in PWID is a tractable problem. Investment in resources aimed specifically at PWID attending specialist drug services can lead to significant increases in engagement and treatment of this “difficult-to-reach” patient group within routine clinical care pathways. We believe the keys to the success of HepCATT were the employment of enthusiastic research nurses with a determination to break down barriers and overcome stigma associated with HCV infection in PWID, an acknowledgement that there was unlikely to be a “one fits all” solution to such a multi-faceted problem, thereby encouraging flexibility in choice of interventional approach on the ground, and a guiding philosophy of placing individual PWID at the centre of the care pathway, with subsequent adjustment of provision of healthcare services, rather than insisting that individual clients should fit in with preconceived ideas of how healthcare should be delivered. We are not claiming that the observed size of the intervention effect in this pilot study will necessarily be replicated across the whole country, but we have clearly shown that a large intervention effect is possible and therefore wider introduction of such an intervention – with evaluation – is recommended. Future research should also address the possible further impact of introducing outreach HCV treatment services within the drug services clinics themselves, an aspect of care delivery that HepCATT was not designed to address.

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RR and MH acknowledge support from the NIHR Health Protection Research Unit in Evaluation of Interventions at University of Bristol

RESEARCH ETHICS APPROVAL

Research ethics committee approval was provided by the Derby East REC (ref 15/EM/0016). The study sponsor was the University of Nottingham.

AUTHOR CONTRIBUTIONS
Study design and funding co-applicants: SDR, BJT, GRF, SS, MHa, MHi, WLI.

Intervention management: GIH, WLI, AC, SS, MHi

Data collection: GIH, KM, RG, PL, SA, PR, AH, MW, WG, EU, KR, AO, KT, CS, SO

Data analysis: GIH, RR, MHi, WLI

Manuscript preparation: All co-authors

All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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### Table 1a Clients and outcomes – Intervention sites

<table>
<thead>
<tr>
<th>Number (%)</th>
<th>Site A</th>
<th>Site B</th>
<th>Site C</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Intervention</td>
<td>Baseline</td>
</tr>
<tr>
<td>All clients</td>
<td>633 (57.0)</td>
<td>572 (54.7)</td>
<td>2043 (34.8)</td>
</tr>
<tr>
<td>PWID (% of all clients)</td>
<td>361 (57.0)</td>
<td>313 (54.7)</td>
<td>710 (34.8)</td>
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<tr>
<td>Tested (% of PWID)</td>
<td>106 (29.4)</td>
<td>139 (44.4)</td>
<td>135 (19.0)</td>
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<td>HCV-positive (% of PWID)</td>
<td>87 (24.1)</td>
<td>100 (31.9)</td>
<td>173 (24.4)</td>
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<td>Referred (% of HCV+ PWID)</td>
<td>29 (33.3)</td>
<td>97 (97.0)</td>
<td>11 (6.4)</td>
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<tr>
<td>Engaged (% of HCV+ PWID)</td>
<td>10 (11.5)</td>
<td>55 (55.0)</td>
<td>3 (1.7)</td>
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<tr>
<td>Treated</td>
<td>2</td>
<td>15</td>
<td>1</td>
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### Table 1b Clients and outcomes – Control sites 1-3

<table>
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<tr>
<th>Number (%)</th>
<th>Control 1</th>
<th>Control 2</th>
<th>Control 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Intervention</td>
<td>Baseline</td>
</tr>
<tr>
<td>All clients</td>
<td>252 (56.0)</td>
<td>189</td>
<td>2124</td>
</tr>
<tr>
<td>PWID (% of all clients)</td>
<td>141 (56.0)</td>
<td>113 (59.8)</td>
<td>685 (32.3)</td>
</tr>
<tr>
<td>Tested (% of PWID)</td>
<td>7 (5.0)</td>
<td>10 (8.8)</td>
<td>85 (12.4)</td>
</tr>
<tr>
<td>HCV-positive (% of PWID)</td>
<td>37 (26.2)</td>
<td>24 (21.2)</td>
<td>146 (21.3)</td>
</tr>
<tr>
<td>Referred (% of HCV+ PWID)</td>
<td>32 (86.5)</td>
<td>10 (41.7)</td>
<td>19 (13.0)</td>
</tr>
<tr>
<td>Engaged (% of HCV+ PWID)</td>
<td>15 (40.5)</td>
<td>1 (4.2)</td>
<td>18 (12.3)</td>
</tr>
<tr>
<td>Treated</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

Baseline period (all sites): Jan–Dec 2014.

\( a \) Many identified through a case-finding study using oral swab testing over a 3-month period.

\( b \) Hepatitis C status derived from self-reported data held in the drug services databases as described in Methods section.

\( c \) Includes 3 (Site A), 2 (Site B) and 1 (Site C) clients later discovered to be PCR negative

### Table 2 Cascade of care for Control sites 4 and 5

<table>
<thead>
<tr>
<th>HCV-infected clients</th>
<th>Control 4</th>
<th>Control 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referred</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Engaged</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Treated</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 3. Reasons for drop-out from the cascade of care pathway.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Referred but did not attend (n = 87)</th>
<th>Attended but did not engage (n = 16)</th>
<th>Engaged but was not treated (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social/lifestyle/mental health issues*</td>
<td>19</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Physical constraints*</td>
<td>17</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Unwilling</td>
<td>23</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Died</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Awaiting decision*</td>
<td>2</td>
<td>5</td>
<td>42</td>
</tr>
<tr>
<td>Became/tested PCR negative</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Not known</td>
<td>23</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

* These terms are defined in the Methods

Table 4. Activities undertaken by facilitators at each site.

<table>
<thead>
<tr>
<th>Intervention activity</th>
<th>Site A</th>
<th>Site B</th>
<th>Site C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facilitator actively &quot;grab &amp; tested&quot; clients via DBS</td>
<td>No</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Arranged for more flexible appointment times at hospital</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Made systematic changes for quicker appointment times at hospital</td>
<td>YES</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Streamlined referral process for service staff including provision of referral templates</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Implemented a system to allow self-referral of clients (and NSP users) to HCV treatment services</td>
<td>YES</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Educational initiatives to educate service staff about HCV and new treatment regimens</td>
<td>Yes</td>
<td>YES</td>
<td>Yes</td>
</tr>
<tr>
<td>After appointment letter is sent to client, send a second more personal letter with contact details ensuring keyworker is cc'd</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Used service provider IT system to identify clients whose HCV status was unknown or untested recently. Followed up with client’s keyworker</td>
<td>Yes</td>
<td>Yes</td>
<td>YES</td>
</tr>
<tr>
<td>Actively contacted clients by phone or SMS immediately prior to their appointments at hospital to remind/encourage them</td>
<td>YES</td>
<td>YES</td>
<td>Yes</td>
</tr>
<tr>
<td>Increased communication with keyworkers of known positive clients and at risk clients who needed to be tested</td>
<td>Yes</td>
<td>Yes</td>
<td>YES</td>
</tr>
<tr>
<td>Actively targeted NSP steroid users</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Establishment/enhancement of a buddy/peer support system</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

The 3 activities that each facilitator worked best are indicated in emboldened capital letters; NSP = Needle and Syringe Programme
FIGURE LEGENDS

Figure 1(a) Change in percentage engagement, by site
Figure 1(b) Intervention effect on engagement, by site

Footnotes:

Intervention Effect: OR 29.2, 95% CI 11.9–71.8, p<0.001

No clients engaged with treatment in either period at site 3 so, to present an approximation to the odds ratio, one engaged client has been added in each period there.

Figure 2 Intervention effect on HCV testing, by site

Footnote:

Intervention Effect: OR 3.9, 95%CI 2.7–5.5, p<0.001
Figure 1(a) Change in percentage engagement, by site

Engagement with HCV treatment

HepCATT sites: A B C
Control sites: 1 2 3

Engagement with HCV treatment

Figure 1(b) Intervention effect on engagement, by site

Engagement with HCV treatment

Odds ratio for intervention period

<table>
<thead>
<tr>
<th>Centre</th>
<th>Odds ratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control sites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.06 (0.01, 0.52)</td>
<td>27.85</td>
</tr>
<tr>
<td>2</td>
<td>0.63 (0.28, 1.38)</td>
<td>53.43</td>
</tr>
<tr>
<td>3</td>
<td>0.85 (0.05, 15.16)</td>
<td>18.72</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0.35 (0.06, 1.56)</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>HepCATT intervention sites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>9.41 (4.37, 20.28)</td>
<td>45.07</td>
</tr>
<tr>
<td>B</td>
<td>22.94 (7.08, 74.33)</td>
<td>29.30</td>
</tr>
<tr>
<td>C</td>
<td>4.29 (1.16, 15.82)</td>
<td>25.63</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>9.99 (4.42, 22.56)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
Figure 2 Intervention effect on HCV testing, by site

Testing for Hepatitis C virus
Odds ratio for intervention period

<table>
<thead>
<tr>
<th>Centre</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.86 (0.68, 5.05)</td>
<td>19.97</td>
</tr>
<tr>
<td>2</td>
<td>0.65 (0.45, 0.93)</td>
<td>50.07</td>
</tr>
<tr>
<td>3</td>
<td>0.60 (0.29, 1.23)</td>
<td>29.96</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.78 (0.46, 1.33)</td>
<td>100.00</td>
</tr>
<tr>
<td>HepCATT intervention sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1.92 (1.40, 2.64)</td>
<td>33.37</td>
</tr>
<tr>
<td>B</td>
<td>1.79 (1.40, 2.29)</td>
<td>33.94</td>
</tr>
<tr>
<td>C</td>
<td>8.60 (5.84, 12.68)</td>
<td>32.69</td>
</tr>
<tr>
<td>Subtotal</td>
<td>3.06 (1.26, 7.47)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis