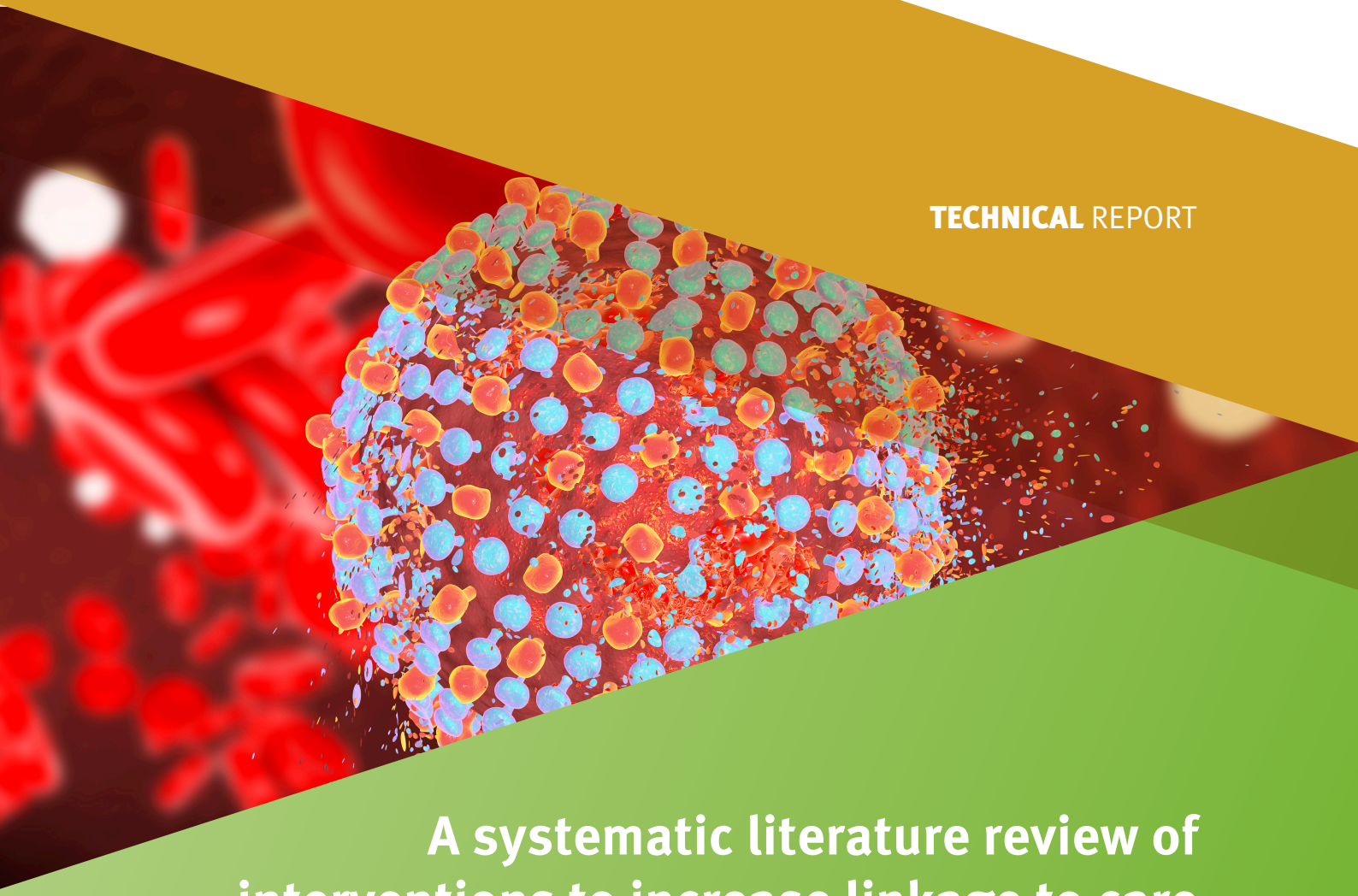

TECHNICAL REPORT

A systematic literature review of interventions to increase linkage to care and adherence to treatment for hepatitis B and C, HIV and tuberculosis among people who inject drugs

From the package of technical documents published to accompany the joint ECDC and EMCDDA update of the guidance, 'Prevention and control of infectious diseases among people who inject drugs' (2023)

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This report was commissioned by the European Centre for Disease Prevention and Control (ECDC) through service contract No. ECD.10793/2020, coordinated by Otilia Mårdh with support from Janelle Sandberg, and produced by the Austrian National Public Health Institute (Gesundheit Österreich, GOEG).

This report is part of a package of technical documents to accompany the joint ECDC and EMCDDA update of the guidance, 'Prevention and control of infectious diseases among people who inject drugs' (2023).

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Acknowledgements

The authors would like to thank Daniela Antony (GOEG) for helping with the development of the search strategy and the extraction form and Ana-Belen Escriva (ECDC) for peer-reviewing the search strategy.

Competing interests

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of this review and there is no financial interest to report.

Suggested citation: European Centre for Disease Prevention and Control. A systematic literature review of interventions to increase linkage to care and adherence to treatment for hepatitis B and C, HIV and tuberculosis among people who inject drugs. Stockholm: ECDC; 2022.

Stockholm, 2022

ISBN 978-92-9498-597-2
doi: 10.2900/257011
Catalogue number TQ-03-22-166-EN-N

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Abbreviations

aHR	adjusted Hazard Ratio
ART	Antiretroviral therapy (HIV)
AtT	Adherence to treatment
CAD	Centre for alcohol and other drug problems
CM	Care management
DAA	Direct-acting antivirals
DOT	Directly observed therapy
EDU	Educational intervention
EEA	European Economic Area
EFTA	European Free Trade Association
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EPHPP	Effective Public Health Practice Project tool
EU	European Union
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Harm reduction
IDU	Injecting drug use(rs)
IFN	Interferon
ITT	Intention-to-treat analysis
LtC	Linkage to care
mDOT	modified directly observed therapy
NCM	Nurse care manager/management
NRS	Non-randomised study
NSP	Needle and syringe programme
OST	Opioid substitution treatment
PHE	Public Health England
PICO	Population, Intervention, Comparison and Outcome
PoC	Point of care
PP	Per-protocol analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
SAT	Self-administered therapy
SES	Socio-economic status
SUD	Substance use disorder
SVR12	Sustained virological response at post-treatment week 12
SVR24	Sustained virological response at post-treatment week 24
TA	Treatment adherence
TC	Treatment completion (outcome)
TI	Treatment initiation
TM	Telemedicine
WHO	World Health Organization

Glossary

Cascade of care model

A model comprised of the key stages of care for people living with a particular disease. It can be adapted for different disease areas but is generally comprised of the following key stages: prevention, identification, treatment and recovery. It is used to guide the monitoring of outcomes and the tailoring of interventions accordingly. It is also called the continuum of care within the context of HIV/AIDS.

Contingency management

A behavioural management technique that involves using incentives such as cash, vouchers, prizes, or other kinds of privileges to reinforce behaviours, or disincentives to discourage them.

Directly observed therapy

A method of treatment administration in which a healthcare professional watches as a person take each dose of a medication to ensure all medications are received and taken as prescribed. It is sometimes called directly administered antiretroviral therapy (DAART) within the context of HIV/AIDS.

Multicomponent intervention

An intervention that delivers a variety of targeted services (e.g. case management, peer mentors, social workers, mental health support) in an integrated manner.

Opioid substitution treatment

Where patients who are dependent on fast-acting opioids (such as heroin) are instead administered slow-acting opioids (such as opioid agonists methadone and buprenorphine). While OST could technically include both opioid agonist treatment (OAT) and opioid antagonist treatment, the overwhelming majority on OST would likely be receiving OAT alone.

Peers

People within a community with equal standing with each other, belonging to the same group and sharing a common experience. Peer support, which can occur informally or formally, refers to support provided and received by people who are peers.

Primary care

Medical care and treatment provided by general practitioners or other healthcare workers. Primary care is typically the first point of healthcare contact; is focused on providing ongoing, comprehensive care; and involves coordinating with specialists as needed.

Sustained Virological Response – SVR12

Where no hepatitis C virus (HCV) RNA is detectable in the blood 12 weeks after treatment has been completed. It is considered a marker for being cured of HCV infection.

Sustained Virological Response – SVR24

Where no HCV RNA is detectable in the blood 24 weeks after treatment has been completed. It is considered a marker for being cured of HCV infection.

Telemedicine

The use of telecommunication technologies to deliver health services when patients and healthcare providers are separated by a distance.

Executive summary

Background

This systematic literature review of interventions to increase linkage to care and adherence to treatment for hepatitis B and C, HIV and tuberculosis (TB) among people who inject drugs was conducted as part of the update process of the joint European Centre for Disease Prevention and Control (ECDC) and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) guidance, 'Prevention and control of infectious diseases among people who inject drugs' (published in 2011). The purpose of this review was to identify and synthesise the existing evidence on effectiveness of interventions targeting people who inject drugs at two stages of the care cascade: linkage to care and adherence to treatment of HIV, hepatitis B/C and TB.

Methods

The systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A protocol was developed and published on PROSPERO together with the search strategy.

The primary research question regarding interventions that impact linkage to care and adherence to treatment of infections among people who inject drugs was formulated based on a PICO format and included the following elements:

- P (population): people who inject drugs or people receiving OST with chronic HBV, HCV, HIV infection and/or TB;
- I (intervention): any intervention to increase linkage to care or enhance adherence to treatment;
- C (comparator): people who inject drugs or OST comparator group with no intervention or receiving usual or routine care; and
- O (outcome): linkage to care: 'visit' and 'treatment initiation' (TI) and adherence to treatment: 'sustained virological response' (SVR12/SVR24), 'treatment adherence' (TA), 'treatment completion' (TC), or change to low viral load/undetectable 'viral load' (VL).

Barriers to linkage to care and adherence to treatment were collected as secondary outcomes from the eligible studies. Searches in five electronic databases covered the period from 1 January 2011 to 8 July 2020 with no language restrictions and included all the European Union (EU)/ European Economic Area (EEA)/European Free Trade Association (EFTA) countries, EU candidate countries, the United Kingdom, the United States, Canada, Australia, and New Zealand. Titles, abstracts, and full texts were reviewed for inclusion by two independent reviewers, with a third reviewer acting as an arbiter. Data were extracted using a pre-specified, previously piloted data extraction form. The study risk of bias was assessed using the Effective Public Health Practice Project (EPHPP) tool [1], while study quality was determined in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system described by Guyatt et al. (2008) [2].

A narrative synthesis of the findings was conducted of publications addressing the impact of interventions on linkage to care and adherence to treatment. The evidence base identified through this review was critically reviewed by a panel of experts appointed by ECDC and EMCDDA.

Results

This systematic literature review of interventions to increase linkage to care and adherence to treatment for infections among people who inject drugs retrieved 25 eligible studies that were included in the analysis. These studies represented a diverse group of interventions spanning various settings and focusing on one or two of the infections of interest. Most studies (20) focused on HCV, with only four studies on HIV and one on TB. There were no eligible studies reporting interventions for HBV. All included studies were conducted in high-income countries (the United States, Canada, Australia, New Zealand, Italy, Germany, Portugal, Austria, the United Kingdom, Spain, and one multicentre trial at sites in the United States and Europe).

For increasing linkage to HCV care, the results suggest that integrated care approaches, nurse case management, and peer involvement, as well as multidisciplinary services and cooperation between providers, especially when involving pharmacies and primary care settings, are promising strategies to facilitate treatment-seeking and improving access to care for people who inject drugs. For increasing linkage to HIV care, identified evidence was sparse and of very low quality. Regarding interventions to increase adherence to treatment, major differences were identified between the four infectious diseases due to a diversity of treatment options and durations. Adherence to HCV treatment was improved by peer mentoring, integrated care, and primary care approaches. For adherence to HIV treatment, only non-randomised and rather low-quality studies were

identified, which resulted in a low certainty of evidence ratings. One study evaluated adherence to TB treatment through cooperation between services, but the unclear certainty of evidence due to low quality did not allow an interpretation of effectiveness.

Conclusions

This review, covering the period between 2011 and 2020, identified several interventions that can improve linkage to care and adherence to treatment of infections (in particular of HCV) among people who inject drugs and can inform public health decision-making and practice. It also highlights the paucity of well-designed randomised control trials (RCTs) or comparative studies evaluating interventions to enhance linkage to care and adherence to treatment, especially in relation to HBV, HIV and TB. There were no studies evaluating interventions to enhance linkage to HBV and TB care, and only one study assessing adherence to TB treatment. This review calls for well-designed studies evaluating interventions for an improved and simplified care cascade for infectious diseases among people who inject drugs. Outcomes of this systematic review provide a direction for policy-makers, public health researchers and national and international programme coordinators involved in the prevention and control of infectious disease among the people who inject drugs in EU/EEA countries and elsewhere.

1. Background

1.1 Infectious diseases among people who inject drugs: current state of knowledge and understanding

People who inject drugs are at a high risk for blood-borne viral infections such as HIV and hepatitis B and C and bacterial infections, including tuberculosis (TB) [3]. These infections are primarily spread through the using and sharing of contaminated injection drug equipment, unsanitary conditions, and low vaccination rates among at-risk populations [4].

Hepatitis C virus (HCV) is the most prevalent blood-borne virus infection among people who inject drugs, who can transmit the virus to others when sharing injecting materials that have been in contact with their blood [3]. If not resolved, HCV can lead to chronic liver disease, cirrhosis, and cancer [5]. In the EU/EEA, 37 733 cases of (HCV) infection were notified in 2019 [6]. Among the cases for which information on the transmission mode is available, injecting drug use was reported as the likely cause for 60% of acute cases and 59% of chronic cases [6].

Hepatitis B virus (HBV) infection is less common than HCV infection, but is still more prevalent among people who inject drugs than in the general population despite the availability of an effective vaccine, which is included in recommended vaccination schedules in most European Union and European Economic Area (EU/EEA) countries [3]. For HBV infection, an estimated 7% of the acute cases reported in 2019 in the EU/EEA were linked to injecting drug use [7]. HBV infection can be either acute or chronic and the associated illness ranges in severity, potentially leading to the development of cirrhosis, liver cancer and death. Monitoring data collected by ECDC show suboptimal linkage to HBV or HCV care in EU/EEA countries and limited progress towards the WHO European Action Plan targets for 2020. Only seven countries had available data on numbers diagnosed and receiving care for HCV. The proportion of diagnosed HCV cases linked to care ranged from 2.3% in Denmark to 55.3% in Romania. None of the countries with available data achieved the 2020 target of having 90% of diagnosed HBV or HCV patients linked to care [8].

Human immunodeficiency virus (HIV) also has the potential to spread rapidly via the sharing of needles and syringes between people who inject drugs, as well as via unprotected sex between people who inject drugs and their injecting and non-injecting partners. While people who inject drugs now account for a smaller proportion of new HIV cases in the WHO European Region, HIV infections linked to injecting drug use are being diagnosed late and local HIV outbreaks among people who inject drugs are still being documented in Europe (Bulgaria, Estonia, Greece, Latvia, Lithuania and Romania) [3]. In 2019, 849 cases (5.5%) were attributed to injecting drug use, a proportion that has remained low and stable for the last decade [9].

Moreover, people who inject drugs are at increased risk of developing TB. TB is an infectious disease caused by a group of Mycobacterium species called the *Mycobacterium tuberculosis* complex [10]. TB typically affects the lungs (pulmonary TB), but it can cause disease in any organ (extrapulmonary TB). Studies recording the prevalence of active TB disease among people who inject drugs report levels from 0.5% to 66% [11]. HIV further increases the risk of TB, and TB is a leading AIDS-defining illness and cause of mortality among people living with HIV who inject drugs [12].

1.2 Purpose, scope, relevance to public health

In October 2011, ECDC and EMCDDA published a joint guidance on 'Prevention and control of infectious diseases among people who inject drugs' [4]. Seven key interventions were recommended based on scientific evidence combined with expert opinion and models of best practice of prevention within the EU/EEA. A stakeholder survey on guidance use carried out in 2018 by ECDC and EMCCDA confirmed the need for an update and identified emerging topics and public health concepts to be covered by the updated guidance. ECDC and EMCDAA initiated the update process in 2019 and commissioned an update of the evidence base retrieved in 2011 and a new collection of evidence for several new areas, including on interventions to increase linkage to care and adherence to treatment of infections of people who inject drugs.

The objective of this systematic review was to identify interventions that can improve linkage to care and adherence to treatment of infections among people who inject drugs for HIV, HBV, HCV, and TB.

2. Review methods

The systematic review was conducted following PRISMA guidelines [13]. A protocol was developed and published on PROSPERO together with the search strategy (https://www.crd.york.ac.uk/prospero, registration no.: CRD42020191116) on 14 July 2020.

Research questions and objectives

The research questions of the systematic review, definitions of linkage to care and adherence to treatment, and the PICOs were agreed between ECDC and Gesundheit Österreich GmbH (GOEG). Additional comments were received from other organisations involved in the guidance update process, including EMCDDA and its contractor from Glasgow Caledonian University, Public Health Scotland, in partnership with the University of Bristol.

The primary research questions were:

- Q1: Which interventions can increase linkage to care for hepatitis B, hepatitis C, human immunodeficiency virus and tuberculosis among people who inject drugs?
- Q2: Which interventions can increase adherence to treatment for hepatitis B, hepatitis C, human immunodeficiency virus and tuberculosis and among people who inject drugs?

Reported barriers to linkage to care and adherence to treatment were collected as secondary outcomes.

2.1 Definitions for linkage to care and adherence to treatment

A scoping search of literature was conducted to identify definitions for linkage to care and adherence to treatment.

Definitions for linkage to care varied across studies and diseases.

Saab et al. (2019) [14] mention some examples for **linkage to care for HCV**: 'confirmatory HCV RNA testing in patients found to have HCV antibodies'; 'referral to specialty clinics among viremic patients'; a combination of these two; 'receiving HCV RNA testing'; 'referral to specialty care and attending the first appointment with the specialist'; 'attending the first appointment with a provider and starting viral treatment' or 'being seen by a specialist'. In a systematic review by Bajis et al. in 2017 [15], the authors differentiated between linkage to care defined as 'clinical assessment of HCV infection or liver disease' and treatment initiation or treatment uptake including interferon-containing and interferon-free regimens.

In Hyun et al. (2019) [16], **linkage to HBV care** is defined as follows: 'a first visit to a physician following the diagnosis of chronic HBV infection […] an essential step in engaging patients chronically infected with HBV and persuading them to get follow-up care. [Linkage to care] involves continual monitoring of the disease and, when indicated, medical and surgical intervention'.

The definition of **linkage to care** in the field of **TB** care also varies across studies. Some examples from the literature are: 'starting TB treatment within 28 days in those with a positive test result' [17]; 'patients diagnosed with TB starting treatment' [18]; and 'attended follow-up: attended at least one session for evaluation of a positive test and/or for treatment services' [19]'.

With regard to definitions of **linkage to care for HIV,** Croxford et al. (2018) [20] defined prompt linkage to care as 'entry into care within three months of diagnosis' (based on research from the US showing that initiation of care within three months of HIV diagnosis is significantly associated with faster time to viral suppression, data from the United Kingdom showing that >95% of people diagnosed with HIV enter care within three months of diagnosis, and the fact that a three-month cut-off has been used widely in the literature from Europe).The International Association of Providers of AIDS Care (IAPAC) Guidelines for Optimizing the HIV Care Continuum for Adults and Adolescents consider a visit after one month as 'failed linkage' or 'delayed entry into care' [21], similar to the National US HIV/AIDS strategy, which defines linkage to care as the 'completion of a visit with an HIV medical provider within one month (30 days) of HIV diagnosis' [22]. It should be noted that factors influencing linkage to HIV care in people who inject drugs or people on OST may be considered very different from those in the general population. For this technical report, a pre-defined time frame may be not directly relevant for the study outcomes.

Definitions for **adherence to treatment** also vary across studies. In a systematic review by Lieveld et al. (2013) [23], **HCV adherence** was defined as 'filling new prescriptions or refilling prescriptions or any other therapeutic interventions on time'. **Non-adherence to TB treatment** was defined as 'having taken less than 80%-90% of TB treatment doses' [24], 'being lost to follow-up' (or default), 'not filling new prescriptions or refilling prescriptions or any other therapeutic interventions on time' or is being assessed through isoniazid (INH) urine tests or appointment keeping rates. **Non-adherence to HIV treatment** is defined using HIV-specific clinical outcomes such as viral load (change or proportion with undetectable levels), CD4/T-cell count (change),

progression to AIDS, and mortality and other co-morbidities, as well as study authors definitions such as 'having taken less than 80%-90% of treatment doses', 'being lost to follow-up' (or default), 'appointment keeping', 'not filling new prescriptions', and 'not refilling prescriptions or any other therapeutic interventions on time'.

As no consistent and widely accepted definitions of linkage to care and adherence to treatment exist, ECDC, EMCDDA and the project team decided on using a pragmatic and broad approach for this systematic review (see Box 1).

Box 1. Definitions of linkage to care, adherence to treatment and outcomes

Linkage to care: Visit with a provider/specialist after positive test for HBV, HCV, HIV or TB and/or starting treatment (treatment initiation). The outcomes for primary research question on linkage to care are 'visit' and 'treatment initiation' (TI).

Adherence to treatment: Filling new prescriptions or refilling prescriptions or any other therapeutic interventions on time, completing treatment, change to low viral load/undetectable virus load (VL). The outcomes for primary research question on adherence to treatment are: SVR12, SVR24, 'treatment adherence' (TA), 'treatment completion' (TC), 'viral load' (VL).

2.2 PICOs

The research questions were formulated using the Population, Intervention, Comparison and Outcome (PICO) model.

Table 1. Population, Intervention, Control, Outcome (PICO) model for linkage to care

Population	People who inject drugs OR people on opioid substitution therapy (OST) with chronic HBV, HCV, HIV infection and/or TB, adults and adolescents over the age of 14 years of any sex
Intervention	Any intervention to increase linkage to care or to decrease the duration between diagnosis and first visit and/or initiation of treatment. » *Linkage to care defined as Visit with a provider/specialist after positive test for HCV, HBV, HIV or TB and/or starting treatment (treatment initiation).*
Comparator	People who inject drugs or OST comparator group with no intervention or receiving usual or routine care as defined by study authors
Outcomes	**Primary outcomes:** » Proportion of study population with chronic HBV, HCV, HIV infection and/or TB, linked to provider/specialist (visit) » Proportion of study population with chronic HBV, HCV, HIV infection and/or TB, initiating treatment (TI) **Secondary outcomes:** » Any reported reasons for seeing/not seeing provider/specialist » Any reported reasons for initiating/not initiating treatment

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; OST: opioid substitution treatment; TB: tuberculosis; TI: treatment initiation.

Table 2. Population, Intervention, Control, Outcome (PICO) model for adherence to treatment

Population	People who inject drugs OR people on opioid substitution therapy (OST) with chronic HBV, HCV, HIV infection and/or TB, adults and adolescents over the age of 14 years of any sex
Intervention	Any intervention to enhance adherence to treatment. » *Adherence to treatment defined as* filling new prescriptions or refilling prescriptions or any other therapeutic interventions on time, completing treatment, change in viral load.
Comparator	People who inject drugs or OST comparator group with no intervention or receiving usual or routine care as defined by study authors
Outcomes	**Primary outcomes:** » Proportion of study population with chronic HBV, HCV, HIV infection and/or TB, already in treatment and adherent to treatment » Viral load as surrogate endpoint **Secondary outcomes:** » Any reported reasons for being or nor not being adherent to therapy (e.g. adverse events, access problems, financial issues) from people who inject drugs

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; OST: opioid substitution treatment; TB: tuberculosis; TI: treatment initiation.

2.3 Inclusion and exclusion criteria

Table 3 lists the inclusion and exclusion criteria for studies related to HCV, HBV, TB, and HIV.

Table 3. Selection criteria

Criteria	Inclusion	Exclusion
Publication date	Publications between 1 January 2011 and 8 July 2020 (date of database search)	Publications before 1 January 2011
Country of study	EU/EEA/EFTA countries + candidate countries + UK + US + CA + AU + NZ (for full list, see Annex 1)	All other countries
Language	No language restrictions	
Publication type	Full text study publication available	Conference abstracts, study protocols, studies that have not been peer-reviewed, repeated/duplicate results
Study design/type	Randomised controlled trials (RCTs), non-randomised control trials, prospective and retrospective cohort studies and case-control studies	Other study design: Non-comparative studies with no control, case studies, case reports, animal studies, ineligible methodologies, epidemiology studies, review studies (only used for citation check)
Study duration	**Adherence:** HCV: at least three months* HBV/TB/HIV: study duration at least one year or follow up within one year	**Adherence:** HCV: less than three months HBV/TB/HIV: study duration less than one year or follow up within one year
Study population	• At least 50% of study sample comprised of PWID or people on OST (age 14 and older, any sex) AND • PWID with co-infections HBV, HCV, HIV, TB	Other study population
Intervention	• Any intervention aimed at enhancing linkage to care targeting PWID/people on OST in any setting OR • Any intervention aimed at enhancing adherence to treatment targeting PWID/people on OST in any setting	• Public health interventions targeting healthcare providers as opposed to individuals** • Interventions targeting testing
Study outcomes	Data on at least one of the outcomes listed in the specific PICO tables must be reported***	None of the defined study outcomes included/ineligible outcomes, no data available

AU: Australia; CA: Canada; EEA: European Economic Area; EFTA: European Free Trade Association; EU: European Union; HBV: Hepatitis B Virus, HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; NZ: New Zealand; OST: opioid substitution treatment; PWID: people who inject drugs; PICO: Population, Intervention, Control, Outcome; UK: the United Kingdom; US: the United States.

** A cut-off duration of at least three months for adherence for the HCV studies was chosen to cover the 12 weeks of DAA therapy that is recommended for most patients under existing guidelines so as to achieve sustained virological response (SVR) [25].*

*** Interventions should target people who inject drugs/OST as individuals, if after first selection of abstracts no studies were identified, then public health interventions targeting healthcare providers were also included.*

**** Adherence reporting: people who inject drugs/OST self-reporting adherence were included in the first step, if enough primary studies were available without self-reporting adherence (more than five studies), self-reporting adherence were excluded due to higher bias risk.*

2.4 Search strategy and information sources

The search strategy followed the Peer Review of Electronic Search Strategies (PRESS) 2015 Guideline Evidence-Based Checklist by McGowan et al. (2016) [26]. The final search strategy was peer-reviewed by an ECDC librarian not involved in the project team. For the detailed search strategies and search terms, see Annex 2.

Searches covered the period from 1 January 2011 to 8 July 2020, with no language restrictions.

Searches in electronic databases were carried out on 8 July 2020 in:

- MEDLINE (Ovid platform: https://ovidsp.tx.ovid.com). Including epub ahead of print, in-process and other non-indexed citations, daily, and versions. Time span: 1946 to 6 July 2020.
- Embase: Elsevier produces the data. Ovid provides the interface (Ovid platform: https://ovidsp.tx.ovid.com). Time span: 1947 to present.

- Cochrane Central Register of Controlled Trials (CENTRAL): Provides high quality evidence of clinical trials worldwide. The Cochrane Collaboration collects the information (https://www.cochranelibrary.com) and Wiley-Blackwell publishes it. Time span: 1991 to present.
- Cochrane Database of Systematic Reviews (CDSR): CDSR includes all Cochrane Reviews (and protocols) prepared by Cochrane Review Groups. CDSR is part of the Cochrane Library (https://www.cochranelibrary.com), which is published by Wiley-Blackwell. Time span: 1995 to present.
- American Psychological Association (APA) PsycINFO: database encompassing psychiatry, psychology, behaviour and mental health. Time span: 1806 to June 2020.

In addition, a grey literature search was undertaken in July 2020 on the websites listed in Table 4 below.

Table 4. Grey literature search

Name	URL
US Preventive Service Task Force (Search Results | United States Preventive Services Taskforce)	uspreventiveservicestaskforce.org
European Monitoring Centre for Drugs and Drug Addiction	https://www.emcdda.europa.eu/publications-database_en?f%5B0%5D=field_search_topic%3A1903
World Health Organization Regional Office for Europe	https://www.euro.who.int/en/health-topics/communicable-diseases/hivaids/publication
Agency for Healthcare Research and Quality	https://www.ahrq.gov/research/publications/search.html
Centre for Reviews and Dissemination	https://www.crd.york.ac.uk/CRDWeb
National Institute for Health Research	https://www.journalslibrary.nihr.ac.uk; https://www.journalslibrary.nihr.ac.uk/advancedsearch
Centers for Disease Control and Prevention (CDC)	https://www.cdc.gov/hepatitis/resources/professionals/mmwrs.htm#hepB https://www.cdc.gov/tb/publications/reportsarticles/default.htm
Organisation for Economic Cooperation and Development (OECD)	https://www.oecd-ilibrary.org
United Nations Office on Drug and Crime	https://unov.tind.io/?ln=en; UN library vienna online
Health Technology Assessment International (HTAi)	https://htai.org
European Public Health Association (EUPHA)	https://eupha.org/publications.php?one=EUPHA+Publications
Joint United Nations Programme on HIV/AIDS (UNAIDS)	https://www.unaids.org/en/resources/publications/all
Health Evidence Network (HEN)	https://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/publications/evidence-reports/evidence-reports
European Network for Health Technology Assessment (EUnetHTA)	https://eunethta.eu
Council of Europe Pompidou Group	https://www.coe.int/en/web/pompidou/publications
European Commission	https://ec.europa.eu/info/index_en
Health Protection Agency (UK) – linked to: Public Health England	https://www.gov.uk/government/organisations/public-health-england
Harm Reduction International (HRI	https://www.correlation-net.org/resource-center-publications
Correlation European Harm Reduction Network	https://www.correlation-net.org/resource-center-publications https://www.hepatitis-c-initiative.eu/index.php/resources/hcv-drug-use
Joint Action HA-REAC	https://www.hareact.eu
HepCare Europe	https://www.ucd.ie/medicine/hepcare
National Institute for Health and Care Excellence (NICE)	https://www.evidence.nhs.uk
The International Network of Agencies for Health Technology Assessment (INAHTA)	https://database.inahta.org

In addition, a search for ongoing or unpublished studies was conducted in the clinicaltrials.gov register in August 2020. An update of the status of the registry entries was carried out in April 2021.

2.5 Selection process

All citations retrieved through electronic databases search were imported into EndNote X9 and duplicates removed. Titles of remaining citations were screened by two reviewers using *Covidence* (https://app.covidence.org), and irrelevant citations were removed. A further screening of abstracts was performed by two reviewers according to pre-defined selection criteria (see Table 3). Any disagreements were resolved by discussion between the two reviewers and a third member of the team until consensus was reached. Assessment of full text of all abstracts that passed eligibility criteria was independently conducted by two reviewers. Full text screening was done in Endnote X9 bibliographic software (Clarivate Analytics, Philadelphia, US). In cases of disagreement, reviewers discussed the paper with a third member of the team to reach agreement. Reasons for exclusion of studies after full text review were recorded. Lists of references of included studies were cross-checked for any potentially missed publications. The results are presented in a PRISMA flow diagram (see Figure 1). Ongoing studies identified through this search are presented in Supplement 1 and were not included.

2.6 Data collection process and data items

Data and information from studies that fulfilled inclusion criteria for primary outcome (quantitative data) were extracted independently by two reviewers in a pre-defined extraction form in MS Excel. Any discrepancies were resolved by discussion. The extraction form was piloted with five publications to ensure clarity and consistency.

The following variables were extracted: first author, title, publication year, study design, study period, study location, population characteristics (population in % of ever- and/or recent-injecting drugs or % of participants on OST), setting, intervention description (including duration), comparator description, sample size (including intervention and control arms), outcome description, number of participants achieving the outcome of interest (and proportions, if applicable) in both intervention and control arms, funding source, and conflict of interest. Additional information regarding secondary outcomes (any reported reasons for seeing/not seeing a provider/specialist, initiating/not initiating treatment or being/not being adherent to therapy) was extracted from included studies and described qualitatively.

2.7 Study risk of bias assessment

The Cochrane Collaboration's Risk of Bias (RoB) 2 tool (revised tool for Risk of Bias in randomised trials) and the ROBINS-1 tool (Risk of Bias in non-randomised studies - of Interventions) were intended for the risk of bias assessment in the systematic review protocol. Both tools were piloted with two non-randomised studies (NRS) and three RCTs. As a result of the pilot, it was decided that the ROBINS-1 tool would not be used for the assessment of NRS studies because the following key criteria of the Cochrane 'Study Quality Guide' [27] were not met:

- There must be at least two intervention sites and two control sites;
- The timing of the periods for study for the control and intervention groups should be comparable (that is, the pre- and post- intervention periods of measurement for the control and intervention groups should be the same); and
- The intervention and control groups should be comparable on key characteristics.

As a result, the tool for risk of bias assessment was changed to the Effective Public Health Practice Project tool (EPHPP), which accounts for the different study designs of the included studies. For consistency reasons, both study types (NRS and RCTs) were assessed with the EPHPP-quality assessment tool taking into account the accompanying EPHPP dictionary.

The EPHPP tool examined each study against six dimensions:

A. Selection bias;
B. Study design;
C. Confounders;
D. Blinding;
E. Data collection method; and
F. Withdrawals/dropouts.

The quality of each study was graded as strong, moderate, or weak according to the individual ratings attributed to each dimension. Weak quality indicates a high risk of bias, strong quality means a low risk of bias. Two reviewers assessed the studies, and any discrepancies were resolved by discussion or, in case of disagreement, consultation with a third reviewer.

2.8 Assessment of external validity

External validity of research findings may reflect applicability/generalisability of interventions beyond the original study settings and usefulness for practice [28]. To ensure that recommendations that would be based on the findings and conclusions of this review are externally valid, and feasible for practice, published standards for guideline development methodology were reviewed and the following determinants of external validity were selected for inclusion in the assessment: population characteristics, details of the intervention (and the comparison), study period, country, and setting of the intervention (see Table 28 in Annex 3).

Information on external validity was included in evidence to decision (EtD) tables that were developed to support external validity assessment of interventions by an Expert Panel. The Expert Panel was convened to examine the evidence gathered through this review and, based on this, advise on updated guidance recommendations. The EtD tables were based on a combination of GRADE [29] and SIGN 50 [30].

2.9 Measurement of effect

The effects of interventions to improve linkage to care and adherence to treatment are presented as Risk Ratio (Relative Risk; RR) or Odds Ratio (OR) with their respective 95% confidence interval (95% CI). RR and corresponding 95% CI was calculated for each study outcome by the project team, using the initial number of eligible participants included and the number achieving the outcome of interest in each arm. The statistical significance of an outcome was inferred from the 95% CI of RR; the outcome is considered not statistically significant if 95% CI included 1.00.

2.10 Data synthesis methods

First, for each of the 25 studies, main intervention characteristics were extracted and summarised in a table (see Table 28 in Annex 3). Characteristics were compared across studies and studies were grouped based on similarity of interventions in eight groups.

For each intervention group, study characteristics and effect size estimates (calculated RR and 95% CI) were tabulated, accompanied by a qualitative analysis of the results. Any other relevant information from contributing studies was also included.

GRADE system (Table 5) was used to assess the overall certainty of evidence. The detailed assessments of certainty in the body of evidence for each outcome indicator including the studies' individual reasons for downgrading are described in section 3.5 Certainty of evidence.

Meta-analysis was intended (as per PROSPERO protocol, if there were three or more sufficiently similar studies available), but considered not feasible due to across studies heterogeneity (i.e. participants characteristics, settings, interventions, comparators, study designs) and numbers of interventions with similar outcome measurement too small to pool. To note that data pooling should be done separately for NRS and RCTs. In addition, reporting and publication bias could not be assessed (e.g. with Eggers test) as there were not enough studies available.

2.11 Certainty of evidence assessment

The certainty of evidence (also called quality of evidence or confidence in estimates effect) was determined using GRADE system. GRADE rates (if possible) the quality of evidence for each outcome across studies as high, moderate, low or very low (see Table 5). The strength of evidence expresses the level of confidence that the identified evidence correctly reflects the effect of the intervention [2].

Table 5. Overall evidence GRADE – Definitions

Evidence GRADE		Definitions
⊕⊕⊕⊕	HIGH	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low.
⊕⊕⊕◯	MODERATE	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different*Error! Bookmark not defined. is moderate.
⊕⊕◯◯	LOW	This research provides some indication of the likely effect. However, the likelihood that it will be substantially different*Error! Bookmark not defined. is high.
⊕◯◯◯	VERY LOW	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high.

* *Substantially different here is defined as meaning a large enough difference that it might affect a decision.*
Source: Guyatt et al. (2008) [2]

GRADE quality of evidence rating was based on the assessment of five conditions: (1) risk of bias (limitations in study designs, methodology quality assessed with EPHPP tool); (2) inconsistency (heterogeneity) in the direction and/or size of the estimates of effect, (3) indirectness of the body of evidence to the populations, interventions, comparators and/or outcomes of interest, (4) imprecision of results (underpowered study size: few participants/events/observations, wide confidence intervals), and (5) indications of reporting publication bias.

The included RCTs and NRS were grouped and rated separately. For RCTs, the assessment began with a high-quality rating (⊕⊕⊕⊕), which was downgraded if there were serious or very serious concerns related to one or more of the five conditions. In this review, a weak EPHPP rating for RCTs was a reason for downgrading the (1) risk of bias dimension in GRADE. For the dimension (4) imprecision of results, the value for underpowered study size was defined with n ≤ 30 per arm, and/or small events ≤ 10.

NRS assessment started with a low-quality rating (⊕⊕◯◯) and were downgraded if there were serious or very serious concerns related on one or more of the five conditions. For each primary outcome, the strength of the evidence has been assessed separately.

Following the recommendations of the Cochrane Effective Practice and Organisation of Care Group [31], standardised statements have been applied to express results of an intervention with GRADE (see Table 6).

Table 6. Cochrane plain language summaries

	Important difference	Small difference (May not be important)	Little or no difference
High certainty evidence	Improves/ decreases/ prevents/ leads to [outcome]	Improves slightly/decreases slightly/leads to slightly fewer (more) [outcome]	Results in little or no difference in [outcome]
Moderate certainty evidence	Probably improves/ decreases/ prevents/ leads to [outcome]	Probably improves slightly/decreases slightly/leads to slightly fewer (more) [outcome]	Probably leads to little or no difference in [outcome]
Low certainty evidence	May improve/ decrease/ prevent/ lead to [outcome]	May slightly improve/slightly decrease/lead to slightly fewer (more) [outcome]	May lead to little or no difference in [outcome]
Very low certainty evidence	It is uncertain whether [intervention] improves, decreases, prevents, leads to [outcome] because the certainty of the evidence is very low		
No data or no studies	[Outcome] was not measured or not reported, or no studies were found that evaluated the impact of [intervention] on [outcome]		

Source: Cochrane Effective Practice and Organisation of Care (EPOC) [31]

Studies on interferon-based HCV therapy

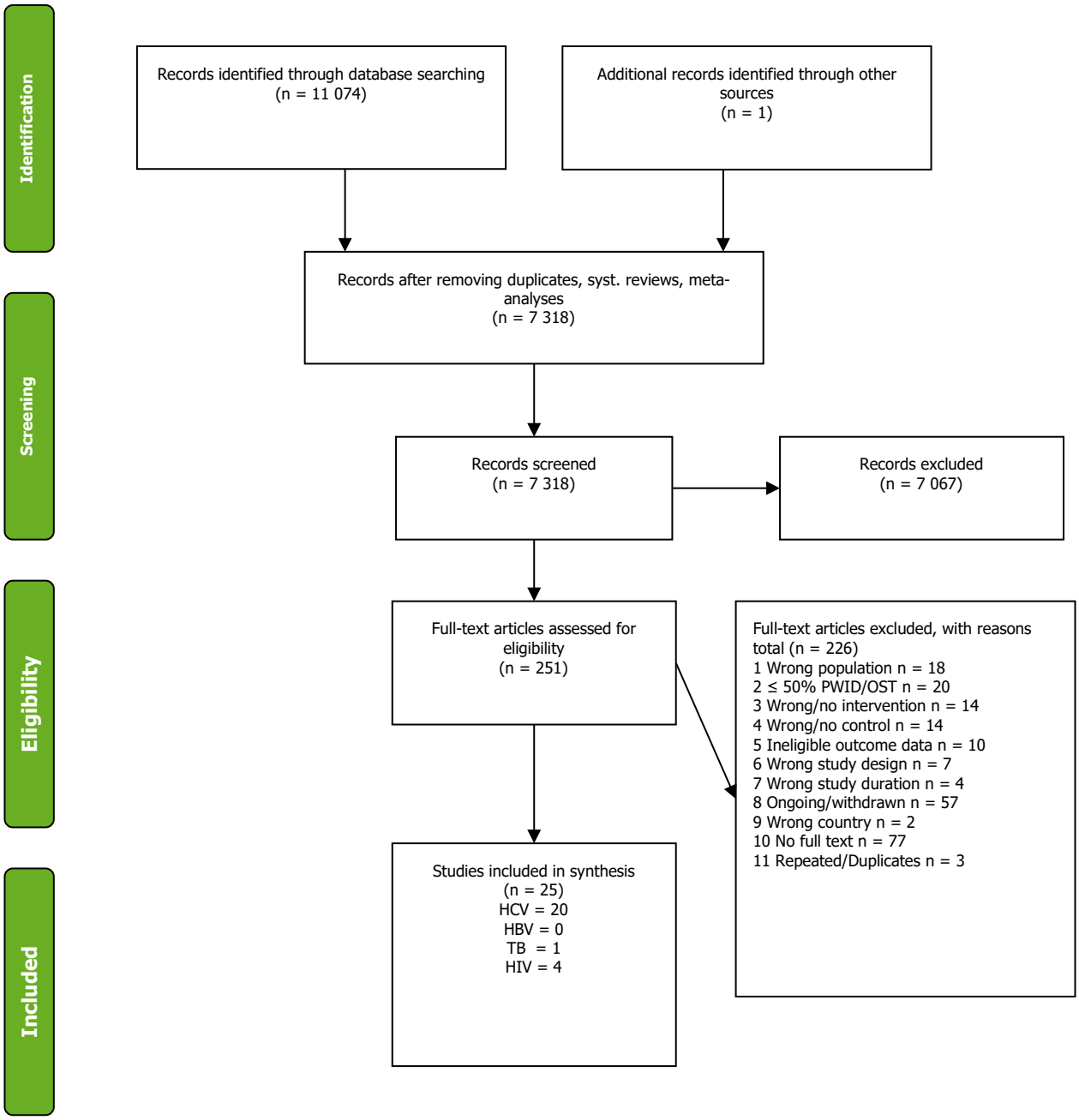
In 2020, the European Association for the Study of the Liver (EASL) updated its clinical guidelines, clearly recommending DAA-based regimens for the treatment of hepatitis C for all patients [25]. As a consequence, it was agreed between ECDC, GOEG, and EMCDDA that studies reporting interventions with interferon-based regimens only will not be included in the evidence synthesis as they are outdated and not relevant for European settings.

3. Review results

3.1 Study selection

The literature search on interventions that can improve linkage to care and adherence to treatment of infections among people who inject drugs and, or people on OST for HCV, HBV, TB and HIV identified in total 11 075 records including one from grey literature search. After excluding duplicates, systematic reviews and meta-analyses, 7 318 remained for title and abstract screening. Of these, 251 were eligible for full text screening. After the full text review, 226 studies were excluded and 25 studies were retained for quantitative and qualitative analysis (Figure 1).

Figure 1. PRISMA flow diagram



An overview of the 57 ongoing, withdrawn or completed studies not eligible for evidence synthesis, identified in study registries, research programmes or from handsearching, is provided in Supplement 1. Twenty-one new or ongoing studies were identified for HCV, one also focusing on HBV. In addition, 35 studies in progress were identified for HIV, with one also including HCV (mainly conducted in the United States and Canada) and one for TB.

The list of all included studies and the list of all excluded studies after full text review with the main reasons for exclusion are provided in Supplement 1.

3.2 Study characteristics

Twenty-five studies were included in the analysis: one study for TB [32], four studies for HIV [33-36], and 20 studies for HCV [37-56] (Table 7). No HBV eligible study could be included after full text review. Of the 25 studies, nine investigated the effect of interventions on both linkage to care and adherence to treatment [36,43,45-47,49,50,55,56]. Thirteen studies were RCTs and 12 were non-randomised studies. All included studies were conducted in high-income countries and published in English. Characteristics of the included studies are summarised in Table 8 and presented in detail in Table 28 in Annex 3.

Table 7. Overview of studies included in the evidence synthesis by area of intervention, study design and geographical region (N=25)

	Total studies	**HCV** Number of studies and references		**TB** Number of studies and references		**HIV** Number of studies and references	
Infection	25	20	[37-56]	1	[32]	4	[33-36]
Area of intervention							
Linkage to care only	4	4	[38,39,48,54]	0	-	0	-
Adherence to treatment only	12	8	[37,40-42,44,51-53]	1	[32]	3	[33-35]
Linkage to care *and* adherence to treatment	9	8	[43,45-47,49,50,55,56]	-	-	1	[36]
Study Design							
RCT	13	13	[37-40,42,44-46,50,52,54-56]	0	-	0	-
Non-randomised studies	12	7	[41,43,47-49,51,53]	1	[32]	4	[33-36]
Geographic region							
AU/NZ	1	1	[44]	0		0	
Europe: 2 UK, 2 DE, 1 AT, 2 PT, 2 IT, 2 ES, 1 BE	12	9	[38,41,46-48,50-53]	1	[32]	2	[33,35]
US, CA	11	9	[37,39,40,42,43,45,49,54,56]	-	-	2	[34,36]
US/Europe multicentre: US, FR, DE, IT, ES, UK	1	1	[44]	-	-	-	-

AU: Australia; BE: Belgium; CA: Canada; DE: Germany; ES: Spain; FR: France; IT: Italy; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; NRS: non-randomised study; NZ: New Zealand; OST: opioid substitution treatment; PT: Portugal; RCT: randomised controlled trial; Ref no.: Reference number; TB: tuberculosis; TI: treatment initiation; UK: the United Kingdom; US: the United States.

3.2.1 Study designs

Thirteen (52%) of the 25 included studies were RCTs [37-40,42,44-46,50,52,54-56] and 12 were non-randomised studies [41,43,47-49,51,53]. Most RCTs were pilot studies or cluster randomised trials with small sample sizes. Four non-randomised studies evaluated interventions on HIV, three retrospectively [33-35] and one prospectively [36]. With regard to TB, one non-randomised study was identified evaluating pre- and post-intervention adherence to TB treatment [32] (see Table 8).

3.2.2 Settings

The interventions were evaluated in a number of settings: primary care, drug treatment centres providing OST services, hospitals, pharmacies, NSP sites and one post-incarceration transitions clinic (see Table 8). Studies performed in addiction centres and specialised infectious disease centres (HIV and HCV care) were most frequently identified. One study recruited participants via outreach [39].

Table 8. Characteristics of studies included in the evidence synthesis (N=25)

First author, publication year; [Ref]	Country	Study design	Setting	Type of intervention vs control (treatment)	Reported outcomes
Hepatitis C					
Akiyama et al. 2019 [37]	US	RCT	OST centres	a) Directly observed therapy vs. self-administered therapy =usual care (DAA+/-IFN) b) Group treatment vs. self-administered therapy =usual care (DAA+/-IFN)	TA; SVR12
Arain et al. 2016 [38]	BE	RCT, pilot	Centre for drug problems	Educational intervention: formal+peer (IFN)	Visit
Broad et al. 2020 [39]	CA	RCT	HCV programme	Linkage to care via outreach testing with peer involvement (DAA) vs. usual care	Visit
Bruce et al. 2012 [40]	US	RCT, pilot	OST centre/spec. clinic	Modified directly observed therapy vs. self-administered therapy =usual care (IFN)	SVR24
Christensen et al. 2018 [41]	DE	NRS	HCV-registry centres of which some also provide OST	OST vs. non-OST =usual care (DAA)	TC; SVR12/24
Coffin et al. 2019 [42]	US	RCT, pilot	Community based clinical research centre	Modified directly observed therapy vs. self-administered therapy =usual care (DAA)	TA; SVR12
Cooper et al. 2017 [43]	CA	NRS	Hospital/regional HCV programme	Telemedicine intervention vs. usual care (IFN+DAA)	TI; SVR12
Grebely et al. 2016 [44]	US, FR, DE, IT, ES, UK	RCT, multicentre	Multicentre trial at sites in US and Europe	OST vs. non-OST =usual care (DAA)	TA; TC; SVR12
Ho et al. 2015 [45]	US	RCT	Veteran HCV centres	Integrated care vs. usual care in Veteran Affair patients (IFN +DAA)	TI; TA; SVR12/24
Lewis et al. 2016 [46]	UK	RCT, cluster	Drug treatment centres/ community outreach clinics	Nurse vs. physician-initiated therapy (IFN)	TI; TA
Marinho et al. 2016 [47]	PT	NRS, cross-sectional, pre/ post	Drug treatment centre	Health educational programme vs. usual care (IFN)	Visit; TI; TC
Messina et al. 2020 [48]	IT	NRS, prospective cohort (pre/post)	Drug treatment centre + Infectious Disease centre	Cooperation between two centres in PWUD and PWID vs. usual care (DAA)	TI
Norton et al. 2019 [49]	US	NRS	NSP centre	Contingency management vs. enhanced usual care (DAA)	Visit; TI; SVR12
Radley et al. 2020 [50]	UK	RCT, cluster	Pharmacies	Pharmacy-led modified directly observed therapy vs. usual care (DAA)	TI; TC; SVR12
Reimer et al. 2013 [51]	DE	NRS	OST centres	Psycho-education groups vs. usual care (IFN)	TC; SVR24

First author, publication year; [Ref]	Country	Study design	Setting	Type of intervention vs control (treatment)	Reported outcomes
Saiz de la Hoya et al. 2014 [52]	ES	RCT	Healthcare centres in prisons	Directly observed therapy vs. self-administered therapy =usual care (IFN)	SVR12/24
Schmidbauer et al. 2020 [53]	AT	NRS	Drug treatment centre (OST)/hospital	Directly observed therapy vs. self-administered therapy =usual care (DAA)	SVR12
Starbird et al. 2020 [54]	US	RCT	Outpatient clinic (HIV+ HCV care)	Nurse Case Management (DAA) vs. usual care	Visit; TI
Wade et al. 2019 [55]	AU; NZ	RCT	Primary care/hospitals	Primary care vs. hospital =usual care (DAA)	TI; SVR12
Ward et al. 2019 [56]	US	RCT	Clinic for HIV care	a) Peer mentors vs. usual care (DAA), b) Contingency Management vs. usual care (DAA)	TI; TC; SVR12
HIV					
Babudieri et al. 2011 [33]	IT	NRS, retrospective	Drug rehab. centres + outpatient	Directly observed therapy vs. self-administered therapy at home =usual care – CON1 Directly observed therapy vs. self-administered therapy at outpatient clinic =usual care – CON2	TA; VL
Masyukova et al. 2018 [34]	US	NRS, retrospective	Post-incarceration Transitions Clinic	Transition clinic for formerly incarcerated (TC) vs non-TC =usual care	TA at 6 m.; TA at 12 m.; VL
Sanchez et al. 2012 [35]	ES	NRS, retrospective	Drug treatment centre	Drug user in multidisciplinary care vs. non-drug users in usual care*	TA (discontinuation); VL
Tu et al. 2013 [36]	CA	NRS, prospective	Primary Care Health Centres for Aboriginals	Chronic Care Model in community health centre (aboriginals) before vs. after	TI, VL
Tuberculosis					
Duarte et al. 2011 [32]	PT	NRS, pre/post	Outpatient TB clinic	Cooperation between institutions and street teams incl. directly observed therapy before vs. after	TA (non-compliance); TA (discontinuation)

ART: antiretroviral therapy; CM: contingency management; COOP: cooperation; CON: control; DAA: direct-acting antivirals; DI: drug interactions; DOT: directly observed therapy; DU: drug use; EDU: educational intervention; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; IC: integrated care; IFN: interferon; mDOT: modified directly observed therapy; NA: not available/applicable; NCM: nurse care manager/management; NRS: non-randomised controlled study; NSP: needle and syringe programme; OST: opioid substitution treatment; PE: psycho-education; PC: primary care; PWID: people who inject drugs; PWUD: people who use drugs; RCT: non-randomised controlled trial; SAT: self-administered therapy; SVR12: Sustained Virological Response at post-treatment week 12; SVR24: Sustained Virological Response at post-treatment week 24; TA: treatment adherence; TB: tuberculosis; TC: treatment completion; TI: treatment initiation; TM: telemedicine; UC: usual care; VL: viral load.

** Different population – INT and CON: INT: active people who use drugs living with HIV-1 admitted for drug treatment and who started their first HAART, CON: people living with HIV-1 (sexually transmitted) attended in a reference hospital under standard care.*

3.2.3 Population

The study populations varied across the studies, and included former and current substance users with or without known psychiatric comorbidities, patients from drug treatment and substance dependence treatment centres, patients visiting outpatient infectious disease units, formerly incarcerated HIV-infected patients [34], and Veteran Affairs (VA) services patients [45]. Injecting drug use and OST characteristics were well documented and defined in the vast majority of studies.

For HCV, the sample size for intervention arms ranged from 20 to 1 365 for linkage to care studies and from nine to 1 365 for adherence to treatment studies. For HIV, the intervention arm sample size was 219 in the linkage to care study [36] and ranged from 28 to 219 participants in the intervention arms in studies reporting on adherence to HIV treatment intervention [33-35]. For the study on TB, the intervention arm sample size was 59 [32]. The mean age of total participants in the included studies ranged from 36 to 55 years, with most participants being men (61% to 100%). High rates of poverty, homelessness, prior incarceration and psychiatric illnesses and other comorbidities including HCV/HIV co-infection have been observed in the study population (see Table 28 in Annex 3).

3.2.4 Interventions

The interventions implemented/studied in the included studies were diverse and highly specific to the setting in which they were offered. The studies were organised in the following intervention groups addressing HCV, HIV and TB:

- Direct observed therapy (DOT) versus self-administered therapy (SAT) for HCV [37,40,42,50,52,53] or HIV [33];
- Different forms of educational interventions, formal and with peers (EDU) for HCV [38,47];
- Contingency management (CM) with financial incentives for participants, e.g. for visits or treatment adherence for HCV [49,56];
- The use of telemedicine (TM) for HCV [43];
- Nurse case management (NCM) with nurses initiating referral, assisting appointments, conducting HCV education and so on for HCV [54];
- Integrated care (IC) with multidisciplinary care coordination and patient case management for HCV [45];
- Cooperation (COOP) between different centres (drug treatment centres/specialised centres for disease for HCV [48] or between institutions and street teams for TB [32];
- Peers: trained former HCV-infected and/or HIV-positive people (=peers) support participants in a programme tailored to people who inject drugs and HCV treatment [56];
- Psychoeducation with weekly regular supervised groups and update sessions for HCV treatment [51]
- Comparison of linkage to care or adherence to treatment interventions in different settings: nurse-led versus physician-led [46]; primary care versus hospital care for HCV [55]; OST centres + DAA vs. non-OST participants for HCV [41,44];
- Chronic care model (CCM) as a multidimensional approach to chronic disease management and empowering patients for HIV [36];
- Services of a specialised transition clinic for patients after discharge from prison (TC) for HIV [34]; and
- Multidisciplinary care (MDC) with a multidisciplinary health team in a drug abuse outpatient treatment facility providing medical care for HIV, drug treatment and psychosocial support [35].

Of the 20 studies targeting HCV treatment initiation or treatment adherence included in the review, six interventions were evaluated in the interferon era [38,40,46,47,51,52] and 11 in the DAA era [39,41,42,44,48-50,53-56]. Three studies evaluated both treatment regimens/eras [37,43,45].

3.2.5 Controls

In the PICOs (see Tables 1 and 2), control groups were generally defined as people who inject drugs or people on OST with no intervention or receiving usual or routine care as defined by study authors. In the identified studies, control groups included:

- participants receiving standard medical care consistent with current treatment guidelines and/or clinic structures;
- self-administered/unobserved treatment or dosing;
- physician-initiated therapy (vs nurse case management);
- treatment in care centres not providing OST; or
- participants treated in the pre-intervention period, before implementation of the intervention.

Control group sample size did not substantially differ from intervention group sample size except for Cooper et al. (2017) [43] (157 vs. 1 130), Christensen et al. (2018) [41] (739 vs. 7 008), Grebely et al. (2016) [44] (70 vs. 1 882) and Masyukova et al. (2018) [34] (38 vs. 100). For details on study control groups see Table 28 in Annex 3.

Outcomes

A total of 13 studies reported on interventions with impact on linkage to care for HCV, HIV and TB. By outcome indicator, five studies reported on Visit with a provider/specialist after positive test (Visit) and 10 on Treatment Initiation (TI).

Twenty-one studies reported on outcomes related to adherence to treatment. Of these, nine reported on Treatment Adherence (TA), six on Treatment Completion (TC), three Viral Load (VL), 12 Sustained Virological Response at week 12 (SVR12) and five Sustained Virological Response at week 24 (SVR24).

Treatment Adherence (TA) definition varied across studies e.g. 'completing 80% of planned treatment', 'receiving ≥80 of treatment doses', '>95% of prescribed pills taken (high adherence)', 'mean weekly visit completion', 'receiving ≥80% of total doses for ≥80% of expected therapy' (assessed by direct questioning and observation, examination of dosette boxes and/or by review of blood tests). Definition of Treatment Adherence (TA) in each individual study are described in detail in Table 28 in Annex 3.

3.3 Risk of bias of individual studies

The results of the quality assessment according to the EPHPP tool [1] are presented in Table 9.

Table 9. Results of quality assessment of included studies using the Effective Public Health Practice Project (EPHPP) tool*

First author, year [ref no.]	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and dropouts	Overall quality score**
Akiyama et al. 2019 [37]	Strong	Strong	Strong	Weak	Strong	Strong	Moderate
Arain et al. 2016 [38]	Moderate	Strong	Moderate	Moderate	Weak	Moderate	Moderate
Babudieri et al. 2011 [33]	Weak	Moderate	Moderate	Weak	Moderate	Weak	Weak
Broad et al. 2020 [39]	Weak	Strong	Moderate	Moderate	Moderate	Moderate	Moderate
Bruce et al. 2012 [40]	Moderate	Strong	Weak	Weak	Moderate	Moderate	Weak
Christensen et al. 2018 [41]	Moderate	Moderate	Weak	Moderate	Weak	Moderate	Weak
Coffin et al. 2019 [42]	Moderate	Strong	Moderate	Weak	Weak	Weak	Weak
Cooper et al. 2017 [43]	Weak	Moderate	Weak	Moderate	Weak	Weak	Weak
Duarte et al. 2011 [32]	Weak	Moderate	Weak	NA	Moderate	NA	Weak
Grebely et al. 2016 [44]	Moderate	Strong	Moderate	Weak	Strong	Strong	Moderate
Ho et al. 2015 [45]	Weak	Strong	Strong	Moderate	Strong	Strong	Moderate
Lewis et al. 2016 [46]	Weak	Strong	Weak	Weak	Weak	Weak	Weak
Marinho et al. 2016 [47]	Weak	Moderate	Weak	Weak	Weak	Weak	Weak
Masyukova et al. 2018 [34]	Weak	Moderate	Weak	Weak	Moderate	Weak	Weak
Messina et al. 2020 [48]	Moderate	Moderate	Weak	Weak	Weak	Moderate	Weak
Norton et al. 2019 [49]	Weak	Weak	Moderate	Weak	Strong	Weak	Weak
Radley et al. 2020 [50]	Weak	Strong	Weak	Weak	Strong	Strong	Weak
Reimer et al. 2013 [51]	Weak	Weak	Moderate	Weak	Strong	Moderate	Weak
Saiz de la Hoya et al. 2014 [52]	Moderate	Strong	Strong	Weak	Weak	Moderate	Weak
Sanchez et al. 2012 [35]	Weak	Moderate	Weak	Weak	Moderate	Moderate	Weak
Schmidbauer et al. 2020 [53]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Starbird et al. 2020 [54]	Strong	Strong	Strong	Moderate	Strong	Strong	Strong
Tu et al. 2013 [36]	Weak	Weak	Weak	Weak	Weak	Moderate	Weak
Wade et al. 2019 [55]	Moderate	Strong	Strong	Weak	Weak	Weak	Weak
Ward et al. 2019 [56]	Moderate	Strong	Strong	Weak	Strong	Moderate	Moderate

** Assessment of six quality dimensions using EPHPP - Quality Assessment Tool: Hamilton, Ontario, Canada [1]*
*** Global Rating of six quality dimensions results in 'weak' = two or more weak ratings (= high risk of bias); 'moderate' = one weak rating; 'strong' = no weak rating*

3.4 Results of individual studies

For each study, the outcome indicator for linkage to care or adherence to treatment, the type of intervention and its comparison, and a summary of effect measurements for both the intervention and control group are presented in Table 10. The calculation of relative risk (RR) or odds ratios (OR) and 95% confidence interval [95% CI] for each study are also presented. Statistically significant outcomes are indicated in bold letters. For hepatitis C studies, the type of therapy, interferon (IFN), direct acting antiviral (DAA) or both (DAA+IFN) are indicated.

Table 10. Outcomes of interventions on linkage to care and adherence to treatment for HCV, HIV and tuberculosis among people who inject drugs by individual studies

First author, publication year; [Ref]	Outcome indicator	Intervention vs. control	Effect measurement intervention n/N; % [95% CI]	Effect measurement Control n/N; % [95% CI]	Relative risk [95% CI]
Hepatitis C					
Akiyama et al. 2019 [37]	TA (DAA+/-IFN)	DOT vs. SAT	NA; 86% [80-92]	NA; 75% [70-81]	RR 1.15 [0.95-1.39]
	SVR12 (DAA+IFN)	DOT vs. SAT	NA; 94% [84-99]	NA; 87% [75-95]	RR 1.08 [0.95-1.22]
	TA (DAA+IFN)	Group treatment vs. SAT	NA; 90% [79-97]	NA; 91% [79-97]	RR 0.99 [0.93-1.15]
	SVR12 (DAA+IFN)	Group treatment vs. SAT	NA; 87% [74-94]	NA; 87% [75-95]	RR 1.00 [0.93-1.15]
Arain et al. 2016 [38]	Visit (IFN)	EDU vs. UC	1/25; 4% [NA]	0/27; 0% [NA]	NA
Broad et al. 2020 [39]	Visit (DAA)	LtC via (outreach) testing vs. UC	6/195; 3% [NA]	5/185; 3% [NA]	RR 1.17 [0.36-3.77]
Bruce et al. 2012 [40]	SVR24 (IFN)	mDOT/Health Centre (OST) vs. SAT/spec. liver clinic	6/10; 60% [NA]	1/33; 33% [NA]	RR 4.5 [0.65-31.08]
Christensen et al. 2018 [41]	TC (DAA)	OST vs. Non-OST/DU	528/739; 71% [NA]	1 126/1 500; 75% [NA]	RR 0.95 [0.90-1.00]
	SVR12/24 (DAA)	OST vs. Non-OST/DU	450/528; 85% [NA]	969/1 126; 86% [NA]	RR 0.99 [0.95-1.03]
Coffin et al. 2019 [42]	TA (DAA)	mDOT vs. SAT	NA; 96.3% [NA]	NA; 96.6% [NA]	RR 1.00 [0.87-1.15]
	SVR12 (DAA)	mDOT vs. SAT	18/20; 89.5% exCI [66.9–98.7]	10/11; 90% exCI [55.5–99.7]	RR 0.99 [0.78-1.27]

First author, publication year; [Ref]	Outcome indicator	Intervention vs. control	Effect measurement intervention n/N; % [95% CI]	Effect measurement Control n/N; % [95% CI]	Relative risk [95% CI]
Cooper et al. 2017 [43]	TI (DAA+IFN)	TM vs. UC	43/157; 27.4% [NA]	608/1,130; 53.8% [NA]	**RR 0.51 [0.39-0.66]**
	TI (DAA)	TM vs. UC	27/43; 62.8% [NA]	319/608; 52.5% [NA]	RR 1.07 [0.83-1.39]
	SVR12 (DAA+IFN)	TM vs. UC	18/19; 94.7% [NA]	236/249; 94.8% [NA]	RR 1.00 [0.90-1.12]
Grebely et al. 2016 [44]	TA (DAA)	OST vs. Non-OST	65/70; 93% [84-98]	1 737/1 882; 92% [91-93]	RR 1.01 [0.94-1.08]
	TC (DAA)	OST vs. Non-OST	68/70; 97% [90-99]	1 846/1 882; 98% [97-99]	RR 0.99 [0.95-1.03]
	SVR12 (DAA)	OST vs. Non-OST	66/70; 94% [86-98]	1 822/1 882; 97% [96-98]	RR 0.97 [0.92-1.03]
Ho et al. 2015 [45]	TI (DAA+IFN)	**IC vs. UC (Veteran Affair patients)**	58/182; 31.9% [NA]	34/181; 18.8% [NA]	**RR 1.70 [1.17-2.46]**
	TA (DAA+IFN)	IC vs. UC (Veteran Affair patients)	95/182; 52% [NA]	80/181; 44% [NA]	RR 1.18 [0.95-1.46]
	SVR12/24 (DAA+IFN)	**IC vs. UC (Veteran Affair patients)**	29/182; 15.9% [NA]	14/181; 7.7% [NA]	**RR 2.06 [1.13-3.77]**
Lewis et al. 2016 [46]	TI (IFN)	Nurse vs. physician	6/62; 9.7% [NA]	6/76; 8% [NA]	RR 1.23 [0.42-3.61]
	TA (IFN)	Nurse vs. physician	5/6; 83.3% [NA]	5/6; 83.3% [NA]	RR 1.0 [0.60-1.66]
Marinho et al. 2016 [47]	Visit (IFN)	EDU vs. UC	250/340; 73.5% [68.8-72.8]	203/273; 74.4% [69.2-79.5]	RR 0.99 [0.90-1.09]
	TI (IFN)	EDU vs. UC	75/130; 57.7% [49.2–66.2]	58/122; 45.5% [38.7-56.4]	RR 1.21 [0.96-1.54]
	TC (IFN)	EDU vs. UC	57/75; 76% [65.2-84.3]	44/58; 75.9% [64.8-86.9]	RR 1.00 [0.83-1.22]
Messina et al. 2020 [48]	TI (DAA)	**COOP (between 2 centres) PWUD vs. UC**	63/75; 84% [NA]	3/18; 17% [NA]	**RR 5.04 [1.79-14.23]**
	TI (DAA)	**COOP (between 2 centres) PWID vs. UC**	45/55; 82% [NA]	3/16; 19% [NA]	**RR 4.63 [1.56-12.19]**

First author, publication year; [Ref]	Outcome indicator	Intervention vs. control	Effect measurement intervention n/N; % [95% CI]	Effect measurement Control n/N; % [95% CI]	Relative risk [95% CI]
Norton et al. 2019 [49]	Visit (DAA)	**CM vs. enhanced UC**	14/19; 74% [NA]	6/20; 30% [NA]	**RR 2.46 [1.19-5.05]**
	TI (DAA)	CM vs. enhanced UC	9/12; 75% [NA]	4/4; 100% [NA]	RR 0.75 [0.54-1.04]
	SVR12 (DAA)	CM vs. enhanced UC	9/9; 100% [NA]	3/4; 75% [NA]	RR 1.33 [0.76-2.35]
Radley et al. 2020 [50]	TI (DAA)	**mDOT – pharmacy-led vs. UC**	112/1365; 8% [NA]	61/1353; 5% [NA]	**RR 1.82 [1.34-2.46]**
	TC (DAA)	**mDOT – pharmacy-led vs. UC**	108/1 365; 8% [NA]	58/1 353; 4% [NA]	**RR 1.85 [1.35-2.52]**
	SVR12 (DAA)	**mDOT – pharmacy-led vs. UC**	98/1 365; 7% [NA]	43/1 353; 3% [NA]	**RR 2.26 [1.59-3.21]**
Reimer et al. 2013 [51]	TC (IFN)	PE vs. UC (in OST)	67/82; 82% [NA]	78/107; 73% [NA]	RR 1.12 [0.96-1.31]
	SVR24 (IFN)	PE vs. UC (in OST)	64/82; 78% [NA]	73/109; 67% [NA]	RR 1.17 [0.96-1.31]
Saiz de la Hoya et al. 2014 [52]	SVR12/24 (IFN)	DOT vs. SAT	66/109; 60.6% [51.17-69.22]	89/135; 65,9% [57.6-73.4]	RR 0.92 [0.746-1.125]
Schmidbauer et al. 2020 [53]	SVR12 (DAA)	DOT vs. SAT (=UC)	70/74; 94.6% [86.7-98.5]	69/71; 97.2% [90.2–99.7]	RR 0.97 [0.91-1.04]
Starbird et al. 2020 [54]	Visit (DAA)	**NCM vs UC**	16/34; 47% CI for difference [3.2-40.9]	8/32; 25% CI for difference [3.2-40.9]	RR 1.88 [0.94-3.78]
	TI DAA)	NCM vs UC	4/34; 12% [NA]	8/32; 25% [NA]	RR 0.47 [0.16-1.41]
Wade et al. 2019 [55]	TI (DAA)	**PC vs. hospital**	43/57; 75% [NA]	18/53; 34% [NA]	**RR 2.48 [1.54-3.95]**
	SVR12 (DAA)	**PC vs. hospital**	28/57; 49% [NA]	16/53; 30% [NA]	**RR 2.22 [1.48-3.33]**
Ward et al. 2019 [56]	TI (DAA)	Peers vs. UC	45/54; 83% [NA]	24/36; 67% [NA]	RR 1.25 [0.96-1.62]
	TC (DAA)	Peers vs. UC	42/54; 78% [NA]	23/36; 64% [NA]	RR 1.22 [0.92-1.62]

First author, publication year; [Ref]	Outcome indicator	Intervention vs. control	Effect measurement intervention n/N; % [95% CI]	Effect measurement Control n/N; % [95% CI]	Relative risk [95% CI]
	SVR12 (DAA)	Peers vs. UC	41/54; 76% [NA]	22/36; 61% [NA]	RR 1.24 [0.92-1.68]
	TI (DAA)	CM vs UC	41/54; 76% [NA]	24/36; 67% [NA]	RR 1.14 [0.86-1.50]
	TC (DAA)	CM vs UC	42/54; 78% [NA]	23/36; 64% [NA]	RR 1.13 [0.84-1.52]
	SVR12 (DAA)	CM vs UC	37/54; 69% [NA]	22/36; 61% [NA]	RR 1.12 [0.82-1.54]
HIV					
Babudieri et al. 2011 [33]	TA	**SAT/home vs. DOT**	NA; NA [NA]	NA; NA [NA]	6 m. **OR 0.22 [0.12-0.39]** 12 m. **OR 0.30 [0.17-0.54]** 24 m. **OR 0.35 [0.20-0.62]** 36 m. OR 0.65 [0.34-1.27]
	TA	**SAT/OUT clinic vs. DOT**	NA; NA [NA]	NA; NA [NA]	6 m. **OR 0.19 [0.10-0.34]** 12 m. **OR 0.19 [0.11-0.35]** 24 m. **OR 0.39 [0.22-0.68]** 36 m. OR 1.70 [0.94-3.07]
	VL	SAT/home vs. DOT	NA; NA [NA]	NA; NA [NA]	aHR 0.98 [0.73–1.32]
	VL	**SAT/OUT clinic vs. DOT**	NA; NA [NA]	NA; NA [NA]	**aHR 0.70 [0.52–0.96]**
Masyukova et al. 2018 [34]	TA at 6 m.	TC for formerly incarcerated vs. non-TC	29/38; 76% [NA]	79/100; 79% [NA]	RR 0.96 [0.78-1.18]
	TA at 12 m.	TC for formerly incarcerated vs. non-TC	24/38; 63% [NA]	67/100; 67% [NA]	RR 0.94 [0.71-1.24]

First author, publication year; [Ref]	Outcome indicator	Intervention vs. control	Effect measurement intervention n/N; % [95% CI]	Effect measurement Control n/N; % [95% CI]	Relative risk [95% CI]
	VL	TC for formerly incarcerated vs. non-TC	21/38; 54% [NA]	63/100; 63% [NA]	RR 0.86 [0.62-1.19]
Sanchez et al. 2012 [35]	TA (treatment discontinuation)	Drug user in MDC vs. non-drug users in UC*	9/71; 12.7% [NA]	4/48; 8.3% [NA]	RR 1.52 [0.50-4.66]
	VL	Drug user in MDC vs. non-drug users in UC*Error! Bookmark not defined.	62/71; 87.3% [NA]	42/48; 87.5% [NA]	RR 1.0 [0.87-1.15]
Tu et al. 2013 [36]	TI	**CCM in community health centre** (aboriginals) before vs. after design	168/219; 77% [NA]	104/219; 47% [NA]	**RR 1.62 [1.38-1.89]**
Tuberculosis					
Duarte et al. 2011 [32]	TA (treatment non-compliance)	**COOP (between institutions and street teams) incl. DOT (pre/ post)**	14/59; 23.7% [NA]	39/82; 47.6% [NA]	**RR 0.50 [0.30-0.83]**
	TA (treatment discontinuation)	**COOP (between institutions and street teams) incl. DOT (pre/ post)**	6/59; 10.2% [NA]	29/82; 35.4% [NA]	**RR 0.29 [0.13-0.65]**

aHR: adjusted Hazard Ratio; ART: antiretroviral therapy; AtT: adherence to treatment; CCM: chronic care model; CI: confidence interval; CM: contingency management; COOP: cooperation; CON: control; DAA: direct-acting antivirals; DOT: directly observed therapy; EDU: educational intervention; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; IC: integrated care; IFN: interferon; mDOT: modified directly observed therapy; NA: not available/applicable; NCM: nurse care manager/management; NRS: non-randomised controlled study; OR: odds ratio; OST: opioid substitution treatment; PE: psycho-education; PC: primary care; PWID: people who inject drugs; PWUD: people who use drugs; RCT: non-randomised controlled trial; RR: risk ratio/relative risk; SAT: self-administered therapy; SVR12/24: Sustained Virological Response at post-treatment week 12/week 24; TA: treatment adherence; TB: tuberculosis; TC: treatment completion; TI: treatment initiation; TM: telemedicine; UC: usual care; VL: viral load.

** Different population - INT and CON: INT: active drug users living with HIV-1 admitted for drug treatment and who started their first HAART, CON: individuals living with HIV-1 (sexually transmitted) attended in a reference hospital under standard care.*

3.5 Certainty of evidence

The assessments of certainty in the body of evidence for each outcome of the studies assessed including reasons for downgrading are summarised in Annex 3.

Hepatitis C: One study by Ward et al. (2019) [56] assessing CM and Peer interventions to *increase linkage to care* was considered to generate high certainty evidence. Four studies [45,50,54,55] reported on interventions NCM, IC, DOT, primary care with outcomes *visits* and *TI* and provide a good indication of the likely effect with moderate certainty of evidence. For two studies [39,43] assessing Peers and TM, the certainty of evidence was considered to be low, suggesting that this research provides some indication of the likely effect. The certainty of evidence of two outcomes of two studies [48,49] was rated very low.

Certainty of evidence for *adherence to treatment* was high in two studies [37,56] assessing SVR12, TA and TC with interventions DOT, group treatment, Peers and CM, providing a very good indication of the likely effect. Certainty of evidence was moderate for four studies [44,45,50,55] assessing interventions OST, IC, DOT, primary care. The certainty of evidence of two studies [41,42] with OST and DOT interventions was graded low, providing only some indication of the likely effect. For three studies [43,49,53] assessing TM, CM and DOT and SVR12 the certainty of evidence was rated very low.

HIV: One study, by Tu et al. (2013) [36], was identified for *linkage to care,* but with a low certainty of evidence rating. Three studies assessing *adherence to treatment* were considered to generate low [33] and very low [34,35] certainty evidence. Overall certainty of evidence for HIV suggests that further studies may show different results.

TB: No studies were identified for linkage to TB care. The certainty of evidence rating for the only available study, by Duarte et al. (2011) [32], for adherence to treatment was very low. For TB, further research might show different results.

3.6 Funding and conflicts of interest in included studies

Conflicts of interest related to funding and author-industry financial relationships can introduce bias in research by influencing the framing of research questions, inclusion and exclusion criteria, study design, choice of drug dosages and comparators, selection of trial outcomes, how analyses are conducted, interpretation of findings, which outcomes are reported and whether or which results are published [57,58].

Funding sources for each of the 25 studies and the conflicts of interest of the authors are presented in Annex 3. Fourteen studies reported financial ties with industry (including provision of financial support, resources e.g., statistical analyses, or inclusion of study personnel beyond those listed as authors), and 12 reported conflicts of interest with the authors.

3.7 Barriers and facilitators

Five of the 25 studies reported on barriers for linkage to care or adherence to treatment [38,40,45,54,56]. Of these five studies, only one study [54] mentioned one facilitator. All five studies were related to HCV (see Table 11 below).

Table 11. Secondary outcomes – reported barriers or facilitators for linkage to care or adherence to treatment from included studies for HCV

First author, year [ref. no]	Linkage to care/Adherence to treatment	Intervention	Setting/ Country	Assessed by	Barriers	Facilitators
Linkage to care						
Arain et al., 2016 [38]	LtC: Visit liver specialist	EDU	Centre for Drug problems/Belgium	Participants/questionnaire	Reasons to decline/postpone treatment, intervention vs control: ° Insufficient knowledge about HCV: 24% vs 24% ° No symptoms: 24% vs 17% ° Injecting drug/drug use: 12% vs 17% ° Financial problems: 17% vs 8% ° Doctor told not necessary: 12.9% vs not reported ° Concerns for side effects: 18% vs not reported ° Other medical problem/other reason: not reported vs 16%	Not reported
Starbird et al., 2020 [54]	LtC: Visit	NCM	HIV primary care centre/US*	Primary care provider	° Too many missed visits: 33% ° Competing co-morbidities: 25% ° Need to stabilise HIV first: 25% ° Need to decrease substance use: 13%	Knowing someone who had been cured of HCV
Starbird et al., 2020 [54]	LtC: TI	NCM	HIV primary care centre/US*	Data health insurance; regression model on factors predicting HCV care continuum	° Insurance denial for detectable HIV viral load: 11% ° Insurance denial for fibrosis: 33% ° Unresolved prior authorisation DAA: 33% ° Lost to follow up: 11% ° Waiting for kidney transplantation: 11%	

First author, year [ref. no]	Linkage to care/Adherence to treatment	Intervention	Setting/ Country	Assessed by	Barriers	Facilitators
Adherence to treatment						
Bruce et al., 2012 [40]	AtT: SVR	mDOT	OST centre/spec. Clinic/US	Interviews + addiction severity index	◦ Treatment never started: due to mental health issues, homelessness, incarceration, missed appointments: 24% ◦ Stopped treatment due to assault, jail, refused SAT wanted DOT: 14%	Not reported
Ho et al., 2015 [45]	AtT: TA	IC	Veteran HCV centre/US	Medical records	Reasons for early discontinuation in the IC (integrated care) and UC (usual care) group: ◦ Adverse events: 39% vs. 44% ◦ Viral nonresponse: 46% vs. 56% ◦ Non-adherence: 15% vs. 0%	Not reported
Ward et al., 2019 [56]	AtT: TC	CM/Peers	Clinic for HIV care/US*	adverse effects + medication adherence assessed at visits	◦ Adverse events: 3 participants ◦ Non-adherence pharmacy visits: 3 participants ◦ Pregnancy: 1 participant	Not reported

AtT: adherence to treatment; BE: Belgium; CM: contingency management; DAA: direct-acting antivirals; EDU: educational intervention; IC: integrated care; HCV: hepatitis C virus; HIV: Human Immunodeficiency Virus; LtC: linkage to care; mDOT: modified directly observed therapy; NCM: nurse care manager/management; OST: opioid substitution treatment; SAT: self-administered therapy; SVR12: Sustained Virological Response at post-treatment week 12; TA: treatment adherence; TC: treatment completion; TI: treatment initiation; US: the United States
** Participants with HIV/HCV coinfection*

3.7.1 Barriers to linkage to HCV care

Arain et al. [38] reports on barriers to testing and treatment initiation among people who inject drugs collected by means of questionnaires. Overall, 60% (31/52) participants of the study postponed or declined the treatment, of whom 55% (17/31) completed the questionnaires over the study period. Barriers reported were (% intervention group; % control group): *insufficient HCV knowledge* (24%; 24%), *not having symptoms* (24%; 17%), *financial problems (17%; 8%), injecting drug/drug use (12%; 17%). Concerns about side effects (18%)* and *doctor told them treatment was not necessary* (12%) were reported by the intervention group, whereas the control group indicated *other medical problems (8%) and other reasons* (8%). The study was conducted in the IFN era. During the study, seven participants were incarcerated, two hospitalised, 24 left the OST programme, and two died.

In Starbird et al. [54], primary care providers specified the following reasons for non-adherence to treatment and end of HCV care: *too many missed visits* (33%), *competing co-morbidities* (25%), *need to stabilise HIV first* (25%) and *need to decrease substance use* (13%). In total, 42 of 66 participants (63%) did not visit HCV care practice. Reasons for not initiating treatment were drawn from electronic medical records. Barriers to initiating DAA HCV treatment within 180 days were *insurance denial for detectable HIV viral load*, *insurance denial for fibrosis* level <F2, *unresolved prior authorisation DAA*, *lost to follow up* and *awaiting to receive an HCV-positive kidney transplant*. However, data were not separated between intervention and control group and included only twelve participants. Patient characteristics predicting the HCV care continuum were determined through a regression model. Participants taking opiate agonist therapy (OAT) were 75% less likely to be prescribed DAA compared to participants not taking OAT, in particular because HCV treatment and drug use therapy were not integrated in study settings.

3.7.2 Facilitators to linkage to HCV care

Among the participants in Starbird et al, 'knowing someone who had cured HCV' was identified as facilitator of linkage to care [54]. The authors stated that this factor 'was associated with greater odds of being prescribed DAAs and initiating treatment'. [54].

3.7.3 Barriers to adherence to HCV treatment

Bruce et al. [40] reported on reasons why participants of the standard-of-care group (self-administered therapy) never started HCV treatment, which were mental health issues, homelessness, incarceration and missed appointments. Five of 21 participants (24%) did not start treatment. The information was collected in a three-hour structured interview assessing demographic and social circumstances, Addiction Severity Index (general psychiatric health status included) and an additional follow-up interview. The authors did not report on facilitators.

Based on medical records, Ho et al. [45] reported on reasons for sub-optimal TA, defined as completions of less than 80% of the planned treatment course, surveyed in both the IC (integrated care) and UC (usual care) group. Reasons for discontinuation of treatment in IC and UC groups include *adverse events (i.e.* any condition that resulted in a hospitalisation, emergency room visit, and/or death) (39% vs. 44%), *viral nonresponse* (46% vs. 56%) and *other reasons of non-adherence* (15% vs. 0%). Overall, 48% in the intervention group and 56% in the usual care group did not complete 80% of the planned treatment course. No facilitators were mentioned.

Ward et al. [56] assessed adverse effects and medication adherence at each visit. Three participants discontinued treatment due to *adverse events* (nausea, peer; tinnitus, peer; insomnia, incentive). One participant from each group (three total) discontinued treatment early due to *non-adherence to pharmacy visits* (reasons for non-adherence not reported), while three participants were lost to follow up. In total, seven of 110 participants (6%) did not complete treatment.

3.8 Results of descriptive synthesis

In the syntheses, results are grouped and presented according to similar interventions.

Of the 20 studies targeting linkage to HCV care or treatment adherence included in the review, six interventions were evaluated in the interferon era [38,40,46,47,51,52], 11 in the interferon-free DAA era [39,41,42,44,48-50,53-56] and three studies evaluated both treatment regimens [37,43,45]. The six studies considering interferon-based regimens only are not included in the synthesis (see Annex 3).

3.8.1 Directly observed therapy

Four studies evaluated directly observed therapy (DOT) interventions for HCV [37,42,50,53] and one for HIV [33].

Table 12. Directly observed therapy to increase linkage to HCV care – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Radley et al. 2020 [50]	**mDOT – pharmacy-led vs. Usual Care**	TI	112/1365; 8%; CI [NA]	61/1353; 5%; CI [NA]	**RR 1.82 [1.34–2.46]**	MODERATE*

CI: confidence interval; mDOT: modified direct observed therapy; RR: relative risk; SAT: self-administered therapy; SD: standard deviation
**Downgraded by one level: risk of bias (selection of those participants already interested; participants with certain conditions, e.g. risk of cirrhosis, HIV or HBV infection, violent participants against pharmacy staff are excluded)*

Radley et al. (2020) [50] (cluster RCT, 2 718 participants) significantly improved **treatment initiation (TI)** for participants receiving OST through pharmacy-led DOT in comparison with usual care provided by a multidisciplinary service from community treatment centres (8% vs. 5% in CON group, RR 1.82, 95% CI 1.34–2.46).

Conclusion based on GRADE: Pharmacy-led DOT versus self-administered therapy (=usual care) probably improves treatment initiation (moderate certainty evidence) [50].

Table 13. Directly observed therapy to increase adherence to HCV treatment – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Akiyama et al. 2019 [37]	DOT vs. SAT (=UC)	TA (DAA +/- IFN)	NA; 86%; CI [80–92%]	NA; 75%; CI [70–81%]	RR 1.15 [0.95–1.39]	HIGH
Coffin et al. 2019 [42]	mDOT vs. SAT (=UC)	TA (DAA)	NA; 96.3%; (SD 19.1)	NA; 96.6%; (SD 18.3)	RR 1.00 [0.87–1.15]	LOW*
Radley et al. 2020 [50]	**mDOT – pharmacy-led vs. UC**	TC (DAA)	108/1 365; 8%; CI [NA]	58/1 353; 4%; CI [NA]	**RR 1.85 [1.35–2.52]**	MODERATE**
Akiyama et al. 2019 [37]	DOT vs. SAT (=UC)	SVR12 (DAA +/- IFN)	NA; 94%; [84–99%]	NA; 87%; [75–95%]	RR 1.08 [0.95–1.22]	HIGH
Coffin et al. 2019 [42]	mDOT vs. SAT (=UC)	SVR12 (DAA)	18/20; 89.5%; 95% exCI [66.9–98.7]	10/11; 90%; 95% exCI [55.5–99.7]	RR 0.99 [0.78–1.27]	LOW*
Radley et al. 2020 [50]	**mDOT – pharmacy-led vs. UC**	SVR12 (DAA)	98/1 365; 7%; CI [NA]	43/1 353; 3%; CI [NA]	**RR 2.26 [1.59–3.21]**	MODERATE**
Schmidbauer et al. 2020 [53]	DOT vs. SAT (=UC)	SVR12 (DAA)	70/74; 94.6%; CI [86.7–98.5%]	69/71; 97.2%; CI [90.2–99.7%]	RR 0.97 [0.91–1.04]	VERY LOW***

CI: confidence interval; DAA: direct-acting antivirals; IFN: interferon; mDOT: modified directly observed therapy; NA: not available; RR: relative risk; SAT: self-administered therapy; TA: treatment adherence; TC: treatment completion; UC: usual care; SD: standard deviation
** Downgraded by two levels due to risk of bias and imprecision (underpowered study - small sample size [N = 31] with 20 participants in intervention and 11 in control arm)*
*** Downgraded by one level due to risk of bias (selection of those already interested; participants with certain conditions, e.g. risk of cirrhosis, HIV or HBV infection, violent participants against pharmacy staff are excluded)*
**** Study design NRS (starting with low quality rating) and downgraded by one level due to indirectness (comparison - intervention and control are not same population =PWID vs. non-PWID or DU)*

Akiyama et al. (2019) [37] assessed the effects of DOT on treatment adherence (TA) in people who inject drugs enrolled in OST. The study was conducted in the transition period from interferon (IFN) to highly effective short-course direct acting antiviral (DAA) treatment, meaning that not all participants received the same therapy. Results show slight, however not significant improvements on TA in the DOT intervention group (86% vs. 75% in CON group, RR 1.15, 95% CI 0.95–1.39). The cluster RCT of Radley et al. (2020) [50] assessed the effect of pharmacy-led DOT on treatment completions (TC) in OST patients receiving DAA. The study showed that pharmacy-led DOT significantly improves TC (8% vs. 4% in CON group, RR 1.85, 95% CI 1.35–2.52), particularly in settings where people who inject drugs receive other harm reduction services through pharmacies (OST).

Coffin et al. (2019) [42] assessed mean number of weekly visits through week 8 and SVR12 for mDOT (mDOT = all participants were compensated for visits) dosing vs. self-administered therapy (SAT) in people who inject drugs. Results show that mDOT with DAA did not increase the mean number of weekly visits (96.3% vs. 96.6% in CON group, RR 1.00, 95% CI 0.87–1.15) and had no effect on SVR12 (89.5% vs. 90% in CON group, RR 0.99, 95% CI 0.78–1.27) when compared to self-administered therapy (SAT) using Wisepill dispenser. However, this study was a pilot study and not powered appropriately to evaluate the primary study outcome (31 participants in total). Radley et al. (2020) [50] assessed the effect of DOT with DAA on SVR12. Results suggest that pharmacy-led DOT significantly improved SVR12 when compared with SAT (7% vs. 3% in control, RR 2.26, 95% CI 1.59–3.21). The non-randomised

study by Schmidbauer et al. (2020) [53] evaluated changes in SVR12 following DOT among people who inject drugs at high risk for non-adherence to DAA therapy (INT) and non-injecting people who use drugss and people who inject drugs with presumed excellent compliance (CON). Overall, the proportion of participants achieving SVR12 in both groups was similarly high (94.6% vs. 97.2% in control, RR 0.97, 95% CI 0.91–1.04).

Conclusion based on GRADE: DOT with direct-acting antivirals +/-IFN (vs SAT) makes little or no difference to treatment adherence and adherence to treatment expressed as SVR12 (both high certainty evidence) [37]. DOT with direct-acting antivirals probably improves treatment completion (moderate certainty evidence) [50]. DOT with direct-acting antivirals may make little or no difference on treatment adherence or SVR12 vs usual care [42,53] (low certainty evidence/very low certainty evidence) [42]; while pharmacy-led DOT with direct-acting antivirals probably improves SVR12 alongside supervised OST (moderate certainty evidence) [50].

Table 14. Directly observed therapy to increase adherence to HIV treatment – Synthesis of results

First author, year [ref no.]	CONTROL vs. INTERVENTION	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Babudieri et al. 2011 [33]	**SAT/home vs. DOT**	TA	NA; NA; NA	NA; NA; NA	6 m. **OR 0.22 [0.12–0.39]** 12 m. **OR 0.30 [0.17–0.54]** 24 m. **OR 0.35 [0.20–0.62]** 36 m. OR 0.65 [0.34–1.27]	LOW*
	SAT/OUT clinic vs. DOT	TA	NA; NA; NA	NA; NA; NA	6 m. **OR 0.19 [0.10–0.34]** 12 m. **OR 0.19 [0.11–0.35]** 24 m. **OR 0.39 [0.22–0.68]** 36 m. OR 1.70 [0.94–3.07]	LOW*
	SAT/home vs. DOT	VL	NA; NA; NA	NA; NA; NA	aHR 0.98 [0.73–1.32]	LOW*
	SAT/OUT clinic vs. DOT	VL	NA; NA; NA	NA; NA; NA	**aHR 0.70** [0.52–0.96]	LOW*

aHR: adjusted Hazard Ratio; CI: confidence interval; aHR: adjusted hazard ratio; DOT: directly observed therapy; NA: not available; OR: odds ratio; OUT: outpatient clinic; SAT: self-administered therapy; TA: treatment adherence; UC: usual care; VL: viral load
**Study design NRS = starting with low quality rating, not downgraded*

The non-randomised study by Babudieri et al. (2011) [33] with 318 participants overall (one intervention group of ex-IDUs admitted to residential drug rehabilitation facilities) and two control groups treated with self-administered ART therapy (one SAT at home, one SAT in outpatient clinic) assessed the effect of DOT for HIV on treatment adherence defined as 'taking more than 95% of prescribed pills' with a long follow-up of 36 months.

The proportion of patients with high level (> 95%) adherence to ART, as measured at the four follow-up visits, ranged from 87% to 90% in the DOT group, 56–65% in the SAT/home group, and 38–53% in the SAT/OUT group (not in the table). Significantly lower treatment adherence was observed in the SAT/home and SAT/OUT groups compared to the interventional DOT group at six, 12, and 24 months from the start of ART therapy (SAT/home vs DOT: 24m. OR 0.35 and SAT/OUT vs DOT: 24m. OR 0.39), but not at the 36-month time point (OR 0.65 for SAT at home vs DOT, and OR 1.70 for SAT in outpatient clinic vs DOT).

Moreover, Babudieri et al. (2011) [33] assessed viral load comparing the DOT group with the two control groups mentioned above. At 24 months follow-up, the adjusted HR (aHR) of observing an undetectable HIV-RNA level was significantly lower in the SAT/OUT group versus DOT (aHR 0.70) but did not reach statistical significance for the SAT/home group (aHR 0.98). Findings suggest that the interventional DOT group (ex-IDU in residential drug rehabilitation facilities) had a significantly better virologic response than the SAT/OUT group, but not when compared to the SAT/home group, although a slightly favourable trend to DOT versus SAT/home seemed to be present.

Conclusion based on GRADE: With regard to 24 months follow-up, DOT may improve treatment adherence (low certainty evidence) and may slightly improve viral load (low certainty evidence) [33].

3.8.2 Contingency management

Two studies, one pilot NRS by Norton et al. (2019) [49] and one RCT by Ward et al. (2019) [56], assessed the effects of cash incentives on linkage to care (visits, TI) and subsequent adherence to treatment (TC, SVR12 as surrogate).

Table 15. Contingency management to increase linkage to HCV care – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Norton et al. 2019 [49]	**CM vs. enhanced UC**	Visit	14/19; 74%; CI [NA]	6/20; 30%; CI [NA]	**RR 2.46 [1.19–5.05]**	VERY LOW*
		TI (DAA)	9/12; 75%; CI [NA]	4/4; 100%; CI [NA]	RR 0.75 [0.54–1.04]	VERY LOW*
Ward et al. 2019 [56]	CM vs UC	TI (DAA)	41/54; 76%; CI [NA]	24/36; 67%; CI [NA]	RR 1.14 [0.86–1.50]	HIGH

CI: confidence interval; CM: contingency management; DAA: direct-acting antivirals; NA: not available; RR: relative risk; TI: treatment initiation; UC: usual care
** Study design NRS; downgraded by one level due to imprecision (underpowered study - small sample size [N = 39] with 19 participants in intervention and 20 in control arm and small events)*

Based on the findings of Norton et al. (2019) [49], participants allocated to interventional contingency management (CM) receiving cash up to $395 for 12 weeks or $540 for 24 weeks were significantly more likely to conduct baseline HCV evaluation (Visit) within three months after enrolment (74% vs. 30% in CON group, RR 2.46, 95% CI 1.19–5.05). In contrast, CM was found to have little or no impact on treatment initiation (TI) defined as receiving prescriptions for at least one DAA within 1 year of baseline visit (75% vs. 100% in CON group, RR 0.75, 95% CI 0.54–1.04) [49].

In the study by Ward et al. (2019) [56], participants received cash incentives of a total maximum of $220 designed to reinforce HCV treatment initiation (TI). Incentives were not based on pill count or HCV RNA response. The initiation rate was higher in people randomised to CM compared to usual care (76% vs. 67% in CON group, RR 1.14, 95% CI 0.86–1.50), however a level of statistical significance was not reached.

Conclusion based on GRADE: It is uncertain whether contingency management improves visits or treatment initiation because the certainty of this evidence is very low [49]; Contingency management makes little or no difference to treatment initiation (high certainty evidence) [56].

Table 16. Contingency management to increase adherence to HCV treatment – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Ward et al. 2019 [56]	CM vs UC	TC (DAA)	42/54; 78%, CI [NA]	23/36; 64%; CI [NA]	RR 1.13 [0.84–1.52]	HIGH
Norton et al. 2019 [49]	CM vs. enhanced UC	SVR12 (DAA)	9/9; 100%; 95% CI [NA]	3/4; 75%; CI [NA]	RR 1.33 [0.76–2.35]	VERY LOW*
Ward et al. 2019 [56]	CM vs UC	SVR12 (DAA)	37/54; 69%; CI [NA]	22/36; 61%; CI [NA]	RR 1.12 [0.82–1.54]	HIGH

CI: confidence interval; CM: contingency management; DAA: direct-acting antivirals; NA: not available; RR: relative risk; SVR12: Sustained Virological Response at post-treatment week 12; TC: treatment completion; UC: usual care
** Study design NRS; downgraded by one level due to imprecision (underpowered study - small sample size and small events)*

Ward et al. (2019) [56] found little effect of CM on the outcome treatment completion (TC) (78% vs. 64% in CON group, RR 1.13, 95% CI 0.84–1.52). Similarly, CM does not substantially increase the proportion of patients achieving SVR12 (69% vs. 61% in CON group, RR 1.12, 95% CI 0.82–1.54). With regard to SVR12, results in Norton et al. (2019) [49] also did not favor interventional CM over the control (100% vs. 75% in CON group, RR 1.33, 95% CI 0.76–2.35). While this study was not powered to show a difference in adherence rates between study arms (9 INT, 4 CON), CM may be advantageous for HCV adherence as treatment is rolled out to a larger population of people who inject drugs.

Findings from Norton et al. (2019) [49] suggest that there is little or no difference between interventional enhanced standard of care and the likelihood of visiting a provider/specialist, demonstrating the need for larger, adequately powered trials. The cash incentives evaluated in Ward et al. (2019) [56] may have been too low to reinforce behavioural changes.

Conclusion based on GRADE: Contingency management makes little or no difference to treatment completion, and it probably makes little or no difference to achieving SVR12 (high certainty evidence) [56]. It is uncertain whether contingency management improves treatment adherence as the certainty of this evidence is very low [49].

3.8.3 Telemedicine

Only one study was identified that evaluated a telemedicine (TM) intervention to increase linkage to HCV care and adherence to treatment [43].

Table 17. Telemedicine to increase linkage to care/adherence to treatment for HCV – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Cooper et al. 2017 [43]	TM vs. UC	TI (IFN+DAA)	43/157; 27.4%; CI [NA]	608/1,130; 53.8%; CI [NA]	**RR 0.51 [0.39–0.66]**	LOW*
	TM vs. UC	TI (DAA)	27/43; 62.8%; CI [NA]	319/608; 52.5%; CI [NA]	RR 1.07 [0.83–1.39]	LOW*
	TM vs. UC	SVR12 (DAA)	18/19; 94.7%; CI [NA]	236/249; 94.8%; CI [NA]	RR 1.00 [0.90–1.12]	VERY LOW**

CI: confidence interval; DAA: direct-acting antivirals; IFN: interferon; NA: not available; RR: relative risk; SVR12: Sustained Virological Response at post-treatment week 12; TI: treatment initiation; TM: telemedicine; UC: usual care
** Study design NRS = starting with low quality rating, not downgraded*
*** NRS downgraded by one level due to imprecision (small sample size in intervention)*

Only one study was identified that evaluated a TM intervention to increase treatment initiation (TI) and the proportion of patients achieving SVR12. Cooper et al. (2017) [43] investigated a TM programme staffed by a multidisciplinary team of HCV-competent healthcare professionals in Canada with statistical significant results for TI with IFN and DAA, however favouring the control (27.4% vs. 53.8% in CON group, RR 0.51, 95% CI 0.39–0.66). When considering only participants receiving DAA, TI rates increased compared to the control, but not significantly (62.8% vs. 52.5% in CON group, RR 1.07, 95% CI 0.83–1.39). With regard to the second outcome, SVR12 (DAA), results did not show any difference between the groups (94.7% vs. 94.8% in CON group, RR 1.00, 95% CI 0.90–1.12). This study by Cooper et al. (2017) [19] aimed to assess that there was no difference in TI when DAA was provided by TM interventions or through attending the clinics (=usual care) in a remote community. Thus, TM can lead to similar results for TI with DAA in remote populations with limited access to healthcare facilities.

Conclusion based on GRADE: Telemedicine with interferon+DAA may reduce treatment initiation (low certainty evidence); Telemedicine with direct-acting antivirals may make little or no difference to treatment initiation (low certainty evidence) and it is uncertain whether it improves viral load because certainty of evidence is very low [43].

3.8.4 Peers

Two studies evaluated the effect of peer involvement on linkage and adherence to HCV care [39,56].

Table 18. Peers to increase linkage to HCV care – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Broad et al. 2020 [39]	LtC via (outreach) testing vs. UC	Visit	6/195; 3%; CI [NA]	5/185; 3% [NA]	RR 1.17 [0.36–3.77]	LOW*
Ward et al. 2019 [56]	Peer mentors vs. UC	TI	45/54; 83%; CI [NA]	24/36; 67%; CI [NA]	RR 1.25 [0.96–1.62]	HIGH

CI: confidence interval; DAA: direct-acting antivirals; LtC: linkage to care; NA: not available; RR: relative risk; TI: treatment initiation; UC: usual care
**Downgraded by two levels: risk of bias (participants were recruited from personal networks) and imprecision (small number of events)*

One RCT evaluated the effect of a peer interventional approach on linkage to HCV care with DAA. Broad et al. (2020) [39] assessed the proportion of participants who had a visit with the HCV nurse within 6 months after point-of-care testing and contact with trained outreach workers with lived HCV experience (=peers). Findings did not show that facilitating linkage to care via outreach workers after testing increased the proportion of participants visiting the HCV nurse within six months (3% vs. 3% in CON group, RR 1.17, 95% CI 0.36–3.77).

Another RCT by Ward et al. (2019) [56] assessed the effect of engagement of peer mentors on the proportion of participants initiating DAA treatment within eight weeks after randomisation/recruitment. Findings suggest that engagement of peer mentors improves treatment initiation in people living with HIV/HCV co-infection from an

outpatient clinic (83% vs. 67% in CON group, RR 1.25, 95% CI 0.96–1.62). However, while a larger proportion of those in the intervention group had the desired outcome (TI), the difference was not statistically significant.

Conclusion based on GRADE: Peers may make little or no effect on visits (low certainty evidence) [39]; Peers may slightly improve treatment initiation (high certainty evidence) [56].

Table 19. Peers to increase adherence to HCV treatment - Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Ward et al. 2019 [56]	Peer mentors vs. UC	TC	42/54; 78%, CI [NA]	23/36; 64%; CI [NA]	RR 1.22 [0.92–1.62]	HIGH
		SVR12	41/54; 76%; CI [NA]	22/36; 61%; CI [NA]	RR 1.24 [0.92–1.68]	HIGH

CI: confidence interval; NA: Not Available; RR: relative risk; SVR12: Sustained Virological Response at post-treatment week 12; TC: treatment completion; UC: usual care.

Ward et al. (2019) [56] also evaluated the effect of engagement of peer mentors on the proportion of participants completing treatment (TC) with DAA and achieving SVR12. With regard to TC, engagement of peer mentors during and after HCV DAA treatments was superior to the control, but the difference was not statistically significant (78% vs. 64% in CON group, RR 1.22, 95% CI 0.92–1.62). SVR12 was achieved by 76% of study participants in the intervention group compared to 61% in the control (RR 1.24, 95% CI 0.92–1.68).

Conclusion based on GRADE: Peers make little or no difference to treatment completion and SVR12 (high certainty evidence) [56].

3.8.5 Primary care

Only one study was identified that assessed the effectiveness of providing DAA in primary care setting to increase linkage to care and adherence to treatment [55].

Table 20. Primary care to increase linkage to care/adherence to treatment for HCV – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Wade et al. 2019 [55]	**PC vs. hospital**	TI	43/57; 75%; CI [NA]	18/53; 34%; CI [NA]	**RR 2.48 [1.54–3.95]**	MODERATE*
	PC vs. hospital	SVR12	28/57; 49%; CI [NA]	16/53; 30%; CI [NA]	**RR 2.22 [1.48–3.33]**	MODERATE*

CI: confidence interval; NA: Not Available; PC: primary care; RR: relative risk; SVR12: Sustained Virological Response at post-treatment week 12; TI: treatment initiation; UC: usual care
** Downgraded by one level: Risk of bias (high withdrawals, ineligible participants)*

Wade et al. (2019) [55] assessed HCV DAA treatment initiation (TI) and the proportion of people who inject drugs achieving SVR12 through DAA in primary care (PC) in settings where general practitioners provided OST, compared to DAA in local hospital-based specialist care (OST still provided in PC). Findings of the RCT show significantly increased TI rates in the interventional PC group compared to the control (75% vs. 34% in CON group, RR 2.48, 95% CI 1.54–3.95). In total, 49% of study participants in the intervention group achieved SVR12 compared to 30% in the control group (RR 2.22, 95% CI 1.48–3.33), also reaching statistical significance.

Conclusion based on GRADE: Primary care probably improves treatment initiation and SVR12 (moderate certainty evidence) [55].

3.8.6 Opioid substitution treatment

Two studies evaluated if the provision of OST is effective in increasing adherence to HCV treatment [41,44].

Table 21. Opioid substitution treatment to increase adherence to HCV treatment – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Grebely et al. 2016 [44]	OST vs. Non-OST	TA	65/70; 93%; CI [84–98%]	1 737/1 882; 92%; CI [91–93%]	RR 1.01 [0.94–1.08]	MODERATE*
Christensen et al. 2018 [41]	OST vs. Non-OST/DU	TC	528/739; 71%; exCI [NA]	1 126/1 500; 75%; exCI [NA]	RR 0.95 [0.90–1.00]	LOW**
Grebely et al. 2016 [44]	OST vs. Non-OST	TC	68/70; 97%; CI [90–99%]	1 846/1 882; 98%; CI [97–99%]	RR 0.99 [0.95–1.03]	MODERATE*
Christensen et al. 2018 [41]	OST vs. Non-OST/DU	SVR12/24	450/528; 85%; CI [NA]	969/1 126; 86%; CI [NA]	RR 0.99 [0.95–1.03]	LOW**
Grebely et al. 2016 [44]	OST vs. Non-OST	SVR12	66/70; 94%; CI [86–98%]	1 822/1 882; 97%; CI [96–98%]	RR 0.97 [0.92–1.03]	MODERATE*

CI: confidence interval; DU: drug use; exCI: exact confidence interval; NA: not available; OST: opioid substitution treatment; RR: relative risk; SVR12: Sustained Virological Response at post-treatment week 12; TA: treatment adherence; TC: treatment completion; UC: usual care
** Downgraded by one level: indirectness (participants were excluded if they had clinically significant drug use).*
*** Study design NRS = starting with low quality rating, not downgraded.*

In their NRS, Christensen et al. (2018) [41] assessed DAA treatment completion (TC) (follow-up documentation after 12–24 weeks with DAA) and SVR12/24 in OST centres vs. non-OST centres. Participants were recruited from a chronic HCV-registry with registration from 254 participating centres, of which about half provided OST. The studied population comprises OST patients in the intervention group and non-OST patients with former/current drug use (non-OST/DU) in the control group. Findings did not indicate that the provision of OST increased HCV treatment completion (71% vs. 75% in CON group, RR 0.95, 95% CI 0.90–1.00) or the proportion of patients achieving SVR12/24 (85% vs. 86% in CON group, RR 0.99, 95% CI 0.95–1.03).

A multicentre RCT at sites in the United States and Europe by Grebely et al. (2016) [44] evaluated DAA treatment adherence (TA), treatment completion (TC) and SVR12 in participants receiving OST (INT) and participants not receiving OST (CON). The total sample sizes ranged from 70 (INT) to 1 882 (CON) individuals. As in Christensen et al. (2018) [41], OST intervention in Grebely et al. (2016) [44] did not increase TA (93% vs. 92% in CON group, RR 1.01, 95% CI 0.94–1.08), TC (97% vs. 98% in CON group, RR 0.99, 95% CI 0.95–1.03) or SVR12 (94% vs. 97% in CON group, RR 0.97, 95% CI 0.92–1.03).

Findings suggest that OST has no or only little effect on outcomes for DAA treatment adherence, however, it should be stressed that the population in both studies was mainly comprised of people receiving OST in contrast to active people who inject drugs. In the study by Christensen et al. (2018) [41], people receiving OST made up 100% of intervention group; Grebely et al. (2016) [44] excluded participants with 'clinically significant drug use within 12 months of screening'.

Conclusion based on GRADE: OST probably makes little or no difference to treatment adherence, treatment completion and viral load (moderate certainty evidence) [44]; OST may make little or no difference to treatment completion and viral load (low certainty confidence) [41]. The results are consistent.

3.8.7 Multicomponent interventions

Interventions with at least three different components were grouped in this intervention group (nurse case management, chronic care model, integrated/multidisciplinary care, group treatment and transition clinic). Two studies on linkage to HCV care [45,54], one study on linkage to HIV care [36], two studies on adherence to HCV treatment [37,45] and two studies on adherence to HIV treatment [34,35] were identified.

Table 22. Multicomponent intervention to increase linkage to HCV care – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Starbird et al. 2020 [54]	NCM vs UC	Visit	16/34; 47%; CI for difference [3.2–40.9%]	8/32; 25%; CI for difference [3.2–40.9%)	RR 1.88 [0.94–3.78]	MODERATE*
	NCM vs UC	TI (DAA)	4/34; 12%; CI [NA]	8/32; 25%; CI [NA]	RR 0.47 [0.16–1.41]	MODERATE*
Ho et al. 2015 [45]	**IC vs. UC (Veteran Affair patients)**	TI (IFN+DAA)	58/182; 31.9%; CI [NA]	34/181; 18.8%; CI [NA]	**RR 1.70 [1.17–2.46]**	MODERATE**

CI: confidence interval; DAA: direct-acting antivirals; IC: Integrated Care; IFN: interferon; NA: Not Available; NCM: Nurse Case Management; RR: relative risk; TI: treatment initiation; UC: usual care.
** Downgraded by one level: imprecision (small number of events in control).*
*** Downgraded by one level: indirectness (highly selective population, veterans).*

Starbird et al. (2020) [54] assessed the effect of nurse case management (NCM) involving nurse-initiated referral to HCV care, strengths-based HCV education, assisted appointment scheduling and strategies to minimise barriers to attending the appointment, on the proportion of participants with HIV co-infections attending hepatitis practice (visits) within 60 days after enrolment and the proportion initiating DAA treatment (TI) within 181 days after enrolment, compared to usual care (UC). The study nurse case manager in the intervention group initiated the referral to HCV care and assisted participants to schedule an appointment in the HCV practice. Strategies to minimise barriers to attending the appointment were discussed. At day 60, 47% of NCM participants were linked to HCV care compared to 25% of UC participants (RR 1.88, 95% CI 0.94–3.78). However, few participants initiated DAA treatment (4/34 in INT vs. 8/32 in CON group, RR 0.47, 95% CI 0.16–1.41). Both outcomes are of moderate certainty.

Ho et al. (2015) [45] investigated in a highly selective group of Veteran Affair patients (US) the proportion of participants initiating IFN and DAA treatment (TI). Results show that integrated care with psychological interventions and case management provided in collaboration with clinic physicians, nurses, and other mental health providers significantly improved TI (31.9% vs. 18.8% in CON group, RR 1.70, 95% CI 1.17–2.46).

Conclusion based on GRADE: Nurse case management probably improves linkage to care. It is uncertain whether it improves treatment initiation (moderate certainty evidence) [54]. Integrated care probably improves treatment initiation (moderate certainty evidence) [45].

Table 23. Multicomponent intervention to increase linkage to HIV care – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Tu et al. 2013 [36]	**CCM in community health centre (aboriginals) before vs. after design**	TI	168/219; 77%; CI [NA]	104/219; 47%; CI [NA]	**RR 1.62 [1.38–1.89]**	VERY LOW*

CCM: Chronic Care Model; CI: confidence interval; NA: not available; RR: relative risk; TI: treatment initiation.
** NRS downgraded by one level: risk of bias (high statistically significant difference in baseline characteristics).*

Tu et al. (2013) [36] assessed treatment initiation (TI) in HIV-positive patients who received primary care in two urban community health centres (CHC) in Canada, before (CON) and after (INT) the implementation of a chronic care model (CCM). Study participants were from a marginalised, largely aboriginal population, with 'most' having injection drug as the presumed route of HIV transmission. The chronic care model is a multidimensional approach to chronic disease management with 6 interrelated components designed to promote uptake of evidence-based clinical recommendations, enhance clinical teamwork, empower patients to better manage their own care. In this framework patients in need of an intervention are easily identified, the quality of care delivery can be objectively examined, and population-based quality improvement initiatives can be evaluated.

Findings indicate that interventional CCM significantly improves TI (77% after vs. 47% before, RR 1.62, 95% CI 1.38–1.89). Besides ART uptake, CCM increased viral load suppression, enabled pneumococcal immunisation, and increased syphilis and TB screening. The quality of evidence was, however, assessed as very low. This is because it was a non-randomised study and there was a statistically significant difference in baseline characteristics among study participants in the two study sites. Furthermore, only limited information about the baseline characteristics of the participants was available.

Conclusion based on GRADE: It is uncertain whether the chronic care model improves treatment initiation because the certainty of this evidence is very low.

Table 24. Multicomponent intervention to increase adherence to HCV treatment – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Akiyama et al. 2019 [37]	Group treatment vs. SAT	TA (DAA+/-IFN)	NA; 90%; CI [79–97%]	NA; 91%; CI [79–97%]	RR 0.99 [0.93–1.15]	HIGH
Ho et al. 2015 [45]	IC vs. UC (Veteran Affair patients)	TA (DAA+IFN)	95/182; 52%; CI [NA]	80/181; 44%; CI [NA]	RR 1.18 [0.95–1.46]	MODERATE*
Akiyama et al. 2019 [37]	Group treatment vs. SAT	SVR12 (DAA+/-IFN)	NA; 87%; CI [74–94%]	NA; 87%; CI [75–95%]	RR 1.00 [0.93–1.15]	HIGH
Ho et al. 2015 [45]	**IC vs. UC (Veteran Affair patients)**	SVR12/24 (DAA+IFN)	29/182; 15.9%; CI [NA]	14/181; 7.7%; CI [NA]	**RR 2.06 [1.13–3.77]**	MODERATE*

CI: confidence interval; IC: Integrated Care; IFN: interferon; RR: relative risk; SVR12/24: Sustained Virological Response at post-treatment week 12 or 24; TA: treatment adherence; UC: usual care.
** Downgraded by one level: indirectness (highly selective population, veterans).*

Two RCTs, Akiyama et al. (2019) [37] and Ho et al. (2015) [45] were identified evaluating effects on treatment adherence and reaching SVR12. Interventional group treatment (weekly meetings with other patients/peers and treatment team, psychosocial support from peers and providers, HCV education, self-administered individual treatment with DAA and IFN) studied by Akiyama et al. (2019) [37] shows no significant effect, either on TA (90% vs. 91% in CON group, RR 0.99, 95% CI 0.93–1.15) or on achieving SVR12 (87% vs. 87% in CON group, RR 1.00, 95% CI 0.93–1.15).

The integrated care approach (which included mental health services) by Ho et al. (2015) [45] demonstrated little effect on DAA and IFN treatment adherence (52% vs. 44% in CON group, RR 1.18, 95% CI 0.95–1.46) but significantly increased the proportion of participants in the study group achieving SVR12/24 (15.9% vs. 7.7% in CON group, RR 2.06, 95% CI 1.13–3.77).

Conclusion based on GRADE: Group treatment makes little or no difference to treatment adherence (high certainty evidence) [37]; integrated care probably makes little or no difference to treatment adherence (moderate certainty evidence) [45]. Integrated care probably improves viral load (moderate certainty evidence) [45]. Group treatment makes little or no difference to viral load (high certainty evidence) [37].

Table 25. Multicomponent intervention to increase adherence to HIV treatment – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Masyukova et al. 2018 [34]	TC for formerly incarcerated vs. non-TC	TA at 6 m.	29/38; 76%; CI NA	79/100; 79%, CI NA	RR 0.96 [0.78–1.18]	LOW *
	TC for formerly incarcerated vs. non-TC	TA at 12 m.	24/38; 63%, CI [NA]	67/100; 67%, CI [NA]	RR 0.94 [0.71–1.24]	LOW *
Sanchez et al. 2012 [35]	MDC (DU) vs. Non-DU in UC	TD	9/71; 12.7%; [NA]	4/48; 8.3%; [NA]	RR 1.52 [0.50–4.66]	LOW **
Masyukova et al. 2018 [34]	TC for formerly incarcerated vs. non-TC	VL	21/38; 54%; CI [NA]	63/100; 63%; CI [NA]	RR 0.86 [0.62–1.19]	LOW *
Sanchez et al. 2012 [35]	MDC (DU) vs. Non-DU in UC	VL	62/71; 87.3%; [NA]	42/48; 87.5%; [NA]	RR 1.0 [0.87–1.15]	LOW **

CI: confidence interval; IC: integrated care; DU: drug use; MDC: multidisciplinary care; NA: not available; RR: relative risk; VL: viral load; TA: treatment adherence; TD: treatment discontinuation; TC: transition clinic.
** NRS downgraded by one level due to indirectness (different population – incarcerated vs community; difference intervention/control not clear).*
*** NRS downgraded by one level due to indirectness (different population – active drug users with HIV versus non-drug users with sexually transmitted HIV).*

The NRS by Masyukova et al. (2018) [34] compared changes in treatment adherence (TA) and viral load (VL) in formerly incarcerated patients living with HIV of a specialised transition clinic (TC) with patient navigation services at different time points with usual care in a community health centre (CHC) and in an infectious disease clinic not directly tailored to formerly incarcerated people. Usual care group has also access to a CHC and infectious disease

clinic specialised in HIV, access to multidisciplinary services incl. nutritional counselling, case management, group programmes, mental health services and substance use disorder treatment. TC intervention neither shows an effect on TA (both time points) nor on VL (54% vs. 63% in CON, RR 0.86, 95% CI 0.62–1.19), even favouring control. Study had a 12-month follow-up period.

Sanchez et al. (2012) [35] assessed the effect of integrated care provided by a multidisciplinary health team on treatment discontinuation (TD) and virological response of <50 copies/mL (viral load) active drug users living with HIV-1 admitted for drug treatment. Services included medical, drug treatment and psychosocial services. The control group was comprised of non-drug users with sexually transmitted HIV-1-infection attending a reference hospital under standard care. The results did not find a statistically significant difference in the risk of permanent treatment discontinuation (stopping treatment >15 days by individuals' choice as defined by the study authors) in the intervention group (12.7% vs. 8.3% in CON group, RR 1.52, 95% CI 0.50–4.66) nor in the effect on viral load (87.3% vs. 87.5% in CON group, RR 1.0, 95% CI 0.87–1.15). Study had a mean follow-up period of 188 weeks (range 24–252 weeks).

Conclusion based on GRADE: For transition clinic (for formerly incarcerated patients) and multidisciplinary care model it is uncertain whether they improve or reduce HIV treatment adherence or viral load as certainty of evidence is very low.

3.8.8 Cooperation

Table 26. Cooperation to increase linkage to HCV care – Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Messina et al. 2020 [48]	**COOP (between 2 centres) PWUD vs. UC**	TI	63/75; 84%; CI [NA]	3/18; 17%; CI [NA]	**RR 5.04 [1.79–14.23]**	VERY LOW*
	COOP (between 2 centres) PWID vs. UC	TI	45/55; 82%; [NA]	3/16; 19%; [NA]	**RR 4.63 [1.56–12.19]**	VERY LOW*

CI: confidence interval; COOP: cooperation; PWID: people who inject drugs; PWUD: people who use drugs; RR: relative risk; TI: treatment initiation; UC: usual care
** NRS downgraded by one level due imprecision (small sample size control)*

In a prospective, interventional, before and after study, Messina et al. (2020) [48] studied the effect of cooperation between a service for substance use disorder (SUD) and an infectious disease unit on treatment initiation rates (TI). The intervention aimed to improve knowledge on HCV infection and on the need to start DAA treatment among SUD staff and ensured fast lane access of people who use drugs/people who inject drugs to the infectious disease unit. Compared with the pre-intervention period, the number of people who were anti-HCV–positive who started DAA treatment increased significantly, with similar results for people who inject drugs and people who use drugs (people who inject drugs: 82% vs. 19%, RR 4.63, 95% CI 1.56–12.19; people who use drugs: 84% vs. 17%, RR 5.04, 95% CI 1.79–14.23). The use of the innovative model with close interaction between the two facilities resulted in a significant increase in linkage to care and start of DAA treatment in the studied population. However, the true effect size of cooperation on the studied outcome should be interpreted with caution as the sample size was small (people who inject drugs: 55 INT vs. 16 CON; people who use drugs: 75 INT vs. 18 CON), resulting in a wide confidence interval in both groups.

The pre-intervention period was January to December 2017, the post-intervention period January to December 2018. Treatment duration was 12 weeks.

Conclusion based on GRADE: For cooperation between SUD staff and infectious disease units, it is uncertain whether it improves or reduces treatment initiation rates as certainty of evidence is very low.

Table 27. Cooperation to increase adherence to tuberculosis treatment - Synthesis of results

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Duarte et al. 2011 [32]	**COOP (between institutions and street teams) incl. DOT (pre/ post)**	TA non-compliance	14/59; 23.7%; CI [NA]	39/82; 47.6%; CI [NA]	**RR 0.50 [0.30–0.83]**	VERY LOW*
	COOP (between institutions and street teams) incl. DOT (pre/ post)	TA treatment discontinuation	6/59; 10.2%; CI [NA]	29/82; 35.4%; CI [NA]	**RR 0.29 [0.13–0.65]**	VERY LOW*

CI: confidence interval; COOP: cooperation; DAA: direct-acting antivirals; DOT: directly observed therapy; NA: not available; RR: relative risk; TA: treatment adherence
** NRS downgraded by one level due risk of bias (no information on participants characteristics)*

One study was identified evaluating an intervention to increase TB treatment adherence (TA). Duarte et al. (2011) [32] assessed the proportion of active-TB participants non-compliant to treatment (not taking all medications) and the proportion of participants discontinuing treatment (treatment interruption for more than two months) before and after the implementation of a cooperation between different institutions (outpatient TB clinic, people who use drugs support centres, public health department, local hospital) and street teams (supporting people who use drugs in the community) for the early detection and treatment of TB including DOT. Findings show that the intervention decreased the absolute risk for non-compliance by 24 percentage points (24% vs. 48% in CON group, RR 0.50, 95% CI 0.30–0.83) and for treatment discontinuation by 25% points (10% vs. 35% in CON group, RR 0.29, 95% CI 0.13–0.65) compared to the control.

The pre-intervention period was 2001 to 2003, the post-intervention period 2005 to 2007.

Conclusion based on GRADE: It is uncertain whether cooperation improves treatment adherence of TB because the certainty of this evidence is very low [32].

4. Discussion

This systematic review aimed to identify and synthesise the existing evidence on effectiveness of interventions to increase linkage to care and adherence to treatment for hepatitis B and C, HIV and TB among people who inject drugs (people who inject drugs).

Generally, to be considered by this review, studies must have been conducted among people who inject drugs or people receiving opioid substitution therapy (OST). The 25 studies that met all eligibility criteria and were included in the evidence synthesis reported on a diverse group of interventions spanning across various settings and focusing on one or two of the infections of interest. Most studies (20) focused on HCV, with only four studies focussing on HIV and one on TB. There were no eligible studies reporting interventions on linkage to care and adherence to treatment for HBV. All included studies were conducted in high-income countries (the United States, Canada, Australia, New Zealand, Italy, Germany, Portugal, Austria, the United Kingdom, Spain and one multicentre trial at sites in the United States and Europe).

4.1 Primary objectives

Studies reporting on linkage to care interventions aimed to increase the likelihood of a 'visit' by people who inject drugs with a provider/specialist after having tested positive for HCV, HIV or TB for an initial evaluation in order to start the treatment. Interventions to enhance linkage to care included: contingency management, telemedicine approaches, peer involvement, cooperation between providers, facilitated referral and the scheduling of specialist appointments through primary care and nurses, and multicomponent approaches. The strongest evidence available for increasing linkage to HCV care was for the use of interventions such as nurse case management (facilitated referral, assisted appointment scheduling and strategies to minimise barriers to attending the appointment), peer involvement, and multicomponent approaches, or integrated care. Multidisciplinary services and cooperation between providers, especially in pharmacy and primary care setting, appear to be a promising approach to facilitate treatment-seeking by people who inject drugs. Due to limited evidence supporting contingency management as a single intervention, it should only be considered as part of a comprehensive package to facilitate linkage to care after adaptation to local circumstances and/or groups or sub-groups of people who inject drugs. There was very little evidence identified for increasing linkage to care through telemedicine approaches. For facilitating linkage to HIV care, little evidence is available (one study, very low quality) for implementation of a chronic care model, that does not allow interpretation of effectiveness.

Publications evaluating interventions to improve adherence to treatment looked at impact on treatment adherence, treatment completion, achieving SVR12 (HCV) or viral load (HIV). Interventions included the same interventions as to increase linkage to care and, in addition, provision of OST services and multicomponent approaches involving group treatments and integrated care. There were differences in the number of studies for interventions to increase adherence to treatment for HCV vs HIV vs TB (20 studies for HCV, 4 studies for HIV, 1 study for TB) revealed by this review. This may be explained by differences in treatment options (regimens) and treatment duration (i.e. short-time DAA treatment for HCV vs. life-long HIV therapy) and by already defined HIV care pathways in many settings. However, across different infectious diseases, patterns do emerge, e.g. for HIV only non-randomised and rather low-quality studies were identified that aimed to assess whether an intervention increased adherence to HIV treatment, resulting in low certainty of evidence ratings, while those interventions focusing on adherence to HCV treatment were shown to be more often effective and of higher quality, with higher certainty of evidence. Adherence to HCV treatment was improved by: peer mentoring, integrated care, and primary care approaches. Limited level certainty of evidence was identified for: contingency management, peer mentoring, provision of OST, multicomponent approaches focusing on group treatment and telemedicine. Regarding directly observed therapy (DOT) interventions, studies provide rather contradictory results: based on the very limited available evidence, DOT may improve short-time adherence to treatment of HIV, however, adherence decreases in the long run. Moreover, DOT did not substantially improve adherence to HCV treatment, with the exception of pharmacy-led DOT alongside supervised opioid substitution treatment. One low-quality study was identified evaluating adherence to TB treatment before and after the implementation of a cooperation between different institutions. Given the very limited evidence, no conclusions can be drawn as to which interventions may improve adherence to TB treatment.

4.2 Secondary objectives

The search was based on the primary objectives; however, data were also extracted to address secondary objectives. Secondary data analyses were not comprehensive and data quality is not assured. Secondary outcomes were reported reasons for not being linked to care or not being adherent to treatment. Among the identified studies, very few addressed barriers or facilitators for linkage to care and adherence to treatment. Only five HCV studies reported barriers or facilitators, albeit in a rather rudimentary form and no patterns can be derived from these results. The only results available rarely refer to directly reported feelings and statements from participants and need to be interpreted in consideration of different settings and countries. For future studies addressing interventions to

increase linkage to care and adherence to treatment, it is strongly recommended to systematically collect additional data on self-reported reasons for (not) initiating or continuing treatment. The same applies for the collection of facilitators, for which no information could be retrieved from the included studies in this report.

Regarding linkage to care, a relevant systematic review by Yanes-Lane et al. (2019) [59] identified individual-, provider- and system-level barriers and facilitators to linkage to HCV and HIV care among released inmates including people who inject drugs and people with risk behaviours such as needle sharing in prisons. Facilitators to linkage to HCV care included social support, having an existing primary care provider, and receipt of methadone, whereas barriers included a perceived lack of healthcare information and a lack of specialised linkage to care programmes. The principal facilitators to linkage to HIV care included social support, treatment for substance use and mental illness, the provision of education, case management, discharge planning and transportation assistance. Important barriers were unstable housing, age <30 years, HIV-related stigma, poor providers' attitudes, and the lack of post-release reintegration assistance [59].

4.3 Gaps in the evidence and outlook

This review identified important research gaps and the need for well-powered RCTs which compare well-characterised interventions to evaluate strategies to enhance linkage to care and adherence to treatment for infectious diseases among people who inject drugs.

For hepatitis C, most of the included studies were conducted outside of Europe. This particularly applies to studies that assessed outcomes for linkage to care, impairing the transferability of the results. In addition, well-powered RCTs to validate the effects of the interventions are lacking. Studies investigating the entire care cascade from testing to cure in one study are urgently needed, whereby the implementation of a variety or combination of different interventions should be pursued further. Depending on the different steps within the care cascade, peer involvement and financial incentives might be promising approaches to increase testing and subsequent linkage to care, whereas DOT or integrated care could support treatment adherence in the target population. Telemedicine services, although not supported by the evidence retrieved in this review, could offer a novel approach in bringing health and health equity into all population groups and regions. An analysis of potentially relevant ongoing studies resulted in 13 trials investigating interventions to increase linkage to care and adherence to treatment for HCV (see Supplement 1). These trials take a promising approach and may contribute to the scarce evidence available. However, based on the trial descriptions, it is not always clear if people who inject drugs are included in the study population. From these trials, two are from Norway, one from Spain, one from Iceland, and one multicentre trial is conducted in Scotland, Wales, and Australia. The other trials are conducted in the United States and Australia.

No study assessing HBV among people who inject drugs could be identified in this review. Further, no upcoming HBV studies which include people who inject drugs could be identified in the trial register (also see Supplement 1), highlighting a considerable lack in evidence in the field of HBV care cascade. One explanation for this lack in evidence could be that HBV vaccination for people who inject drugs and other high-risk groups is a time-limited challenge in most high-income countries, as new cohorts of people who inject drugs will increasingly have been immunised at birth [60].

Only one NRS [36] with low certainty of evidence was identified that assessed HIV treatment initiation, with an interventional comprehensive chronic care model among a largely aboriginal group of people who inject drugs, in British Columbia, Canada. Regarding adherence to HIV treatment among people who inject drugs, three NRS [33-35] with a study duration of >1 year were available from Italy, Spain, and the United States. Those studies assessed interventional DOT, multidisciplinary care, and specialised care in a transition clinic for formerly incarcerated with low [33] to very low [34,35] certainty of evidence. For HIV, there is an urgent need for well-conducted studies (ideally RCTs but also well performed NRS) examining interventions targeting both linkage to care and adherence to treatment over a longer study period. Further, it would be beneficial if such studies were also conducted in European countries to increase the transferability of the results. As with HCV, it would be advantageous if these studies included the full care cascade for HIV, from testing to viral suppression. Considering that HIV requires life-long therapy and acknowledging the conclusive evidence of the power of (long-term) viral suppression in preventing HIV transmission, results clearly highlight the need for more long-term studies with durations of ideally more than 1 year or studies with longer follow-ups. Study protocols of 14 ongoing studies were retrieved from the clinical trial register evaluating interventions to increase linkage to care or adherence to treatment for HIV (see Supplement 1). However, as it is the case in many registered trials if the study population also includes people who inject drugs is not always reported. All identified trials are conducted in the United States.

Scarce evidence is available for TB treatment among people who inject drugs. No study could be identified that assessed linkage to TB care for people who inject drugs. One NRS [32] with small sample size and providing only very low certainty of evidence evaluated an intervention that facilitated cooperation between institutions and street teams. The aim was to support the early detection (screening) of TB and to increase people who inject drugs's adherence to treatment in Portugal. Screening of studies registered in the clinical trial register identified only one study potentially relevant for TB evaluating 'Traditional Directly Observed Therapy (DOT) and Electronic DOT for Tuberculosis Treatment'. However, detailed information on the study population and if people who inject drugs are

included is not available (see Supplement 1). The surveillance report of ECDC/WHO [61] shows that despite the notable progress achieved in the fight against TB in the European Union/European Economic Area (EU/EEA), TB remains a public health issue; 'TB predominantly affects vulnerable populations, such as migrants, prison inmates or people coinfected with HIV'. To achieve the SDG target to end TB by 2030, further efforts are required. The limited evidence identified in this review on interventions to increase linkage and adherence to TB treatment in people who inject drugs highlights the urgent need for well-conducted studies in the European area. Studies assessing interventions along the complete TB care cascade to enforce screening and treatment should be the focus.

4.4 Strengths and limitations

The strengths of this review are that it is based on an in-depth and well-defined search strategy, which was applied to a comprehensive set of databases. Input from ECDC, EMCDDA and experts from a range of disciplines ensured that the appropriate research questions, objectives, search strategy and eligibility criteria were used. Primary peer-reviewed journal publications from 2011 onward with no language restrictions were included to cover a broad spectrum of infectious diseases among people who inject drugs and different interventions across various settings to provide data on the most recent strategies and approaches to increase linkage to care and adherence to treatment among people who inject drugs and people in OST. A comprehensive quality assessment of included studies was conducted using the EPHHP Quality Assessment tool to address the public health sector's need for evidence to support practice and GRADE certainty rating providing a sensible and transparent approach to grading certainty of evidence and strength of recommendations.

Another strength of the review was that a comparison group was required in order to measure impact, thus improving the quality of the evidence. Though the goal of the review is to inform policy-makers in the EU/EEA countries, the geographic scope was extended to include not only EU/EEA/EFTA Member States but also candidate countries to the European Union and comparable countries as Australia, Canada, New Zealand, the United Kingdom, and the United States. The criterion to include only publications with study populations comprised of at least 50% people who inject drugs or people receiving OST in intervention and control group is an important strength. A comparison with the general population is not reasonable, as study outcomes of interventions targeting e.g. HCV-infected individuals without injecting drug use would not be transferable to the highly specific and vulnerable population of people who inject drugs.

This review has several limitations. Firstly, the search was based on the primary research questions, so data on secondary outcomes, barriers and facilitators of interventions for linkage to care and adherence to treatment for infections of people who inject drugs are incomplete or of uncertain quality.

Secondly, the quality of studies was limited, with almost half of all studies included for review being non-randomised studies. Most studies were small in sample size with high risk of bias and confounding. In addition, publication bias was probable given that many of the studies retrieved were only available as posters; studies with less favourable outcome and/or quality are in general less likely to be published in peer-reviewed journals.

Thirdly, due to the review's wide remit, there was a large amount of heterogeneity in the papers included, not only in terms of intervention strategies, definition of populations (i.e. former, recent, and current injection drug use or people in OST), and outcomes, but also in the presentation of the data. For linkage to care, different definitions of successful linkage with different time intervals were presented, including first visit with a provider e.g. within 60 days, three or six months or initiating treatment in general or e.g. within eight weeks. Different measures were also used to assess adherence to treatment, including treatment adherence defined as e.g. completing ≥80% or >95% of planned treatment, treatment completion in general or limited within a certain time frame or sustained virological response at week 12 or 24 (SVR12/24). In this context, it is important to note that for this review it was not feasible to measure long term or final endpoints and that the mentioned outcomes are intermediate endpoints that do not offer further information on cure or morbidity/mortality.

Fourthly, study populations differed in terms of former, recent, and current injection drug users or participants in OST and may therefore not be directly comparable with one another. Very few studies could be included despite comparing people who inject drugs in the intervention groups to non-people who inject drugs (but active drug users) to improve the very limited evidence base. Due to the heterogeneity of data extracted and the limited number of studies with similar interventions, it was not possible to conduct a meta-analysis. However, estimates of the size of effect and confidence intervals were generated to evaluate individual studies providing an overview of the effectiveness of interventions. In addition, we performed a narrative synthesis from which a number of patterns emerged.

Finally, the review excluded interventions focusing on screening and (point of care) testing and did not include costs or cost-effectiveness, as this was beyond the scope of the review's remit. Reviewing the cost-effectiveness of the interventions with the strongest evidence-base and incorporating provider perspectives would enable decision-makers to combine the impact evidence synthesis with implementation cost and provider acceptability of the strategy, to make an informed choice.

5. Conclusions

This review provides evidence-based data on the effectiveness of interventions that can increase linkage to care and adherence to treatment for infections among people who inject drugs and people in OST. The resulting 25 studies meeting eligibility criteria represent a diverse group of interventions spanning different settings and focusing on different infectious diseases. For each infectious disease, the evidence is reviewed and presented. For increasing linkage to HCV care, results show that integrated care approaches, nurse case management, peer involvement as well as multidisciplinary services and cooperation between providers, especially in pharmacy and primary care setting, appear to be promising strategies to facilitate treatment seeking and outreach to the studied population. For increasing linkage to HIV care, the identified evidence was sparse and of very low quality. Regarding interventions to increase adherence to treatment, major differences arise between the various infectious diseases due to diversity of treatment options and durations. Adherence to HCV treatment was improved by peer mentoring, integrated care, and primary care approaches. For adherence to HIV treatment, only non-randomised and rather low-quality studies were identified, which resulted in a low certainty of evidence ratings. One low-quality study was identified evaluating adherence to TB treatment that does not allow for interpretation of effectiveness.

Several areas have been identified in which more research could be helpful in producing a stronger evidence base to inform future public health decision-making and practice. The results highlight the paucity of well-designed RCTs or comparative studies evaluating interventions to enhance linkage to care and adherence to treatment, especially in the field of HIV. In addition, there were no studies evaluating interventions to enhance linkage to HBV and TB care, and only one study assessing adherence to TB treatment. This review calls for well-designed studies evaluating interventions for an improved and simplified care cascade for infectious diseases among the key population of people who inject drugs. The outcomes of this systematic review provide a direction for policy-makers, public health researchers and national and international programme coordinators involved in the prevention and control of infectious diseases among highly vulnerable groups, both in EU/EEA countries and elsewhere.

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Annex 1. List of countries included in systematic search

European Union		
Austria (AT)	France (FR)	Malta (MT)
Belgium (BE)	Germany (DE)	The Netherlands (NL)
Bulgaria (BG)	Greece (EL)	Poland (PL)
Croatia (HR)	Hungary (HU)	Portugal (PT)
Republic of Cyprus (CY)	Ireland (IE)	Romania (RO)
Czechia (CZ)	Italy (IT)	Slovakia (SK)
Denmark (DK)	Latvia (LV)	Slovenia (SI)
Estonia (EE)	Lithuania (LT)	Spain (ES)
Finland (FI)	Luxembourg (LU)	Sweden (SE)
European Free Trade Association (EFTA)/European Economic Area (EEA)		
Iceland (IS)	Norway (NO)	
Liechtenstein (LI)	Switzerland (CH)	
Candidate countries and potential candidates to the EU		
Albania (AL)	Republic of North Macedonia (MK)	Türkiye (TR)
Bosnia and Herzegovina (BA)	Montenegro (ME)	
Kosovo[1] (XK)	Serbia (RS)	
Other countries included		
Australia (AU)	New Zealand (NZ)	United States (US)
Canada (CA)	United Kingdom (UK)	

[1] This designation is without prejudice to positions on status, and is in line with UNSCR 1244 and the ICJ Opinion on the Kosovo Declaration of Independence.

Annex 2. Search strategies

EBM Reviews: Cochrane Central Register of Controlled Trials May 2020 via Ovid

ID	Search	Hits
1	exp Hepatitis B/	2 674
2	exp Hepatitis B virus/	763
3	exp Hepatitis B Antigens/	1 055
4	exp Hepatitis B Antibodies/	604
5	"hep B".ti,ab.	83
6	HBV.ti.	979
7	"hepatitis B".ti,ab.	8 261
8	exp Hepatitis C/	3 313
9	exp Hepacivirus/	1 247
10	exp Hepatitis C Antibodies/	112
11	exp Hepatitis C Antigens/	14
12	"hepatitis C".ti,ab.	7 938
13	"hep c".ti,ab.	30
14	HCV.ti.	2 403
15	hepaciviru*.ti,ab.	0
16	exp Tuberculosis/	2 324
17	"tuberculos*".ti,ab.	5 907
18	TB.ti.	711
19	exp hiv/	3 060
20	exp hiv infections/	12 377
21	"human immunodeficiency virus".ti,ab.	4 394
22	HIV.ti.	16 554
23	"acquired immunodeficiency syndrome".ti,ab.	477
24	AIDS.ti.	2 682
25	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	44 810
26	(substance* or drug*).ti,ab.	214 739
27	(abuse* or depend* or use* or misus* or addict*).ti,ab.	152 349
28	(inject* or intravenous).ti,ab.	138 938
29	26 and 27	35 125
30	26 and 28	27 871
31	exp Drug Users/	116
32	"people who inject*".ti,ab.	167
33	"person* who inject*".ti,ab.	25
34	PWID.ti,ab.	132
35	IDU.ti,ab.	179

ID	Search	Hits
36	((inject* or "shooting up" or intraven* or needle* or syringe*) adj4 (substance* or drug* or opiat* or opioid* or opium or heroin* or diamorphin* or morphin* or morfin* or narcot* or cocaine or methamphetamine or "crystal meth" or "N methylamphetamine") adj4 (user* or abuser* or misuser* or addict* or depend*)).ti,ab.	750
37	exp Substance Abuse, Intravenous/	395
38	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	58 511
39	((uptake or retain* or retention or linkage or link* or initiat* or begin* or began or start* or enter* or entry or commenc* or refer*) adj5 (care or healthcare or treat* or therap*)).ti,ab.	68 367
40	((care or treatment) adj4 (continuum or continuity or cascade or coordination)).ti,ab.	2 099
41	((first or initial) adj1 (appointment or consultation)).ti,ab.	767
42	((link* or identify* or connect*) adj4 (specialist* or "medical provider*" or "long term medical case*" or "prevention service*" or "social service*" or "ambulatory care")).ti,ab.	118
43	exp "Continuity of Patient Care"/	645
44	((adhere* or comply* or compliance or complied) adj5 (care or healthcare or treat* or therap*)).ti,ab.	19 772
45	exp patient compliance/	11 753
46	39 or 40 or 41 or 42 or 43 or 44 or 45	95921
47	25 and 38 and 46	815
48	limit 47 to yr="2011 -Current"	530

Date of search: 8 July 2020

Cochrane Library: Cochrane Reviews

ID	Search	Hits
1	MeSH descriptor: [Hepatitis B] explode all trees	2 667
2	MeSH descriptor: [Hepatitis B virus] explode all trees	749
3	MeSH descriptor: [Hepatitis B Antigens] explode all trees	1 057
4	MeSH descriptor: [Hepatitis B Antibodies] explode all trees	604
5	("hep B"):ti,ab,kw	206
6	(HBV):ti	937
7	("hepatitis B"):ti,ab,kw	8 546
8	MeSH descriptor: [Hepatitis C] explode all trees	3 282
9	MeSH descriptor: [Hepacivirus] explode all trees	1 217
10	MeSH descriptor: [Hepatitis C Antibodies] explode all trees	108
11	MeSH descriptor: [Hepatitis C Antigens] explode all trees	14
12	("hepatitis C"):ti,ab,kw	8 124
13	("hep c"):ti,ab,kw	40
14	(HCV):ti	2 262
15	(hepaciviru*):ti,ab,kw	1 220
16	MeSH descriptor: [Tuberculosis] explode all trees	614
17	(tuberculos*):ti,ab,kw (Word variations have been searched)	6 309
18	(TB):ti (Word variations have been searched)	661
19	MeSH descriptor: [HIV] explode all trees	3011
20	MeSH descriptor: [HIV Infections] explode all trees	12 316
21	("human immunodeficiency virus"):ti,ab,kw	10 969
22	(HIV):ti	15 572
23	("acquired immunodeficiency syndrome"):ti,ab,kw	2 245
24	(AIDS):ti	2 612
25	(OR 1-24)	44 939
26	(substance* or drug*):ti,ab,kw (Word variations have been searched)	604 801
27	(abuse* or depend* or use* or misus* or addict*):ti,ab,kw (Word variations have been searched)	837 827
28	(inject* or intravenous):ti,ab,kw (Word variations have been searched)	169 809
29	26 AND 27	408163
30	26 AND 28	104 083
31	MeSH descriptor: [Drug Users] explode all trees	110
32	(people who inject*):ti,ab,kw (Word variations have been searched)	2 182
33	(person* who inject*):ti,ab,kw	1 692

ID	Search	Hits
34	(PWID):ti,ab,kw (Word variations have been searched)	132
35	IDU:ti,ab,kw	194
36	((inject* or "shooting up" or intraven* or needle* or syringe*) NEAR/4 (substance* or drug* or opiat* or opioid* or opium or heroin* or diamorphin* or morphin* or morfin* or narcot* or cocaine or methamphetamine or "crystal meth" or "N methylamphetamine") NEAR/4 (user* or abuser* or misuser* or addict* or depend*)):ti,ab,kw	769
37	MeSH descriptor: [Substance Abuse, Intravenous] explode all trees	387
38	(OR 29-37)	442 964
39	((uptake or retain* or retention or linkage or link* or initiat* or begin* or began or start* or enter* or entry or commenc* or refer*) NEAR/5 (care or healthcare or treat* or therap*)):ti,ab,kw (Word variations have been searched)	60 733
40	((care or treatment) NEAR/4 (continuum or continuity or cascade or coordination)):ti,ab,kw	2 316
41	((first or initial) NEAR/1 (appointment or consultation)):ti,ab,kw	693
42	((link* or identify* or connect*) NEAR/4 (specialist* or "medical provider*" or "long term medical case*" or "prevention service*" or "social service*" or "ambulatory care")):ti,ab,kw	51
43	MeSH descriptor: [Continuity of Patient Care] explode all trees	24 214
44	MeSH descriptor: [Treatment Adherence and Compliance] explode all trees	27 949
45	((adhere* or comply* or compliance or complied) NEAR/5 (care or healthcare or treat* or therap*)):ti,ab,kw (Word variations have been searched)	18 578
46	(OR 39-45)52	122 773
47	25 AND 38 AND 46 with Cochrane Library publication date Between Jan 2011 and Jul 2020, in Cochrane Reviews	52

Date of search: 8 July 2020

Embase

ID	Search	Hits
1	'hepatitis b'/exp	103 057
2	'hepatitis b virus'/exp	54 861
3	'hepatitis b antigen'/exp	55 158
4	'hepatitis b antibody'/exp	18 883
5	'hepatitis b':ab,ti	109 876
6	'hep b':ab,ti	411
7	hbv:ti	13 592
8	'hepatitis c'/exp	115 910
9	'hepacivirus'/exp	65, 671
10	'hepatitis c antibody'/exp	8 740
11	'hepatitis c antigen'/exp	876
12	'hepatitis c':ab,ti	111 636
13	'hep c':ab,ti	387
14	hcv:ti	25 033
15	'hepaciviru*':ab,ti	286
16	'human immunodeficiency virus'/exp	193 582
17	'human immunodeficiency virus infection'/exp	379 520
18	'human immunodeficiency virus':ab,ti	93 199
19	hiv:ti	243 156
20	'acquired immunodeficiency syndrome':ab,ti	16 504
21	aids:ti	73 766
22	'tuberculosis'/exp	264 030
23	tuberculos*:ab,ti	225 077
24	tb:ti	10 760
25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	1 036 089
26	'substance abuse'/exp	53 428
27	substance*:ab,ti OR drug*:ab,ti	2 539 734
28	abuse*:ab,ti OR depend*:ab,ti OR use*:ab,ti OR misus*:ab,ti OR addict*:ab,ti	10 946 029
29	inject*:ab,ti OR intravenous:ab,ti	1 284 050
30	#27 AND #28	1 327 295
31	#27 AND #29	217 858
32	'intravenous drug abuse'/exp	10 209
33	'injection drug user'/exp	2 122
34	'people who inject*':ab,ti	3 010
35	'person* who inject*':ab,ti	521
36	pwid:ab,ti	2 313
37	idu:ab,ti	4 243

ID	Search	Hits
38	((inject* OR 'shooting up' OR intraven* OR needle* OR syringe*) NEAR/4 (substance* OR drug* OR opiat* OR opioid* OR opium OR heroin* OR diamorphin* OR morphin* OR morfin* OR narcot* OR cocaine OR methamphetamine OR 'crystal meth' OR 'n methylamphetamine') NEAR/4 (user* OR abuser* OR misuser* OR addict* OR depend*)):ab,ti	15 068
39	#26 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	1 436 858
40	'linkage to care'/exp	31
41	'continuum of care'/exp	18
42	((uptake OR retain* OR retention OR linkage OR link* OR initiat* OR begin* OR began OR start* OR enter* OR entry OR commenc* OR refer*) NEAR/5 (care OR healthcare OR treat* OR therap*)):ab,ti	456 430
43	((first OR initial) NEAR/1 (appointment OR consultation)):ab,ti	5 839
44	((care OR treatment) NEAR/4 (continuum OR continuity OR cascade OR coordination)):ab,ti	29 345
45	((link* OR identify* OR connect*) NEAR/4 (specialist* OR 'medical provider*' OR 'long term medical case' OR 'prevention service*' OR 'social service*' OR 'ambulatory care')):ab,ti	1 403
46	'patient compliance'/exp	156 639
47	'adherence'/exp	61
48	((adhere* OR comply* OR compliance OR complied) NEAR/5 (care OR healthcare OR treat* OR therap*)):ab,ti	85 063
49	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	675 465
50	#25 AND #39 AND #49	14 026
51	#50 AND [2011-2020]/py	9 185
52	#51 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	4 752

Date of search: 8 July 2020

Ovid MEDLINE(R) ALL 1946 to 6 July 2020

ID	Search	Hits
1	exp Hepatitis C/	63 826
2	"hepatitis C".ab,ti.	76 514
3	exp Hepacivirus/	33 040
4	Hepatitis C Antibodies/	6 306
5	exp Hepatitis C Antigens/	946
6	hepaciviru*.ab,ti.	243
7	"hep c".ab,ti.	60
8	HCV.ti.	13 252
9	exp Hepatitis B/	58 028
10	"hepatitis B".ab,ti.	78 182
11	exp Hepatitis B virus/	26 895
12	exp Hepatitis B Antigens/	31 044
13	exp Hepatitis B Antibodies/	9 733
14	"hep B".ab,ti.	117
15	HBV.ti.	7 701
16	exp Tuberculosis/	191 667
17	tuberculos*.ab,ti.	188 748
18	TB.ti.	7 660
19	exp HIV/	98 587
20	exp HIV Infections/	282 243
21	"human immunodeficiency virus".ab,ti.	86 218
22	HIV.ti.	196 510
23	"Acquired Immunodeficiency Syndrome".ab,ti.	15 906
24	AIDS.ti.	64 077
25	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	756 271
26	exp Substance Abuse, Intravenous/	15 143
27	(substance* or drug*).ab,ti.	1 848 261
28	(abuse* or depend* or use* or misus* or addict*).ab,ti.	8 651 311
29	(inject* or intravenous).ab,ti.	961 534
30	27 and 28	943 389
31	27 and 29	156 804
32	exp Drug Users/	3 127
33	IDU.ab,ti.	2 926
34	"people who inject*".ab,ti.	2 298
35	"person* who inject*".ab,ti.	373
36	PWID.ab,ti.	1 588
37	((inject* or "shooting up" or intraven* or needle* or syringe*) adj4 (substance* or drug* or opiat* or opioid* or opium or heroin* or diamorphin* or morphin* or morfin* or narcot* or cocaine or	12 716

ID	Search	Hits
	methamphetamine or "crystal meth" or "N methylamphetamine") adj4 (user* or abuser* or misuser* or addict* or depend*)).ab,ti.	
38	26 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	1 012 971
39	((adhere* or comply* or compliance or complied) adj4 (care or healthcare or treat* or therap*)).ab,ti.	46 051
40	exp "Treatment Adherence and Compliance"/	243 073
41	"Continuity of Patient Care"/	19 060
42	((uptake or retain* or retention or linkage or link* or initiat* or begin* or began or start* or enter* or entry or commenc* or refer*) adj5 (care or healthcare or treat* or therap*)).ab,ti.	284 108
43	((first or initial) adj1 (appointment or consultation)).ab,ti.	3 078
44	((care or treatment) adj4 (continuum or continuity or cascade or coordination)).ab,ti.	21 022
45	((link* or identify* or connect*) adj4 (specialist* or "medical provider*" or "long term medical case*" or "prevention service*" or "social service*" or "ambulatory care")).ab,ti.	842
46	39 or 40 or 41 or 42 or 43 or 44 or 45	570 020
47	25 and 38 and 46	8 700
48	limit 47 to yr="2011 -Current"	4 754

Date of search: 8 July 2020

APA PsycInfo 2002 to June Week 5 2020

ID	Search	Hits
1	"hepatitis C".ab,ti.	2 605
2	hepaciviru*.ab,ti.	1
3	"hep c".ab,ti.	5
4	HCV.ti.	325
5	exp hepatitis/	2 517
6	"hepatitis B".ab,ti.	982
7	"hep B".ab,ti.	6
8	HBV.ti.	41
9	exp hepatitis/	2 517
10	exp HIV/	30 652
11	"human immunodeficiency virus".ab,ti.	3 560
12	HIV.ti.	26 443
13	"Acquired Immunodeficiency Syndrome".ab,ti.	440
14	AIDS.ti.	6 954
15	exp Tuberculosis/	998
16	tuberculos*.ab,ti.	1 629
17	TB.ti.	110
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	39 685
19	(substance* or drug*).ab,ti.	182 225
20	(abuse* or depend* or use* or misus* or addict*).ab,ti.	1 252 167
21	(inject* or intravenous).ab,ti.	43 073
22	19 and 20	140 792
23	19 and 21	14 371
24	exp intravenous drug usage/	3 006
25	IDU.ab,ti.	832
26	"people who inject*".ab,ti.	1 056
27	"person* who inject*".ab,ti.	139
28	PWID.ab,ti.	784
29	((inject* or "shooting up" or intraven* or needle* or syringe*) adj4 (substance* or drug* or opiat* or opioid* or opium or heroin* or diamorphin* or morphin* or morfin* or narcot* or cocaine or methamphetamine or "crystal meth" or "N methylamphetamine") adj4 (user* or abuser* or misuser* or addict* or depend*)).ab,ti.	2 777
30	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	144 133
31	exp "continuum of care"/	1 719
32	((care or treatment) adj4 (continuum or continuity or cascade or coordination)).ab,ti.	5 257
33	((first or initial) adj1 (appointment or consultation)).ab,ti.	604

ID	Search	Hits
34	((uptake or retain* or retention or linkage or link* or initiat* or begin* or began or start* or enter* or entry or commenc* or refer*) adj5 (care or healthcare or treat* or therap*)).ab,ti.	40 815
35	((link* or identify* or connect*) adj4 (specialist* or "medical provider*" or "long term medical case*" or "prevention service*" or "social service*" or "ambulatory care")).ab,ti.	254
36	((adhere* or comply* or compliance or complied) adj4 (care or healthcare or treat* or therap*)).ab,ti.	11 452
37	exp compliance/	13 386
38	exp treatment compliance/	10 945
39	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	64 448
40	18 and 30 and 39	1 567
41	limit 40 to yr="2011 -Current"	986

Date of search: 8 July 2020

Annex 3. Quality assessment and certainty of evidence (GRADE) by outcome of intervention reported in studies included in the evidence synthesis on linkage to care and adherence to treatment

HCV

Outcomes	First author, year [ref no.]	Intervention	Study type	Quality EPHHP	Certainty GRADE	Reason for downgrading*	GRADE conclusion**
Linkage to care							
Visit	Broad et al. 2020 [39]	Peers	RCT	Moderate	⨁⨁◯◯	Risk of bias; Imprecision	Little/no difference
Visit	Starbird et al. 2020 [54]	Multi/NCM	RCT	Strong	⨁⨁⨁◯	Imprecision	Probably improved
TI	Messina et al. 2020 [48]	COOP (PWID)	NRS	Weak	⨁◯◯◯	Imprecision	Uncertain
TI	Messina et al. 2020 [48]	COOP (PWUD)	NRS	Weak	⨁◯◯◯	Imprecision	Uncertain
TI	Ho et al. 2015 [45]	Multi/IC	RCT	Moderate	⨁⨁⨁◯	Indirectness	Probably improved
TI	Radley et al. 2020 [50]	DOT	RCT	Weak	⨁⨁⨁◯	Risk of bias	Probably improved
TI	Starbird et al. 2020 [54]	Multi/NCM	RCT	Strong	⨁⨁⨁◯	Imprecision	Favours control
TI	Wade et al. 2019 [55]	Primary care	RCT	Weak	⨁⨁⨁◯	Risk of bias	Probably improved
TI	Ward et al. 2019 [56]	CM	RCT	Moderate	⨁⨁⨁⨁	-	Little/no difference
TI	Ward et al. 2019 [56]	Peers	RCT	Moderate	⨁⨁⨁⨁	-	Slightly improved
TI	Cooper et al. 2017 [43]	TM (DAA + INF)	NRS	Weak	⨁⨁◯◯	-	Favours control
TI	Cooper et al. 2017 [43]	TM (DAA)	NRS	Weak	⨁⨁◯◯	-	Little/no difference[2]
TI	Norton et al. 2019 [49]	CM	NRS	Weak	⨁◯◯◯	Imprecision	Favours control
Adherence to treatment							
TA	Akiyama et al. 2019 [37]	Multi/Group treatment	RCT	Moderate	⨁⨁⨁⨁	-	Little/no difference
TA	Coffin et al. 2019 [42]	DOT	RCT	Weak	⨁⨁◯◯	Risk of bias; Imprecision	Little/no difference
TA	Grebely et al. 2016 [44]	OST	RCT	Moderate	⨁⨁⨁◯	Indirectness	Little/no difference
TA	Ho et al. 2015 [45]	Multi/IC	RCT	Moderate	⨁⨁⨁◯	Indirectness	Little/no difference
TC	Ward et al. 2019 [56]	CM	RCT	Moderate	⨁⨁⨁⨁	-	Little/no difference
TC	Ward et al. 2019 [56]	Peers	RCT	Moderate	⨁⨁⨁⨁	-	Slightly improved

[2] However, the initiation rate is higher than with INF + DAA.

Outcomes	First author, year [ref no.]	Intervention	Study type	Quality EPHHP	Certainty GRADE	Reason for downgrading*	GRADE conclusion**
TC	Radley et al. 2020 [50]	DOT	RCT, cluster	Weak	⨁⨁⨁◯	Risk of bias	Probably improved
TC	Grebely et al. 2016 [44]	OST	RCT	Moderate	⨁⨁⨁◯	Indirectness	Little/no difference
TC	Christensen et al. 2018 [41]	OST	NRS	Weak	⨁⨁◯◯	-	Little/no difference
SVR12	Akiyama et al. 2019 [37]	DOT	RCT	Moderate	⨁⨁⨁⨁	-	Little/no difference
SVR12	Akiyama et al. 2019 [37]	Multi/Group treatment	RCT	Moderate	⨁⨁⨁⨁	-	Little/no difference
SVR12	Ward et al. 2019 [56]	CM	RCT	Moderate	⨁⨁⨁⨁	-	Little/no difference
SVR12	Ward et al. 2019 [56]	Peers	RCT	Moderate	⨁⨁⨁⨁	-	Slightly improved
SVR12	Radley et al. 2020 [50]	DOT	RCT, cluster	Weak	⨁⨁⨁◯	Risk of bias	Probably improved
SVR12	Coffin et al. 2019 [42]	DOT	RCT	Weak	⨁⨁◯◯	Risk of bias, imprecision	Little/no difference
SVR12	Grebely et al. 2016 [44]	OST	RCT	Moderate	⨁⨁⨁◯	Indirectness	Little/no difference
SVR12	Ho et al. 2015 [45]	Multi/IC	RCT	Moderate	⨁⨁⨁◯	Indirectness	Probably improved
SVR12	Wade et al. 2019 [55]	Primary care	RCT	Weak	⨁⨁⨁◯	Risk of bias	Probably improved
SVR12	Christensen et al. 2018 [41]	OST	NRS	Weak	⨁⨁◯◯	-	Little/no difference
SVR12	Cooper et al. 2017 [43]	TM (DAA + INF)	NRS	Weak	⨁◯◯◯	Imprecision	Uncertain
SVR12	Norton et al. 2019 [49]	CM	NRS	Weak	⨁◯◯◯	Imprecision	Uncertain
SVR12	Schmidbauer et al. 2020 [53]	DOT	NRS	Weak	⨁◯◯◯	Indirectness	Uncertain[3]

CM: contingency management; COOP: cooperation; DAA: direct-acting antivirals; DOT: directly observed therapy; HCV: Hepatitis C Virus; IC: integrated care; IFN: interferon; NCM: nurse care manager/management; NRS: non-randomised controlled study; OST: opioid substitution treatment; RCT: non-randomised controlled trial; SVR12: Sustained Virological Response at post-treatment week 12; TA: treatment adherence; TC: treatment completion; TI: treatment initiation; TM: telemedicine

** For more details, see the results tables in section 3.7, Results of descriptive synthesis.*

*** Standardised statements have been applied to express results of an intervention with GRADE (see Table 6).*

[3] Comparator group was non-PWID.

HIV

Outcomes	First author, year [ref no.]	Intervention	Study type	Quality EPHHP	Certainty GRADE	Reason for downgrading*	GRADE conclusion
Linkage to care							
TI	Tu et al. 2013 [36]	Multi/CCM	NRS	Weak	⊕◯◯◯	Risk of bias	Uncertain
Adherence to treatment							
TA	Babudieri et al. 2011 [33]	DOT vs. SAT home	NRS	Weak	⊕⊕◯◯	-	May improved
TA	Babudieri et al. 2011 [33]	DOT vs. SAT outpatient clinic	NRS	Weak	⊕⊕◯◯	-	May improved
TD	Sanchez et al. 2012 [35]	Multi/MDC	NRS	Weak	⊕◯◯◯	Indirectness	Uncertain
VL	Babudieri et al. 2011 [33]	DOT vs. SAT home	NRS	Weak	⊕⊕◯◯	-	May slightly improved
VL	Babudieri et al. 2011 [33]	DOT vs. SAT outpatient clinic	NRS	Weak	⊕⊕◯◯	-	May slightly improved
VL	Masyukova et al. 2018 [34]	Multi/TC	NRS	Weak	⊕◯◯◯	Indirectness	Uncertain
VL	Sanchez et al. 2012 [35]	Multi/MDC	NRS	Weak	⊕◯◯◯	Indirectness	Uncertain

CCM: chronic care model, COOP: cooperation; DOT: directly observed therapy; HIV: Human Immunodeficiency Virus; MDC: multidisciplinary care; NRS: non-randomised controlled study; RCT: non-randomised controlled trial; SAT: self-administered treatment; TA: treatment adherence; TC: treatment completion; TD: treatment discontinuation; TI: treatment initiation; VL: viral load
** For more details, see the results tables in section 3.7, Results of descriptive synthesis.*
*** Standardised statements have been applied to express results of an intervention with GRADE (see Table 6).*

Tuberculosis

Outcomes	First author, year [ref no.]	Intervention	Study type	Quality EPHHP	Certainty GRADE	Reason for downgrading*	GRADE conclusion
TB Adherence to treatment							
TA - non-compliance	Duarte et al. 2011 [32]	COOP	NRS	Weak	⊕◯◯◯	Risk of bias	Uncertain
TA - treatment discontinuation	Duarte et al. 2011 [32]	COOP	NRS	Weak	⊕◯◯◯	Risk of bias	Uncertain

Excluded interferon studies

Six studies [38,40,46,47,51,52] targeting linkage to care and/or adherence to treatment for HCV with **interferon-based treatment regimens** were excluded from the main synthesis and are presented below. Following the structure of the main synthesis (see 0 3.8 Results of descriptive synthesis), results are grouped and reported according to similar interventions. For each intervention group, study characteristics, effect estimates (calculated Risk Ratios and Confidence Intervals) were tabulated and assisted by a descriptive interpretation of results and other relevant information on the contributing studies. The overall certainty of evidence based on the GRADE system (see Table 5) is reported.

Directly observed therapy to increase adherence to HCV treatment (IFN)

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Bruce et al. 2012 [40]	mDOT with OST vs. SAT at spec. liver clinic	SVR24 (IFN)	6/10; 60%; CI [NA];	1/33; 33% CI [NA]	RR 4.5 [0.65-31.08]	⨁⨁◯◯*
Saiz de la Hoya et al. 2014 [52]	DOT vs. SAT	SVR12/24 (IFN)	66/109; 60.6%; CI [51.17-69.22]	89/135; 65,9%; CI [57.59-73.38]	RR 0.92 [0.75-1.13]	⨁⨁⨁◯**

CI: confidence interval; IFN: interferon; DOT: directly observed therapy; mDOT: modified DOT; RR: risk ratio; SAT: self-administered therapy; SVR12/24: Sustained Virological Response at post-treatment week 12/24.
** Downgraded by two levels: Risk of bias (weak study quality) and imprecision (small sample size).*
*** Downgraded by one level: Risk of Bias (weak study quality, 'follow-up losses were not considered failures for the efficacy analysis'; as treated principle: nine patients crossed over from DOT to non-DOT).*

Two RCTs, Bruce et al. (2012) [40] and Saiz de la Hoya et al. (2014) [52], evaluated if DOT with IFN increases the proportion of patients achieving **SVR12/24.** The study by Bruce et al. (2012) [40] was conducted among OST patients of a methadone maintenance clinic (INT) and at a liver specialty clinic (CON). Patients in the intervention group were treated with IFN and received modified DOT (mDOT) and were more likely to achieve SVR12/24 (60% vs. 33% in CON group, RR 4.5, 95% CI 0.65-31.08). However, the confidence interval around the RR is wide and not statistically significant and certainty of evidence is low. On the contrary, Saiz de la Hoya et al. (2014) [52] studied DOT with IFN given to prison inmates with chronic HCV in prisons' healthcare centres by the study nurse. Results on SVR12/24 are not significant (60.6% vs. 65.9% in CON group, RR 0.92, 95% CI 0.75-1.13).

Overall results of the two studies show that the proportion of participants assigned to interventional DOT with IFN achieving SVR12/24 did not (substantially) increase [40,52]. It should be noted, however, that interferon no longer conforms with state-of-the-art HCV therapy and that it causes many more adverse events compared to DAA, e.g. Bruce et al. (2012) [40] reported that 93.4% of participants experienced adverse events.

Conclusion based on GRADE: DOT with IFN may improve viral load (low certainty evidence) [40] and DOT probably makes little or no difference to viral load (moderate certainty evidence) [52]. To sum up: results for DOT on SVR12/24 are not consistent, but predominantly showed zero or little effect.

Multicomponent interventions to increase adherence to HCV treatment (IFN)

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Reimer et al. 2013 [51]	PE vs. UC (in OST)	TC (IFN)	67/82; 82%, CI [NA]	78/107; 73%, CI [NA]	RR 1.12 [0.96-1.31]	⨁⨁◯◯*
	PE vs. UC (in OST)	SVR24 (IFN)	64/82; 78%, CI [NA]	73/109; 67%; CI [NA]	RR 1.17 [0.96-1.31]	⨁⨁◯◯*

CI: confidence interval; IFN: interferon; OST: opioid substitution treatment; PE: psychoeducation; RR: risk ratio; TC: treatment completion; UC: usual care.
**Study design NRS, not downgraded.*

Adherence to HCV treatment: The NRS by Reimer et al. (2013) [51] assessed IFN **treatment completion rates (TC)** and achievement of **SVR24** in an OST population with interventional psychoeducation group sessions under supervision (PE). PE slightly improved TC in the study population (82% vs. 73% in CON group, RR 1.12, 95% CI 0.96-1.31), however not significantly. A higher proportion of participants (not sign.) in the INT group achieved SVR24 (78% vs. 67% in CON group, RR 1.17, 95% CI 0.96-1.31).

Conclusion based on GRADE: PE may make little or no difference to viral load (low certainty evidence) [51].

Nurse-led care to increase linkage and adherence to HCV treatment (IFN)

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Lewis et al. 2016 [46]	Nurse vs. Physician	TI (IFN)	6/62; 9.7%; CI [NA]	6/76; 8%; CI [NA]	RR 1.23 [0.42-3.61]	⨁⨁◯◯*
	Nurse vs. Physician	TA (IFN)	5/6; 83.3%; CI [NA]	5/6; 83.3%; CI [NA]	RR 1.0 [0.60-1.66]	⨁⨁◯◯*

CI: confidence interval; IFN: interferon; TA: treatment adherence; TI: treatment initiation
** Downgraded by two levels: Risk of bias (weak study quality; selective participants - due to safety criteria i.e. psychiatric comorbidity), imprecision (number of events was very small: 6 intervention, 6 control)*

Linkage and adherence to HCV treatment: One study was identified that evaluated a nurse-led care intervention to increase **treatment initiation (TI)** and **treatment adherence (TA).** Findings of the cluster RCT by Lewis et al. (2016) [46] indicate that nurse compared to physician-induced IFN treatment may slightly improve TI (9.7% vs. 8% in CON group, RR 1.23, 95% CI 0.42-3.61). With regard to TA, only few participants remained in both the intervention and control group (decline from to 6 participants each) and no difference between the groups could be detected (83.3% vs. 83.3% in CON group, RR 1.0, 95% CI 0.60-1.66, low certainty of evidence).

Conclusion based on GRADE: Nurse-led intervention may make little or no difference to TI and TA (low certainty evidence) [46].

Education interventions to increase linkage and adherence to HCV treatment (IFN)

First author, year [ref no.]	INTERVENTION vs. CONTROL	Outcomes	Outcomes INTERVENTION	Outcomes CONTROL	RR [95% CI]	GRADE Certainty
Arain et al. 2016 [38]	EDU vs. UC	Visit (IFN)	1/25; 4%; CI [NA]	0/27; 0%; CI [NA]	NA	⨁◯◯◯*
Marinho et al. 2016 [47]	EDU vs. UC	Visit (IFN)	250/340; 73.5%; CI [68.8-72.8]	203/273; 74.4%; CI [69.2-79.5]	RR 0.99 [0.90-1.09]	⨁⨁◯◯**
	EDU vs. UC	TI (IFN)	75/130; 57.7%; CI [49.2–66.2 %]	58/122; 45.5%; CI [38.7-56.4]	RR 1.21 [0.96-1.54]	⨁⨁◯◯**
	EDU vs. UC	TC (IFN)	57/75; 76%; CI [65.2-84.3]	44/58; 75.9%; CI [64.8-86.9%]	RR 1.00 [0.83-1.22]	⨁⨁◯◯**

CI: confidence interval; EDU: education; IFN: interferon; NA: not available; RR: relative risk; TC: treatment completion; TI: treatment initiation; UC: usual care
** Downgraded by three levels: Risk of bias (randomisation not described), indirectness (primary aim was 'knowledge increase') and imprecision (underpowered study)*
***Study design NRS, not downgraded*

Linkage to HCV care: The RCT by Arain et al. (2016) [38] evaluated the effect of small-group information sessions with care providers and peers sharing personal experiences on **visiting a liver specialist** in IFN era. The educational intervention (EDU) was conducted for clients of a centre for alcohol and other drug (CAD) problems providing OST and treatment for other comorbidities and compared to usual care in the CAD. Due to the small sample size and available data, calculation and interpretation of the intervention effect on the basis of

relative risk/risk ratio was not possible (1/25 in INT vs. 0/27 in CON group). Marinho et al. (2016) [47] explored if their health educational programme (HEP) increases the proportion of patients **visiting** and **initiating IFN treatment (TI)** in substance dependence treatment centres compared to the pre-interventional time period. The intervention shows no increase in the proportion of patients visiting a provider (73.5% vs. 74.4% in CON group, RR 0.99, 95% CI 0.90-1.09) and only little effect on TI (57.7% vs. 45.5% in CON group, RR 1.21, 95% CI 0.96-1.54).

Adherence to HCV treatment: Results of the NRS by Marinho et al. (2016) [47], whose primary goal was to increase knowledge about HCV (which significantly increased), reveal that EDU intervention had no effect on **treatment completion** (76% vs. 75.9% in CON group, RR 1.00, 95% CI 0.83-1.22, low certainty of evidence).

Conclusion based on GRADE: EDU may make little or no difference to visits, TI and TC (low certainty evidence) [47].

Detailed study characteristics

Table 28 summarises the detailed characteristics and results of studies included in the evidence synthesis, sorted in alphabetical order by authors. Information on Funding and Conflicts of interest for each study is presented on page 79.

Table 28. Detailed study characteristics

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
Akiyama et al. 2019 [37]	RCT	October 2013 – April 2017	US	HCV infected PWID from three OST programmes, mean age 51 years, mostly male, Latino, unemployed, HCV GT1, 77% received combination DAA, psychiatrically stable	75%; NA; 100%	Three OST centres/Bronx	INT 1: DOT HCV medications linked to OST methadone visits, for non-pick-up days doses packed in electronic blister packs for self-administration at home. IFN+DAA treatment in INT1+2. INT 2: Group treatment (weekly meetings with other patients and treatment team), self-administered individual treatment	SAT Self-administered medication at home (one-month supply was given at OST visit)	Treatment adherence estimated from mixed-effects models using the daily timeframe; SVR12
Arain et al. 2016 [38]	RCT, pilot	February 2014 – December 2014	BE	Clients of centre for alcohol and other drug problems (CAD) providing OST and treats/refers patients for other comorbidities, former and current substance users (69% ever used IV drugs); mean age 39; 77% male, 52% secondary school, 63% had health insurance, 10% were homeless, 85% reported incarceration;	69%; 49%; NA	Centre for alcohol and other drug problems (CAD); OST provision and treatment for other comorbidities/ Limburg	EDU formal + peer: Information sessions at CAD, small groups (5-10 clients), one hour. Information was given by a video and a PPT presentation (+ supp. information) by care provider. Peers sharing personal experiences, questions, and discussion. FibroScan incl. transport to the hospital (taxi) accompanied by study team, communication of outcome directly afterwards + further explanation by a	UC: information brochures on HCV infection available in the waiting room of the CAD	Visiting liver specialist (Visit)

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				excl: cognitive disorder problems, non-Dutch speakers			hepatologist. IFN regimen		
Babudieri et al. 2011 [33]	NRS, retrosp., convenience sampling	NA (36 months)	IT	HIV-infected ex-IDUs admitted to residential drug rehabilitation facilities, not on OST, free from any significant psychiatric diseases; significant higher proportion of participants in DAART group (vs both CON groups) previously diagnosed with AIDS; significantly higher CD4 level at baseline in SAT group	100%; 0%; 0%	Residential drug rehabilitation communities and infectious disease outpatient units/throughout Italy	DOT: antiretroviral drugs are administered by nonmedical community staff who observe the patient taking every dose and receiving therapies	SAT: patients housed in community and treated with self-administered therapy (pills for one week) (CON 1) Home/OUT: patients followed as outpatient and treated with self-administered therapy approach (quarterly visit) (CON 2)	High adherence defined as >95% of prescribed pills taken (TA); undetectable viral load (<50 copies/mL) (VL)
Broad et al. 2020 [39]	RCT	November 2018 – February 2019	CA	Participants were recruited from peer outreach worker's personal networks or were strangers/acquaintances found in non-healthcare settings (i.e. drop-ins, public places, and private homes), mean age 42.8 years, 66% reported recent injection drug use, mostly male (68.4%), white (68.4%), about 54% without	100%; 65.8%; NA	Three HCV programme sites/Toronto	Point of care HCV testing and linkage to care via outreach workers (research assistants with lived experience of HCV hired, trained and supported to deliver HCV education and POC HCV antibody testing). DAA therapy offered.	UC: testing as usual (no POC testing)	Visit at one of the three programme sites within six months

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				stable housing and high rates of poverty, 50% reported negative healthcare provider experience					
Bruce et al. 2012 [40]	RCT, pilot	2007 – 2010	US	Patients of a methadone maintenance clinic with HCV, mean age 40 (INT) and 43 (CON) years, most Caucasian, HIV co-infected, psychiatric comorbidities, especially in INT group	NA; NA; 100%	Methadone maintenance clinic with integrated healthcare team/New Haven	mDOT: with IFN treatment weekly and methadone bottles to take home with a MEMS® cap	SAT at a liver specialty clinic	SVR24
Christensen et al. 2018 [41]	NRS, prosp. cohort	September 2015 – June 2016	DE	Patients from chronic HCV-registry with information from 254 centres of which 123 centres provide OST; mean age: 45.6 years (OST), 48.3 years (non-OST with DU), 55.4 years (non-OST with non-DU); male (OST 79%, non-OST/DU 73%, non-OST/non-DU 53%); majority in all 3 groups with HCV GT1, and nearly 90% in all 3 groups with	NA; NA; 100%	HCV-registry centres also providing OST	OST: DAA treatment	Non-OST patients comprised patients with former/current drug use (non-OST/DU) and patients never consuming drugs (non-OST/NDU) in non-OST centres	At least at one follow up documentation after 12-24 weeks after treatment completion (TC); SVR12/24

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				psychiatric disorders					
Coffin et al. 2019 [42]	RCT, pilot	2015 – 2017	US	Patients recruited from HCV incidence cohort study, mean age 42 years, 74% white, 77% unemployed, 45% with no income, 48% not housed, 77% having regular healthcare provider, all HCV GT1; 45% daily IDU, in intervention group more participants using same syringe. Excl.: hepatitis cirrhosis, fibrosis, chronic liver disease, HIV positive	100%; 45%; NA	Community based clinical research centre/San Francisco	mDOT: incl. motivational interviewing, counselling for injection risk reduction and medication adherence. DAA regimen	UC: unobserved treatment/dosing, each participant received seven tablets weekly in *Wisepill* dispenser at each weekly visit (SAT)	Mean weekly visit completion through week 8 (TA); SVR12
Cooper et al. 2017 [43]	NRS	January 2012 – August 2016	CA	Patients from Ottawa Hospital and Regional Viral Hepatitis Program with chronic HCV, mostly with GT1 and white; groups comparable: mean age 48.9 years, 64.7% male, fibrosis stage 24% cirrhotic, in INT group more frequently indigenous, more frequently history of IDU and excess of alcohol use, incarcerated and	TM: 70,1%; NA; NA; Non-TM: 54,9%; NA; NA	Hospital and Regional HCV Program/Ottawa	TM: having the majority of clinic visits conducted utilising the Ontario TeleHealth Network video and audio system. The patient and remote site TM nurse are linked by audio and video to The Ottawa Hospital site at which the HCV clinician, nurse and allied healthcare providers are located. IFN+DAA regimen	UC: all assessments conducted at The Ottawa Hospital outpatient clinic based within a tertiary care centre	Initiating treatment (TI); SVR12

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				materially deprived					
Duarte et al. 2011 [32]	NRS pre/post	Pre: 2001 – 2005; Post: 2005 – 2007	PT	Drug users visiting outpatient TB clinic (screening and treatment for TB), pre-intervention 100% male, mean age 32 years, post-intervention 86% male, mean age 36 years	100%; 100%; NA	Outpatient TB clinic/Porto Metropolitan Area	COOP: cooperation between institutions and street teams for the early detection and treatment of TB, key partners were trained in TB treatment and screening, counselling, negotiation skills and referral, street teams facilitated transport, care was free of charge	Pre intervention	Non-adherence of patients who commenced treatment for active TB: not taking all the medications in the manner prescribed (TA); Treatment discontinuation: interrupting treatment for >2 months (TA)
Grebely et al. 2016 [44]	RCT, post hoc analysis, multic.	May 2013 – March 2014	US, FR, DE, IT, ES, UK	Patients receiving OST with chronic HCV GT1, mean age 47 years (OST), 53 years (non-OST), mainly white, OST-group: 73% from US, non-OST group: 82%, other participants from Europe, 90% non-cirrhotic, excl.: participants with clinically significant drug use within 12 months of screening	OST: NA; NA; 100%; Non-OST: NA	Multicentre trial at sites in the United States and Europe	OST. DAA treatment	UC: Not receiving OST, DAA treatment	Treatment completion; Treatment adherence (≥80 of treatment doses); SVR12
Ho et al. 2015 [45]	RCT	March 2009 – May 2013	US	Veteran Affairs (VA) patients with confirmed active HCV infection with	NA; 47%; NA	3 VA HCV medical centres/San	Integrated care protocol with case management, incl. brief psychological	Usual care within the HCV clinic or referral to standard mental	Initiating treatment (TI); Treatment

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				substance use and/or psychiatric risk factors for antiviral treatment, attending VA HCV clinics, mean age 55 years, 97.8% male, 39% African American, 36% White, 18% Hispanic; 39% unemployed, 38% disabled, 51% homeless, 80% GT1, 11% HIV/HCV co-infected, 64% prior psychiatric illness and 65% prior substance abuse		Diego, Palo Alto, Bronx	interventions and contingent cash incentives provided in collaboration with clinic physicians, nurses, and other mental health providers (IFN+DAA)	health and substance use clinics for further treatment (IFN+DAA)	adherence (≥80% of planned treatment); SVR12/24
Lewis et al. 2016 [46]	RCT, cluster	September 2011 – July 2012	UK	Patients from three specialist addiction units (INT) and six outreach clinics (CON) diagnosed with chronic HCV; median age 40 years (INT) and 42 (CON); majority of participants in both arms men (80% and 74%), 36% (INT) and 55% (CON) had psychiatric comorbidities; excl.: patients with cirrhosis, renal failure, sepsis or	100%; 31%; NA	Three specialist addiction clinics (INT); six community outreach clinics (CON)	Nurse-led initiation of therapy in specialist addiction clinics. IFN treatment	UC: physician-initiated therapy in control clinics. IFN treatment	Initiating treatment (TI); Receiving ≥80% of total doses for ≥80% of expected therapy, assessed by direct questioning and observation, examination of dosette boxes and by review of blood tests (TA)

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				unstable psychiatric disorders					
Marinho et al. 2016 [47]	NRS, cross-sectional, pre/ post	Pre-INT: April – September 2012; Post-INT February – December 2013	PT	Patients with confirmed HCV infection, registered in substance dependence treatment centres (providing psychosocial, OST and screening of HIV, HBV and HCV services), mean age 42.3 years, 78% male, 62% unemployed, 66% IDU route of HCV infection, most patients received OST, 26% HIV co-infected, 12% HBV, 16% mental disorders. note: before DAA regime	66%; 3.6%; 84%	Seven substance dependence treatment centres/ mainland Portugal	EDU: Health Educational Programme (HEP) consisting of patient workshops, educational videos, leaflets, healthcare professionals' workshops. IFN treatment	UC: before introduction of HEP. IFN treatment	Confirmed hospital visit in relation to patients referred (Visit); starting at least one medication intake confirmed by liver specialist (TI); Treatment completion or maintenance (still on treatment) in relation to treatment initiations (TC)
Masyukova et al. 2018 [34]	NRS, retrosp.	January 2009 – December 2013	US	INT: formerly incarcerated HIV-infected patients of a post-incarceration Transitions Clinic (TC); CON patients receiving HIV care in the same community; mean age 49 years, ~90% male, mostly black	23%; NA; 9%[4] INT: 53%; NA; 29% CON: 12%; NA; 2%	Three ambulatory sites (Post-incarceration Transitions Clinic, community health centre, infectious disease clinic)/Bronx	TC: Services of specialised Transition Clinic (TC) for patients after discharge from prison with patient navigation services. Primary care physicians at transition clinic also provide care in transition clinic and practicing in a community health centre, were other	UC: in Community Health Centre (CHC) and infectious disease clinic specialised in HIV (IDC), patients have access to multidisciplinary services incl. nutritional counselling, case management,	Retention in care at six months (TA): defined as having at least two visits, separated by at least 90 days, within the 180-day period after care initiation; Retention in

[4] Ever or recent IDU not clearly stated in study.

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				American or Hispanic; IDU 53% (INT) vs 12% (CON); chronic illness (63% INT, 67% CON), HCV (66% INT, 19% CON) and psychiatric illness (INT 53%, CON 39%)			services including social work, mental health and substance abuse treatment and speciality care are available to transition clinic patients	group programmes, mental health services and substance use disorder treatment, no services directly tailored to formerly incarcerated people	care at 12 months (TA): required 6-month retention and one more visit between 180 and 360 days from treatment initiation (i.e. at least three visits total); Viral load (VL) suppression at 12 months
Messina et al. 2020 [48]	NRS, prosp. cohort, pre/ post	Pre-INT: January – December 2017; Post-INT: January – December 2018	IT	Clients of an outpatient service for substance use disorders, incl.: previous or current PWUD, former or active PWID; median age 39 years, 91% males *PWID-only subgroup analysis available*	42.7%; NA; NA *PWID-only 100%; NA; NA*	Facility for SUD/southern Italy	COOP: Cooperation between SUD and Infectious Disease Unit including three periodic pros. audits conducted by the infectious disease consultants in the SUD facility to improve knowledge on HCV infection and on the need to treatment; including screening, testing and starting treatment. DAA treatment	UC: Pre-INT period without cooperation and HCV education. DAA treatment	Initiating treatment (TI)
Norton et al. 2019 [49]	NRS, convenience sampling	March 2015 – April 2016	US	NSP clients, median age 47 years, 67% men, 69% Hispanic, HCV-positive (GT1a, GT1b)	NA; 44%; NA	NSP centre providing mental health counselling, referrals and other services/New York	CM: participants received financial incentives for HCV visits, return of medication blister packs and successful early clinical outcome. DAA treatment	Enhanced UC: expedited appointment at centre, round-trip transit fare card, reminders from care coordinator. DAA treatment	Conducting baseline HCV evaluation within three months (Visit); receiving prescriptions for at least one DAA within 1 year of baseline

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
									visit (TI); SVR12
Radley et al. 2020 [50]	RCT, cluster	December 2016 – May 2018	UK	Patients receiving OST in pharmacies (for at least three months), willing to test for HCV and agreement for HCV treatment (DAA), HCV positive (only GT 1 or 3), male 63% (INT), 70% (CON), between 30-39 years 56% (INT) and 46% (CON), Excl.: HCV GT other than 1 or 3; risk of cirrhosis, evidence of current liver disease, HIV or HBV infection	NA; NA; 100%	55 randomly assigned community pharmacies/ Scotland	mDOT: in pharmacy with DAA alongside supervised OST	UC: UC pharmacist pathway: HCV infection discussed with patients, testing offered if HCV status unknown, referral to treatment centre offered if HCV positive. DAA	Referred to conventional care provider, receiving prescriptions and initiating treatment (TI); Completing 8- or 12-week HCV treatment (TC); SVR12
Reimer et al. 2013 [51]	NRS, prosp. cohort	January 2005 – December 2008	DE	Patients of 24 study sites on OST, HCV GT1-4 for about 8.5 years (mean); mean age 36.4 years (INT group younger than CON), 74% male, 46% employed, 40% antidepressant medication before/during treatment; excl.: HIV or HBV co-infected, severe comorbid mental disorders (e.g.	NA; NA; 100%	24 study sites offering OST (7 INT, 16 CON), all with several years of experience in OST	PE-groups: 60 minutes psychoeducation group sessions under supervision. Manualised programme especially tailored to PWID in HCV treatment; Module 1: HCV infection, symptoms, course of illness, interaction with opioid dependence, and risk factors; Module 2: HCV treatment, side effects, psychiatric and somatic comorbidities, reinfection and DU, risk behaviour; Module	UC: treatment as usual in 16 of 24 study sites with IFN	Treatment completion (TC); SVR24 (regardless of treatment completion)

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				untreated major depression or acute psychosis)			3: Coping strategies, resources and self-help, effective use of healthcare support, role of social environment, healthy living, nutrition. Particular topics were repeated. IFN treatment		
Saiz de la Hoya et al. 2014 [52]	RCT	July 2006 – September 2008	ES	Prison inmates with chronic HCV (mainly GT1 or 4), mean age 35.8 years, 94.3% men, 72.1% IDU, 21.3% HIV co-infected, about one third on treatment for mental health; excl.: comorbidities like hepatic disease other than HCV, high risk anaemia, coronary and cerebrovascular disease, severe psychiatric disorders etc.	72%; NA; 32%	Healthcare centres in 25 prisons/Spain	DOT: with IFN (ribavirin) given by the study nurse	UC: SAT self-administered IFN (ribavirin)	SVR12/24
Sanchez et al. 2012 [35]	NRS, retrosp.	January 2005 – December 2010	ES	INT: active drug users living with HIV-1 admitted for drug treatment and who started their first HAART, CON: people living with HIV-1 (sexually transmitted) attended in a reference hospital	NA; 94.3%; 90.1%	Drug abuse outpatient centre/ Barcelona	MDC with DU: HAART provided in a drug abuse outpatient treatment facility with a multidisciplinary health team through comprehensive integrated care that includes medical, drug treatment and psychosocial support	Non-DU in UC: HIV-1+ treatment-naive non-DUs infected through sexual transmission (STG) receiving standard medical care at the Infectious Diseases Unit of	Treatment discontinuation defined as stopping treatment >15 days, death, or loss to follow up (TA); virological response (<50 copies/ml)

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				under standard care; mean age: 41.3 (INT), 37.4 years (CON), majority male and white, incarcerated (33.4% INT vs. non CON), HCV/HBV co-infection (95.8%/7% INT, 6.2%/14.6% CON); more psychiatric disorders, more advanced CDC stages and lower baseline CD4+ in INT group				the reference hospital	during a median follow-up of 118 weeks (range 24-252) (VL)
Schmidbauer et al. 2020 [53]	NRS, convenience sampling	Oct. 17 - Dec. 18	AT	Patients with chronic HCV (GT1-4), median age 41.1 years, 62.8% male, 2.8% HIV co-infected, 4.1% with cirrhosis; 71 patients treated in outpatient clinic with presumed excellent compliance (CON), 74 PWIDs on OST treated at pharmacy or in drug treatment facility (INT), all receiving DAA treatment; SES significantly poorer in INT group (85.5%	NA; 67.6%; 58.6%	Pharmacies and drug treatment facility (INT) and outpatient clinic of a tertiary care centre (CON)	Directly observed DAA treatment together with OST at pharmacy or drug treatment facility for PWID at high risk for non-adherence (Mon-Sat, self-administered doses for Sunday)	Usual care via SAT for non-injecting PWUDs and PWID with excellent compliance (received prescriptions every month and were only seen for routine laboratory tests at the outpatient clinic)	SVR12

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				unemployed, 52.7% no own housing, 66.2% previously imprisoned), 67.6% ongoing IDU, relevant psychiatric comorbidity present in all of them					
Starbird et al. 2020 [54]	RCT	Jul 16 - Aug. 18	US	Patients from clinic providing HIV primary care and HCV specialty care (88% HCV GT1/2); not engaged in HCV care, 46% illicit drug use (24% IDU), 52 % on OST, mean age 55 years, 62% male, 81% Black/African American, income mainly from government benefits, 13% no income, 97% prescribed ART; excl.: pregnant women, people unable to provide independent informed consent	NA; 24%; 52%	Outpatient clinic for HIV and HCV care/Maryland	NCM: Nurse case manager-initiated HCV referral and assisted to schedule an appointment, discussion of barriers, reminders; HCV education (coaching participants, identify their strengths)	UC: standard outpatient processes plus HCV Fact Sheet	Visiting hepatitis practice within 60 days (Visit); initiating DAA treatment within 180 days (TI)
Tu et al. 2013 [36]	NRS, prosp.	NA (18-months period)	CA	HIV-positive patients who received primary care at either of	NA; NA; NA[5]	Two urban community health/primary care centres for	CCM: post-intervention period after implementation of chronic care model by	UC: Pre-intervention period before	Initiating ART treatment (TI); CD4,

[5] '... **most** participants had a history of injection drug use that was the presumed route of HIV transmission' – p. 650

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
				the study sites; patients at Prince George site were more likely to be aboriginal, younger, female, and stably housed; patients in Vancouver were more likely to be taking ART and to have CD4 cell counts of 200 cells/mL or greater; excl.: NA		the aboriginal population/ Vancouver, Prince George, BC	Wagner et al.: multidimensional approach to CCM through six interrelated components; designed to promote uptake of evidence-based clinical recommendations, enhance clinical teamwork, empower patients to better manage their own care; framework in which patients in need of intervention are easily identified, the quality of care delivery can be objectively examined, and population-based quality improvement initiatives can be evaluated	implementation of the CCM	undetectable viral load (VL)
Wade et al. 2019 [55]	RCT	Nov. 15 – Jun. 18	AU; NZ	Patients with HCV GT1/3 adherence to treatment ending a primary care study site and not linked to HCV care, mean age 47 (INT) and 46 years (CON), more than two third male, 83% on OST, 50% IDU in last 6 months, over 70% unemployed, 50% ever incarcerated; excl.: patients with cirrhosis	INT: 100%; 49%; 77% CON: 95%; 49%; 69%	13 primary care sites (INT) and specialist based local hospitals (CON)/Australia and New Zealand	PC: hospital employed community hepatitis nurses provided HCV education, assessments, linkage to treatment and support while patients were in treatment at the PC site, general practitioners provided OST. DAA treatment	UC: treatment in local hospital specialist clinic, OST provided in PC. DAA treatment	Initiating treatment (TI); SVR12

Authors, year [ref no.]	Study design	Study period	Country	Population	Ever IDU %; recent IDU %; OST %	Setting	Intervention	Control	Outcomes
Ward et al. 2019 [56]	RCT	Aug. 15 - Oct. 16	US	Patients from an outpatient clinic, HIV/HCV co-infected, PWUD, HCV GT1, median age 54.9 years, 61% male, 93% black, 85% unemployed, 33% moderate to heavy alcohol use, 61% with active depression and 97% on ART; excl.: evidence of hepatocellular carcinoma or decompensated liver disease	NA; 46%; 28%	John Hopkins Moore Clinic for HIV care/Maryland	INT 1: Peer mentors (successfully treated for HIV and HCV): peers had face-to-face meeting with mentees, contacted mentees before, during and after HCV DAA treatments INT 2: Contingent cash incentives (CM)	UC: participants linked to HCV provider, treated according to standard protocol (involving clinical visits and calls delivered by a nurse-led multidisciplinary team, all participants had study-specific visits receiving $10 to $30 per visit	Initiating treatment within eight weeks (TI); Treatment completion after 12 weeks DAA treatment (TC); SVR12 (per-protocol and on ITT-basis)

ART: antiretroviral therapy; AtT: adherence to treatment; CAD: Centre for alcohol and other drug problems; CM: care management; CON: control; DAA: direct-acting antivirals; DI: drug interactions; DU: drug use; EDU: educational intervention; GT: genotype; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HR: harm reduction; IC: integrated care; IDU: injection drug use(rs); IFN: interferon; INT: intervention; ITT: intention-to-treat analysis; IV: intravenous; mDOT: modified directly observed therapy; NA: not available/applicable; NCM: nurse care manager/management; NRS: non-randomised study; NSP: needle and syringe programme; OST: opioid substitution treatment; PC: primary care; PE: psycho-education; PoC: point of care; PP: per-protocol analysis; PWID: people who inject drugs; PWUD: people who use drugs; RCT: randomised controlled trial; RR: risk ratio; SAT: self-administered therapy; SES: socioeconomic status; SUD: substance use disorder; TA: treatment adherence; TC: treatment completion; TI: treatment initiation; TM: telemedicine; UC: usual care; VA: Veteran Affairs.

Funding and conflicts of interest in the studies included in the evidence synthesis

First author, year [ref no.]	Funding	Conflict of interest
Akiyama et al. 2019 [37]	With Industry Financial Ties	With Industry Financial Ties
Arain et al. 2016 [38]	Non-industry	Not reported
Babudieri et al. 2011 [33]	Not reported	None declared
Broad et al. 2020 [39]	Non-industry	None declared
Bruce et al. 2012 [40]	Non-industry	None declared
Christensen et al. 2018 [41]	With Industry Financial Ties	With Industry Financial Ties
Coffin et al. 2019 [42]	With Industry Financial Ties	None declared
Cooper et al. 2017 [43]	Non-industry	Not reported
Duarte et al. 2011 [32]	Not reported	None declared
Grebely et al. 2016 [44]	With Industry Financial Ties	With Industry Financial Ties
Ho et al. 2015 [45]	Non-industry	With Industry Financial Ties
Lewis et al. 2016 [46]	With Industry Financial Ties	With Industry Financial Ties
Marinho et al. 2016 [47]	With Industry Financial Ties	With Industry Financial Ties
Masyukova et al. 2018 [34]	Non-industry	None declared
Messina et al. 2020 [48]	With Industry Financial Ties	None declared
Norton et al. 2019 [49]	With Industry Financial Ties	With Industry Financial Ties
Radley et al. 2020 [50]	With Industry Financial Ties	With Industry Financial Ties
Reimer et al. 2013 [51]	With Industry Financial Ties	None declared
Saiz de la Hoya et al. 2014 [52]	With Industry Financial Ties	With Industry Financial Ties
Sanchez et al. 2012 [35]	Not reported	None declared
Schmidbauer et al. 2020 [53]	Non-industry	With Industry Financial Ties
Starbird et al. 2020 [54]	Non-industry	With Industry Financial Ties
Tu et al. 2013 [36]	With Industry Financial Ties	Not reported
Wade et al. 2019 [55]	With Industry Financial Ties	With Industry Financial Ties
Ward et al. 2019 [56]	With Industry Financial Ties	None declared

Note: classification of funding sources and indicated conflicts of interest: (1) With Industry Financial Ties (incl. provision of financial support, resources e.g., statistical analyses, or inclusion of study personnel beyond those listed as authors), (2) Non-industry (e.g. public granting agency and private not-for- profit granting agency), (3) None declared (i.e. the authors declare that there are no conflicts of interest regarding the publication of their work), (4) Not reported (= missing). Studies reported as funded 'in part' by the pharmaceutical industry with no other indication of funding source were classified as 'With Industry Financial Ties'.

TQ-03-22-166-EN-N

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Publications Office of the European Union

ISBN 978-92-9498-597-2