Grebely, J., Tran, L., Degenhardt, L., Dowell-Day, A., Santo, T., Larney, S., Hickman, M., Vickerman, P., French, C., Butler, K., Gibbs, D., Valerio, H., Read, P., Dore, G. J., & Hajarizadeh, B. (2021). Association between opioid agonist therapy and testing, treatment uptake, and treatment outcomes for hepatitis C infection among people who inject drugs: A systematic review and meta-analysis. *Clinical Infectious Diseases*, *73*(1), e107-e118. Article ciaa612. https://doi.org/10.1093/cid/ciaa612

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Webappendices for Effect of opioid agonist therapy on testing, treatment uptake, and treatment outcomes for hepatitis C infection among people who inject drugs: A systematic review and meta-analysis

Contents

Appendix 1: Search strings and number of results for electronic literature searches

Database	Search group	Search terms
Medline*	HCV	Hepatitis C or HCV **exp Hepatitis C**
	PWID and OST	opioid substitution* or OST or opioid agonist* or OAT or opioid maintenance* or opiate substitution* or opiate maintenance* or opiate agonist* or methadone therap* or methadone treat* or methadone maintenance* or MMT or buprenorphine therap* or buprenorphine treat* or medication-assisted treat* or medication assisted treat* or MAT or opioid treat* or buprenorphine maintenance* or inject drug* or injecting drug* or injection drug* or drug inject* or drug use* or PWID or IDU or IVDU or drug depend* or substance use* or substance misuse* or substance abuse* or drug addict* **exp Opiate Substitution Treatment/ or exp Substance Abuse, Intravenous/**
	Testing and treatment	treat* or therap* or test or tests. or testing or tested or diagnos*or screen* **exp Therapeutics/ or exp Antiviral Agents/ or exp Treatment Outcome/ or exp diagnosis/ or exp Patient Care/ or exp Disease Management/ or exp "Treatment Adherence and Compliance"/**
Scopus	HCV	"hepatitis c" or hcv
	PWID and OST	"opioid* substitution*" or ost or "opioid* agonist*" or oat or "opioid maintenance*" or "opiate* substitution*" or "opiate* maintenance*" or "opiate* agonist*" or "methadone therap*" or "methadone treat*" or "methadone maintenance*"or mmt or "buprenorphine therap*" or "buprenorphine treat*" or "buprenorphine maintenance*" or "medication-assisted treat*" or "medication assisted treat*" or mat or "opioid treat*" or "inject* drug*" or "drug* inject*" or "drug* use*" or pwid or idu or ivdu or "drug* depend*" or "substance* use*" or "substance* misuse*" or "substance* abuse*" or "drug* addict*"
	Testing and treatment	treat* or therap* or test* or diagnos* or screen*
Web of Science	HCV	"hepatitis c" or hcv
	PWID and OST	TS=("opioid* substitution*" or ost or "opioid* agonist*" or oat or "opioid maintenance*" or "opiate* maintenance*" or "opiate* substitution*" or "opiate* agonist*" or "methadone therap*" or "methadone treat*" or "methadone maintenance*" or mmt or "buprenorphine therap*" or "buprenorphine treat*" or "medication-assisted treat*" or "medication assisted treat*" or MAT or "opioid treat*" or "buprenorphine maintenance*" or "inject drug*" or "injecting drug*" or "injection drug*" or "drug inject*" or "drug use*"

Database	Search group	Search terms
		or pwid or idu or ivdu or "drug depend*" or "substance use*" or "substance misuse*" or "substance abuse*" or "drug addict*")
	Testing and treatment	treat* or therap* or test* or diagnos* or screen*
Cochrane	HCV	"hepatitis c" or hcv
	PWID and OST	(opioid* NEXT substitution*) or ost or (opioid* NEXT agonist*) or oat OR (opioid NEXT maintenance*) or (opiate* Next substitution*) or (opiate* NEXT maintenance*) or (opiate* NEXT agonist*) or (methadone NEXT therap*) or (methadone NEXT treat) or (methadone NEXT maintenance*) or mmt or (buprenorphine NEXT therap*) or (buprenorphine NEXT treat*) or (buprenorphine NEXT maintenance*) or (medication-assisted NEXT treat*) or (medication NEXT assisted) or MAT or (opioid NEXT treat) or (inject* NEXT drug*) or (drug* NEXT inject*) or (drug* NEXT use*) or pwid or idu or ivdu or (drug* NEXT depend*) or (substance* NEXT *use) or (drug* NEXT addict*)
	Testing and treatment	treat* or therap* or test* or diagnos* or screen*
PsychINFO	HCV	"hepatitis c" or hcv
	PWID and OST	"opioid substitution*" or ost or "opioid* agonist*" or oat or "opioid maintenance*" or "opiate* substitution*" or "opiate* maintenance*" or "opiate* agonist*" or "methadone therap*" or "methadone treat*" or "methadone maintenance*" or mmt or "buprenorphine therap*" or "buprenorphine treat*" or "buprenorphine maintenance*" or "medication-assisted treat*" or "medication assisted treat*" or MAT or "opioid treat*" or "inject drug*" or "injecting drug*" or "injection drug*" or "drug inject*" or "drug use*" or pwid or idu or ivdu or "drug depend*" or "substance use*" or "substance misuse*" or "substance abuse*" or "drug addict*"
	Testing and treatment	treat* or therap* or "direct acting antiviral*" or test* or diagnos* or screen*

* 'key-words' in lowercase, 'MeSH' terms in **bold;** all key-word searches were limited to title and abstract

	Search terms	Database				
		EMBASE	Scopus	Web of Science	Cochrane	PsycINFO
1.	HCV + PWID and OST + Testing and treatment	4635	6975	5974	405	1240

Appendix 2: List of extracted items

For each study, the following items were extracted:

Population	Variable name	Description
Study characteristics	Author	Surname of the first author
	Year	Year of study publication
	Journal/conference	Whether the data was published in a journal or presented at a conference
	Country	Country of study
	Study design	How the study was conducted (e.g., cross-sectional, observational cohort)
	Single/multi-centre	Were participants recruited from one site or multiple sites?
	Define recent drug use	How the study defined recent drug use
All	N	Total number of participants
	Age	Age summary
	Age median/mean	Noted whether the age summary was for mean age or median age
	n male	Number of male participants
	n HIV	Number of HIV+ participants
	n OST	Number of participants exposed to OAT
	Define OST	How was OAT exposure defined (e.g., currently undergoing OAT, lifetime OAT)
	n Methadone	Of those exposed to OAT, number who were prescribed methadone
	n Buprenorphine	Of those exposed to OAT, number who were prescribed buprenorphine
	n other OST or unknown	Of those exposed to OAT, number who were prescribed another form of OAT or unspecified
	n no OST	Number of participants not exposed to OST
	n HCV antibody testing	Number of participants who underwent HCV antibody testing
	HCV antibody testing interval	What HCV antibody testing time frame was reported (e.g., recent – past 12 months or lifetime)
	n HCV antibody- no OST	From those who were not exposed to OAT, number of people who underwent HCV antibody testing
	n no HCV antibody- no OST	From those who were not exposed to OAT, number of people who did not undergo HCV antibody testing
	n HCV antibody- OST	From those who were exposed to OAT, number of people who underwent HCV antibody testing
	n no HCV antibody- OST	From those who were exposed to OAT, number of people who did not undergo HCV antibody testing
	HCV_Ab effect size	If reported, what was the effect size reported by the study
	HCV_Ab LCI	Lower confidence interval of reported effect size
	HCV_Ab UCI	Upper confidence interval of reported effect size
	HCV_Ab testing effect size definition	Type of pooled analysis conducted (e.g., odds ratio, hazard ratio)
	HCV_Ab testing adjusted effect size	If reported, what was the adjusted effect size reported by the study
	HCV_Ab testing adjusted effect size definition	Type of pooled adjusted analysis conducted (e.g., adjusted odds ratio, adjusted hazard ratio)
	HCV_Ab adjusted for	What did the adjusted analysis adjust for
HCV antibody positive	n overall HCV antibody positive	Number of people who tested HCV antibody positive and therefore eligible for HCV RNA testing
	Age	Age summary
	Age median/mean	Noted whether the age summary was for mean age or median age
	n male	Number of male participants

Population	Variable name	Description
	n HIV	Number of HIV+ participants
	n OST	Number of participants exposed to OAT
	Define OST	How was OAT exposure defined (e.g., currently undergoing OAT, lifetime OAT)
	n Methadone	Of those exposed to OAT, number who were prescribed methadone
	n Buprenorphine	Of those exposed to OAT, number who were prescribed buprenorphine
	n other OST or unknown	Of those exposed to OAT, number who were prescribed another form of OAT or unspecified
	n no OST	Number of participants not exposed to OST
	HCV RNA testing interval	What HCV RNA testing time frame was reported (e.g., recent – past 12 months or lifetime)
	n HCV RNA- no OST	From those who were not exposed to OAT, number of people who underwent HCV RNA testing
	n no HCV RNA- no OST	From those who were not exposed to OAT, number of people who did not undergo HCV RNA testing
	n HCV RNA- OST	From those who were exposed to OAT, number of people who underwent HCV RNA testing
	n no HCV RNA- OST	From those who were exposed to OAT, number of people who did not undergo HCV RNA testing
	HCV_RNA effect size	If reported, what was the effect size reported by the study
	HCV_RNA LCI	Lower confidence interval of reported effect size
	HCV_RNA UCI	Upper confidence interval of reported effect size
	HCV_RNA testing effect size definition	Type of pooled analysis conducted (e.g., odds ratio, hazard ratio)
	HCV_RNA testing adjusted effect size	If reported, what was the adjusted effect size reported by the study
	HCV_RNA testing adjusted effect size definition	Type of pooled adjusted analysis conducted (e.g., adjusted odds ratio, adjusted hazard ratio)
	HCV_RNA adjusted for	What did the adjusted analysis adjust for
HCV RNA positive	n overall HCV RNA positive	Number of people who tested positive from the HCV RNA testing and therefore eligible to start HCV treatment
	Age	Age summary
	Age median/mean	Noted whether the age summary was for mean age or median age
	n male	Number of male participants
	n HIV	Number of HIV+ participants
	n OST	Number of participants exposed to OAT
	Define OST	How was OAT exposure defined (e.g., currently undergoing OAT, lifetime OAT)
	n Methadone	Of those exposed to OAT, number who were prescribed methadone
	n Buprenorphine	Of those exposed to OAT, number who were prescribed buprenorphine
	n other OST or unknown	Of those exposed to OAT, number who were prescribed another form of OAT or unspecified
	n no OST	Number of participants not exposed to OST
	n cirrhosis	Number of participants with cirrhosis
	n HCV treated	Number of participants who started treatment
	n interferon-based	Number of participants who started an interferon-based treatment
	n DAA-based	Number of participants who started a DAA-based treatment
	n other/unknown treatment	Number of participants who started another form or unspecified treatment
	n no treatment- no OST	From those who were not exposed to OAT, number of people who did not start HCV treatment

Population	Variable name	Description
	n treatment – no OST	From those who were not exposed to OAT, number of people who did start HCV treatment
	n no treatment - OST	From those who were exposed to OAT, number of people who did not start HCV treatment
	n treatment - OST	From those who were exposed to OAT, number of people who did start HCV treatment
	HCV_treatment effect size	If reported, what was the effect size reported by the study
	HCV_treatment LCI	Lower confidence interval of reported effect size
	HCV_treatment UCI	Upper confidence interval of reported effect size
	HCV_treatment effect size definition	Type of pooled analysis conducted (e.g., odds ratio, hazard ratio)
	HCV_treatment adjusted effect size	If reported, what was the adjusted effect size reported by the study
	HCV_treatment adjusted effect size definition	Type of pooled adjusted analysis conducted (e.g., adjusted odds ratio, adjusted hazard ratio)
	HCV_treatment adjusted for	What did the adjusted analysis adjust for
Entering HCV treatment	n treatment uptake	Number of individuals who started HCV treatment and therefore eligible to complete treatment
	Age	Age summary
	Age median/mean	Noted whether the age summary was for mean age or median age
	n male	Number of male participants
	n HIV	Number of HIV+ participants
	n OST	Number of participants exposed to OAT
	Define OST	How was OAT exposure defined (e.g., currently undergoing OAT, lifetime OAT)
	n Methadone	Of those exposed to OAT, number who were prescribed methadone
	n Buprenorphine	Of those exposed to OAT, number who were prescribed buprenorphine
	n other OST or unknown	Of those exposed to OAT, number who were prescribed another form of OAT or unspecified
	n no OST	Number of participants not exposed to OST
	n cirrhosis	Number of participants with cirrhosis
	n interferon-based	Number of participants who started an interferon-based treatment
	n DAA-based	Number of participants who started a DAA-based treatment
	n other/unknown treatment	Number of participants who started another form or unspecified treatment
	n completion	Number of participants who completed treatment
	n no completion - no OST	From those who were not exposed to OAT, number of people who did not complete HCV treatment
	n completion – no OST	From those who were not exposed to OAT, number of people who did complete HCV treatment
	n no completion - OST	From those who were exposed to OAT, number of people who did not complete HCV treatment
	n completion - OST	From those who were exposed to OAT, number of people who did complete HCV treatment
	HCV_completion effect size	If reported, what was the effect size reported by the study
	HCV_completion LCI	Lower confidence interval of reported effect size
	HCV_completion UCI	Upper confidence interval of reported effect size
	HCV_completion testing effect size definition	Type of pooled analysis conducted (e.g., odds ratio, hazard ratio)
	HCV_completion testing adjusted effect size	If reported, what was the adjusted effect size reported by the study
	HCV_completion testing adjusted effect size definition	Type of pooled adjusted analysis conducted (e.g., adjusted odds ratio, adjusted hazard ratio)

Population	Variable name	Description
	HCV_completion adjusted for	What did the adjusted analysis adjust for
	n SVR	Number of people who achieved SVR status
	n no SVR - no OST	From those who were not exposed to OAT, number of people who did not reach SVR status
	n SVR – no OST	From those who were not exposed to OAT, number of people who did reach SVR status
	n no SVR - OST	From those who were exposed to OAT, number of people who did not reach SVR status
	n SVR - OST	From those who were exposed to OAT, number of people who did reach SVR status
	HCV_SVR effect size	If reported, what was the effect size reported by the study
	HCV_SVR LCI	Lower confidence interval of reported effect size
	HCV_SVR UCI	Upper confidence interval of reported effect size
	HCV_SVR testing effect size definition	Type of pooled analysis conducted (e.g., odds ratio, hazard ratio)
	HCV_SVR testing adjusted effect size	If reported, what was the adjusted effect size reported by the study
	HCV_SVR testing adjusted effect size definition	Type of pooled adjusted analysis conducted (e.g., adjusted odds ratio, adjusted hazard ratio)

Appendix 3: ROBINS-I tool

For more detailed guidance regarding the ROBINS-I tool, please see http://www.bristol.ac.uk/media-library/sites/social-community-medicine/images/centres/cresyda/ROBINS-I_detailed_guidance.pdf

Bias domain	Signalling questions	Elaboration	Response options
Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomized trial. There is no NI (No information) option for this signalling question.	Y / PY / PN / N
	If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, proceed to question 1.3.	If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions.	NA / Y / PY / PN / N / NI
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required.	NA / Y / PY / PN / N / NI
	Questions relating to baseline confounding only		

	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardization, and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding.	NA / Y / PY / PN / N / NI

	1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings.	NA / Y / PY / PN / N / NI
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Controlling for post-intervention variables that are affected by intervention is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce bias. Controlling for common effects of intervention and outcome introduces bias.	NA / Y / PY / PN / N / NI
	Questions relating to baseline and time-varying confounding		
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	Adjustment for time-varying confounding is necessary to estimate the effect of starting and adhering to intervention, in both randomized trials and NRSI. Appropriate methods include those based on inverse probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present.	NA / Y / PY / PN / N / NI
	1.8. **If Y/PY to 1.7**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	See 1.5 above.	NA / Y / PY / PN / N / NI
	Risk of bias judgement	See Table 1.	Low / Moderate / Serious / Critical / NI

	Optional: What is the predicted direction of bias due to confounding?	Can the true effect estimate be predicted to be greater or less than the estimated effect in the study because one or more of the important confounding domains was not controlled for? Answering this question will be based on expert knowledge and results in other studies and therefore can only be completed after all of the studies in the body of evidence have been reviewed. Consider the potential effect of each of the unmeasured domains and whether all important confounding domains not controlled for in the analysis would be likely to change the estimate in the same direction, or if one important confounding domain that was not controlled for in the analysis is likely to have a dominant impact.	Favours experimental / Favours comparator / Unpredictable

Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	This domain is concerned only with selection into the study based on participant characteristics observed *after* the start of intervention. Selection based on characteristics observed *before* the start of intervention can be addressed by controlling for imbalances between experimental intervention and comparator groups in baseline characteristics that are prognostic for the outcome (baseline confounding).	Y / PY / PN / N / NI
	2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention **and** an effect of either the outcome or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome.	NA / Y / PY / PN / N / NI
	2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
	2.4. Do start of follow-up and start of intervention coincide for most participants?	If participants are not followed from the start of the intervention then a period of follow up has been excluded, and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses.	Y / PY / PN / N / NI
	2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	It is in principle possible to correct for selection biases, for example by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions of the missing participants or follow up times and outcome events and including them using missing data methodology. However such methods are rarely used and the answer to this question will usually be "No".	NA / Y / PY / PN / N / NI
	Risk of bias judgement	See Table 1.	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to selection of participants into the study?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in classification of interventions	3.1 Were intervention groups clearly defined?	A pre-requisite for an appropriate comparison of interventions is that the interventions are well defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level interventions, criteria for considering individuals to have received each intervention should be clear and explicit, covering issues such as type, setting, dose, frequency, intensity and/or timing of intervention. For population-level interventions (e.g. measures to control air pollution), the question relates to whether the population is clearly defined, and the answer is likely to be 'Yes'.	Y / PY / PN / N / NI
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Collection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to control air pollution), the answer to this question is likely to be 'Yes'.	Y / PY / PN / N / NI
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification.	Y / PY / PN / N / NI
	Risk of bias judgement	See Table 1.	Low / Moderate / Serious / Critical / NI

	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias due to deviations from intended interventions	**If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2**		
	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Deviations that happen in usual practice following the intervention (for example, cessation of a drug intervention because of acute toxicity) are part of the intended intervention and therefore do not lead to bias in the effect of assignment to intervention. Deviations may arise due to expectations of a difference between intervention and comparator (for example because participants feel unlucky to have been assigned to the comparator group and therefore seek the active intervention, or components of it, or other interventions). Such deviations are not part of usual practice, so may lead to biased effect estimates. However these are not expected in observational studies of individuals in routine care.	Y / PY / PN / N / NI
	4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	Deviations from intended interventions that do not reflect usual practice will be important if they affect the outcome, but not otherwise. Furthermore, bias will arise only if there is imbalance in the deviations across the two groups.	NA / Y / PY / PN / N / NI
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
	4.3. Were important co-interventions balanced across intervention groups?	Risk of bias will be higher if unplanned co-interventions were implemented in a way that would bias the estimated effect of intervention. Co-interventions will be important if they affect the outcome, but not otherwise. Bias will arise only if there is imbalance in such co-interventions between the intervention groups. Consider the co-interventions, including any pre-specified co-interventions, that are likely to affect the outcome and to have been administered in this study. Consider whether these co-interventions are balanced between intervention groups.	Y / PY / PN / N / NI
	4.4. Was the intervention implemented successfully for most participants?	Risk of bias will be higher if the intervention was not implemented as intended by, for example, the health care professionals delivering care during the trial. Consider whether implementation of the intervention was successful for most participants.	Y / PY / PN / N / NI

	4.5. Did study participants adhere to the assigned intervention regimen?	Risk of bias will be higher if participants did not adhere to the intervention as intended. Lack of adherence includes imperfect compliance, cessation of intervention, crossovers to the comparator intervention and switches to another active intervention. Consider available information on the proportion of study participants who continued with their assigned	Y / PY / PN / N / NI

		intervention throughout follow up, and answer 'No' or 'Probably No' if this proportion is high enough to raise concerns. Answer 'Yes' for studies of interventions that are administered once, so that imperfect adherence is not possible. We distinguish between analyses where follow-up time after interventions switches (including cessation of intervention) is assigned to (1) the new intervention or (2) the original intervention. (1) is addressed under time-varying confounding, and should not be considered further here.	
	4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	It is possible to conduct an analysis that corrects for some types of deviation from the intended intervention. Examples of appropriate analysis strategies include inverse probability weighting or instrumental variable estimation. It is possible that a paper reports such an analysis without reporting information on the deviations from intended intervention, but it would be hard to judge such an analysis to be appropriate in the absence of such information. Specialist advice may be needed to assess studies that used these approaches. If everyone in one group received a co-intervention, adjustments cannot be made to overcome this.	NA / Y / PY / PN / N / NI
	Risk of bias judgement	See Table 2	
	Optional: What is the predicted direction of bias due to deviations from the intended interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	

Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	"Nearly all" should be interpreted as "enough to be confident of the findings", and a suitable proportion depends on the context. In some situations, availability of data from 95% (or possibly 90%) of the participants may be sufficient, providing that events of interest are reasonably common in both intervention groups. One aspect of this is that review authors would ideally try and locate an analysis plan for the study.	Y / PY / PN / N / NI
	5.2 Were participants excluded due to missing data on intervention status?	Missing intervention status may be a problem. This requires that the *intended* study sample is clear, which it may not be in practice.	Y / PY / PN / N / NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	This question relates particularly to participants excluded from the analysis because of missing information on confounders that were controlled for in the analysis.	Y / PY / PN / N / NI
	5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	This aims to elicit whether either (i) differential proportion of missing observations or (ii) differences in reasons for missing observations could substantially impact on our ability to answer the question being addressed. "Similar" includes some minor degree of discrepancy across intervention groups as expected by chance.	NA / Y / PY / PN / N / NI
	5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?	Evidence for robustness may come from how missing data were handled in the analysis and whether sensitivity analyses were performed by the investigators, or occasionally from additional analyses performed by the systematic reviewers. It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate answer. Review authors should seek naïve (complete-case) analyses for comparison, and clear differences between complete-case and multiple imputation-based findings should lead to careful assessment of the validity of the methods used.	NA / Y / PY / PN / N / NI
	Risk of bias judgement	See Table 2	Low / Moderate / Serious / Critical / NI

	Optional: What is the predicted direction of bias due to missing data?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Some outcome measures involve negligible assessor judgment, e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low.	Y / PY / PN / N / NI
	6.2 Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be 'No'. In other situations, outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators; the answer this question would then also be 'No'. In studies where participants report their outcomes themselves, for example in a questionnaire, the outcome assessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves.	Y / PY / PN / N / NI
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome detection methods and thresholds, same time point, same definition, and same measurements.	Y / PY / PN / N / NI
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present, could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship. This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls being in place.	Y / PY / PN / N / NI
	Risk of bias judgement	See Table 2	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to measurement of outcomes?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in selection of the reported result	Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ....multiple outcome *measurements* within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Because of the limitations of using data from non-randomized studies for analyses of effectiveness (need to control confounding, substantial missing data, etc), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously scaled outcome converted to categorical data with different cut-points; different sets of covariates used for adjustment; and different analytic strategies for dealing with missing data. Application of such methods generates multiple estimates of the effect of the intervention versus the comparator on the outcome. If the analyst does not pre-specify the methods to be applied, and multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	7.3 ... different *subgroups*?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	Risk of bias judgement	See Table 2	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to selection of the reported result?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall bias	**Risk of bias judgement**	See Table 3.	Low / Moderate / Serious / Critical / NI
	Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Appendix 4: ROBINS-I Risk of Bias Assessments

Study	Overall	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result
Ever OST + Ever Antibody testing								
Butler, 2015[1]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Butler, 2019[2]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Iakunchykova, 2018[4]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Roux, 2016[5]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Ti, 2013[6]	Moderate	Moderate	Moderate	Low	Low	Low	Low	Low
Ever OST + Recent Antibody testing								
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Roux, 2016[5]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Current/recent OAT + Ever Antibody testing								
Bajis, 2019[7]	Serious	Serious	Moderate	Low	Low	Moderate	Low	Low
Butler, 2015[1]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Butler, 2019[2]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Iakunchykova, 2018[4]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Roux, 2016[5]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Valerio, 2019[8]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Current/recent OAT + Recent Antibody testing								
Day, 2008[9]	Serious	Serious	Moderate	Low	Low	Low	Low	Low
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Roux, 2016[5]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Valerio, 2019[8]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Ever OST + Ever RNA testing								
Butler, 2015[1]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Butler, 2019[2]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Iakunchykova, 2018[4]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Ever OST + Recent RNA testing								
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Current/recent OAT + Ever RNA testing								
Butler, 2015[1]	Serious	Serious	Serious	Low	Low	Low	Low	Low

Study	Overall	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result
Butler, 2019[2]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Iakunchykova, 2018[4]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Valerio, 2019[8]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Current/recent OAT + Recent RNA testing								
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Valerio, 2019[8]	Serious	Moderate	Serious	Low	Low	Moderate	Low	Low
Ever OST + Treatment uptake								
Butler, 2015[1]	Serious	Serious	Serious	Low	Low	Moderate	Low	Low
Butler, 2019[2]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Iversen, 2014[10]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Iversen, 2019[11]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Valerio, 2019[8]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Current/recent OAT + Treatment uptake								
Butler, 2015[1]	Serious	Serious	Serious	Low	Low	Moderate	Low	Low
Butler, 2019[2]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Gibbs, 2019[3]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Iversen, 2014[10]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Makarenko, 2019[12]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Socias, 2019[13]	Serious	Moderate	Serious	Low	Low	Moderate	Low	Low
Valerio, 2019[8]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Current/recent OAT + Treatment completion								
Boglione, 2017[14]	Serious	Serious	Moderate	Low	Low	Low	Low	Low
Bouscaillou, 2018[15]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Eckhardt, 2018[16]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Grebely, 2018[17]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Magel, 2019[18]	Serious	Serious	Serious	Low	Low	Low	No information	Low
Morris, 2017[19]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Norton, 2017[20]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Read, 2019[21]	Serious	Serious	Serious	Low	Low	Moderate	Low	Low
Selfridge, 2019[22]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Current/recent OAT + SVR status								
Boglione, 2017[14]	Serious	Serious	Moderate	Low	Low	Low	Low	Low

Study	Overall	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result
Bouscaillou, 2018[15]	Serious	Moderate	Serious	Low	Low	Low	Low	Low
Eckhardt, 2018[16]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Grebely, 2018[17]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Magel, 2019[18]	Serious	Serious	Serious	Low	Low	Low	No information	Low
Morris, 2017[19]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Norton, 2017[20]	Serious	Serious	Serious	Low	Low	Low	Low	Low
Read, 2019[21]	Serious	Serious	Serious	Low	Low	Moderate	Low	Low
Selfridge, 2019[22]	Serious	Serious	Serious	Low	Low	Low	Low	Low

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Appendix 5: Supplementary Table 1 - Studies evaluating HCV treatment outcomes

Table 5.1. Characteristics of the studies evaluating HCV treatment outcomes among people who are HCV RNA positive who initated HCV treatment

												Treatment completion				SVR			
First author, year (Country)	**Study design**	**Definition of recent injecting drug use**	**Total number of participants**	**Age mean or median, year**	**Male (%)**	**Cirrhosis (%)**	**Used opioids ever (%)**	**OAT ever (%)**	**OAT recently (%)**	**HCV treatment completion (%)**	**SVR (%)**	**no OAT ever**	**OAT ever**	**No recent OAT**	**OAT recently**	**no OAT ever**	**OAT ever**	**No recent OAT**	**OAT recently**
Boglione, 2017 (Italy)	Observational cohort	Previous 12 months	174	51.5	90%	63%	96%	NA	34%	90%	93%	NA	NA	107/115 (93%)	49/59 (83%)	NA	NA	114/115 (99%)	48/59 (81%)
Bouscaillou, 2018 (Georgia)	Observational cohort	Previous 6 months	138	46	100%	58%	NA	NA	25%	98%	80%	NA	NA	101/103 (98%)	34/35 (97%)	NA	NA	84/103 (82%)	27/35 (77%)
Eckhardt, 2018 (USA)	Observational cohort	Previous 1 month	53	47.2*	83%	23%	NA	NA	45%	94%	91%	NA	NA	26/29 (90%)	24/24 (100%)	NA	NA	27/29 (93%)	21/24 (88%)
Grebely, 2018 (Interntional)	Clinical Trial	Previous 6 months	103	48	72%	9%	97%	NA	56%	97%	94%	NA	NA	43/45 (96%)	57/58 (93%)	NA	NA	43/45 (96%)	54/58 (93%)
Morris, 2017 (Australia)	Observational cohort	Previous 12 months	127	45.2*	69%	11%	NA	NA	35%	96%	77%	NA	NA	77/82 (94%)	45/45 (100%)	NA	NA	61/82 (74%)	37/45 (82%)
Norton, 2017 (USA)	Observational cohort	Ongoing/active	31	56	87%	32%	NA	NA	68%	100%	94%	NA	NA	10/10 (100%)	21/21 (100%)	NA	NA	9/10 (90%)	20/21 (95%)
Read, 2019 (Australia)	Observational cohort	Previous 6 months	178	42.5	72%	10%	NA	NA	43%	65%	64%	NA	NA	43/79 (54%)	56/76 (74%)	NA	NA	42/79 (53%)	55/76 (72%)
Magel, 2019 (Canada)	Observational cohort	Previous 6 months	226	52	77%	NA	NA	NA	58%	99%	78%	NA	NA	86/94 (91%)	123/132 (93%)	NA	NA	79/94 (84%)	97/132 (73%)
Selfridge, 2019 (Canada)	Observational cohort	Previous 6 months	132	51	68%	28%	NA	NA	66%	98%	92%	NA	NA	43/45 (96%)	86/87 (99%)	NA	NA	40/45 (89%)	82/87 (94%)

* denotes mean