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MR. DAVOUD POURMARZI (Orcid ID : 0000-0002-1970-3609)

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Clinical effectiveness, cost effectiveness and acceptability of community-based treatment of Hepatitis C Virus infection: a mixed method systematic review

Running title: effectiveness and acceptability of HCV treatment in community

Davoud Pourmarzi: School of Public Health and Social Work, Faculty of Health, Institute of Health and Biomedical Innovation (IHBI), Queensland University of Technology, Brisbane, Australia.

Lisa Hall: School of Public Health, Faculty of Medicine, The University of Queensland, Brisbane, Australia. School of Public Health and Social Work, Faculty of Health, Institute of Health and Biomedical Innovation (IHBI), Queensland University of Technology, Brisbane, Australia.

Julie Hepworth: Mater Research Institute, The University of Queensland, Brisbane, Australia.

Andrew Smirnov: School of Public Health, Faculty of Medicine, The University of Queensland, Brisbane, Australia.

Tony Rahman: School of Nursing, Faculty of Health, Queensland University of Technology. Department of Gastroenterology and Hepatology, The Prince Charles Hospital, Brisbane, Australia.

Gerrard FitzGerald: School of Public Health and Social Work, Faculty of Health, Institute of Health and Biomedical Innovation (IHBI), Queensland University of Technology, Brisbane, Australia.

Correspondence to: Davoud Pourmarzi, O Block, Kelvin Grove Campus, QUT, Victoria Park Road, Kelvin Grove, QLD, 4059, Australia

Email: D.pourmarzi@qut.edu.au
Telephone: +61 (0)7 3138 5815

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Abstract

Several community-based models for treating Hepatitis C Virus (HCV) infection have been implemented to improve treatment accessibility and health outcomes. However, there is a lack of knowledge regarding how well these models achieve the desired goals. We conducted a mixed-method systematic review of quantitative and qualitative evidence about clinical effectiveness, cost effectiveness and acceptability of community-based HCV treatment models. Seventeen databases were researched for published and unpublished studies. Methodological quality was assessed using The Joanna Briggs Institute Critical Appraisal tools. Quantitative findings were synthesised in narrative form and qualitative findings were synthesised using meta-synthesis. Forty-two quantitative and six qualitative studies were included. No relevant cost effectiveness studies were found. Five categories of community-based models were identified: telehealth, integration of HCV and addiction services, integration of HCV and HIV services, integration of HCV and primary care, and implementation by a home care and health care management company. The range of reported outcomes included; end of treatment response: 48.7% to 96%, serious side effects: 3.3% to 27.8%, sustained virological response: 22·3% to 95·5%, relapse: 2·2% to 16·7%, and treatment completion: 33·4% to 100%. Inconsistent measures of uptake and adherence were used; uptake ranged from 8·3% to 92%, and 68·4% to 100% of patients received ≥80% of prescribed doses. Patient reported experiences included trusted and supportive care providers, safe and trusted services, easily accessible care, and positive psychological and behavioural changes. The clinical effectiveness and acceptability reported from the included studies are similar to or better than reported outcomes from systematic reviews of studies in tertiary settings. Studies of the cost-effectiveness of community-based models for treating HCV are needed.

Keywords: Hepatitis C, community-based, treatment, direct acting antivirals, primary health care

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Introduction:

Treatment of HCV improved dramatically when direct acting antivirals (DAAs) were introduced.[1, 2] The previous interferon based regimens were poorly tolerated because of adverse side effects and low treatment success rates were achieved.[3] The DAA based regimens have fewer side effects, shorter treatment duration and higher sustained virological response (SVR).[1, 2] The DAAs provide an opportunity to develop and implement new models for treating HCV and to provide HCV treatment near targeted populations to increase the treatment uptake, compliance and completion rates.[2, 4, 5] The administration of DAAs is less complicated, requiring minimal monitoring and the provision of HCV treatment in community settings is emphasised as an alternative model for HCV treatment.[3, 6, 7] Several community-based models for treating HCV have been implemented and evaluated in different regions to improve the treatment accessibility and outcomes. The community-based models for treating HCV should be clinically effective to improve quality of care and decrease burden of HCV infection.[3, 6, 7] Also, the HCV treatment service needs be acceptable for patients in order to successfully engage and commence treatments. The cost effectiveness of these models is an important area where further research is urgently required, to help policy-makers invest wisely.[7, 8] Currently, there is a lack of knowledge regarding clinical effectiveness, cost effectiveness and acceptability of providing HCV treatment in different community settings.

To develop a better understanding of the outcomes of community-based models of care a range of outcomes and patients' experience should be considered and context of the community-based settings needs to be taken into account in the analyses. The current systematic review is a mixed methods review aimed to develop an aggregated synthesis of quantitative, qualitative and economic evidence to have a better understanding of the clinical effectiveness, acceptability and cost-effectiveness of providing HCV treatment in community settings. The overarching question is: What is the clinical effectiveness, acceptability and cost-effectiveness of community-based models for treating chronic HCV?

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Method:

The protocol for this review is registered on the PROSPERO database (PROSPERO 2017 CRD42017064250) and published.[9]

Inclusion criteria

The review considered all quantitative and economic studies that evaluated community-based models for treating adults who were diagnosed with chronic HCV. The review also included qualitative studies of adult patients' experiences of community-based models for treating chronic HCV. The community services were defined as any medical services which were not provided in hospital or academic tertiary settings. Telehealth services were included. Excluded studies were those that were based on mathematical modelling or reported HCV management in prisons, or were based solely in private gastroenterologist or hepatologist clinics. We have excluded studies that reported HCV treatment in gastroenterologist or hepatologist clinics outside hospital (i.e. specialists who were practicing in their private clinic) as the focus of this study was on community and primary care based models.

Search strategy

Studies published after 2000 (when pegylated interferon was introduced)[10] were considered for inclusion. No language limits were used. The initial search of databases was carried out in September 2016 and updated on 18 September 2017.

Published studies were sought through: CINAHL, Cochrane Library, Embase, MEDLINE (PubMed), ProQuest, Primary Health Care Research and Information Service, PsycINFO, Scopus, Web of Science. Unpublished studies were sought through Canada Theses Portal, Clinicaltrials.gov, Google Grey, Mednar, Open Gray, ProQuest Dissertations and Theses Global, Trove, Websites of relevant organizations included WHO, World Gastroenterology Organization, American Association for the Study of Liver Diseases and European Association for the Study of the Liver. The search strategy in PubMed is provided in appendix A.

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Assessment of methodological quality

Methodological validity of all relevant studies prior to inclusion in the review was assessed using The Joanna Briggs Institute (JBI) Critical Appraisal tools by first author (DP) and was independently reviewed by a second author (LH). Disagreements between the two reviewers were resolved through discussion and referral to the other authors in a group discussion until consensus was reached.

Data extraction

Quantitative outcomes were extracted based on 'intention to treat' when possible. Authors of some included papers were contacted to obtain information that was not reported in the methods and results. Extracted data was independently reviewed by two reviewers (DP and LH), and differences were reviewed and discussed until consensus was reached.

Data synthesis

Quantitative findings were synthesised in narrative form including categorising models based on their similarity of setting, description of each models and reporting measured outcomes to aid in data presentation. Qualitative research findings were synthesised to generate a set of statements using a meta-synthesis method.[11] The findings and their supporting quotes were extracted and organised into tentative categories based on their similarity of meaning. Subsequently, the categories were combined and synthesised.

Results

Search results

Among 8532 identified titles, 42 quantitative and 6 qualitative research studies were included for data extraction. No relevant research articles reporting cost effectiveness of implementing a community-based model were found. Two studies were excluded after reading the full text as they re-reported findings of already included studies (i.e. duplication). [12, 13] (figure 1)

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Methodological quality appraisal

Three quantitative studies were excluded because their methodological quality was assessed as poor.[14-16] Other studies were included for data extraction.

Quantitative studies:

Among 38 cross-sectional studies, inclusion criteria were not clearly defined in only one study.[17] One study failed to describe the study participants and setting in detail,[18] one study did not clearly mention how the exposure (receiving care at the community settings) was measured.[19] The majority of studies failed to address confounders such as patients' socioeconomic characteristics, HIV or HBV co-infections, history of HCV treatment and types of healthcare providers.[17-38] The other criteria (standard criteria for measuring the condition, valid and reliable way for measuring the outcomes and appropriate statistical analysis) were met by all studies. Sixteen studies fulfilled all the eight criteria.[39-54]

There were three cohort studies - in one study there was a subgroup analysis with significant differences in some baseline characteristics between the two groups.[55] In one study it was not clear how the exposure (receiving treatment at community settings) was measured.[56] Strategies to address incomplete follow-up were not applied in two studies,[55, 56] and in one retrospective cohort study, it was not applicable.[57] The other criteria (measuring exposure similarly to assign people to both exposed and unexposed groups, identifying and dealing with confounders, participants being free of outcomes at the start of the studies, measuring outcomes in a valid and reliable way, sufficient follow up time, and appropriate statistical analysis) were met by all studies.

In the only randomised controlled trial (RCT), there were some differences in baseline characteristics between the two groups. Based on the characteristics of the intervention it was not possible for participants and care providers to be blinded. It was not clear if the outcomes assessor was blinded during treatment assignment and analysis. Deviations from the standard RCT design were not accounted in statistical analysis of the trial.[58]

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Qualitative studies:

Among the six qualitative studies none reported the researchers' cultural or theoretical positions.[59-64] In one study the research methodology (qualitative approach for evaluation) and data collection method (telephone structured interview) were incongrous.[61] Three studies also did not address the influence of the researcher on the research and vice-versa,[60, 63, 64] and this issue was also unclear in one another study.[61] The other criteria were met by all studies.

Characteristics of included studies

Data in published articles was collected between November 1998 and February 2017. Fourteen studies were from USA, 13 from Australia, 10 from Canada, six from the UK, two from Switzerland, and three studies were from the Netherlands, France and Pakistan.

Various exclusion and inclusion criteria for treatment were applied in different studies. Six studies excluded treatment-experienced patients.[27, 39, 43, 46, 55, 57] Six studies mentioned HIV co-infected patients were excluded[45, 46, 49, 50, 55, 57] and four studies also excluded hepatitis B virus co-infected patients.[46, 50, 55, 57] In eight studies active drug users were excluded.[20, 22, 23, 26, 27, 44, 46, 57, 58] Fourteen studies excluded patients with severe or uncontrolled mental health problems.[12, 18, 20, 22, 23, 27, 36, 41, 44-46, 48, 50, 57]

Prescribed medicines in the majority of studies were Pegylated-interferon (Peg-IFN) plus ribavirin (RBV). In three studies patients received RBV plus interferon or Peg-IFN[12, 24, 45] and in three others interferon and RBV were prescribed for all patients.[18, 35, 37] In five studies patients received interferon free or Peg-IFN plus RBV with or without DAAs[19, 21, 29, 34, 50] and in four studies all patients were treated with interferon free treatment.[29, 47, 52, 53] Characteristics of included quantitative and qualitative studies are presented in table 1 and 2.

Describing the models of care:

A variety of community-based models for treating HCV were implemented in various settings. The models were organised into five categories based on the similarity of the

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models' settings including: 1) Telehealth models[32, 55-57] based on videoconferencing or teleconferencing among patients, community healthcare providers and a hospital based team. One of these models was a hepatology nurse-led telehealth.[32] 2) Integration of HCV and addiction services where HCV services were added to existing addiction services to make services more accessible for the patients and create more opportunities for engagement with the service's clients.[17-19, 22, 23, 27, 28, 30, 31, 33, 36-39, 41, 43, 45, 46, 48-50, 52, 54, 58-60, 62-64] 3) Integration of HCV and HIV services where HCV services were added to existing HIV programs in a primary care clinic and a multidisciplinary team including an on-site hepatologist provide HCV care.[35] 4) Integration of HCV and primary care models where HCV services was provided in settings where patients received routine primary care,[12, 21, 24, 25, 29, 34, 40, 42, 47, 51, 53, 61] and 5) home care and health care management company models where HCV treatment was provided by a home care nurse in collaboration with a hospital liver clinic or a care management nurse supervised by a multidisciplinary committee in a care management company.[20, 26]

Most of the models were physician-led, but in some of the models, nurse practitioners or nurses were programme coordinators.[17, 19, 27, 32, 46] They also initiated treatment and managed the patients in consultant with hepatologists or gastroenterologists in some models.[26, 28, 38, 46, 47, 55, 56]

Quantitative Synthesis:

Clinical Outcomes of the Models

The included studies measured a wide range of outcomes. We examined outcomes of clinical effectiveness including: rapid virological response (RVR) at week 4 of treatment, early virological response (EVR) at week 12 of treatment, end of treatment response (ETR), SVR, incidence of serious side effects requiring termination of treatment and relapse rate; and acceptability including: uptake, adherence to treatment, and treatment completion (Table 3).

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Clinical effectiveness:

Rapid virological response and early virological response:

In the integrated HCV and addiction services models, in two studies 68%[50] and 62%[43] of patients achieved RVR and in one study EVR of 86% was reported.[43] In one study EVR in the community setting was higher (83·3%) than in the tertiary centre (75%).[58] In the integrated HCV and primary care models in the Baker et al study[40] RVR and EVR were 65·9% and 75·6, respectively, and in another study EVR of 90% in patients with genotype one was reported.[25]

End of treatment response:

In the integrated HCV and addiction services models, ETR ranged from 48·7% in interferon plus RBV based regimen[18] to 89% in interferon free therapy.[52] In integrated HCV and primary care models ETR was 76·7% in a study on interferon based treatment [25] and 96% in a study using a interferon free regimen.[29] In a home HCV care model ETR was 11·3%.[26]

Incidence of serious side effects requiring termination of treatment:

In a nurse-led telehealth model, 10% of patients ceased treatment because of adverse events[32] and in a study comparing two approaches this figure in a telehealth model was significantly lower than a tertiary centre (4·2% vs. 8·9%, P = 0·02).[55] In the integrated HCV and addiction services this figure ranged between 10·5%[18] and 27·8%.[22] In the HIV/HCV integrated model incidence of serious side effects requiring termination of treatment was reported in 23·1% of patients.[35] In the integrated HCV and primary care models in the Ho et al study[25] 6·7% of patients experienced intolerable adverse events, and in the Kattakuzhy et al study[47] where patients were treated with DAAs, treatment was stopped in 3·3% of patients because of adverse events.

Sustained virological response:

In telehealth models, SVR ranged from 55%[57] to 72%[32] and there were no significant differences between telehealth and the tertiary centre. In the integration of HCV and addiction services SVR ranged from 22·3% in Peg-IFN plus RBV based treatment[22] to 80·3% in interferon free therapy.[52] In six studies SVR rate was less than 50%[18, 22, 31, 36-38] - in two of these studies patients received interferon plus RBV[18, 37]. In the Bruce et al study[58] SVR in

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community setting was 50% and in a tertiary centre was 25%. In the models integrating HCV and primary care, SVR ranged from 40% in Peg-IFN plus RBV treatment[51] to 95·5% in a study where most of the patients received interferon free based regimen.[34] In the home care and health care management companies' models, 45%[26] and 27·5%[20] of patients achieved SVR, respectively.

Relapse rate:

In the nurse-led telehealth model the relapse rate was reported in a study as 4%.[32] In the integration of HCV and addiction services in two studies, relapse was 14%[17] and 8·6%.[54] In Lewis et al study[28] 16·7% relapse rate was reported in patients who received treatment from nurse. In the integrated HCV and primary care models the relapse rate was reported as 5·8%,[47] 3%[21] and 2·2%[34] in studies where patients received DAAs based treatment.

Acceptability:

Treatment uptake:

Treatment uptake was measured in different ways in different models. In addition, different inclusion and exclusion criteria applied in different studies and there was a wide range of uptake rates. In integrated HCV and addiction services models uptake rate ranged from 8·3%[48] to 69·7%.[27] In one study providing HCV treatment in an addiction clinic improved the uptake rate significantly in comparison with a traditional hospital-based approach (2% vs. 38%, P< 0·001).[31] In the HCV/HIV integrated model only 10·5% of HCV patients initiated treatment.[35] In the models integrating HCV and primary care, uptake ranged from 19%[51] to 77%.[24] In the home HCV care model 92% of eligible patients initiated treatment.[26]

Adherence to treatment:

Patients' adherence to treatment was measured in different ways in different models. In integrated HCV and addiction services, in three studies 68·4%,[18] 83%[28] and 86%[43] of patients received at least 80% of scheduled doses and 80% of scheduled treatment period. In one study it was reported that all patients took at least 80% of prescribed Peg-IFN and RBV[33] and in another study 87·5% did not have any missed Peg-IFN.[42] In Litwin et al study[50] 74% and 64% of patients took at least 90% of the prescribed RBV and telaprevire/ bocoprevir,

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respectively. In Morris et al study[52] where patients received interferon free treatment 97% of patients took at least 90% of expected doses.

In integrated HCV and primary care model in the Ho et al study,[25] 77% of patients attended at least 80% of recommended visits and 80% took at least 80% of prescribed doses. In studies on interferon free based treatment in one study 41% of patients missed at least one dose[29] and in another study 62·2% of expected visits were attended by patients and 86·6% of expected prescriptions were picked up.[47]

Treatment completion:

The completion rate was 70% in nurse-led telehealth.[32] In one study treatment completion in a telehealth model was significantly higher than a tertiary based model (78% vs. 53%, P = 0·03).[57] In models integrating HCV and addiction services completion rates ranged between 33·4%[22] in Peg-IFN based treatment to 96·1% in an interferon free regimen.[52] Except in two studies which reported the completion rate as 33·4%[22] and 55%,[48] in other studies more than 60% of patients completed the treatment.[17, 18, 23, 27, 33, 37, 38, 41, 46] In the HCV/HIV integrated model this figure was 47·8%.[35] In the integrated HCV and primary care models, completion rate ranged from 60%[51] to 100%.[34] In the home HCV care model 92·5%[26] and in the health care management company model 52·6% of patients completed the treatment.[20]

Qualitative Synthesis

Thirty three findings were extracted and rated based on a JBI level of credibility.[65] Eighty five percent of findings were rated as "unequivocal" (U) and the rest were "equivocal" (E). Based on the similarity in meaning, findings were collated into five categories including trusted and supportive care providers, safe and trusted settings, easy to access care, psychological changes, and behavioural changes (Table 4).

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Category 1: Trusted and supportive care providers

The relationship between community health care providers and patients was a key factor for engaging patients with the services. Being listened to, especially during the initial appointment,[63] access to emotional support and high level of trust in care providers,[61] familiarity with care providers,[60] and being recognised beyond their drug use[63] were mentioned as a catalyst to initiate the treatment. The quality of the therapeutic interaction was important for patients to improve adherence to treatment.[63] Providing convenience, safe, personal[61] and respectful care[64] welcoming and non-judgmental staff,[64] being guided and supported rather than pushed into treatment,[64] and a deep relationship with care providers[60] were characteristics of HCV treatment in the community settings which helped patients feel comfortable. On the other hand some studies reported the negative experience of patients in relationships with OST prescribers in collocated HCV and addiction services can negatively affect patients' perceptions of HCV care providers.[60, 64]

Category 2: Safe and trusted setting:

The community setting was reported by patients as being a safe and trusted setting compared with hospitals.[64] Familiarity and feeling safe in the community settings[60, 62] and seeing other patients in a similar situation[60] increased patients' willingness to initiate their treatment and helped patients to feel comfortable. On the other hand unintended disclosure of HCV because of the design of the OST was seen as a barrier.[64]

Category 3: Easy to access care

Collocation of HCV treatment and drug and alcohol services was mentioned as easy to access care[62, 64] and facilitated initiating and continuing treatment.[64] The availability of all needed services under one roof[62, 64] and reduced travel cost were highlighted by patients.[64]

Category 4: Psychological changes as a result of undertaking HCV treatment

Taking more care about their life, enabling better self-control, developing a sense of hope, and recovery from internalised stigma were mentioned by patients as resulting from undertaking HCV treatment in a community setting.[59]

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Category 5: Behavioural changes as a result of undertaking HCV treatment:

The desire to disclose HCV status, reduction in drug and alcohol use, looking for stable housing, transitioning into a healthier lifestyle, increased sense of responsibility in their lives, and a desire to help others were changes that patients experienced by taking HCV treatment in community-based models.[59]

Synthesised finding: *Community based models of care for HCV treatment allow easy to access care provided in a trusted, safe and supportive environment which can engage patients to treatment and improve their quality of life.*

Discussion

In this review we systematically searched for all published and unpublished papers which reported evaluation results of models for treating HCV in any community setting. A majority of studies used a descriptive cross-sectional design (n= 38) to describe the outcomes of community-based models which showed comparable or better health outcomes for community based in comparison with published tertiary based studies. All three cohort studies compared the outcomes of telehealth with tertiary based treatment and showed the telehealth model is as effective as tertiary based models.[55-57] One randomised controlled trial compared the outcomes of community-based models in a methadone maintenance program with a university based liver speciality clinic where outcomes of community based models were better than the tertiary service.[58] The qualitative studies showed the acceptability of providing HCV treatment in the community settings. Overall, the results of this review suggest that community-based models are acceptable and clinically effective and, where comparisons have been made with tertiary-based models of care, comparable outcomes were found.

Various community-based models of care were developed and implemented based on different settings and target groups. Because HCV is prevalent in people who use drugs, a majority of models were designed and implemented in drug and alcohol services to make services more accessible for the patients and allow for more opportunities to engage with the drug and alcohol services' clients.

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Strengths and limitations of the study

This systematic review is the first mixed method systematic review on HCV treatment in community settings. We included all types of quantitative and qualitative studies and considered all important outcomes of HCV treatment to produce a comprehensive review of the evidence on the provision of HCV treatment in different community settings.

However, our systematic review has some limitations. A majority of included quantitative studies were descriptive studies without comparison groups. Different exclusion and inclusion criteria were used, medicines were prescribed and ways were applied to measure some outcomes such as treatment adherence and uptake across the different studies.

Clinical effectiveness

Rapid virological, early virological and end of treatment responses are comparable for community based and tertiary models. Based on the reviewed studies at least 62% and 75% of patients achieved RVR and EVR, respectively.[25, 40, 43, 50, 58] In a meta-analysis, RVR of about 31% and EVR of about 68% were reported for patients who received Peg-IFN plus RBV.[66] For interferon based treatment, because EVR and RVR are predictors of SVR, care providers would test clients at these intervals to monitor treatment effectiveness and decide whether to continue, change or terminate the treatment regimen.[67] However, in DAA regimens, HCV RNA testing during treatment is not necessary, but is recommended in cases with concern about non-adherence to treatment and patients with decompensated liver disease.[2] Included studies reported ERT of 48·7% in interferon plus RBV based treatment[18] and 96% in interferon free regimen.[29] In a systematic review of RCTs, ETR were 53% and 67% in patients who received interferon plus RBV and Peg-IFN plus RBV, respectively.[68] In another systematic review, ETR was reported as about 77% among patients who receive Peg-IFN plus RBV.[66]

The incidence of serious side effects requiring treatment termination in community-based models is similar to or less than the tertiary based models and varied from 3·3% in interferon free treatment[47] to 27·8% where patients received Peg-IFN plus RBV.[22] In a systematic review of 18 RCTs, discontinuation of treatment because of severe side effects was reported in 17% and 21% of patients who received Peg-IFN plus RBV and interferon plus RBV,

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respectively.[69] A systematic review on 41 studies including RCTs and cohort studies reported a range from 2% to 16% of treatment discontinuation in patients who received Peg-IFN plus RBV and from 9% to 26% and 8% to 25% in patients who received telaprevir or boceprevir plus Peg-IFN plus RBV, respectively.[70]

The SVR from community-based models is compatible with or higher than SVR reported in systematic review on tertiary based treatment. Included studies reported SVR in a range from 22·3%[22] where patients were treated by PEG-IFN plus RBV to 95·5%[34] where the majority of patients received interferon free treatment. Only in six studies SVR rate was less than 50%[18, 22, 31, 36-38] where in two of them patients received interferon plus RBV.[18, 37] In three systematic reviews, 32%, 33% and 38% of patients who received interferon plus RBV achieved SVR.[69, 71, 72] In another systematic review on 18 RCTs, only 50% for patients who received Peg-IFN plus RBV achieved SVR.[69] In a systematic review on studies among people who inject drug (PWID) in Europe median of SVR was 55% ranged from 19% to 88% for PEG-IFN plus RBV regimen.[73] In a systematic review SVR12 among treatment naïve HCV genotype 1 in all DAA regimens without Peg-IFN plus RBV ranged from 93% to 100% and in patients who received Peg-IFN plus RBV was 48%.[74] Two systematic reviews on interferon free treatment reported SVR12 in a range from 80% to 96%.[75, 76]

Relapse rates in community based models are comparable with tertiary based models. Risk of relapse after SVR achievement is reported as a challenge to treatment scale-up. Based on the findings of this review, relapse rates in community settings ranged from 16·7% in a study on Peg-IFN plus RBV based treatment[28] to 2·2 in a study where patients received DAA regimens.[34] In a systematic review on RCTs 4·5% relapse was reported for interferon free therapy.[75] Relapse is more highlighted in HIV infected patients due to their impaired immune system.[77] Among included studies in this systematic review which reported relapse rate, in one study,[28] HIV infection was not mentioned as an exclusion criteria and in another study[34] 24% of the patients were HIV positive.

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There is insufficient knowledge about HCV treatment uptake in community settings. Globally HCV treatment uptake is about 1%.[3, 78] Treatment uptake was measured in different ways in different studies due to varying inclusion and exclusion criteria. The conclusion of the reviewed studies is that treatment uptake was greater in community settings. The qualitative studies revealed that patients are more likely to initiate treatment in the community setting as they experience primary care providers as being friendly and understanding, and that community settings are perceived as familiar, safe, trusted and easy to access.[60-63] It was also mentioned by some patients that they are not comfortable to receive HCV treatment at OST clinics.[60, 64] In a systematic review it was demonstrated that co-location of HCV treatment with mental health and addiction services cannot significantly improve the treatment uptake.[79] Treatment uptake between 0% and 60% (median 30%) was reported among PWID and between 24% and 76% (median 55%) among PWID plus additional criteria e.g. HCV genotype or drug use status.[80] In a review of evidence it was reported that only about 30% to 40% of evaluated patients in referral centres initiated the treatment.[81]

Based on this review providing HCV care in community settings increased adherence to HCV treatment. The included studies used different measures to assess patients' adherence to treatment. Overall adherence to treatment in terms of attending expected visits and receiving prescribed medicines was more than reported figures from tertiary based treatment. In a systematic review on RCTs, 66% of patients remained in the trials for at least 80% of duration and received at least 80% of prescribed medicines.[68] In another systematic review the adherence to treatment among patients who received treatment at tertiary centres was reported from 38% (taking at least 80% of Peg-IFN plus RBV) to 89% (taking at least 80% of RBV).[82] Adherence to treatment is a strong predictor for SVR. SVR among patients who at least took 80% of the prescribed PEG-IFN and RBV for at least 80% of the recommended treatment course was higher than those who did not.[68, 83]

The completion rate in this review was better than reported in systematic review on tertiary based treatment and ranged from 33·4% in Peg-IFN plus RBV based treatment[22] to 100%[34] in interferon free regimen. In five studies the completion rate was less than 60%.[20, 22, 35, 36, 48] Included qualitative studies revealed that in community setting patients are more likely to

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continue the treatment as they feel comfortable[60, 61, 64] and experience positive psychological and behavioural changes.[59] In a systematic review it was shown that co-location of HCV treatment with mental health and addiction services improved treatment completion rate.[79] In a study on national cohort of HCV infected veterans in USA where patients received PEG-IFN (26·9%) or interferon (73·1%) reported only 22·5% of veterans completed a 48 week course of treatment for HCV.[84]

Further research

We could not find any studies of the cost-effectiveness of community-based models. It would be helpful to have a better understanding of the cost-effectiveness of these models for treating HCV. There is also a lack of knowledge regarding the effects of community-based models on re-infection rates. We only found one study from low and middle income countries. More research in these countries is urgently needed to support equitable HCV treatment access and global HCV elimination goals. Strategies such as international collaboration may be helpful for facilitating this research.[21] The organisational and operational elements of successful community-based models, and barriers and enablers to obtaining HCV treatment in community settings, need to be understood, especially in the context of DAA regimens.

The application of this review in the era of DAA regimens

This review provides lessons for developing clinically effective and acceptable community-based models for treating HCV, using efficacious DAAs in routine practice. In terms of clinical effectiveness, all community-based models included in this review provided supports for health care practitioners, such as specialist mentoring and training. These supports may have enabled practitioners to achieve clinical outcomes similar to or better than tertiary based models. Although the efficacy and safety of DAAs, compared with the interferon-based therapies, has removed major treatment-related barriers, primary health care practitioners require training and support to provide HCV care as part of routine practice, so that the opportunities to increase uptake in community settings can be maximised.

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To reach the HCV elimination target for treatment uptake of 80% in 2030, the characteristics of HCV patients need to be understood to ensure the DAA regimens are easily accessible. Based on this review, community-based models implemented in various settings appeared to make treatment easy to access for different groups of patients. However, although we found that providing HCV treatment in community settings increased treatment uptake, there is still some uncertainty regarding the level of uptake achieved, and the contribution of service accessibility on the willingness of patients to initiate treatment. In the DAA era, various models are needed to facilitate access to treatment for different population groups. This is especially important in 'hard to reach' groups such as PWID. Further, data on the geographical distribution of HCV infection should be developed to plan for locally accessible services.

Acceptability of treatment is another factor that needs to be considered. Apart from the efficacy of HCV therapies, many factors related to service provision, including the appropriateness of the clinic environment and support for patients, are likely to influence rates of uptake and cure. This review demonstrates that communication between care providers and patients in a safe and trusted environment are the key factors to making the HCV treatment service acceptable. In studies of both the interferon-based and DAA regimens, various initiatives were implemented to support patients during treatment to increase treatment adherence and completion rates. In routine practice, HCV care providers need to be trained and supported to understand HCV patients' expectations. Also, patients' characteristics need to be assessed and where needed psychological and social supports should be provided to improve patients' engagement with the service. A model involving a 'one-stop shop', wherein a multidisciplinary service was provided to respond holistically to patient's health needs, was highlighted in this review as a factor that increased patient's willingness to initiate treatment. The co-location or linking of HCV treatment with related services, such as harm reduction and drug and alcohol services, also should be considered.

Only one study was from low- and middle-income countries. A likely issue in low and middle income countries relates to the limited available research. There may some types of community-based models implemented but they are not evaluated, reported or published. It is important to consider the health service infrastructure and availability of DAAs in these

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countries. In many low and middle-income courtiers there is more of a focus on increasing the HCV diagnosis rate and addressing medicine affordability.[85] Consequently, the development of models for provision of community-based treatment may be less of a priority. It is important that both HCV testing and DAA treatment are affordable and available. In low and middle income countries opportunities for implementing various community-based models need to be assessed and appropriate approach taken to provide accessible, affordable, effective and acceptable HCV treatment.

Conclusion

The community-based models for treating hepatitis C viral infection that were included in this systematic review have shown impressive outcomes. Although a majority of the included studies examined the provision of interferon-based therapies, which were more complicated than the recent DAA therapies, the outcomes reported by the listed studies are similar to or better than outcomes reported in published systematic reviews on studies from tertiary settings. Treatment clearly needs to be provided in community settings so that HCV cures rates can be increased and global elimination goals met. Support for health care providers and patients is critical and should be carefully considered in developing community-based models. Overall, this mixed methods systematic review demonstrates that the provision of hepatitis C viral treatment in community settings is clinically effective, can increase treatment uptake, adherence and completion rates, and is favourably received by patients.

Contributors

DP, LH were involved in study design, data collection, data analysis and manuscript writing. JH, AS, TR, and GF were involved in data analysis and manuscript writing.

Ethics approval

Not applicable.

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Declaration of interests

We declare no competing interests.

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Figure 1: PRISMA flow diagram of search and study selection process

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Table 1: Characteristics of included quantitative studies

Study	Study design	Date of data collection	Country	Sample size	Setting	Medicine	Outcomes	HIV and HBV Co-infections
Alavi et al[39]	Cross sectional	February 2009-December 2012	Australia	387	Opioid substitution treatment clinics, community health clinics, aboriginal community controlled health organisation	PEG-IFN α 2a/2b + RBV	Uptake: 22%	Not mentioned as an exclusion criterion but data was not reported
Arora et al[55]	Cohort	September 2004-December 2009	USA	407 (261 in ECHO vs. 146 in University of New Mexico (UNM) clinics)	Primary care clinics vs. UNM clinic-based	PEG-IFN + RBV	UNM vs. Echo SVR: 57·5% vs. 58·2% (non-significant). Serious adverse events requiring termination of treatment 8·9% vs. 4·2% (P = 0·05).	excluded
Baker et al[40]	Cross sectional	November 2010-June 2012, follow up March 2013	Australia	41	Primary care clinics	PEG-IFN α-2a/2b+ RBV	Completion: 83%, RVR: 65·9%, EVR: 75·6%, ETR: 78%, SVR: 71%, hospitalization: 12%	HIV^+: 4·9%
Beste et al[56]	Cohort	April 2011- June 2015	USA	6947 initiated treatment (total regimens= 7785)	Primary care clinics	Unclear	non-ECHO vs. VA-ECHO SVR: 53·9% vs. 58·2% (p= 0·32)	HIV^+: 1·8% of exposed, 2·3% of unexposed
Bruce et al[58]	randomized controlled trials	2007-2010	USA	Methadone maintenance program (n= 12) vs. university liver specialty clinic (n= 9)	Community-based methadone maintenance program vs. university based liver speciality clinic	PEG-IFN α-2a + RBV	Methadone maintenance program vs. university liver specialty clinic EVR: 83·3% vs, 75%, SVR: 50% vs, 25%.	HIV^+: 25% Methadone maintenance program vs. 33% university liver specialty clinic
Burunner et al[41]	Cross sectional	2002-2010	Switzerland	66	Opioid maintenance treatment	PEG-IFN α 2a/2b + RBV	Completion: 68·2%, SVR: 62%	HIV^+: 11%
Calvert et al[20]	Cross sectional	January 2000-December 2002	USA	40 eligible for treatment	Health maintenance organization health care management company	PEG-IFN + RBV	Completion: 52·6%, SVR: 27·5%	Not mentioned as an exclusion criterion but data was not reported
Capileno et al[21]	Cross sectional	February to December 2015	Pakistan	169 initiated treatment	Community-based primary care clinic	Sofosbuvir + Ribavirin and for G1 + Peg-IFN	SVR 12: 83·4%, Relapse: 3%	Was not an exclusion criterion but data were not reported

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Charlebois et al[42]	Cross sectional	March 2007- July 2010	Canada	110 CHCV^{+}, 24 initiated treatment	Community health centres	PEG-IFN + RBV	(Before vs. After new model) Assessed by specialist: 18·6% vs. 58·9%, adherence (only after): 87·5%, 3 patients had missed PEG-IFN, SVR (only after): 70·8%	HIV^{+}: 6·1%, HBV^{+}: 0·9%
Grebely et al[23]	Cross sectional	January 2002- march 2005	Canada	40 initiated	Community health centre	PEG-IFN α 2a/2b + RBV	Completion: 62%, SVR: 55%, ETR: 70%, Treatment limiting adverse events: 12·5%	HIV^{+}: 7·5%
Grebely et al[22]	Cross sectional	March 2005- over a period of 80 weeks	Canada	80 referred, 18 initiated treatment at the study site	Community health centre	PEG-IFN α 2a/2b + RBV	Uptake: 26·2%, adherence: 57·8%, completion: 33·4%, ETR: 67%, treatment limiting adverse events: 27·8%, SVR: 22·3%	HIV^{+}: 22%
Grebely et al[44]	Cross sectional	March 2005- March 2008	Canada	109 assessed, 57 initiated treatment, outcome data of 19 patients	Community health centre	PEG-IFN α 2a/2b + RBV	Uptake: 60%, SVR: 63%	HIV^{+}: 11%
Grebely et al [43]	Cross sectional	February 2009- December 2012, follow-up: June 2014	Australia	101	Opioid substitution treatment clinics, community health clinics, aboriginal community controlled health organisation	PEG-IFN α 2a or PEG-IFN α 2b + RBV	Adherence (80% of scheduled doses and 80% of scheduled treatment period): 86%, RVR: 62%, EVR: 86%, ETR: 76%, SVR: 74%	HBV^{+}:3%, HIV^{+} persons were not excluded but data were not reported
Hampton et al[17]	Cross sectional	Pilot 2008-2009 and main study 2009-2011	UK	Pilot =10, Main study = 33	Community drug and alcohol service	PEG-IFN + RBV	Completion: 95·3%, SVR: 72·1%, relapse: 14%	Not mentioned as an exclusion criterion but data was not reported
Hill et al[24]	Cross sectional	September 2001- December 2005	Canada	471 eligible, 363 initiated treatment	Rural and small town health centres	IFN + RBV Or PEG-IFN + RBV	Uptake: 77%, SVR: 61%	Not mentioned as an exclusion criterion but data was not reported
Ho et al[25]	Cross sectional	Not mentioned	USA	30 initiated treatment	Community-based clinic	PEG-IFN α 2 + RBV	Adherence to medical plan (attending > 80% of recommended visits): 77%, Adherence to medicine (taking ≥ 80% of prescribed doses): 80%, Completion: 80%, intolerable adverse events: 6·7%, EVR (only for G1): 90%, ETR: 76·7%, SVR: 63·3%	Not mentioned as an exclusion criterion but data was not reported

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Jack et al[27]	Cross sectional	February 2005-January 2008	UK	43 eligible for treatment, 30 initiated treatment	General practitioner clinics	PEG-IFN α 2a/2b + RBV	Uptake: 69·7%, Completion: 81%, SVR: 81%	Not mentioned as an exclusion criterion but data was not reported
Jack et al[26]	Cross sectional	February 2004-January 2012	UK	88 referred for treatment, 81 initiated (87 episode)	Home care	PEG-IFN α 2a/PEG-IFN α 2a/2b + RBV	Uptake: 92%, Completion: 92·5%, ETR: 11·3%, SVR: 45%	Among 88: HIV^+: 5, HBV infected patients were excluded from analysis for this paper
Jeffrey et al[45]	Cross sectional	October 2002-March 2005	Australia	50 initiated treatment	Community clinic	IFN α 2b + RBV Or PEG-IFN α 2b + RBV	ETR: 66%, SVR: 62%	HIV^+ excluded
John-Baptiste et al[46]	Cross sectional	November 2002-January 2006	Canada	109	Addiction treatment centres	PEG-IFN α 2a/2b + RBV	Completion: 65%, SVR: 56%	Excluded
Kattakuzhy et al[47]	Cross sectional	20 Jan 2015-24 Nov 2015	USA	600	Community base clinics	ledipasvir (LDV) and sofosbuvir (SOF)	Adherence to all treatment visits: 62·2%, adherence to prescriptions: 86·6%, SVR: 86, Relapse: 5·8%, Treatment limiting adverse events: 3·33%	HIV: 23%, HBV included but data was not reported
Keats et al[48]	Cross sectional	February 2009-June 2014	Australia	242 attended an assessment by HCV clinician, 20 initiated treatment	Opioid substitution treatment clinic	PEG-IFN + RBV	Uptake: 8·3%, Completion: 55%, SVR: 75%, Treatment limiting adverse events: 20%	Not mentioned as an exclusion criterion but data was not reported
Lewis et al[28]	randomized controlled trials (both community based then we considered it as a cross-sectional)	September 2011-July 2012	UK	76 standard care (specialist) (control) and 62 nurse-led	Specialist addiction units at community and community outreach clinics	PEG-IFN α 2a + RBV	(specialist and nurse-led) Uptake: 9% and 10% (P = 0·53), Adherence (receiving ≥80% of interferon and ribavirin doses for ≥80% of the expected duration of therapy): 83% and 83%, ETR: 83% and 83%, SVR: 50% and 66·7% (no difference), relapse: 0 and 16·7	Not mentioned as an exclusion criterion but data was not reported

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Lindenburg et al[49]	Cross sectional	January 2005-September 2010	Netherland	58 initiated treatment	Community health centres	PEG-IFN α 2a/2b + RBV	Uptake: 76%, ETR: 82·8%, Relapse: 20·8%, SVR: 65%, Adherence to medical plane: 95% attended the scheduled plan	HIV^+ excluded
Litwin et al[50]	Cross sectional	January 2011-April 2013	USA	50	Methadone maintenance treatment clinics	Telaprevir or boceprevir + PEG-IFN α 2a + RBV	RVR: 68%, EVR: 60%, ETR: 70%, SVR: 62%, Adherence (≥ 90) to ribavirin: 74%, to telaprevire/ bocoprevir: 64%	Exclude
Mason et al[51]	Cross sectional	January 2011-2012	Canada	78 patients, 15 initiated treatment	Community-based primary care centres	Not reported	(Baseline vs. 1 year after new model) HCV specialist access: 15% vs. 54% (P= 0·002), Uptake: 4% vs. 19%, completion: 60%, SVR: 40%	Not mentioned as an exclusion criterion but data was not reported
Mason et al[29]	Cross sectional	2015	Canada	74 initiated, 69 due to SVR at the study time	Community-based primary care centres	DAAs or sofosbuvir and ribavirin	Completion:97%, ETR: 96%, SVR: 87%, 41% of participants had at least one missed dose	Not excluded but data was not reported
Milne et al[30]	Cross sectional	2004-2014	Canada	131 initiated treatment	Community health centre	PEG-IFN α 2a + RBV	SVR: 77%	HIV^+ between 2012-2014: 23·9%
Morris et al[52]	Cross sectional	March 2016-February 2017	Australia	127	Community based alcohol and drug health services	DAAs with and without ribavirin	Completion: 96·1%, SVR: 80·3%, ETR: 89%, Adherence (defined as taking at least 90% of doses): 97%	Not excluded but data was not reported
Moussalli et al[31]	Cross sectional	January 2002-December 2004	France	337, 85 initiated treatment	Addiction centre vs. hospital	Not mentioned	Uptake: 2% in hospital, 38% in addiction centre (P < 0·001), SVR: 44%	Not mentioned as an exclusion criterion but data was not reported
Nazareth et al[32]	Cross sectional	August 2006-2010	Australia	Telehealth (TH) 53 referred 50 initiated treatment (3 ineligibles), face-to-face (FTF) 559	Telehealth clinics vs. face-to-face hospital clinic	PEG-IFN + RBV	TH: Completion: 70%, Adverse effects: 10%, SVR: 72%, Relapse: 4% FTF: SVR: 55·6%	Not mentioned as an exclusion criterion but data was not reported
Newman et al[33]	Cross sectional	June 2006-Decemper 2008	Canada	34, 14 initiated treatment	Community health centre providing addiction services	PEG-IFN α 2a or PEG-IFN α 2a + RBV	Uptake: 41%, Completion: 71·4%, Adherence (≥ 80% prescribed dose): 100%, ETR: 78·6%, SVR: 57%	Not mentioned as an exclusion criterion but data was not reported

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Norton et al[34]	Cross-sectional	Jan 2015- Aug 2015	USA	89 initiated	Community-based primary care clinic	DAAs or Sofosbuvir and ribavirin or Sofosbuvir, peglyated-interferon and ribavirin,	Completion: 100%, Relapse: 2·2%, SVR: 95·5%	HIV^+: 24%
Read et al[53]	Cross-sectional	2015-2016	Australia	72 initiated treatment	Community-based primary health care facility	DAAs ± ribavirin	Completion: 96%, SVR: 82%	HIV^+: 11%, HBV^+: 0
Rossaro et al[57]	Cohort	2006-2010 (months are not mentioned)	USA	40= Telemedicine (TM), 40= hepatology clinic (HC)	Telemedicine vs. hepatology clinic	PEG-IFN + RBV	(HC vs. TM) Completion: 53% vs. 78% (P= 0·03), SVR: 43% vs. 55% (P= 0·36)	Excluded
Seidenberg et al[54]	Cross sectional	January 2002-May 2008	Switzerland	85, 35 initiated treatment	Office based opioid maintenance treatment	PEG-IFN α 2a + RBV	Uptake: 41·2%, ETR: 80%, SVR: 71·4%, relapse: 8·6%	HIV^+ : 14·7% in 1 patient data was missed
Stringari-Murray et al[35]	Cross sectional	November 1998-December 2002	USA	248, 26 initiated treatment	HIV/AIDS Specialty clinic in the community	IFN+ RBV	Uptake: 10·5%, Completion: 47·8%, Treatment stopping adverse events: 23·1%	Not mentioned as an exclusion criterion but data was not reported
Sylvestre et al[37]	Cross sectional	Not reported	USA	71	Community-based clinic	IFN α 2a + RBV	Adherence (took >80% of prescribed interferon and >80% of prescribed ribavirin for at least 80% of the recommended treatment course): 68%, completion: 76%, SVR: 29·6%, Intolerable side effects: 11·3%	HIV^+:1·4%
Sylvestre et al[18]	Cross sectional	Not reported	USA	76	Community-based clinics	IFN α 2a + RBV	Adherence (>80% of prescribed interferon and >80% of prescribed ribavirin for at least 80% of the recommended treatment course): 68·4%, Completion: 76·3%, ETR: 48·7%, SVR: 27·6%, Intolerable systemic side effect: 10·5%	HIV^+: 1·3%
Sylvestre[36]	Cross sectional	Not reported	USA	28	Community-based clinics	PEG-IFN α 2a + RBV	(One patient ongoing treatment) Completion: 92·5%, ETR: 78%, SVR: 44·4%	Not mentioned as a exclusion criteria but data was not reported

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Wade et al[19]	Cross sectional	April 2011-August 2014	Australia	279, 55 initiated treatment	Outreach clinics	PEG-IFN + RVB, or PEG-IFN +RBV+ DAAs	Uptake: 20%, SVR: 61%	HIV^+: 1·8%, HBV^+: 5·5%
Wilkinson et al[38]	Cross sectional	2005-2007	UK	441, 63 initiated treatment	Outreach clinic in the central specialist addiction unite	PEG-IFN α 2a	Uptake: 14·3%, completion: 92·1%, adherence (taking >80% of the prescribed drugs for 80% of the time): 81%, SVR: 43%	HIV^+: 0, HBV^+: 0

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Table 2: Characteristics of included qualitative studies

Study	Date of data collection	Methodology, method, data analysis method	Participant	Setting and geographical location	Medicine
Batchelder et al[59]	June 2011 to March 2013	Not mentioned, Interview, thematic analysis	31, of whom 26 completed treatment, 5 discontinued	Methadone maintenance clinic, USA	Only mentioned interferon-based treatment
Harris et al[60]	June 2011- January 2012	Qualitative case study, in-depth interview facilitated by a topic guide, thematic analysis	35 PWID of whom 12 completed treatment (9 successful), 6 in midst of treatment, 13 waiting for or contemplating treatment, and for 4 treatment were interrupted	Drug and alcohol service, UK	Not reported
Hopwood and Treloar[61]	September 2010 to	Qualitative program evaluation, two brief structured telephone interview 9 open-ended questions, Descriptive content analysis	8 male patients with G2 and G3 completed treatment	General practice, Australia	Not reported
Norman et al[62]	September 2006	Qualitative program evaluation, Semi-structured interview (group interview), thematic analysis	9 clients of healthy liver clinic. Five undergoing HCV treatment and four who were eligible and waiting to commence HCV treatment	Community drug and alcohol clinic, Australia	Peg-IFN and RBV
Rance and Treloar[63]	Between 2009 and 2012	Qualitative program evaluation, semi-structured interview, thematic analysis	57 clients (17 no assessment, 21 initial assessment, 19 awaiting or initiated treatment)	Opioid substitution therapy clinics, Australia	Not reported but based on ETHOS model Peg-IFN α 2a,/PEG-IFN α 2b + RBV
Treloar et al[64]	Between 2009 and 2012	Program evaluation, semi-structured interview, thematic analysis	57 clients (17 no assessment, 21 initial assessment, 19 awaiting or initiated treatment)	Opioid substitution therapy clinics, Australia	Not reported but based on ETHOS model Peg-IFN α 2a,/PEG-IFN α 2b + RBV

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Table 3: Outcomes of the different community-based models for treating HCV

Type of model	Locations	Clinical effectiveness					Acceptability		
		RVR and EVR	ETR	Serious side effects	SVR	Relapse rate	Treatment uptake	Adherence to treatment	Completion
Telehealth	USA[55-57] Australia[32]	-	-	4·2%[55] and 10%[32]	Ranged from 55% to 72%	4%[32]	-	-	78%[57] and 70%[32]
Integration of HCV and addiction services	Australia[19, 39, 43, 45, 48, 52] Canada[22, 23, 30, 33, 44, 46] USA[18, 36, 37, 50, 58] UK[17, 27, 28, 38] Switzerland[41, 54] France[31] Nederland[49]	RVR: 68%[50] and 62% [43] EVR: 86%[49] and 83·3%[64]	Ranged from 48·7% to 89%	Ranged from 11% to 27·8%	Ranged from 22·3% to 80·3%	8·6%,[60] 14%[23] and 16·7%[28]	Ranged from 8·3% to 69·7%	Ranged from 68·4% to 100% of patients who received ≥80% of prescribed doses.	Ranged from 33·4% to 96·1%
HIV/HCV integration model	USA[35]	-	-	23·1%[35]	-	-	10·5%[35]	-	47·8%[35]
Integration of HCV and primary care models	Canada[24, 29, 42, 51] USA[25, 34, 47] Australia[40, 53] Pakistan[21]	RVR: 65·9%[40] EVR: 75·6, [40] 90%[25]	76·7[25] and 96%[29]	3·3%[47] and 6·7%[30]	Ranged from 40% to 95·5%	2·2%,[34] 3%[21] and 5·8%[47]	Ranged from 19% to 77%	≥80% of patients received ≥80% of prescribed doses.	Ranged from 60% to 100%
Home care and health care management companies	UK[26] USA[20]	-	11·3[26]	-	27·5%[20] and 45%[26]	-	92%[26]	-	92·5%[26] and 52·6%[20]

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Table 4: Results of meta-synthesis of qualitative research findings under synthesised findings 2

Findings	Supporting quotes	Categories	Synthesised finding
Being listened to (U)	"The doctor that's runnin' the show . . . he treats me like a friend,. . .. . . 'Cause some people need to be listened to ... and he just listened" [63] *p.456.*	Trusted and supportive care providers	*Community based model of care for HCV treatment is an easy to access care in a trusted, safe and supportive environment which can engage patients to treatment and improve their quality of life.*
Access to emotional support, and high levels of trust in GPs (U)	"… the reason I took it up was … purely because my GP sort of assured me that, "If anything goes wrong, we're there for you all the time." So … I felt more comfortable" [61] *p.901.*		
Familiarity with individual service providers aids engagement, (U)	"I wouldn't have gone to that [service] if it hadn't been for her [BBV nurse]" [60] *p.22.*		
Experience of being recognized beyond the immediate and instrumental needs of their daily dose (U)	"It was nice to know that somebody actually looked out for Tracy, not just 'Methadone Tracy' . . . I had other issues. And it [HCV] was something I didn't wanna address. And she [the ETHOS clinician] helped me address it" [63] *p.456.*		
The quality of the therapeutic interaction was equally noteworthy, if somewhat more clinically orientated (E)	"… she [the ETHOS nurse] helps me, tells me nothing but the truth about it [HCV] and I do everything she says . .. . Explained it to me properly why I should take it [HCV medication], … Why I should keep taking it. Nobody in the gaol told me that" [63] *p.456.*		
convenience, safety and personal care provided by their GPs and practice nurses (U)	"… [My GP] has people to do the blood tests. … . And, since you've known them for a while, you do feel comfortable" [61] *p.902.*		
Respectful treatment (U)	"Whereas you think you're more likely to be treated respectfully in a context like [the OST clinic] … 'cause we see 'em each day and they get to know you. … yeah, they treat you normal." [64] *p.531.*		
Welcoming and non-judgmental attitude of HCV staff (U)	"… You can talk to 'em a lot better. They don't look down on you. … They explain every- thing..." [64] *p.531.*		
Feeling guided and supported rather than rushed or pushed into treatment (U)	"...they don't push it on people. … So it's the person's choice, … And if they don't want to be involved with it, they don't have to" [64] *p.531.*		
develop long-standing relationships with particular 'keyworkers' (U)	"was like a big brother _ we were close" [60] *p.22.*		
The co-location of HCV and OST services raised concerns around confidentiality and the risk of losing access to OST (E)	"… people who "aren't connected to the OST clinic" should run HCV treatment in OST, fearing that "personal grudges" of OST staff could result in clients not receiving their "dose"" [64] *p.532.*		
Co-location of HCV care providers with OST prescribers could pose a symbolic barrier to trust for service users (E)	It's just sit there and keep your head down and shut up because they're writing your scripts. … the person who writes the script, they hold the power; you're not going do anything to piss them off. [60] *p.24.*		
Feeling safe place (U)	"We come here [OST] anyway. We feel safe coming here …" [64] *p.531.*	Safe and trusted setting	
Feeling at ease and comfortable at the clinic (E)	"I don't worry when I'm here" [62] *p.3.*		
Familiarity of the setting (U)	Because you're more familiar with the place … So you're more likely to talk about it. [60] *p.22.*		
Inevitable, if unintended, disclosure of HCV status because of physical layout of	".. the only thing that I could think of is their privacy. Like they'd be too ashamed. … 'Cause it's not a very big		

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OST clinic (U)	clinic..." *p.532.*[64]		
Integrated HCV treatment within a specialist alcohol and drug treatment centre was viewed as easy to access (E)	"making it easier" *p.3.* [62]	Easy to access care	
The continual reminders about HCV in collocated services (U)	"… when you come to the methadone service it's bang in your face. … . Do it while you're here" *p.531.*[64]		
Immediacy of access to care facilitate initiation the treatment (U)	"… I wouldn't have been able to do this if it wasn't accessible through this clinic here and now. …" *p.531.*[64]		
Colocation facilitate continuing the treatment process (U)	"… they've only just gotta walk upstairs and, or ask somebody in the clinic, ... I think havin' all places in the one place make it a lot easier." *p.530.*[64]		
Having multiple needs met at the one place (U)	"...my needs are met in a whole lot of different ways, from personal to support, to my addiction to ramifications from the addiction …" *p.3.*[62]		
Integrated model reduce travel costs (U)	"Well obvious reasons: transport. … it's public transport and going to the one venue for all your appointments is excellent. …" *p.530.*[64]		
Valuing or caring more after undergoing HCV treatment (U)	"At first I didn't want to take care of myself. … . Today, I care how I look, how I dress, what people think of me, how they see the way I've changed," *p.68.*[59]	Psychological changes as a result of undertaking HCV treatment	
Change in ability to regulate emotions and be present for themselves (U)	"Before I used to just get pissed off and give up. I haven't given up on myself since [treatment]," *p.68.*[59]		
A new sense of hope after learning HCV viral load was undetectable (U)	"I'm feeling good because now I got hope for [a] long life, I'm feeling good because I am undetectable. … ." *p.68.*[59]		
Recovery from internalized stigma and shame (U)	"Everything I did during my addiction—I am not ashamed of it because I'm doing something to change," [59] *p.68.*		
Change in HCV disclosure (U)	"I'm on Hep C medication and …. I changed completely and I was okay with telling anybody who wanted to hear about the medication so they could get motivated," *p.68.*[59]	Behavioural changes as a result of undertaking HCV treatment	
Reductions in substance use behaviours. (U)	"… I stopped drug use. I stopped everything because I said if I beat the Hep C, I could beat that too…," *p.68.*[59]		
Sobriety and progression toward stable housing (U)	"I noticed that I wanted to be sober. That getting high was no more fun—a waste of time, waste of money. …. right now we are in transition for housing, …," *p.69.*[59]		
Transitioning into a healthier lifestyle (U)	"… I take care of myself, from my weight to my diet-everything. I'm real conscious of that," *p.69.*[59]		
Increased sense of responsibility in their lives (U)	"… when I started [HCV treatment], I guess I started being responsible. … making responsible decisions about my life. …" *p.69.*[59]		
HCV treatment and broader life transformation (U)	"… saving my life,… So, coming into the hepatitis treatment really was a big turnaround," *p.69.*[59]		
Desire to help others with HCV (U)	"After the treatment, … What can I do to wake them up and let them know … ," *p.69.*[59]		

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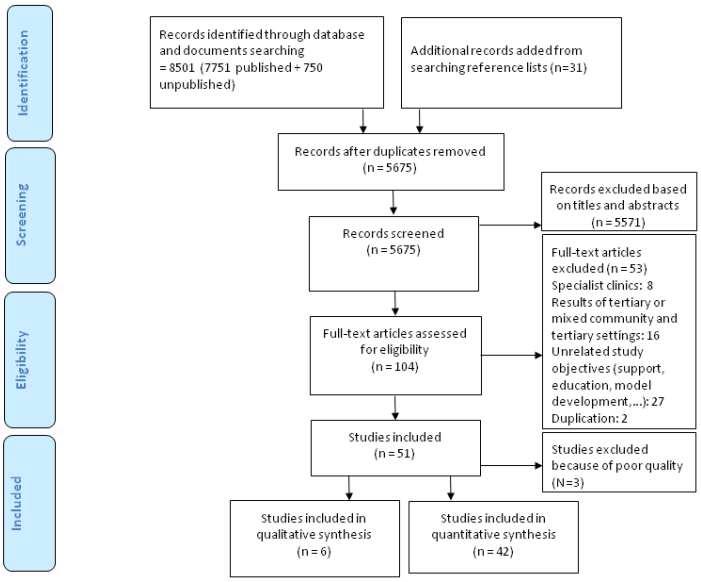

Figure 1: **PRISMA flow diagram of search and study selection process**

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