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Clinical effectiveness of pharmacist-led versus conventionally delivered antiviral treatment for hepatitis C virus in patients receiving opioid substitution therapy: a pragmatic, cluster-randomised trial

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Summary

Background Highly effective direct-acting antiviral drugs provide the opportunity to eliminate hepatitis C virus (HCV) infection, but established pathways can be ineffective. We aimed to examine whether a community pharmacy care pathway increased treatment uptake, treatment completion, and cure rates for people receiving opioid substitution therapy, compared with conventional care.

Methods This cluster-randomised trial was done in Scottish community pharmacies. Before participants were recruited, pharmacies were randomly assigned (1:1) to refer patients with evidence of HCV antibodies to conventional care or offered them care in the pharmacy (pharmacist-led care). Pharmacies were stratified by location. All pharmacies were trained to offer dried blood spot testing. All eligible participants had received opioid substitution therapy for approximately 3 months, and those eligible to receive treatment in the pharmacist-led care pathway were HCV PCR positive, were infected with HCV genotype 1 or 3, and were willing to have a pharmacist supervise their antiviral drug administration. Neither pharmacists nor patients were masked to treatment allocation. In both groups, assessment blood samples were taken, infection with HCV was confirmed, and daily oral ledipasvir–sofosbuvir (90 mg ledipasvir plus 400 mg sofosbuvir) for 8 weeks for genotype 1 or daily oral sofosbuvir (400 mg) plus oral daclatasvir (60 mg) for 12 weeks for genotype 3 was prescribed by a nurse (conventional care group) or pharmacist (pharmacist-led care group). In the conventional care group, the patient received care at a treatment centre. Once prescribed, medication in both groups was delivered as daily modified directly observed therapy alongside opioid substitution therapy in the participants' pharmacy where treatment was observed on 6 days per week. The primary outcome was the number of patients with sustained virological response 12 weeks after completion of treatment (SVR12) as a proportion of the number of people receiving opioid substitution therapy at participating pharmacies. Participants were monitored at each visit for nausea and fatigue; other adverse events were recorded as free text. Secondary outcomes compared key points on treatment pathway between the two groups. These key points were the proportion of patients having dry blood spot testing, the proportion of patients initiating HCV treatment, the proportion of patients completing the 8 or 12 week HCV course of treatment, and the proportion of patients with sustained virological response at 12 months. This study is registered with ClinicalTrials.gov, NCT02706223.

Findings 56 pharmacies were randomly assigned (28 to each group; one pharmacy withdrew from the conventional care group). The 55 participating pharmacies included 2718 patients receiving opioid substitution therapy (1365 in the pharmacist-led care group and 1353 in the conventional care group). More patients met the primary endpoint of SVR12 in the pharmacist-led care group (98 [7%] of 1365) than in the conventional care group (43 [3%] of 1353; odds ratio 2·375, 95% CI 1·555–3·628, p<0·0001). More users of opioid substitution therapy in the pharmacist-led care group versus the conventional care group agreed to dry blood spot testing (245 [18%] of 1365 *vs* 145 [11%] of 1353, 2·292, 0·968–5·427, p=0·059); initiated treatment (112 [8%] of 1365 *vs* 61 [4%] of 1353, 1·889, 1·276–2·789, p=0·0015) and completed treatment (108 [8%] of 1365 *vs* 58 [4%] of 1353, 1·928, 1·321–2·813, p=0·0007). The data for sustained virological response at 12 months are not reported in this study: patients remain in follow-up for this outcome. No serious adverse events were recorded.

Interpretation Using pharmacists to deliver an HCV care pathway made testing and treatment more accessible for patients, improved engagement, and maintained high treatment success rates. The use of this pathway could be a key part of an integrated and effective approach to HCV elimination at a community level.

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Research in context

Evidence before this study

Direct-acting antiviral drugs have a higher cure rate for hepatitis C virus (HCV) infection than previous medication regimens containing pegylated interferon alpha and ribavirin, and a lower treatment burden and monitoring requirement. Consequently, direct-acting antiviral drugs have replaced these older drugs in current practice and are advocated by WHO as a key tool in the elimination of HCV by 2030. Guidance on the prevention, care, and treatment of people with HCV recommends task-shifting to optimise available human resources and decentralisation of care to places where people with HCV infection already visit, so that the scale and reach of provision can be increased to achieve elimination. Direct-acting antiviral drugs could be delivered in the community by affiliated care professionals, including pharmacists. Databases (Cinahl; Embase; Medline; PsycINFO; PubMed) were searched between Jan 1, 2013, and Dec 31, 2017, for studies published in English of treatment with direct-acting antiviral drugs in non-specialist settings to achieve a sustained virological response. Relevant studies were identified, including those containing a comparison between a community and specialist services where available. A narrative synthesis and linked meta-analysis were done on suitable studies with a strength of evidence assessment. We did a systematic review and meta-analysis of community-based treatment pathways and identified 17 studies showing that locally delivered care for patients with HCV is feasible and can facilitate increased uptake of treatment. Such community-based pathways might be able to show similar cure rates to those achieved by specialist clinics in secondary care. However, stronger study designs comparing community pathways with specialist care are needed to give more certainty about the effect size seen in current studies.

Added value of this study

This cluster-randomised controlled study shows that community pharmacists are more likely to recruit patients prescribed opioid substitution therapy to an HCV care pathway than standard care, and that such patients are more likely to engage with treatment when the entire process of diagnosis and treatment is offered in the pharmacy. There was no evidence of disadvantageous effects, such as lower treatment completion or success rates.

Implications of all the available evidence

Transferring the primary responsibility for HCV diagnosis and treatment of patients prescribed opioid substitution therapy to community pharmacies, with guidance available from specialist teams, is likely to increase HCV treatment uptake and cure rates. This intervention could have an important role in a system-wide strategy aimed at eradicating HCV. Such services are in line with the WHO guidance for decentralisation of service delivery to primary care-based sites and of task-sharing. Close collaboration between specialist teams and community pharmacists offers an effective option for addressing HCV in this patient group and supports efforts aimed at HCV elimination at a community level.

Introduction

Hepatitis C virus (HCV) is a blood-borne infection that causes liver disease. The worldwide burden of HCV has been estimated as 71·1 million infections (95% CI 62·5–79·4 million).[1] In high-income countries, people who inject drugs are the group most commonly infected with HCV and approximately 60% (10 million people) of the global population of people who inject drugs have an HCV infection.[2] It has been estimated that 50% of HCV infections in western Europe are caused by injecting drug use.[3] In current testing and treatment pathways within the UK, only a small proportion of patients who had a positive HCV test had evidence of ever receiving treatment (11·9%), and even fewer had a sustained virological response (5·9%).[4]

The conventional care pathway in the UK recommends that patients with a history of intravenous drug use, or who are prescribed opioid substitution therapy, should be offered HCV testing annually. Testing might be available from their general practitioner, drug workers, drug agencies, social workers, community pharmacies, and needle exchanges. Once diagnosed, patients can be referred to established treatment pathways, usually based around hepatology or infectious disease teams in secondary care.[5] The inefficiency of established treatment pathways, with many patients lost from care, leads to increased preventable deaths from hepatitis C and viral transmission among people who inject drugs.[6]

Various reasons might explain the low rates of HCV testing, treatment uptake, and treatment completion. At the patient level, people who inject drugs might encounter several barriers that prevent them from accessing care, including stigma and discrimination, issues with the organisation of care, and the treatment policies of providers or payers.[7] Low levels of health literacy might also limit understanding of their health, illness, and treatments, and people who inject drugs might find it difficult to consistently attend medical clinics.[8,9] Simplifying care pathways to enable treatment initiation, clinical monitoring, and close treatment supervision in a familiar and convenient setting might be effective in overcoming these barriers.[8] Offering hepatitis C care in primary care and community settings might increase uptake of treatment and maintain high rates of cure.[6]

In the UK, people who have injected drugs and are taking opioid substitution therapy receive treatment regularly from their local community pharmacy.[10] Community pharmacists are contractors to the UK National Health Service (NHS), as are general

practitioners and optometrists, and provide services according to financial arrangements. Patients visit pharmacies much more often than secondary care sites, and pharmacies are often located nearer to areas of socioeconomic disadvantage, have longer opening hours, and can be accessed without an appointment. Pharmacy staff can be trained to offer dry blood spot testing to screen for HCV infection. In conventional care, after a positive HCV antibody test, patients are referred to a secondary care-based team; however, the opportunity to provide all diagnostic and treatment prescription services from pharmacies might represent a much more convenient and non-threatening route to HCV treatment for people who inject drugs and are taking opioid substitution therapy. Moreover, at the pharmacist level, having primary responsibility for HCV testing and treatment, and being able to offer potential patients with HCV a more convenient and acceptable treatment pathway, could enhance pharmacists' motivation and effort to recruit patients to the pathway.

WHO has set targets to eliminate HCV as a public health threat by 2030.[11] Creating the complex public health interventions necessary to eliminate HCV requires well designed cross-disciplinary programmes to be put in place to increase screening, testing, and diagnosis.[12] Strategies advocated to increase linkage to care include integration with other services, decentralisation of primary care providers, and task-shifting to non-specialists.[6]

We aimed to evaluate whether a pharmacist-led care pathway compared with conventional care could increase HCV testing, treatment uptake and completion, and cure rates for the population of opioid substitution therapy recipients who are infected with HCV.

Methods

Study design and participants

This cluster-randomised controlled trial compared different HCV care pathways for patients receiving opioid substitution therapy in 55 community pharmacies in Scotland, overseen by three health boards. Ethics approval was granted by East of Scotland Research Ethics Committee 2 (15/ES/0086); sponsor, research and development, and Caldicott approvals were granted by University of Dundee, NHS Tayside, NHS Grampian, and NHS Greater Glasgow and Clyde. The protocol has been published elsewhere.[13]

Eligible pharmacies were community-based, were trained to offer dry blood spot testing for HCV by trained pharmacy staff, and had approximately 30 patients attending to receive opioid substitution therapy to ensure adequate recruitment to the trial. Within those pharmacies, all patients taking opioid substitution therapy were included in the trial, because they were the population at risk of HCV infection. Not all of the patients accepted testing.

Patients eligible to receive treatment in the pharmacist-led care pathway were HCV PCR positive, were infected with HCV genotype 1 or 3, were using opioid substitution therapy, had attended the pharmacy for approximately 3 months, and were willing to have a pharmacist supervise their antiviral drug administration. Patients were ineligible for receiving treatment in the context of this study if they had a HCV genotype other than 1 or 3, had a risk of cirrhosis (fibrosis-4 [FIB-4] score >3·25), had evidence of current or previous decompensated liver disease, had HIV infection, tested HBsAg positive with detectable hepatitis B virus (HBV) DNA, behaved aggressively or violently towards pharmacy staff, were pregnant, or were not able to provide informed consent. There were no age restrictions on study eligibility. Pan-genotypic medicines were not available at the time of this study. All participants gave written informed consent.

Randomisation and masking

The unit of randomisation was eligible pharmacies. Before the start of recruitment, pharmacies were randomly assigned 1:1 to provide conventional care (group 1) or pharmacist-led care (group 2) using www.randomization.com (by SKI) to generate randomly permuted blocks. SKI generated the sequence and allocated pharmacies to the conventional care group or the pharmacist-led care group. Participants were enrolled by the pharmacists in each pharmacy. Neither pharmacists nor patients were masked to treatment allocation, because knowledge of the intervention provided was necessary to enter the pathway—ie, undergoing HCV testing and initiating HCV treatment. Pharmacies were stratified by location so that each Scottish Health Board had equivalent numbers of treatment and control pharmacies.

Procedures

Before initiation of the study, good clinical practice training was provided to all participating pharmacy staff. In addition, training was provided on testing for bloodborne viruses, the interpretation of laboratory test results, FIB-4 score calculation to assess risk of cirrhosis, and the pathophysiology and treatment of HCV.[14]

Conventional care in the comparator group was provided by a highly developed multidisciplinary service from community treatment centres. During the study, pharmacists in the conventional care pathway opportunistically discussed HCV infection with patients taking opioid substitution therapy who attended the community pharmacy. Patients with unknown HCV status or previous negative results could be offered testing using a dry blood spot test in the pharmacy. Dry blood spot tests were sent to the local laboratory where they were analysed for HCV, HBV, and HIV infection. If PCR was required, this test was done at the regional laboratory. Results were usually communicated directly to the pharmacist within 7 days. Patients who were recently or previously identified as having HCV were provided with an information leaflet explaining that their pharmacy was participating in a study and asking them to provide informed consent to

See Online for appendix

having their data collected. Patients who were tested for HCV during the trial had a post-test discussion with the pharmacist using a standard infographic (appendix p 1) and were offered referral to a treatment centre. When the patient attended an appointment at a treatment centre, a member of the specialist hepatitis team assessed the patient for treatment for HCV as per standard of care. Assessment comprised medical history, concurrent medication, a full blood count, urea and electrolytes, liver function testing, and viral parameters (HCV genotype and viral load). Prescriptions for direct-acting antiviral treatment were provided by a nurse prescriber and dispensed at the participant's community pharmacy.

Similarly to the conventional pathway, in the pharmacist-led care pathway, pharmacists opportunistically discussed HCV infection with patients taking opioid substitution therapy who attended the pharmacy, and offered dry blood spot testing and communicated the possibility of receiving direct-acting antiviral treatment in the pharmacy to patients who tested positive for HCV (including patients who tested positively on a previous occasion, but who had not had treatment). People who identified as being HCV antibody-positive provided informed consent to receive their treatment from the pharmacist rather than conventional care, and for their data to be collected. In the pharmacist-led care pathway, the pharmacist assessed the participant for treatment, solely within the pharmacy. The pharmacist completed a pretreatment checklist of medical comorbidities, took a medicines history, and identified factors—such as history of non-attendance or treatment instability—that were likely to impinge on treatment compliance. A phlebotomist or nurse visited the pharmacy for assessment blood tests and the pharmacist determined suitability for treatment. When there were no contra-indications to therapy, the patient commenced treatment. In patients with contraindications or about whom there were queries about suitability, the pharmacist contacted the specialist hepatitis team for advice. Potential participants with a FIB-4 score of more than 3·25 (and at risk of having cirrhosis) were referred to a hospital consultant. In Scotland, prescribing of direct-acting antiviral drugs is not limited to specialists but can be done by general practitioners, nurses, and pharmacists, as well as being made available by protocolised prescribing through patient group directions. Prescriptions for treatment in the pharmacist-led care pathway were provided by a pharmacist prescriber or through use of a patient group direction.[15]

The direct-acting antiviral treatment provided in both pathways was daily administration of oral ledipasvir–sofosbuvir for 8 weeks for patients with genotype 1 infections, and oral sofosbuvir plus oral daclatasvir for 12 weeks for patients with genotype 3 infections. Ledipasvir–sofosbuvir (90 mg ledipasvir plus 400 mg sofosbuvir; Gilead Sciences, Foster City, CA, USA), sofosbuvir 400 mg (Gilead Sciences, Foster City, CA, USA), and daclatasvir 60 mg (Bristol-Myers Squibb, Princeton, NJ, USA) were provided free of charge through investigator sponsored research grants. The direct-acting antiviral treatment was administered concurrently with supervised opioid substitution therapy by the participant's pharmacist, who observed consumption (modified directly observed therapy). In both study groups, medications were usually carried away to be self-administered on Sundays when the pharmacy was closed. For doses that patients self-administered, the pharmacist and patient made a brief if–then action plan (an implementation intention) and coping plan (to overcome anticipated barriers).[16]

In both groups, daily monitoring was done at the pharmacy (excluding Sundays), including recording of any side-effects or adverse events. Participants were monitored at each visit for nausea and fatigue; other adverse events were recorded as free text. Participants who did not attend the pharmacy for 7 consecutive days had treatment discontinued and were deemed to have left the study. Fidelity of the intervention in both groups was promoted through standardised training and concurrent support from the study coordinators, who gave advice on implementation of the study protocol. Any breaches of protocol were reported to the sponsor. A comparison of treatment pathways between the two groups is shown in figure 1. An estimate of HCV prevalence from national surveillance data and within-study testing was used in an exploratory analysis to describe the numbers of participants who might have HCV infection.[17]

Outcomes

The primary outcome of the study was the proportion of patients with sustained virological response 12 weeks after completion of treatment (SVR12) and was analysed in the intention-to-treat population.

Secondary outcomes were analysed in the intention-to-treat population or per-protocol population, depending on the stage of the care cascade.[18] These key points were the proportion of patients having dry blood spot testing, the proportion of patients initiating HCV treatment, the proportion of patients completing the 8 or 12 week HCV course of treatment, and the proportion of patients with sustained virological response at 12 months (to assess potential reinfection).

Statistical analysis

Sample size calculations assumed that approximately 3% of HCV-positive patients on opioid substitution therapy enter HCV therapy per year via conventional pathways, with 2·5% of the total eligible population reaching a sustained virological response per annum. We estimated that the new pathway would increase the proportion of patients with sustained virological response to 15%, and on that basis, we calculated that a sample of 141 patients in each group (total 282 patients) would be needed for 90% power (α=0·05). The clustered design requires inflation to account for intracluster correlation,

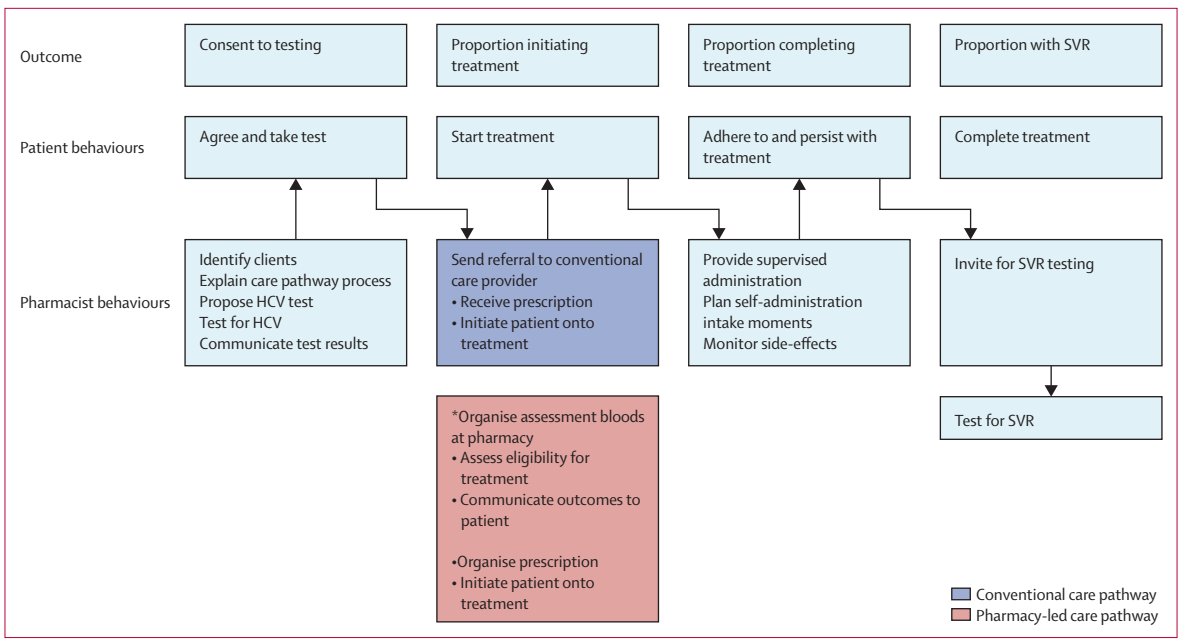

Figure 1: **Comparison of patient and pharmacist behaviours in the conventional care and pharmacist-led care pathways**
HCV=hepatitis C virus. SVR=sustained virological response. *This stage in the pharmacist-led care pathway follows "Agree and take test" and leads to "Start treatment", as in the conventional care pathway.

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so if the average number of HCV-positive patients per pharmacy is 12, the inflation factor for sizes of cluster, assuming an intracluster correlation of 0·05, is 1·55. We therefore aimed to recruit 437 patients across both groups. The analysis was verified by an independent statistician.

The primary outcome of SVR12 was assessed as a binary outcome for patients and used logistic regression modelling in Stata MP. The primary analysis was done at the individual level in the intention-to-treat population, which included the number of patients on opioid substitution therapy in each treatment group, because this represents the population at risk of infection. All patients with missing SVR12 results were assumed to be treatment failures, therefore there were no missing data in the primary outcome. To account for the use of clustered randomisation, we used a mixed-effects logistic regression model with a parameter for study group, a random parameter to account for within-cluster correlation, and stratified by hub (Scottish Health Board). A sensitivity analysis was done assuming missing data represented treatment success, based on documentation of completion of treatment.[19] Regression modelling was preplanned in the statistical analysis for type of therapy (ledipasvir–sofosbuvir, daclastavir plus sofosbuvir) and genotype (genotype 1, genotype 3), as well as hub data on the time between testing and initiating treatment. p values of less than 0·05 were assumed to be significant.

Secondary outcomes were also assessed as binary outcomes using the same procedure, initially in the intention-to-treat population, then as per protocol analysis of eligible patients at each stage.

We did a post-hoc analysis to investigate differences in attrition rates at individual steps between the two pathways, to explore any differences in patients' behaviours once they had reached that stage. Cure rates were also calculated for the notional population at risk of infection and for the population diagnosed with HCV infection. The diagnosed population cure rate was the number of patients with SVR12 as a proportion of diagnosed patients. The notional population cure rate was the number of patients with SVR12 as a proportion of patients estimated to have an HCV infection. This study is registered with ClinicalTrials.gov, NCT02706223.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Dec 9, 2016, and May 31, 2018, 2718 opioid substitution therapy recipients attended the 55 pharmacies that were randomly assigned to one of the two care pathways (28 pharmacies in the pharmacist-led care pathway group, 27 in the conventional care pathway group; figure 2).

Pharmacy and patient characteristics were similar between the two groups (tables 1, 2). Detailed information is only available for patients who consented to

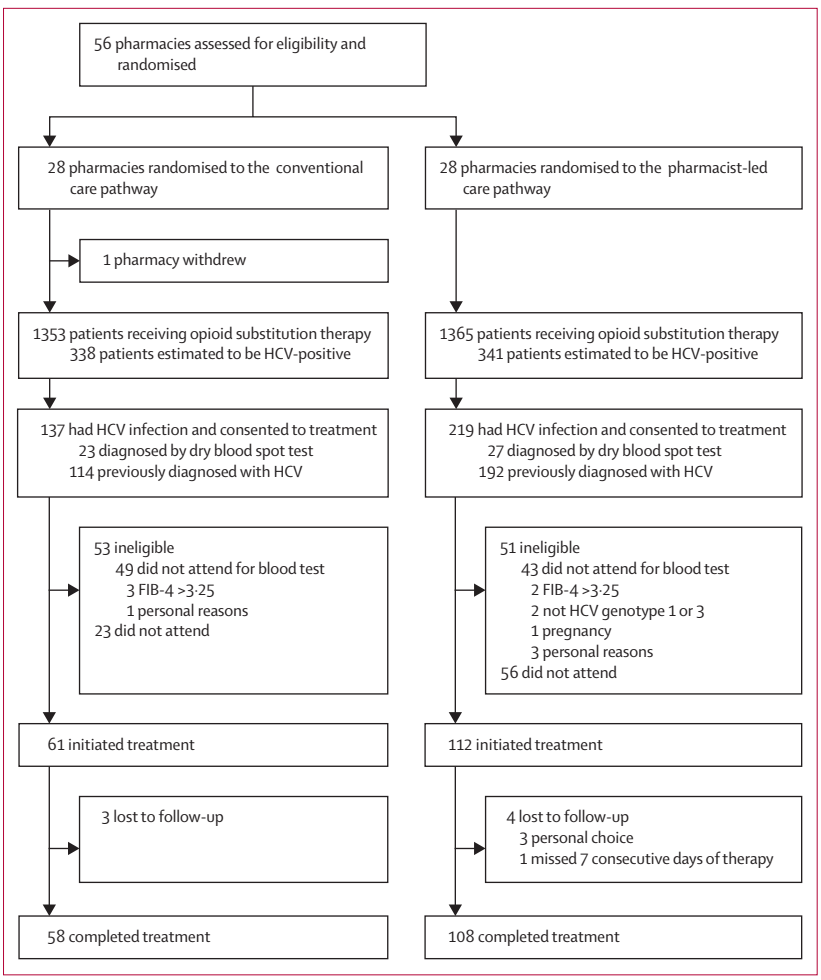

Figure 2: **Trial profile**
HCV=hepatitis C virus. FIB-4=fibrosis 4.

	Conventional care (n=27)	Pharmacist-led care (n=28)
Number of patients receiving opioid substitution therapy at start of study		
20–29	4 (15%)	3 (11%)
30–39	6 (22%)	13 (46%)
40–49	7 (26%)	2 (7%)
50–59	6 (22%)	2 (7%)
≥60	4 (15%)	8 (29%)
SIMD quintile for pharmacy address		
1	17 (63%)	14 (50%)
2	8 (30%)	7 (25%)
3	1 (4%)	4 (14%)
4	1 (4%)	1 (4%)
5	0	2 (7%)

SIMD=Scottish Index of Multiple Deprivation (1 being most deprived, 5 being least deprived).

Table 1: **Characteristics of pharmacies included in the study**

have data collected when they elected to receive therapy. Of the 356 participants who had HCV infection and consented to take part in the study (137 in the conventional care pathway group, 219 in the pharmacist-led care pathway group), 197 (55%) completed further blood tests and 185 (52%) completed assessments to define FIB-4 score and HCV genotype (figure 2). The 2362 patients receiving opioid substitution therapy who did not commence treatment as part of this study were HCV-negative, had been previously treated, or declined testing. Through access to region-wide prescribing data, to the best of our knowledge, no eligible patients were treated outside the study.

Data on the number of patients at each site who were recruited, who were tested, who initiated and completed treatment, and who achieved SVR12 are shown in the appendix (p 2). 98 (7%) of 1365 participants in the pharmacist-led treatment group had SVR12 compared with 43 (3%) of 1353 participants in the conventional care group (odds ratio [OR] 2·375, 95% CI 1·555–3·628, p<0·0001; table 3). There were two treatment failures in each group. Of the 108 patients in the pharmacist-led care group who completed treatment, six (6%) did not attend for an SVR12 test (two patients died from unrelated causes); 12 (21%) of 58 patients in the conventional care group who completed treatment did not attend for an SVR12 test. Two (2%) of 108 patients in the pharmacist-led treatment group and one (2%) of 58 patients in the conventional care group attended for an SVR12 test, but had an insufficient sample taken to complete the PCR test. Results from multiple logistic regression modelling exploring the patient and pharmacy characteristics that were associated with the primary and secondary outcomes were not significant (data not shown). For the sensitivity analysis, in which we assumed that patients who completed treatment had SVR12 (rather than treatment failure), a smaller effect size was shown because of the higher number of dropouts in the conventional care group. In this analysis, 106 (8%) of 1365 patients in the pharmacist-led care group had SVR12 compared with 56 (4%) of 1353 patients in the conventional care group (OR 1·95, 1·397–2·72, p<0·0001).

For the uptake of HCV testing, 245 (18%) of 1365 patients on opioid substitution therapy in the pharmacist-led care group had a dry blood spot test, 77 of whom tested antibody positive; 145 (11%) of 1353 in the conventional care group had a dry blood spot test, 31 of whom tested antibody positive (OR 2·292, 95% CI 0·968–5·427; p=0·06). 27 (11%) of the 245 participants in the pharmacist-led care group and 23 (16%) of the 145 participants in the conventional care group were HCV PCR positive. The prevalence of HCV-positive tests from in-study testing across both groups was 50 (13%) of 390. The most frequent reason for not proceeding with the treatment pathway in both groups was non-attendance (56 in the pharmacist-led care group, 23 in the conventional care group), with non-eligible genotypes (two participants in the pharmacist-

led care group, zero in the conventional care group) and a FIB-4 score of more than 3·25 (two participants in the pharmacist-led care group, three in the conventional care group) being infrequent (figure 2). Other secondary outcomes analysed in the intention-to-treat population are shown in table 3.

In a per-protocol analysis of secondary outcomes, with denominators depending on stage of the cascade of care, 219 (16%) of 1365 patients in the pharmacist-led pathway and 137 (10%) of 1353 in the conventional care pathway who were either newly diagnosed (27 in the pharmacist-led care group, 23 in the conventional care group) or previously diagnosed (192 in the pharmacist-led care group, 114 in the conventional care group) consented to receiving direct-acting antiviral treatment after being approached by their pharmacists. 112 (51%) of 219 participants initiated treatment in the pharmacist-led care group compared with 61 (44%) of 137 participants in the conventional care group. The median time between testing and commencement of treatment for the pharmacist-led care group was 46·5 days (IQR 16·1–76·9) and for the conventional care pathway was 71 days (17·5–124·5).

108 (49%) of 219 patients in the pharmacist-led care group and 58 (42%) of 137 in the conventional care group completed treatment. The proportion of patients who completed treatment among those who initiated treatment were similar between the two groups: 108 (96%) of 112 in the pharmacist-led care group and 58 (95%) of 61 in the conventional care group. The proportion of patients with a sustained virological response at 12 months (to assess potential reinfection) will be reported elsewhere; patients are still in follow-up for this outcome.

One participant in the pharmacist-led care group withdrew after assessment but before initiating therapy because of pregnancy. One patient in the pharmacist-led care group was discontinued from treatment because they missed 7 consecutive days of therapy. Six participants dropped out during treatment (three in the pharmacist-led care group, three in the conventional care group) through personal choice. During the study no adverse events, including serious adverse events, were identified.

In the post-hoc analysis, population cure rates more than doubled in the pharmacist-led care pathway compared with in the conventional care pathway (table 3). The results of our exploratory analysis using national surveillance data[17] and within-study testing to describe the estimated numbers of participants who might have HCV infection at each stage in the care pathway are shown in figure 3.

	Conventional care (n=61)	Pharmacist-led care (n=112)
Age, years		
20–29	3 (5%)	3 (3%)
30–39	28 (46%)	63 (56%)
40–49	24 (39%)	43 (38%)
50–59	4 (6%)	3 (3%)
≥60	2 (3%)	
Sex		
Male	43 (70%)	70 (63%)
Female	18 (29%)	42 (37%)
FIB-4 score		
<1·45	46 (75%)	68 (61%)
1·46–3·24	14 (23%)	42 (37%)
>3·25	0	2 (2%)*
HCV genotype		
1	30 (49%)	37 (33%)
3	31 (51%)	75 (70%)

Proportions (%) have been rounded to the nearest whole number and might not total 100%. FIB-4=fibrosis 4. HCV=hepatitis C virus. *Patients continued to treatment despite meeting exclusion criteria after discussion between the pharmacy and multidisciplinary team. [A: footnote ok?]

Table 2: **Baseline characteristics of participants who initiated treatment with direct-acting antiviral therapy**

	Conventional care pathway (n=1353)	Pharmacist-led care pathway (n=1365)	Odds ratio (95% CI)	p value
SVR12	43 (3%)	98 (7%)	2·375 (1·555–3·628)	<0·0001
Dry blood spot test	145 (11%)	245 (18%)	2·292 (0·968–5·427)	0·059
Consented	137 (10%)	219 (16%)	1·696 (1·350–2·131)	<0·0001
Initiated treatment	61 (5%)	112 (8%)	1·889 (1·276–2·798)	0·0015
Completed treatment	58 (4%)	108 (8%)	1·928 (1·321–2·813)	0·0007
Diagnosed population cure rate*	137 (31%)	219 (45%)	..	..
Notional population cure rate†	338 (13%)	341 (29%)	..	..

SVR12=sustained virological response 12 weeks after completion of treatment. *The number of patients with SVR12 as a proportion of diagnosed patients. †The number of patients with SVR12 as a proportion of patients estimated to have infection.

Table 3: **Outcomes of the primary, secondary, and post-hoc analyses in the intention-to-treat population**

Discussion

Our findings show that by making care more convenient for patients, the pharmacist-led care pathway led to more participants with SVR12 than did the conventional care pathway. We found that centralising the primary responsibility for HCV care in pharmacies led to more HCV testing and increased treatment uptake by patients who had previously tested HCV-positive, and maintained the high proportion of treatment success observed in the conventional care pathway.[20] From the post-hoc notional population cure rates, treatment success rates more than doubled in this study. Also, because patient care was transferred out of hospital clinics and into pharmacies that the participants were already attending, the use of secondary care resources and the burden on patients are likely to have reduced. In a UK benchmark study, 11·9% of the included population had evidence of ever receiving treatment and a smaller proportion (5·9%) were thought to have SVR12.[4] A US study reported that 15% of patients with

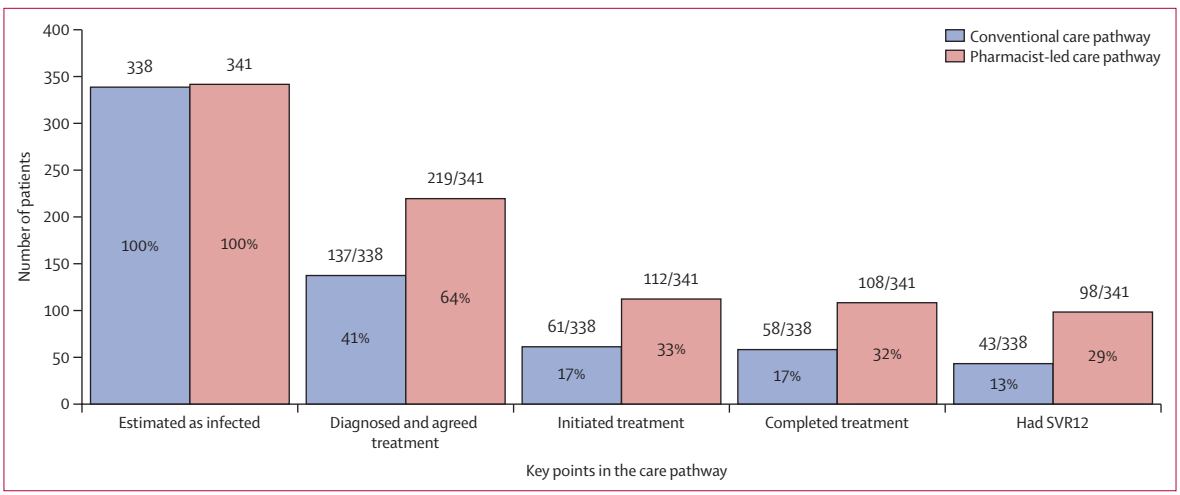

Figure 3: **Progress of participants to SVR12 through the cascade of care**
Numbers of patients at each stage of the care pathway as a proportion of the estimated number of cases.[17]

an HCV diagnosis attending an urban health network initiated treatment and 8% achieved SVR12.[21] In the pharmacist-led care group in our study, the proportions were higher than in both these previous studies, with 51% of patients with a diagnosis of HCV starting treatment and 45% achieving SVR12.

Using community pharmacies as the focal point of this intervention enabled a number of barriers to care that we identified in the literature and intervention development work to be overcome.[22,23] Participants' perceptions (recorded as part of our pilot work)[22–25] were that the close proximity of the pharmacies and the trusting relationships formed between the pharmacists and people attending for opioid substitution services were important factors in encouraging HCV treatment participation, making service attendance easier (eg, no need to find money to travel),[8,9] and removing the challenges of navigating the health system.[26] These factors were expected to enhance uptake of HCV testing and treatment initiation, as was observed in this study; however, the increased uptake could also suggest that a less motivated and less selected group of patients initiated HCV treatment than normally would.[27] It is noteworthy that the proportions of patients completing treatment compared with those initiating treatment was similar in both pathways, despite the higher treatment uptake in the pharmacist-led care group. We suggest that the proximity of pharmacies to where patients live, and the fact that the patients were already attending the pharmacy, might underlie the observed difference in treatment uptake in the intention-to-treat population and in the per-protocol populations.

The safety of direct-acting antiviral drugs means that many routinely measured analytes are no longer required (full blood count, liver function tests, viral load) and monitoring of safety outcomes can be simplified. The only outstanding issue is fibrosis estimation, which cannot be tested using capillary blood but can be managed with portable imaging methods such as elastography. The introduction of pangenotypic treatments of HCV reduces the complexity of clinical assessment, with an assessment for fibrosis being the main requirement, and further reduces the need for monitoring.[28] However, it is important to ensure support from a specialist hepatitis team and a peripatetic phlebotomist when making this transition from conventional care to pharmacist-led care. The use of rapid RNA tests, currently being introduced and already being used in suitable environments, is expected to reduce the time taken to provide results to patients, increase the number of patients who remain engaged in the process, and reduce the time between diagnosis and treatment uptake.

The change from conventional care to pharmacist-led care was also expected to modify the behaviour of the pharmacist. Being assigned the primary responsibility for HCV testing and treatment was expected to prompt pharmacists to more actively participate in a novel clinical service. Community pharmacies received financial incentivisation for participation in this service, as contractors within the NHS. The incentives provided might have motivated pharmacists to participate in the study and to complete follow-up with patients who were receiving antiviral treatment, although the exact mechanisms are impossible to disentangle from the effects of the intervention on participants. Participants self-selected to join the pharmacy pathway and it is unsurprising that many completed the course of treatment after electing to do so. The efficacy of direct-acting antiviral treatment is likely to deliver an SVR12 result if participants continued to attend for their opioid substitution therapy.

Pharmacists did not have access to skills and information sources that are available to hospital clinics, such as a phlebotomist and detailed medical histories

for the patients. This was not a barrier to care and no adverse events were observed. Close working with the specialist hepatitis team meant that any queries raised by the pharmacists could be efficiently dealt with through email or telephone; a visiting phlebotomist was able to meet with patients in their pharmacy. Although the full HCV treatment pathway could be delivered by pharmacies, ensuring support by a visiting phlebotomist and relationships with specialist teams seem to be important factors in making this pathway both safe and effective.

In a systematic review, we evaluated the performance of care pathways that use direct-acting antiviral drugs in a range of community and primary care settings, including studies based in opioid treatment services and integrated care arrangements (Extension for Community Health Outcomes, ECHO).[29] We identified some evidence that HCV treatment provided in primary care and community environments could result in similar proportions of patients with SVR12 to specialist care, and increase the numbers of people who could access care. From the 17 studies included, just two were randomised controlled trials, one of which was the feasibility study[24] we did in preparation for this study. The feasibility study also showed an increase in testing uptake and increased retention in care in pharmacist-led care compared with conventional care. The second randomised controlled trial[30] showed increased treatment uptake and proportions of patients with SVR12 in primary care sites compared with standard of care, and provided evidence of the applicability of moving care to primary care and community settings in an international context.

Our study has shown greater effectiveness of a pharmacist-led treatment pathway, which included close collaboration between specialist clinics and pharmacies and directly observed treatment of HCV at the pharmacies, compared with a gold standard comparator (the conventional care pathway).[20] The use of pharmacists to deliver care to different patient groups is expanding rapidly because of the availability of safer medicines, the need to access disadvantaged communities, and the widening of the multidisciplinary team. Cost-effectiveness of the pharmacist-led care pathway is being evaluated as part of our programme of ongoing work.

We believe that our comparator care pathway was innovative, being community-facing, multidisciplinary, and involving nurse prescribing. The Tayside region of Scotland has been a test bed for sequential development of integrated services for HCV care over the past two decades,[31] moving from standard secondary care-based hospital outpatients, onto nurse-supported treatment services, to a HCV managed care network, and finally to a development in the managed care network model, which included a widespread dry blood spot testing programme in drug services and development in outreach services across the region, including providing treatment within drug services and prisons.[20] That we nevertheless observed such an increase in treatment uptake and effectiveness in the pharmacist-led care group provides strong additional support for the WHO guidelines on care and treatment of individuals diagnosed with chronic HCV infection (ie, the importance of simplified service delivery models, integration with other services, decentralised services supported by task-sharing, and community engagement to address stigma and increase reach).[6] Increasing access to care by lowering barriers to treatment will be essential to achieve the goals outlined in the WHO guidelines. This study shows a way that this increase in access to care can be accomplished.

This cluster-randomised controlled study had several strengths: the intervention was developed iteratively and pragmatically using Medical Research Council guidance for developing and evaluating complex interventions;[32] pilot work was done using focus groups, examination of patient preferences, testing of elements of the pathway, and implementation of a feasibility trial to aid the design of the pharmacist-led pathway;[22–25] and the intervention was based on a pilot study, was feasible, and was well powered.

The main weaknesses of our study are, first, that we could only collect participant data after dry blood spot testing from participants who consented to treatment, which did not represent true baseline data (which would have required us to collect data on the full randomised sample of all patients prescribed opioid substitution therapy in the participating pharmacies). Second, the number of study participants who did not present for a confirmatory SVR12 blood test was slightly higher in the conventional care group than in the pharmacist-led care group, which could inflate the treatment effect. However, a sensitivity analysis assuming that all participants who completed treatment had SVR12 confirmed the effect shown in the pharmacist-led care group. Finally, the participating pharmacies might have been a selection of those already interested in taking on this additional HCV test-and-treat responsibility, hence, the success of the pathway should be closely monitored when it is implemented in routine health services.

The pharmacist-led care pathway is a safe and effective approach to improving the reach and impact of HCV treatment. The use of direct-acting antiviral drugs means that monitoring and management of patients are straightforward: risk of cirrhosis can be assessed using routine blood tests, and ongoing monitoring of participants can be done during routine attendance for opioid substitution therapy. This study shows that conveniently organising the entire HCV treatment pathway in community pharmacies—compared with a pathway comprising state-of-the-art HCV care by pharmacies in collaboration with secondary care treatment centres—can double HCV testing and treatment consent rates, and retain excellent treatment outcomes. This intervention could be an important

complementary strategy for achieving the WHO target of eliminating HCV.

Contributors

AR, MdB, SKI, PTD, STB, AF, and JFD conceived, planned, and designed the study, prepared the protocol, and prepared the manuscript. JFD was chief investigator, AR was principal investigator for Tayside sites, STB was principal investigator for Glasgow, and AF was principal investigator for Grampian. SKI coordinated the trial as study manager, developed the operating procedures, and did the randomisation. AR, SKI, STB, and AF contributed to intervention development, local implementation of the study, practice and patient recruitment, training, study monitoring, and data collection. AR, SKI, PTD, AH, and JFD devised the statistical analysis plan. AR and AH did the analysis. AR wrote the first draft of the paper. All authors revised the paper critically for intellectual content and approved the final version.

Declaration of interests

AR has received grants from Gilead and Bristol-Myers Squibb during the conduct of the study; and grants from Roche, and grants and personal fees from AbbVie, outside of the submitted work. PTD has received grants from Gilead and Bristol-Myers Squibb during the conduct of the study; and grants from Novo Nordisk, Shire, and GlaxoSmithKline, outside of the submitted work. PTD is also a member of the New Drugs Committee of the Scottish Medicines Consortium. STB has received grants and personal fees from Gilead and AbbVie outside of the submitted work. JFD has received non-financial support from Gilead and Bristol-Myers Squibb, and grants from the Scottish Government Department of Health, during the conduct of the study; and grants and personal fees from Gilead, AbbVie, MSD, Janssen, and Roche, and grants from Genedrive, outside of the submitted work. All other authors declare no competing interests.

Data sharing

The anonymised dataset will be held by the chief investigator. Consideration will be given to applications from other researchers who apply for access to the data for their own research. Any such application would require approval from the chief investigator and funders.

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