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Integrated models of care for people who inject drugs and live with hepatitis C virus: A systematic review

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ABSTRACT

Background: Despite the key role that people who inject drugs (PWID) play in the hepatitis C virus (HCV) epidemic, HCV treatment rates among this population have been historically low. Integrated models of HCV and substance use care have the potential to overcome some barriers to access; however, the evidence base is uncertain. This systematic review assesses the impacts of integrated HCV and substance use services on engagement in HCV care among PWID.

Methods: We searched five databases up to December 2018 to identify original quantitative studies evaluating the impacts of co-location of HCV and substance use services on engagement in the HCV cascade of care among adult PWID. We conducted a narrative synthesis, categorizing models based on patient entry point (a: HCV facility, b: substance use disorder (SUD) facility, and c: other facilities), and levels of integrated services offered (a: HCV/substance use testing only, b: HCV/substance use treatment, and c: testing/treatment + other services).

Results: A total of 46 articles corresponding to 44 original studies were included. Almost all studies (n = 42) were conducted in high-income countries and only six studies in the Direct-Acting Antiviral (DAA) era. Twenty-six studies discussed the integration of services at SUD facilities, one at HCV facilities, and seventeen at other facilities. Analysis of included studies indicated that overall integrated care resulted in improved engagement in HCV care (e.g., testing, treatment uptake and cure). However, the quality of evidence was predominantly low to moderate.

Conclusions: Available evidence suggests that integration of HCV and substance use services may improve engagement along the continuum of HCV care among PWID. Given limitations in data quality, and very few studies conducted in the DAA era and in low- and middle-income settings, further research is urgently needed to inform strategies to optimize HCV care access and outcomes among PWID globally.

Introduction

People who use drugs, and in particular those who inject drugs are a key population within the hepatitis C (HCV) epidemic (Grebely et al., 2018; Scheinmann et al., 2007). Indeed, in most middle- and high-income countries, injection drug use is the primary route of HCV transmission, contributing to high HCV incidence and prevalence rates among people who inject drugs (PWID). Globally, it is estimated that the chronic HCV prevalence among PWID is 40% (approximately 6 million PWID), and that injection drug use accounts for 23% of new HCV infections (Degenhardt et al., 2016; Grebely et al., 2018). PWID are not only at greater risk of infection and re-infection, but also at increased risk of disease progression, mortality, and onward HCV transmission (Degenhardt et al., 2016; Simmons, Saleem, Hill, Riley, & Cooke, 2016; Suryaprasad et al., 2014).

Fortunately, the increasing availability of highly efficacious, tolerable and shorter Interferon-free Direct Acting Antiviral (DAA)-based therapies has resulted in HCV cure (i.e., sustained virologic response

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[SVR]) rates of over 95% in most scenarios (Webster, Klenerman, & Dusheiko, 2015). Achieving a SVR not only reduces HCV-related morbidity, mortality, and health care costs (Hill, Saleem, Heath, & Simmons, 2014), but also has a potentially secondary benefit by virtually eliminating the risk of onward transmission (Grebely, Matthews, Lloyd, & Dore, 2013; Martin et al., 2013).

Despite comparable treatment outcomes to non-PWID populations when appropriately supported (Aspinall et al., 2013; Dimova et al., 2013), access to HCV care and treatment for PWID has been historically low, with studies indicating that less than 6% of HCV-positive PWID have ever been treated for HCV (Grebely et al., 2011; Iversen et al., 2014; Mehta et al., 2008). While factors underlying these figures are multifactorial, a major barrier is the poor fit between treatment settings and multiple care needs of this marginalized population (Bruggmann & Litwin, 2013). Accordingly, there has been growing interest in the potential role of low-threshold, one-stop shop models providing multidisciplinary care for PWID (Bruggmann & Litwin, 2013). While integration of care of related diseases is intuitively appealing, and has shown to be effective in improving access to and quality care in other chronic conditions, the impact of integrated substance use and HCV services for PWID on HCV outcomes has not been comprehensively assessed (Atun, de Jongh, Secci, Ohiri, & Adeyi, 2010; Mounier-Jack, Mayhew, & Mays, 2017). Therefore, the aim of the present review was to comprehensively assess the literature to evaluate the impacts of integrated substance use and HCV services on engagement in the HCV cascade of care (from testing to SVR) among PWID.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & Group, 2009) to conduct and report this systematic review (please see Supplementary Table 1 for the PRISMA checklist). Inclusion criteria and analysis plan were specified a priori and are documented in a PROSPERO protocol (CRD42017078445), as well as a peer-reviewed publication (Ti, Parent, & Socias, 2018).

Eligibility criteria

The population, interventions, comparators, outcomes and study designs (PICOs) considered for this systematic review are presented in Table 1.

Search strategy

The search strategy was developed in consultation with an experienced medical librarian at the University of British Columbia, and is presented in Supplementary Table 2. We searched MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science from January 1, 1980 to December 31, 2018, for empirical quantitative studies using relevant subject heading terms or key words for three key concepts (i.e., HCV, illicit drug use, integrated health services) combined with appropriate Boolean operators. Additionally, we searched the grey literature (i.e., grey literature databases, dissertations, reports, and clinical trials registries (http://www.clinicaltrials.gov), and hand searched references of included studies and reviews for other relevant citations. Searches were restricted to studies published in English, French or Spanish.

Study selection and data extraction

After removing duplicates, two reviewers (S.P. and J.B.) independently screened and assessed the citations for inclusion in two separate phases (i.e., titles and abstracts, and full-text screening). At each phase, studies not meeting our eligibility criteria were excluded from further assessment, and reasons for exclusion were recorded. Disagreements were resolved by consensus and discussion at team meetings. Data were also extracted by two independent reviewers using a standard data extraction sheet, collecting information on study characteristics (e.g., study design and location), participant characteristics (e.g., target population, age, HIV status, substance use characteristics), integrated services provided (e.g., point of entry, services offered), and outcomes (e.g., main study findings).

Data synthesis

Given the significant conceptual heterogeneity among the studies due to their various study designs, populations, interventions, and outcomes, we did not conduct a meta-analysis. We synthesized the evidence in a narrative fashion and summarized the study characteristics and their findings using structured tables. Findings were categorized based on three levels of patient entry point (i- HCV care facility, ii- substance use disorder (SUD) care facility, and iii- other facilities), and types of integrated services offered (i- HCV or substance use screening and counseling only, ii- incorporating treatment for either HCV or SUD, and iii- combination with other health or social services). These groupings were informed by a previous systematic review evaluating integrated care for HIV and substance use (Haldane et al., 2017). Data for each study were summarized with respect study and participant characteristics, interventions and outcomes, including numbers and proportions of PWID engaged at each step of the HCV cascade of care, as well as differential effects between groups, when available.

Risk of bias assessment

Risk of bias (RoB) assessment was completed based on the type of study design. Randomized clinical trials (RCT)' RoB was assessed using the Cochrane RoB tool for RCTs (Higgins et al., 2011). Studies were examined for selection bias (e.g., allocation concealment), performance

Table 1
Population, interventions, comparisons, outcomes and study design (PICOS) criteria for study inclusion.

Criteria	Definition/Description
Population	≥18-year-old adults[a] who have a history of injection drug use[b] and are living with hepatitis C infection
Interventions	Service integration[c] interventions at varying degrees of integration (e.g., HCV testing and/or treatment within opioid use disorder treatment clinics or multidisciplinary care addressing medical, psychological, social and addiction-related needs)
Comparators	Placebo or other/no interventions (if available)
Outcomes	HCV testing, linkage to HCV care, HCV assessment, HCV treatment uptake, HCV treatment compliance, sustained virologic response (SVR), HCV recurrence, mortality
Study designs	Empirical quantitative studies (including observational and experimental)[d]

[a] Mean/Median age of > 18 was considered for studies with a mixed population of people who inject drugs (PWID).
[b] Studies were considered eligible if at least 50% of their participants were PWID or on opioid agonist therapy. It was assumed that people who use illicit drugs and are screened for HCV or received HCV care/treatment are predominantly PWID.
[c] Integrated care was defined as co-location of HCV and substance use services.
[d] Commentaries, viewpoints, letters to editors, reviews, and editorials were excluded.

Table 2
Study and participants characteristics of the included studies on integrated care for PWID living with HCV.

Author (year)	Study period/ Study Location	N/Age/%Male	Ethnicity (%)	HIV-positive (%)	Baseline substance use type and history of injection drug use[a]	Inclusion criteria
Randomized clinical trials						
Ebner et al. (2009)	2003-2006/ Austria	N: 300 screened, 17 treated/ Mean age: 34 (range 20-45)/ 29.4% of those treated were Male	100% Caucasian	0%: HIV-positivity was an exclusion criterion	*Substance type: Opioids *Injection drug use: NR	HCV positive with no major liver damage, or other major medical and psychiatric comorbidities; Abstinent from drug use for the past 6 months or on OAT; Not pregnant.
Bruce et al. (2012)	2007–2010/U.S.	N: 21/Mean age: 41/52% Male	9.5% African American; 14.2% Hispanic; 76.2% Caucasian	29%	*Substance type: Poly-substance use *Injection drug use: NR	Age ≥18 years; Prescribed methadone; Opioid negative in the past 30 days (urine test); Documented HIV testing; Detectable HCV RNA & genotype.
Single-arm intervention studies (Non-randomized clinical trials)						
Fried et al. (2008)	2002-2004/ Switzerland	N: 67/Mean age: 34 (range 21-56)/73.1 % Male	NR	0%; HIV-positivity was an exclusion criterion	*Substance type: Opioids *Injection drug use: 100%	On OAT; Chronic HCV; 18 and 65 years of age; Not previously treated with interferon-ribavirin combination therapy; Elevated serum ALT documented on at least one occasion within the past 6 months; No evidence of hepatocellular carcinoma; Regular attendance at the treatment center.
Jack et al. (2009)	2005-2008/United Kingdom	N: 353/Mean age: 34.7 (range 21-53)/72.5% Male	NR	0% (HIV testing was performed in 234/353 patients)	*Substance type: Opioids *Injection drug use: NR	Patients attending OAT clinics in primary care settings.
Schulte et al. (2010)	2002-2007/ Germany	N: 310/Mean age: 37 (range 23-54)/81% Male	NR	NR	*Substance type: Opioids *Injection drug use: 100%	Randomisation to heroin OAT; At least six months' participation in the heroin trial; Co-consumption of licit and illicit drugs limited to an extent that it did not interfere with antiviral treatment, and HCV-RNA positive.
Taylor et al. (2011)	18-month recruitment period/U.S.	N: 11/Mean age: 46 (range: 37-61)/36% Male	36.3% Black; 45.5% White; 18.2% Hispanic	100%	*Substance type: Poly-substance use *Injection drug use: 100%	HCV infected individuals aged 18-65; HCV treatment naïve; HIV-coinfected; CD4 > 100 cells/mm3 or HIV RNA < 10,000 copies/ml and CD4 ≤ 200 cells/mm3; On OMT; No contraindications for Peg-IFN; No active opportunistic disease; No active alcohol use; No pregnancy of breastfeeding.
Malnick et al. (2009)	NR/Israel	N: 114/NR/95% Male	NR	NR	*Substance type: Opioids *Injection drug use: NR	Enrollment in methadone OAT, HCV seropositive
Kikvidze et al. (2018)	2015/Georgia	N: ~2,600 HR clients/NR/NR	NR	NR	*Substance type: NR *Injection drug use: 100%	PWID attending the harm reduction center.
Cohort studies						
Backmund et al. (2001)	1997-2000/ Germany	N: 50/Mean age: 32.5 (range 19-48)/50% Male	NR	0%; HIV-positivity was an exclusion criterion	*Substance type: Poly-substance use *Injection drug use: 100%	Tested positive for HCV RNA, had volunteered to participate in a 12- or 24-month study, and had met the current diagnosis of opioid dependence with an additional dependence on alcohol, benzodiazepine, or cocaine.
Mauss et al. (2004)	NR/Germany	N: 100/Age range: 22-53/ 88% Male	NR	NR	*Substance type: NR *Injection drug use: NR	Patients had to have been on stable methadone OAT without the concomitant use of illicit drugs for 6 months. To be enrolled in the control group, patients had to have no history of injection drug use, illicit drug use, or opioid maintenance therapy for less than 5 years.
Guadagnino et al. (2007)	2002-2003/Italy	N: 53/Mean age: 32.5 (SD 5.8, 22-55)/86.8% Male	NR	0%: HIV-positivity was an exclusion criterion	*Substance type: Opioids *Injection drug use: 100%	PWID (18-60 years old) who were HCV- positive for at least 6 months, with a histological or clinical diagnosis of chronic HCV, high alanine- aminotransferase concentration, HCV-RNA detected with a sensitive PCR technique, and regular attendance to the detoxification program.
Jeffrey et al. (2007)	2002-2005/ Australia	N: 50/Mean age: 35 (19-54)/ 68.0% Male	NR	0%: HIV-positivity was an exclusion criterion	*Substance type: Opioid *Injection drug use: 100%	Active HCV infection and aged between 18-65 years old.

(*continued on next page*)

Table 2 (*continued*)

Author (year)	Study period/ Study Location	N/Age/%Male	Ethnicity (%)	HIV-positive (%)	Baseline substance use type and history of injection drug use[a]	Inclusion criteria
Belfiori et al. (2009)	2003-2006/Italy	N: 52/Mean age: 33 (range 18–57)/94.2% Male	NR	0%: HIV-positivity was an exclusion criterion	*Substance type: NR *Injection drug use: 100%	Chronic HCV, diagnosed by: persistent elevated aminotransferases and/or histological evidence of hepatitis or fibrosis; no other form of hepatitis; No co-infection with HIV and HBV; Diagnosis of substance abuse or opioid addiction; No problematic alcohol use (less than 50 gr/day); Drug-free for at least 3 months as shown by negative urine drug tests at recruitment, stable treatment with methadone or buprenorphine; No severe pre-existing psychiatric conditions, psychiatric assessment as suitable candidate for the study; > 18 years old.
Wilkinson et al. (2009)	2005-2007/United Kingdom	N: 83/Mean age: 42.2/77% Male	NR	0%	*Substance type: Poly-substance use *Injection drug use: 100% (ever); 30.1% (current)	PWID expressing interest in HCV treatment
Moussalli et al. (2010)	2002-2004/France	N: 337/Mean age of treated patients: 42 (SD 5.2)/NR	NR	NR	*Substance type: Opioids *Injection drug use: 100% (ever)	Patients attending the centre during the study period.
Lindenburg et al. (2011)	2005-2010/ Netherlands	N: 497/Mean age: 43.9 (SD 7.6)/68.8% Male	NR	14%	*Substance type: Poly-substance use *Injection drug use: 67.4% (ever)	Population I: Participants from the Amsterdam Cohort Studies for drug users; Population II: Drug users referred from opioid-substitution clinics.
Abou-Saleh et al. (2013)	12-month/United Kingdom	N: 556/Mean age: 32.7 (SD 8.2)/73% Male	NR	NR	*Substance type: Poly-substance use *Injection drug use: 90.3% (ever)	Drug users attending national health services, community-based NSP and incarcerated persons.
Alavi et al. (2013)	2009-2014/ Australia	N:387/Mean age: 41 (SD 9)/ 71% Male	15% Aboriginal	NR	*Substance type: Poly-substance use *Injection drug use: 51%	≥18 years old with a history of injection drug use and chronic HCV infection.
Newman et al. (2013)	2006-2008/Canada	N: 34/Median age: 42 (range 21-67)/59% Male	NR	NR	*Substance type: NR *Injection drug use: 100% (ever)	≥18 years old interested in undergoing HCV treatment with HCV infection confirmed by HCV RNA testing.
Keats et al. (2015)	2009-2014/ Australia	N: 378/Mean age: 40.2 (SD 9.1)/75% Male	5% Indigenous	NR	*Substance type: Opioids *Injection drug use: 100%	Clients attending the Newcastle Pharmacotherapy Service, 18 years and older, with a history of injecting drug use and chronic HCV infection.
Morris et al. (2017)	2016-2017/ Australia	N: 127/Mean age: 45.2 (SD 10.5)/69% Male	10% Aboriginal	NR	*Substance type: Poly-substance use *Injection drug use: 50% (current)	HCV positive individual prescribed DAA who injected drugs in the last 12 months, received OAT, received drug counselling or were clients from a rehabilitation community, and who were due to SVR before September 2016.
Read et al. (2017)	2015-2016/ Australia	N: 72/Median age: 45 (range 25-69)/67% Male	32% Aboriginal	11%	*Substance type: Poly-substance use *Injection drug use: 100% (ever)	All patients receiving IFN-free, DAA-based therapy for HCV and had due SVR12 testing by the end of study period.
Nouch et al. (2018)	2015-2017/ Canada	N: 138/Median age: 53 (Q1-Q3 46-60)/75% Male	70% White; 12% First Nations; 1% Black; 3% Other; 17% No response	7%	*Substance type: Poly-substance use *Injection drug use: 75% (ever)	Clients initiating DAA-based HCV therapy within any of the study sites receiving at least 1 dose of medications and due to SVR12 before 1 August 2017.
Trabut et al. (2018)	2014-2017/ France	N: 50/Mean age: 46.2 (SD 7.3)/84% Male	NR	8%	*Substance type: Poly-substance use *Injection drug use: 100% (ever), 12% (current)	Patients with history of SUD or currently on OAT, chronic HCV, advanced fibrosis (FibroScan® ≥ 9.6 kPA).
Cross-sectional studies						
Taylor et al. (2005)	NR/ U.S.	N: 146/NR/NR	NR	100%	*Substance type: NR *Injection drug use: 94%	HIV/HCV coinfected individuals attending a multidisciplinary clinic.
Hennessy et al. (2007)	2000-2004/ U.S.	N: 279/NR/NR	NR	4%	Substance type: NR *Injection drug use: 100%	Clients who sought services at a publicly funded STD clinic and self-identified as PWID.
Heseltine et al. (2007)	2000-2005/ U.S.	N: 9130 tests/NR/NR	NR	NR	*Substance type: NR *Injection drug use: 79%	NR.
McCormick et al. (2008)	NR/Ireland	N: 13/NR/NR	NR	NR	*Substance type: NR *Injection drug use: 100%	PWID attending drug treatment clinic assessing HCV treatment uptake and SVR.
Witteck et al. (2011)	2009/Switzerland	N: 196/Median age: 41 (range 20-63)/75% Male	NR	19%	*Substance type: Opioids *Injection drug use: 88%	Patients enrolled in the OAT program.

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Table 2 (*continued*)

Author (year)	Study period/ Study Location	N/Age/%Male	Ethnicity (%)	HIV-positive (%)	Baseline substance use type and history of injection drug use[a]	Inclusion criteria
Xia, Chen et al. (2013, 2013b)	2008/China	N: 13270/82.6% aged 20-40 years old/93.9% Male	NR	6%	Substance type: 99.6% Heroin *Injection drug use: 83.0%	People attending the methadone clinic.
Bregenzer et al. (2017)	2013-2015/ Switzerland	N: 205/Median age: 38.5 (Q1-Q3 32.4-44.7)/ 79.5% Male	NR	7%	*Substance type: Poly-substance use *Injection drug use: 70.6% (ever)	Patients receiving OAT within the canton of Aargau.
Hashim et al. (2018)	2013-2016/ United Kingdom	N: 485/Mean age: 41 (SD 9.9)/80% Male	NR	NR	*Substance type: Poly-substance use *Injection drug use: 69% (ever)	Patients receiving care within a nurse-led SUD clinic during study period.
Case-series studies						
Knott et al. (2006)	2003-2004/ U.S.	N: 184/Mean age: 51.7 (SD 6.2)/98.9% Male	65.8% Caucasian; 21.2% African American; 3.3% Hispanic; 1.6% Native American; 1.0% Asian American; and 7.1% unknown	NR	*Substance type: NR *Injection drug use: 51%	HCV antibody positive patients seen at the clinic.
Grebely et al. (2007, 2010)	2005-2008/ Canada	N: 204/Median age: 47 (range 24-62)/83% Male	NR	NR	*Substance type: NR *Injection drug use: NR	Aged ≥19 years with documented HCV viremia, elevated liver enzymes or liver biopsy demonstrating at least Knodell stage 2; No decompensated cirrhosis and adherent to pre-treatment assessment visits; No pregnancy, breastfeeding, concomitant liver disease or uncontrolled depression.
Litwin et al. (2009)	2003-2005/ U.S.	N: 73/Mean age: 46 (SD 8)/ 71% Male	67% Latino; 12% African American; 21% Caucasian	32%	*Substance type: 100% Opioids *Injection drug use: 90%	NR.
Senn et al. (2009)	2002-2008/ Switzerland	N: 387/Median age: 38.5 (IQR 33.6 – 44.5)/ 69.3% Male	NR	18%	*Substance type: Opioids *Injection drug use: 62.7% (ever)	Patients who were more than 3 months on OAT during study period.
Harris et al. (2010)	2003-2005/ U.S.	N: 291/Mean age: 47 (SD NR)/60% Male	60% Hispanic; 27% African American; 13% White	17%	*Substance type: 100% Opioids *Injection drug use: NR	All patients enrolled in the methadone program as of July 1, 2003, plus all new patients admitted through December 15, 2004.
Charlebois et al. (2012)	2007-2010/ Canada	N: 129/Mean age: 47.8 (SD 7.43)/71% Male	82.8% White; 9.4% Aboriginal; 5.5% Black; 1.6% Asian; 0.8% Other	6%	*Substance type: Poly-substance use *Injection drug use: 86.8% (past-month)	HCV antibodies and HCV RNA positive at baseline who attended one or more structured group sessions.
Islam et al. (2012)	2006-2010/ Australia	N: 479/Mean age: 35 (SD 9)/ 77% Male.	13% Aboriginal/ Indigenous	NR	*Substance type: Poly-substance use *Injection drug use: 86% (ever)	PWID attending a nurse-led service primary-care, PWID-targeted facility.
Martinez et al. (2012)	2006-2008/U.S.	N: 401/Mean age: 49 (30-55)/66% Male	51% Caucasian; 34% Hispanic; 13% African American	15%	*Substance type: Opioids *Injection drug use: NR	HCV, active enrollment in methadone maintenance program.
Taylor et al. (2012)	2005-2009/U.S.	N: 61/NR/74% Male	62% Caucasian; 33% Hispanic; 20% Black; 15% unknown; 3% Native American	100%	*Substance type: Opioids *Injection drug use: NR	HIV-infected individuals receiving buprenorphine OAT.
Brunner et al. (2013)	2002-2010/ Switzerland	N: 66/Median age: 40 (IQR 33.7-44.2)/80% Male	NR	14%	*Substance type: Poly-substance use (predominantly opioids) *Injection drug use: 70.7% (ever)	All patients in the primary care-based outpatient clinics for addiction medicine with HCV treatment.
Seidenberg et al. (2013)	2002-2008/ Switzerland	N: 85/Median age: 38.8 (IQR 35-44.4)/61.2% Male	NR	16%	*Substance type: Poly-substance use *Injection drug use: 92.9% (ever)	≥18 years old with ≥3 months participating in OAT and documented chronic HCV infection.
Scherz et al. (2018)	2014-2017/ Switzerland	N: 64/Mean age: 48 (SD 8)/ 80% Male	NR	13%	*Substance type: Poly-substance use *Injection drug use: 14%	Patients on OAT treated with DAA-based therapy between October 2014 and August 2017 within the study sites.

Abbreviations: CD4: cluster of differentiation 4; DAA: direct acting antiviral; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IFN: interferon; IQR: Inter-quartile range; NR: not reported; NSP: Needle and syringe program; OAT: opioid agonist treatment; PWID: people who inject drugs; RNA: ribonucleic acid; SD: standard deviation; STD: sexually transmitted diseases; SUD: substance use disorder; SVR: sustained virologic response.

[a] The timeline for history of injection drug use is reported when available.

bias (e.g., blinding of personnel), detection bias (e.g., blinding of outcome assessors), attrition bias (e.g., incomplete outcome data), reporting bias (e.g., selective reporting), and other potential sources of bias (e.g., funding conflict of interest). RCTs were reported as 'high risk' of bias when at least one criterion was assessed as high risk of bias. For single-arm intervention, prospective observational and cross-sectional studies, RoB was assessed using the modified Newcastle Ottawa Scale (Wells et al., 2013). Studies were evaluated for selection bias (e.g., representativeness), comparability (e.g., comparable subjects), and outcome assessment (e.g., sufficient follow-up). We also assessed the quality of case-series using a recommended tool that assesses case-series for selection (e.g., representativeness), ascertainment (e.g., exposure measurement), causality (e.g., sufficient follow-up), and reporting (e.g., inference) biases (Murad, Sultan, Haffar, & Bazerbachi, 2018).

Results

Our database and hand search yielded a total of 1,600 unique citations, of which 1,400 were removed after an initial screening of title and abstract. Of the 200 full-text records assessed, 46 articles corresponding to 44 studies met the eligibility criteria and were included in the present qualitative synthesis (Fig. 1).

Study and participant characteristics

There were two RCTs, six single-arm intervention studies, sixteen cohort-studies, eight cross-sectional studies, and twelve retrospective case-series. The majority of the studies were conducted in Western Europe (n = 21) and North America (n = 14). The remainder of the studies were conducted in Australia (n = 6), Georgia (n = 1), Israel (n = 1) and China (n = 1). The median sample size of the 44 included studies was 131 (Interquartile range: 66–317). Selected characteristics of study participants are presented in Table 2.

Intervention characteristics and outcomes

Twenty-six studies discussed integration of services at SUD care facilities, one at HCV care facilities, and seventeen at other facilities (Table 3). Of note, only six studies assessed integration of newer DAA-based HCV treatments with substance use services for PWID. Four of them had SUD care facilities as point of entry (Hashim, O'Sullivan, Williams, & Verma, 2018; Morris et al., 2017; Scherz, Bruggmann, & Brunner, 2018; Trabut et al., 2018), and two, primary care facilities (Nouch et al., 2018; Read et al., 2017).

Point of entry: HCV care facilities

Substance use screening at HCV care facilities. No studies evaluated substance use screening in HCV facilities.

SUD treatment at HCV care facilities. Only one study assessed integration of SUD treatment at HCV care facilities (Knott et al., 2006). This study was conducted in a Veterans Affairs (VA) HCV clinic in the United States (U.S.), and evaluated a model of routine integrated care for mental health and SUD. Under this model, all patients with positive screens for SUD or mental disorders were referred to a psychiatric nurse who provided behavioural (i.e., motivational interviewing, cognitive behavioural) and pharmacological treatment (e.g., antidepressants) as needed and targeted to the specific diagnosis onsite. The study reported positive outcomes, including higher HCV assessment and treatment initiation rates among patients with follow-up by the co-located psychiatric nurse (90%/49%) than those with no substance use/psychiatric care (59%/27%, $P < 0.001$ and 0.08, respectively) or receiving care offsite (56%/14% both $P < 0.001$). Interestingly, patients receiving integrated psychiatric/substance use care also had higher rates of HCV treatment completion than those with no psychiatric/SUD comorbidities (76% versus 41% $P = 0.012$).

Substance use disorder treatment and other services at HCV care facilities. No studies evaluated integration of substance use and other services for PWID in HCV care facilities.

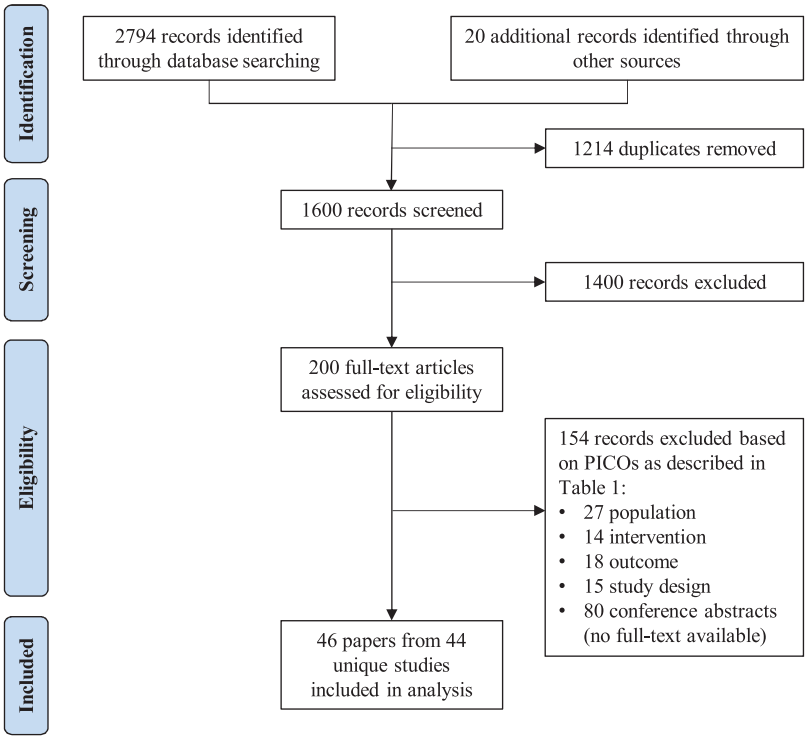

Fig. 1. Flow diagram of included studies.

Table 3
Interventions characteristics of the included studies on integrated care for PWID living with HCV.

Author (year)	Type of integration		Description of the intervention/ Type of HCV treatment	Study outcomes/Main findings	Risk of bias
	Point of entry	Services offered			
Randomized clinical trials					
Ebner et al. (2009)	SUD care facility	*OUD MAT *HCV treatment	*HCV treatment as well as psychopharmacological medication and counselling /Peg-IFN + RBV/Group A: RBV 800 mg/day, Group B: RBV 400 mg/day *No placebo group	*HCV seroprevalence: 63% (190/300) *HCV RNA positive: 47% (141/190) *HCV treatment uptake: 23% of genotype 2/3 participants (17/75) *ETR: 23% (17/75) *SVR24: 23% (17/75) *HCV recurrence: 11.8% (2/17)	High
Bruce et al. (2012)	Primary care facility	*OUD MAT *HCV testing *HCV assessment *HCV treatment *HIV testing	*mDOT for HCV (Peg-IFN based treatment) within a methadone maintenance program *Control group: Self-administered therapy (SAT)	*HCV treatment uptake: 12/12 in mDOT vs. 4/9 in SAT *EVR: 10/12 in mDOT vs. 3/9 in SAT *SVR24: 6/12 mDOT vs. 1/9 SAT	High
Single-arm intervention studies (Non-randomized clinical trials)					
Fried et al. (2008)	SUD care facility	*OUD MAT *HCV testing *HCV treatment	*HCV treatment injection once per week in the OUD MAT centres /Peg-IFN + ribavirin *No control group	*ETR: 75% (50/67). *SVR24: 61% (41/67)	High
Jack et al. (2009)	Primary care facility	*OUD MAT *HCV testing *HCV treatment *HIV and HBV testing *Primary care	*HCV assessment (testing, staging) and Peg-IFN based treatment *No control group	*HCV testing uptake: 64% (226/353) *HCV seroprevalence: 65% (174/226) *HCV RNA tested: 95% (165/174) (94.8%) *HCV RNA positive: 75% (124/165) *New HCV diagnosis and treatment naïve: 118 *HCV treatment uptake: 70% of those eligible (30/43) *HCV treatment compliance > 85% *SVR24: 38% (13/34, 9 still on treatment)	High
Schulte et al. (2010)	SUD care facility	*OUD MAT *HCV treatment	*Supervised heroin up to three times a day; Randomised to a combination of drug counselling and psychoeducation or case management plus motivational interviewing *No placebo group	*HCV treatment uptake: 9% (26/301) *Completed HCV treatment: 7% (21/301) *ETR: 7% (20/301) *SVR24: 6% (18/301)	Moderate
Taylor et al. (2011)	HIV care facility	*HCV treatment *OUD MAT *HIV care	*Nurse-administered Peg-IFN based HCV therapy *No control group	During the 18-month recruitment period: *11 HIV/HCV PWID initiated HCV treatment *EVR: 25% (3/12) *ETR: 18% (2/11) *SVR24: 18% (2/11)	High
Malnick et al. (2009)	SUD care facility	*OUD MAT *HCV treatment	*Regular services/Peg-IFN + RBV *No control group	*114 HCV+ *50 (44%) attended the initial meeting *HCV treatment uptake: 80% of those eligible (20/25) *SVR24: 32% (8/25)	High
Kikvidze et al. (2018)	Harm reduction centre	*HCV testing *HCV assessment *Needle exchange	*Peer-led intervention providing help with referrals to clinic for those eligible for treatment *HCV rapid testing and liver elastometry *No control group	*HCV testing uptake: 21% (554/≈2600) *HCV linkage to care: 97% (338/350)	High
Cohort studies					
Backmund et al. (2001)	SUD care facility	*OUD MAT *HCV testing *HCV treatment *Medical care for other comorbidities *Psychotherapy	* HCV treatment/Peg-IFN and ribavirin (6 injections) *No control group	*HCV sero-prevalence: 65% (161/246) *HCV-RNA positive: 43% (106/246) *HCV treatment uptake: 47% (50/106) *ETR: 22% (24/106) *SVR24: 17% (18/106)	Moderate
Mauss et al. (2004)	SUD care facility	*OUD MAT *HCV treatment	*HCV treatment/Peg-IFN offered to all patients	*ETR: 50% (25/50) of methadone group vs 76% (38/50) in control group (p = 0.01). *SVR24 in 42% (21/50) methadone group vs 56% (28/50) in control group (p = 0.16).	Moderate
Guadagnino et al. (2007)	SUD care facility	*OUD MAT *HCV testing *HCV treatment	*Counselling, HCV screening, and intravenous HCV treatment /Peg-IFN + RBV *No control group	*RVR: 88.7% (n = 47) *EVR: 77.4% (n = 41) *ETR: 58.5% (n = 31) *SVR24: 54.7% (n = 29)	Moderate
Jeffrey et al. (2007)	SUD care facility	*OUD MAT *HCV treatment	*HCV and substance use harm reduction education; Following treatment patients were visited monthly /Peg-IFN *No control group	*ETR: 68% (34/50) *Early discontinuation: 22 (11/50) *SVR24: 62% (31/50) *HCV recurrence: 6% (2/34)	Moderate
Belfiori et al. (2009)	SUD care facility	*OUD MAT *HCV treatment	*Addiction specialist monitored compliance in the clinical interview, adjusted MAT dosage, and collected routine blood and urine samples/ Peg-IFN *No control group	*Completed HCV treatment: 87% (45/52) *7.6% (4/52) discontinued due to poor compliance *ETR: 71.1% (37/52) *SVR24: 50% (26/52)	Moderate
Wilkinson et al. (2009)	SUD care facility	*OUD MAT *HCV treatment *Needle exchange *Primary care	*HCV treatment/Peg-IFN + RBV *No control group	*HCV treatment uptake: 76% (63/83) *Completed HCV treatment: 70% (58/83) *SVR24: 30% (25/83)	Moderate

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Table 3 (*continued*)

Author (year)	Type of integration		Description of the intervention/ Type of HCV treatment	Study outcomes/Main findings	Risk of bias
	Point of entry	Services offered			
Moussalli et al. (2010)	SUD care facility	*OUD MAT *HCV treatment *Needle exchange *SUD counselling *Primary care	*Evaluation, treatment and medical/psych/motivation support /Peg-IFN *Control group: Time comparison from when patients received HCV treatment at the hospital (2002)	*HCV liver fibrosis assessment: 66% (224/337) vs 5% (6/113) control ($p < 0.001$). *HCV treatment uptake: 38% (85/224) vs 2% (2/113) control ($p < 0.001$). *Completed HCV treatment 31% (70/224) *SVR24: 17% (37/224)	High
Lindenburg et al. (2011)	Primary care facility	*OUD MAT *HCV treatment *Psychiatric care *HIV testing	*HCV testing and Peg-IFN based HCV treatment *No control group	*HCV testing uptake: 90% (449/497) *HCV seroprevalence: 59% (267/449) *HCV RNA positive: 69% (183/267) *HCV assessment uptake among HIV-negative participants: 63% (84/134) *HCV treatment uptake among HIV-negative participants: 73% (44/60) *SVR24: 65% (37/57) *HCV reoccurrence: 21% (10/48)	Moderate
Abou-Saleh et al. (2013)	Harm reduction centre	*HCV testing *Needle exchange	*DBS HCV testing and pre and post-test counseling; HCV-positive patients were referred to specialized liver clinics and Peg-IFN based therapy *No control group	*HCV testing uptake: 556 PWID during 12 months *HCV seroprevalence: 30% (169/556) *HCV linkage to care: 46% (45/169) *HCV treatment uptake: 4% (7/169)	Moderate
Alavi et al. (2013)	SUD care facility	*OUD MAT *HCV assessment *HCV treatment	*Clinical assessment and case note review collected information on HCV testing and treatment as well as medical and psychiatric history/Peg-IFN *No control group	*86% (331/387) willing to receive treatment *61% (236/387) referred to an HCV specialist *81% (191/236) attended their appointment *22% (84/387) started treatment	Moderate
Newman et al. (2013)	Primary care facility	*Primary care *OUD MAT *HCV treatment *SUD counselling *Psychiatric care *Needle exchange *Peer support	*Peg-IFN based HCV treatment within a multidisciplinary primary-care clinic *No control group	*HCV treatment uptake: 41% (14/34) *ETR: 32% (11/34) *SVR24: 24% (8/34) *HCV recurrence: 27% (3/11)	Moderate
Keats et al. (2015)	SUD care facility	*OUD MAT *HCV testing *HCV treatment *Needle exchange *Peer navigator	*Upon HCV treatment initiation, clients were seen at baseline, week 2 and week 4, then every 4 weeks through the completion of treatment with Peg-IFN + RBV *No control group	*HCV testing uptake: 26% (378/1447) *HCV RNA positive: 17% (242/1447) *HCV treatment uptake: 8% (20/242) *SVR24: 6% (15/242)	Moderate
Morris et al. (2017)	SUD care facility	*SUD counselling *HCV treatment *Primary care *Needle exchange *Peer education	*DAA-based HCV treatment *No control group	*HCV treatment completion: 96% (122/127) *HCV treatment adherence: 97% (118/122) *ETR: 69% (88/127) *SVR12: 80% (102/127)	Moderate
Read et al. (2017)	Primary care facility	*HCV treatment *OUD MAT *Needle exchange *Primary care *HIV and STI care	*DAA-based, IFN-free HCV treatment within a primary-care facility providing services to PWID *No control group	* HCV treatment completion: 96% (69/72) *SVR12: 82% (59/72) *SVR12 among current PWID: 79% (42/53), 82% (14/17) among patients on MAT and 78% among those not on MAT (28/36)	Moderate
Nouch et al. (2018)	Primary care facility	*HCV testing *HCV assessment *HCV treatment *OUD MAT *Primary care *Counselling	*DAA-based HCV therapy within a primary-care based model of care *No control group	*Completed HCV treatment: 96% (132/138) *SVR12: 86% (118/138) *HCV recurrence: 2% (3/132) *Co-location of MAT and HCV treatment was associated with attendance to SVR12 visit (aOR 11.1 95% CI 2.2-50)	Moderate
Trabut et al. (2018)	SUD care facility	*OUD MAT *HCV treatment	DAA-based HCV therapy under the supervision of hepatologists *No control group	*SVR12: 90% (45/50) *No significant differences in adherence versus historical controls.	Moderate
Cross-sectional studies					
Taylor et al. (2005)	HIV care facility	*HCV testing *HCV treatment *HIV care *Psychiatric/SUD care	*Peg-IFN based HCV treatment *No control group	*HCV linkage to care: 635 (92/146) *HCV assessment: 69/92 *HCV treatment uptake: 33% (17/51) *HCV treatment completion: 15% (7/46) *SVR: 2% (1/46)	High
Hennessy et al. (2007)	STI care facility	*HCV testing *HIV testing *STI testing and treatment *HBV and HAV vaccination	*Integration of viral hepatitis services into a publicly funded STI clinic in New York *No control group	*HCV testing uptake: 92% (95/103) *HCV seroprevalence: 93% (88/95)	Moderate
Heseltine and McFarlane (2007)	SUD care facility	*HCV testing *HIV and STD counselling	*Pre- and post-test counseling offered to people requesting HCV testing *No control group	*24% (n = 9130) of all HCV tests were conducted in drug treatment facilities *HCV seroprevalence in drug treatment facilities: 26% (2345/9130)	Moderate
McCormick et al. (2008)	SUD care facility	*OUD MAT *HCV treatment	*Integration of HCV treatment services into drug treatment clinic/ pegylated interferon and ribavirin *No control group	*HCV treatment uptake: 46% (6/13) *HCV treatment completion: 46% (6/13) *SVR24: 46% (6/13)	High

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Table 3 (*continued*)

Author (year)	Type of integration		Description of the intervention/ Type of HCV treatment	Study outcomes/Main findings	Risk of bias
	Point of entry	Services offered			
Witteck et al. (2011)	SUD care facility	*OUD MAT *HCV testing *HCV assessment *HCV treatment *HIV testing	*HCV testing, fibrosis staging and Peg-IFN treatment for those eligible within an OST clinic *No control group	*HCV testing uptake: 99% (194/196) *HCV seroprevalence: 75% (146/194) *HCV RNA testing: 91% (133/146) *HCV RNA positive: 59% (78/133) *HCV treatment uptake: 23% of those eligible (21/91) vs. 36%-65% in non-PWID *SVR24: 9% (8/86, 5 were still on treatment)	High
Xia, Chen et al. (2013, 2013b)	SUD care facility	*OUD MAT *HCV testing	*HCV testing *No control group	*HCV testing uptake: 79% (8663/11011)	Moderate
Bregenzer et al. (2017)	SUD care facility	*OUD MAT *HCV testing *HCV assessment *HIV testing	*HIV/HCV testing, liver fibrosis staging, referral for HCV therapy for those eligible *No control group	*HCV testing uptake (rapid tests): 94% (192/205) vs 76% (156/205) in before period *HCV seroprevalence: 54% (109/203) *HCV RNA positive: 52% (44/85) *Liver fibrosis assessment: 93% (41/44) *HCV treatment uptake: 43% (28/65) *SVR24: 32% (21/65)	Moderate
Hashim et al. (2018)	SUD care facility	*OUD MAT *HCV testing *HCV assessment *HCV treatment *Peer-navigators	*HCV assessment and Peg-IFN or DAA-based treatment within a nurse-led SUD-focused clinic *No control group	*HCV testing uptake: 97% (472/485) *HCV seroprevalence: 56% (262/472) *HCV RNA positive: 81% (211/262) *HCV treatment uptake: 60% of eligible patients (87/145) *HCV treatment compliance: 98% *SVR12: 50% (69/138, 5 patients still on treatment)	Moderate
Case-series studies					
Knott et al. (2006)	HCV care facility	*HCV treatment *Mental health and substance use screening *Behavioral interventions for SUD	*Psychotherapy and prescribed Peg-INF/4 to four groups: i) patients without positive screens; ii) patients with positive screens who saw the PCNS; iii) patients with positive screens who saw an existing MH provider only; and iv) patients with positive screens who declined referral for psychiatric and SUD *No control group	Among patients with SUD/psychiatric comorbidities in integrated care: *HCV assessment: 90% (63/70) *HCV treatment uptake: 49% (34/70) *HCV treatment completion: 76% (26/34) *SVR24: 38% (13/34)	High
Grebely et al. (2007, 2010)	Primary care facility	*HCV assessment *HCV treatment *OUD MAT *Counselling	*HCV assessment and Peg-IFN based HCV treatment, weekly peer support group to illicit drug users within an urban multidisciplinary health clinic *No control group	*HCV assessment: 53% (109/204) *HCV treatment uptake: 66% among those eligible (57/87) *SVR24: 63% of those with complete follow-up (12/19)	High
Litwin et al. (2009)	SUD care facility	*OUD MAT *HCV testing *HCV treatment	*HCV evaluation and treatment/Peg-IFN + RBV *No control group	*86% (63/73) completed at least 12 weeks of treatment *ETR: 55% (40/73) *SVR24: 45% (33/73)	High
Senn et al. (2009)	Primary care facility	*HCV testing *OUD MAT *Primary care	*HCV testing among patients attending a primary-care clinic for OUD MAT *No control group	*HCV testing uptake: 91% (327/360) *HCV seroprevalence: 42% (136/327) *HCV RNA positive: 63.2% (86/136)	Moderate
Harris et al. (2010)	SUD care facility	*OUD MAT *HCV testing *HCV treatment	*HCV testing, counselling, and treatment with Peg-IFN + RBV *No control group	During the 2-year study period: *HCV testing uptake: 99% (281/291) *HCV seroprevalence 65% (188/281) *HCV RNA-positive: 71% (98/139), 66% of those eligible for on-site care (83/125) *HCV treatment uptake: 28% of those eligible for treatment (21/76) vs. 5% (3/58) of patients receiving HCV care off-site *SVR24: 10% (8/76) *HCV recurrence: 26% (3/11)	Moderate
Charlebois et al. (2012)	Primary care facility	*HCV treatment *Primary care *Needle exchange *Social services	*Peg-IFN based HCV treatment and group sessions for 16 weeks to HCV-infected patients *No control group	*129 HCV-positive PWID *HCV RNA testing: 88% (114/129) *HCV RNA positive: 97% (110/114) *HCV treatment uptake: 26% (24/92) *SVR24: 18% (17/92)	High
Islam et al. (2012)	Harm reduction centre	*HCV testing *Needle exchange *Primary care	*HCV testing and assessment and referral to a tertiary liver clinic *No control group	*HCV testing uptake: 74% (353/479) *HCV seroprevalence: 60% (212/353) (60%) *HCV RNA testing: 93% (197/212) *HCV RNA positive: 73% (143/197) *Linkage to HCV care: 48% (68/143) *HCV treatment uptake: 16% (11/68) (16%) *SVR24: 10% (7/68)	High
Martinez et al. (2012)	SUD care facility	*OUD MAT *HCV testing *HCV assessment *HCV treatment	*HCV assessment and treatment/Peg-IFN *No control group	*HCV seroprevalence: 64% (257/401) *HCV RNA positive: 71% (157/222) *HCV assessment: 61% (76/125) *HCV treatment uptake: 59% (24/41) *HCV treatment completion: 46% (19/41) *SVR24: 32% (13/41)	Moderate
Taylor et al. (2012)	HIV care facility	*HCV testing *HCV treatment *OUD MAT *HIV care	*Peg-IFN based HCV therapy within integrated HIV and OUD MAT related services *No control group	*HCV testing uptake: 100% (61/61) *HCV seroprevalence: 93% (57/61) *HCV RNA positive: 84% (48/57) *HCV treatment uptake: 17% (8/48) *SVR24: 2% (1/48)	Moderate

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Table 3 (*continued*)

Author (year)	Type of integration		Description of the intervention/ Type of HCV treatment	Study outcomes/Main findings	Risk of bias
	Point of entry	Services offered			
Brunner et al. (2013)	SUD care facility	*OUD MAT *HCV assessment *HCV treatment *Psychiatric care *HIV care	*HCV assessment, Peg-IFN based therapy within a primary care-based facility focused on SUD *No control group	*HCV treatment completion: 68% (45/66) *SVR24: 41/66 (62%) *HCV recurrence: 15% (9/60)	Moderate
Seidenberg et al. (2013)	Primary care facility	*HCV treatment *OUD MAT *Primary care	*Chronic HCV assessment and Peg-IFN based HCV treatment among patients receiving OUD MAT within a primary-care clinic *No control group.	*HCV treatment uptake: 31% (35/85) *SVR24: 29% (25/85)	High
Scherz et al. (2018)	SUD care facility	*OUD MAT *HCV treatment *Primary care *Psychiatric care *Social work	DAA-based HCV therapy *No control group	*SVR12: 92% (59/64)	Moderate

Abbreviations: aOR: adjusted odd ratio; CI: confidence interval; DAA: direct-acting antiviral; DBS: dried blood spot; ETR: end of treatment response; EVR: early virological response; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IQR: interquartile range; ITT: intention to treat; MAT: medication assisted treatment; mDOT: modified directly observed therapy; OUD: opioid use disorder; Peg-IFN: pegylated interferon; PWID: people who inject drugs; PWUD: people who use drugs; RBV: Ribavirin; RNA: ribonucleic acid; RVR: rapid virological response; STI: sexually transmitted infection; SUD: substance use disorder; SVR12: sustained virological response at 12 weeks post-treatment; SVR24: sustained virological response at 24 weeks post-treatment.

Point of entry: SUD care facilities

HCV testing at SUD care facilities. Two studies described HCV testing activities at SUD care clinics (Heseltine & McFarlane, 2007; Xia, Chen, Tucker, Wang, & Ling, 2013; Xia, McLaughlin, Chen, Ling, & Tucker, 2013). One study described a statewide program that aimed to integrate HCV counselling and testing into different settings in the U.S. (Heseltine & McFarlane, 2007). Specifically, in SUD treatment settings the prevalence of HCV was around one quarter, underscoring the potential of this strategy. In addition, while managers of these facilities agreed that these services addressed an unmet need for their population, they also acknowledged that the limited access to HCV and SUD treatment for clients with positive screens for HCV undermined these efforts. The other study evaluated a model of routine HCV/HIV testing at methadone clinics in one Chinese province, demonstrating high testing uptake rates (79%) (Xia, Chen et al., 2013; Xia, McLaughlin et al., 2013).

HCV treatment at SUD care facilities. Fifteen studies assessed integration of HCV treatment at SUD facilities; thirteen were conducted in the Peg-Interferon era (Guadagnino et al., 2007; Alavi et al., 2013; Belfiori et al., 2009; Ebner et al., 2009; Fried et al., 2008; Guadagnino et al., 2007; Harris, Arnsten, & Litwin, 2010; Jeffrey et al., 2007; Litwin et al., 2009; Malnick, Sheidvasser, Basevitz, & Levit, 2009; Martinez et al., 2012; Mauss, Berger, Goelz, Jacob, & Schmutz, 2004; McCormick, Keavney, O'Toole, & Moloney, 2008; Schulte et al., 2010) and two in the DAA era (Hashim, O'Sullivan, Williams, & Verma, 2018; Trabut et al., 2018). All of them integrated HCV treatment into the context of medication-assisted treatment (MAT) for opioid use disorder (OUD). Though methadone was the most commonly prescribed MAT, there were studies across the range of MAT, including buprenorphine, naltrexone, slow-release oral morphine and diacetylmorphine. Overall, these studies observed high HCV treatment uptake (22%–80%), completion (46–98%) and SVR rates (10–90%), when HCV treatment was integrated in these settings. Importantly, ongoing substance use was not associated with worse outcomes. Only four studies evaluated HCV recurrence after treatment, documenting rates between 6%–26% (2–9 patients) among patients with End of Treatment Response (ETR) (Brunner, Senn, Rosemann, Falcato, & Bruggmann, 2013; Ebner et al., 2009; Harris et al., 2010; Jeffrey et al., 2007).

HCV treatment and other services at SUD care facilities. Nine studies evaluated integration of care for HCV and other comorbidities at SUD care facilities; six from the Peg-IFN era (Backmund, Meyer, Von Zielonka, & Eichenlaub, 2001; Brunner et al., 2013; Keats, Micallef, Grebely, Hazelwood, Everingham, Shrestha, Jones, Bath, Treloar, Dore, Dunlop et al., 2015; Moussalli et al., 2010; Wilkinson et al., 2009; Witteck et al., 2011) and three from the DAA era (Bregenzer et al., 2017; Morris et al., 2017; Scherz et al., 2018). Four studies described the integration of HCV care alongside management of other conditions in SUD clinics in Switzerland (Bregenzer et al., 2017; Brunner et al., 2013; Scherz et al., 2018; Witteck et al., 2011). The first one evaluated HCV management practices in three large MAT programs, finding high rates of HCV and HIV screening (95–99%). In addition, while rates of treatment uptake were lower compared to non-PWID populations (23% versus 58%, $P < 0.001$), among those treated, SVR rates were similar (9% versus 16%, $P = 0.09$) (Witteck et al., 2011). Bregenzer et al. showed that point-of-care diagnostic tests (HCV and HIV antibody rapid tests and mobile liver elastometry) offered in OUD MAT settings resulted in substantial improvements in HCV testing (94% versus 76%, $P < 0.001$) and liver fibrosis assessment rates (93% versus 36%, $P < 0.001$) compared to the before period (Bregenzer et al., 2017). The two remainder studies from Switzerland demonstrated that providing HCV treatment to individuals on MAT within low-threshold addiction clinics that also provides primary care for HIV and other comorbidities was feasible and resulted in high SVR rates both with Peg-IFN (66%) (Brunner et al., 2013) and DAA-based treatments (92%)

(Scherz et al., 2018). The positive impacts of low-threshold integrated care for PWID on HCV treatment outcomes was also documented in another study conducted during the DAA era in Australia, reporting SVR rates of 80% (Morris et al., 2017). Another study from Australia described an integrated peer-support based model (Keats, Micallef, Grebely, Hazelwood, Everingham, Shrestha, Jones, Bath, Treloar, Dore, Dunlop, Haber et al., 2015) within a MAT program. While the peer-support intervention did not result in improved HCV treatment uptake rates compared to other populations of PWID, high SVR rates were documented among clients who started HCV treatment (75%). One study from France evaluated the impacts of a one-stop-shop model of care (including HCV care, MAT, needle exchange, primary care, and social support) at a SUD clinic (Moussalli et al., 2010). The evaluation of this program, which also implemented non-invasive liver fibrosis assessment, showed improved HCV assessment (66% versus 5%, $P < 0.001$) and treatment initiation (38% versus 2%, $P < 0.001$) rates compared to the year before the program was implemented. Another study described initiation of HCV treatment, alongside medical management of other common comorbidities in PWID in an OUD detox unit (Backmund et al., 2001). Though most of the patients relapsed to opioid use, high HCV SVR rates were documented (17%). Finally, one study conducted in the U.K. demonstrated that a nurse-led model of care in a community-based addiction clinic could be successful in delivering low-threshold HCV treatment to people who use drugs, as suggested by HCV treatment uptake and SVR rates of 76% and 30%, respectively (Wilkinson et al., 2009).

Point of entry: other facilities

Primary care facilities. Of the seventeen studies in this category, the majority (n = 10) described the integration of substance use and/or HCV services in primary care community settings (Bruce et al., 2012; Charlebois, Lee, Cooper, Mason, & Powis, 2012; Grebely et al., 2007, 2010; Jack, Willott, Manners, Varnam, & Thomson, 2009; Lindenburg et al., 2011; Newman et al., 2013; Nouch et al., 2018; Read et al., 2017; Seidenberg, Rosemann, & Senn, 2013; Senn, Seidenberg, & Rosemann, 2009). Four of these studies were conducted in Canada and assessed the uptake and outcomes of HCV treatment among PWID delivered within a one-stop-shop and multidisciplinary model of care in primary care settings (Charlebois et al., 2012; Grebely et al., 2007, 2010; Newman et al., 2013; Nouch et al., 2018). Under this model, clients could also access a range of relevant health and social services, including addiction and infectious diseases care, needle exchange, and peer-support groups. All of them showed improved HCV treatment uptake (26%–41%) and SVR rates (18%–86%). Similarly encouraging high rates of engagement in the HCV cascade of care among PWID were found in multidisciplinary primary care settings in the Netherlands (treatment uptake: 90%, SVR: 65%) (Lindenburg et al., 2011) and Australia (SVR 79%) (Read et al., 2017). Two studies examined integration of HCV services among individuals receiving OUD MAT in a primary care setting, demonstrating that this strategy was feasible and resulted in favorable outcomes (HCV testing uptake: 91%, treatment uptake: 31%, SVR: 29%), particularly among those with longer duration of MAT (Seidenberg et al., 2013; Senn et al., 2009). One pilot RCT conducted in the U.S. demonstrated higher HCV treatment uptake (100% versus 44%, $P = 0.012$) and efficacy rates (50% versus 11%, $P = 0.049$) among participants receiving methadone-based MAT and HCV care in an integrated, multidisciplinary primary care setting (including a modified direct observed therapy component) compared to those receiving methadone-based MAT and HCV treatment in different settings (Bruce et al., 2012). One study reported on a nurse-led community-based model of HCV care in the U.K. and involved a clinical nurse specialist in hepatitis working under the supervision of a consultant in infectious diseases in a primary care setting that also provided MAT for OUD. (Jack et al., 2009). In this model, the nurse performed testing for viral hepatitis and HIV, as well as urine drug tests. The decision to offer treatment for HCV was made between the nurse and all the treating physicians. This study found high numbers of previously undiagnosed chronic HCV infection (95%), as well as better compliance rates than patients treated in the hospital setting (> 85% versus < 40%), and high SVR rates (38%).

Harm reduction centres. Three studies reported on HCV testing among attendees of harm reduction centres (Abou-Saleh, Rice, & Foley, 2013; Islam et al., 2012; Kikvidze et al., 2018), with two of them evaluating point-of-care HCV diagnostic tools, including dried blood spot (DBS) antibody testing (Abou-Saleh et al., 2013) and rapid HCV testing and liver elastometry (Kikvidze et al., 2018). Overall, studies found high rates of HCV testing uptake, HCV prevalence and referrals to specialized HCV care, though one study found that recent injection drug use was negatively associated with attending the referral (Islam et al., 2012).

HIV care facilities. Two studies described the integration of first HCV treatment (Taylor, 2005), and later on buprenorphine-based MAT (Taylor et al., 2012) in an HIV clinic in the U.S. While a preliminary evaluation of the HCV/HIV coinfection clinic suggested the feasibility and potential of the strategy (Taylor, 2005), the additional introduction of onsite buprenorphine-based MAT did not result in improved HCV treatment uptake rates (Taylor et al., 2012). Authors speculate that this may be partially explained by the fact that many patients had still uncontrolled HIV disease, and therefore were not good candidates for HCV treatment. A third study from the same group evaluated the efficacy of Peg-IFN treatment among HIV/HCV co-infected individuals enrolled in methadone-based MAT receiving integrated care at two HIV clinics (Taylor et al., 2011). While limited by the small sample size, and low completion rates due to adverse events, SVR rates (18%) were similar to historical controls (14%).

Sexually transmitted infection (STI) clinic. Lastly, one study from the U.S. showed that integration of hepatitis services into an STI clinic resulted in high HCV testing (92%) and referral rates, as well as high uptake of other services (e.g., STI exam, HIV testing) among PWID (Hennessy, Weisfuse, & Schlanger, 2007).

Methodological quality assessment

Overall the quality of evidence was low to moderate. The only two included RCTs were assessed as having a high risk of bias. Similarly, none of the single-arm intervention or observational studies was assessed to be at low risk of bias, with 21 of them being deemed to be at moderate risk of bias and 9 at high risk of bias. Of the 12 case-series studies, 6 were assessed as moderate risk of bias and 6 as high risk of bias. Table 3 presents an overall risk of bias for each study, and the full details are shown in Supplementary Tables 3–5.

Discussion

HCV is prevalent among PWID, and likewise, many people living with HCV struggle with problematic substance use. Despite these overlapping epidemics, research shows that only a minority of PWID referred for evaluation to a HCV specialty clinic show up, and even less initiate treatment (Fishbein, Lo, Reinus, Gourevitch, & Klein, 2004; Gonzalez, Fierer, & Talal, 2017). Therefore, there has been increasing interest on the role of one-stop shop models of substance use and HCV services to improve access to HCV care and treatment outcomes among PWID. Our systematic review suggests that, indeed, integration of HCV and substance use services may facilitate engagement along the continuum of care of HCV among PWID. However, overall the quality of evidence was low to moderate. Of note, of the 44 included studies, only two were RCT (Bruce et al., 2012; Ebner et al., 2009), and both were deemed at high risk of bias. In addition, only one of the two RCT had a non-integrated care arm as control, but included only 21 participants (Bruce et al., 2012), further limiting our ability to draw strong

conclusions on the relative benefits of integrated and non-integrated care approaches. Likewise, the diversity of integration approaches adopted made it difficult to compare outcomes across studies. Our review also found that almost all studies (except for two) were conducted in high-income countries, with no studies from settings with high HCV prevalence among PWID, such as Eastern Europe and Southeast Asia, and only six studies were conducted in the DAA era, limiting the applicability of findings to other populations of PWID living with HCV or current HCV treatment standards.

The heterogeneity of integration interventions implemented and treatment settings documented in this review indicates that a variety of models could be successful and that this is highly context-specific. Indeed, we found evidence of improved HCV treatment outcomes in diverse settings ranging from HCV facilities to OAT programs, to HIV clinics, to community health clinics, to harm reduction centres. Similarly, although the number of services (e.g., testing, treatment) and type of intervention implemented (e.g., nurse-led, peer-led) also differed, a common theme among successful models was its multidisciplinary, people-centered approach. Altogether, these findings suggest that understanding the population dynamics, including their needs, priorities and points where they are already accessing services is a critical first step for an effective and acceptable integrated substance use and HCV care model (Savic, Best, Manning, & Lubman, 2017).

The majority of the studies included in this review were conducted in specialized SUD care settings (e.g., MAT programs), with only one conducted in a HCV care facility. The lack of more studies evaluating integrated models of care for PWID in HCV facilities is not surprising, and probably reflect common reservations among HCV clinicians about treating PWID for HCV (Asher et al., 2016), despite growing evidence indicating that when appropriately supported, PWID achieve similar rates of SVR compared to the general population both with older Peg-IFN- (Aspinall et al., 2013; Dimova et al., 2013) and newer DAA-based regimens (Hajarizadeh et al., 2018). Accordingly, more empirical research is needed to determine the feasibility, acceptability, and effectiveness of integrating HCV and substance use services for PWID in HCV care settings.

Our review also identified some innovative integrated care models. Specifically, we found some evidence that integration of HCV and substance use services in primary care or community settings, including nurse-led models, may improve engagement along the continuum of HCV care even with complex and lengthy IFN-regimens. Easier and safer-to-administer DAA-based regimens offer a unique opportunity for task-shifting and further integration of HCV care into community settings, improving coverage and potentially reaching more hidden populations of PWID (Yoo, Perumpail, Cholankeril, Jayasekera, & Ahmed, 2017). For example, a recent large community-based trial found similarly high SVR rates of over 85% when DAAs were administered by specialist or non-specialist providers (primary care physician or nurse practitioner) (Kattakuzhy et al., 2017). In addition, given the chronic nature of SUD and related comorbidities (including HCV), primary care settings offer a particularly attractive venue to provide longitudinal continuity of care and integrated services to meet the multiple needs of PWID in a more people-centered way (McLellan & Woodworth, 2014; Samet, Friedmann, & Saitz, 2001).

Finally, as some studies have shown, the integration of healthcare services is challenging. Among this, programs' limited capacity and staff resistance to taking on the additional training and increased workload have been documented as key implementation barriers (Heseltine & McFarlane, 2007). While some models with less integration (e.g., only testing activities) also faced challenges with referrals for continuing and timely care due to fragmented communication or absence of specific services (Heseltine & McFarlane, 2007), this obstacle was overcome when HCV testing was integrated within low-threshold community-based centres with additional supports (e.g., peer-navigators) and organized referral pathways (Abou-Saleh et al., 2013; Islam et al., 2012; Kikvidze et al., 2018). Collectively, these findings suggest the need to consider contextual factors and available resources, as well as to involve relevant stakeholders when developing any integrated care strategy.

This study has a number of limitations. First, our categories of integrated care models only describe one way of integrating HCV and substance use services (i.e., co-location). We decided to focus on one-stop shop models given the evidence demonstrating attrition when patients need to travel from one location to another one (Fishbein et al., 2004; Gonzalez et al., 2017). Second, we excluded 80 conference abstracts that did not have a published full-text available, and thus we may have excluded relevant work, particularly from the DAA era. Furthermore, our findings may have been affected by publication bias, where undesired outcomes (e.g., null or negative findings) may have influenced decisions to publish. Third, while some studies reported short-term HCV recurrence (i.e., at 24 weeks post-treatment), the small sample size of these studies precludes drawing any significant conclusion. Similarly, none of the studies reported long-term HCV outcomes (e.g., re-infection, mortality), limiting our ability to evaluate whether the impacts of integrated models were sustained. Fourth, we only identified one small pilot RCT comparing head-to-head an integrated and non-integrated care approach and no studies comparing outcomes of different models of integrated care. Therefore, we cannot ascertain the relative advantages and disadvantages of different models. Finally, the heterogeneity of integration approaches makes it difficult to extrapolate findings from one setting to another one. This is particularly true for low- and middle-income countries given the lack of studies conducted in these settings. That said, overall positive integration outcomes suggest that integrated models of HCV and substance use care can be successfully implemented in diverse settings.

Conclusion

In summary, this review found low to moderate quality evidence that integrated models of HCV and substance use care (i.e., one-stop shop models) may improve engagement along the continuum of HCV care among PWID. The diversity of integration approaches suggests that there is no single model that should be pursued and that the ideal model for a particular setting should consider contextual factors, such as population needs and available resources. As such, there is an urgent need for higher quality studies, particularly in low- and middle-income settings, to inform integrated care strategies to optimize HCV care access and outcomes among PWID globally.

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Conflict of interest

Nothing to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2019.05.023.

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