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MAJOR ARTICLE

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

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(See the Editorial Commentary by Kattakuzhy and Rosenthal on pages e119–21.)

Background. People who inject drugs (PWID) experience barriers to accessing testing and treatment for hepatitis C virus (HCV) infection. Opioid agonist therapy (OAT) may provide an opportunity to improve access to HCV care. This systematic review assessed the association of OAT and HCV testing, treatment, and treatment outcomes among PWID.

Methods. Bibliographic databases and conference presentations were searched for studies that assessed the association between OAT and HCV testing, treatment, and treatment outcomes (direct-acting antiviral [DAA] therapy only) among PWID (in the past year). Meta-analysis was used to pool estimates.

Results. Of 9877 articles identified, 22 studies conducted in Australia, Europe, North America, and Thailand were eligible and included. Risk of bias was serious in 21 studies and moderate in 1 study. Current/recent OAT was associated with an increased odds of recent HCV antibody testing (4 studies; odds ratio (OR), 1.80; 95% confidence interval [CI], 1.36–2.39), HCV RNA testing among those who were HCV antibody–positive (2 studies; OR, 1.83; 95% CI, 1.27–2.62), and DAA treatment uptake among those who were HCV RNA–positive (7 studies; OR, 1.53; 95% CI, 1.07–2.20). There was insufficient evidence of an association between OAT and treatment completion (9 studies) or sustained virologic response following DAA therapy (9 studies).

Conclusions. OAT can increase linkage to HCV care, including uptake of HCV testing and treatment among PWID. This supports the scale-up of OAT as part of strategies to enhance HCV treatment to further HCV elimination efforts.

Keywords. HCV; PWID; IDU; care cascade; injecting drug use.

Globally, 6.1 million people who inject drugs (PWID) are estimated to be living with hepatitis C virus (HCV) infection [1, 2]. The development of simple, effective, direct-acting antiviral treatments (DAAs) for the treatment of HCV infection [3] has been transformative, with evidence that DAAs are having a population-level impact on liver disease burden in settings where treatment scale-up has been broad at the population level [4–7]. The World Health Organization (WHO) has set a goal to eliminate HCV infection as a global public health threat [8]. However, in many settings, HCV testing and treatment uptake remain below the WHO elimination targets, especially among PWID [8]. People who have injected drugs comprise the majority of existing infections in many countries [1, 2, 9]. Strategies to improve HCV testing and treatment outcomes for PWID, therefore, are critical for global HCV elimination efforts.

Opioid agonist therapy (OAT) improves antiretroviral therapy outcomes for human immunodeficiency virus (HIV) infection [10] and reduces the risk of HIV and HCV acquisition [11, 12]. It is hypothesized that OAT may similarly increase engagement of PWID in the HCV care cascade. Although there are studies that have evaluated the uptake of HCV testing [13–20] and treatment uptake [14, 16, 20–24] among PWID, to our knowledge, the association between OAT and HCV testing, treatment uptake, and treatment outcomes has not been systematically reviewed. Understanding the impact of OAT on the cascade of HCV care is critical to inform the implementation of successful strategies to enable progress toward global HCV elimination efforts among PWID.

In order to address this gap, we conducted a systematic review to evaluate the association between OAT and HCV testing and treatment uptake among PWID and to evaluate the association between OAT and adherence, treatment completion, and

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sustained virologic response (SVR) following DAA treatment among PWID.

METHODS

The study is reported in accordance with PRISMA [25], and the protocol was registered with PROSPERO (CRD42019138921).

Eligibility Criteria

We included observational (cohorts and cross-sectional studies) or experimental studies that investigated HCV testing and treatment if the study met the following criteria: population of people with recent injecting drug use (injecting in the previous 12 months, including active/ongoing/current drug use); reported a comparison of outcomes among people who had and had not received OAT with either methadone or buprenorphine (ever or currently/recently [past 6 months]); and reported 1 of the following outcomes: HCV antibody testing (ever or recently [past year]), HCV RNA testing (ever or recently [past year]), HCV treatment uptake (interferon-based and DAA), and DAA HCV treatment outcomes (adherence, completion, and SVR).

Information Sources and Search

Literature searches of 5 bibliographic databases, including Medline (PubMed), Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO, were performed. Presentations at key viral hepatitis conferences were searched, including the International Liver Congress, the Liver Meeting, the Conference on Retroviruses and Opportunistic Infections, and the International Conference on Hepatitis Care in Substance Users. Reference lists of the articles included in the analysis and relevant review articles were hand-searched. Forward citation tracking was carried out using Scopus. Searches were performed in September 2018. For searches of HCV testing and treatment uptake, there was no time restriction. For searches of DAA treatment outcomes, searches were limited to studies published since January 2013 (interferon-free DAA therapies available after this date). Combinations of search terms relating to HCV, drug use, OAT, HCV testing, and treatment were used (Supplementary Materials).

Study Selection

Records identified through primary searches were screened by title and abstract after the removal of duplicates. The full text of potentially eligible records was retrieved, reviewed, and eligible studies included. In the case of multiple publications of a single study, the one with the most up-to-date data was included.

Data Collection Process and Data Items

Data extracted included study characteristics, participant characteristics, testing outcomes, treatment uptake, and treatment outcomes (Supplementary Materials, pp 4–7). Authors were contacted if supplementary data were required and updated/unpublished data were used in analyses.

Risk of Bias in Individual Studies

The risk of bias for the included studies was assessed using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool [26]. Studies were ranked as having low, moderate, serious, or critical risk of bias across 7 domains, and the overall risk of bias was derived.

Study selection, data extraction, and risk of bias appraisal was undertaken by 2 reviewers independently (study selection: J. G. and B. H.; data extraction: A. D., L. T., T. S., and J. G.; and risk of bias appraisal: H. V. and L. T.), with discrepancies discussed with a third reviewer (study selection: L. D.; data extraction: B. H.; and risk of bias appraisal: L. D.).

Synthesis of Results

The primary outcomes of interest were recent or ever HCV antibody testing, recent or ever HCV RNA testing (among those HCV antibody–positive), HCV treatment uptake (among those HCV RNA–positive), and DAA treatment outcomes (adherence, completion, and SVR). Treatment completion was defined as completion of the full course of the prescribed treatment among those who initiated treatment. SVR was defined as unquantifiable HCV RNA at 12 or 24 weeks after the end of treatment for those who initiated treatment (intent-to-treat). The proportion of people with each outcome of interest was assessed, and odds ratios (ORs) were calculated for the association between ever having received OAT and between currently received OAT on each outcome. For HCV treatment uptake, additional analyses were performed to evaluate the association between OAT and DAA treatment. For each study, the outcome measures and corresponding standard errors and 95% confidence intervals (95% CIs) were calculated.

Meta-analysis was used to synthesize the outcome measure estimates. Heterogeneity across studies was assessed using the I^2 statistic, with an I^2 of less than 25%, 25%–75%, and more than 75% considered as low, moderate, and high heterogeneity, respectively [27]. Random-effect models were used when heterogeneity was medium or high ($I^2 \geq 25\%$).

Logit transformed outcome estimates were used in all meta-analyses, while the estimates were back-transformed for reporting. A fixed continuity correction of 0.5 was applied where there was a zero cell in calculating ORs. Two-sided *P* values of less than .05 were deemed to be statistically significant. All analyses were done with Stata version 14.0.

RESULTS

A total of 9877 records in bibliographic databases and 12 records from other sources were identified, with 22 studies included (Figure 1) [13–24, 28–37].

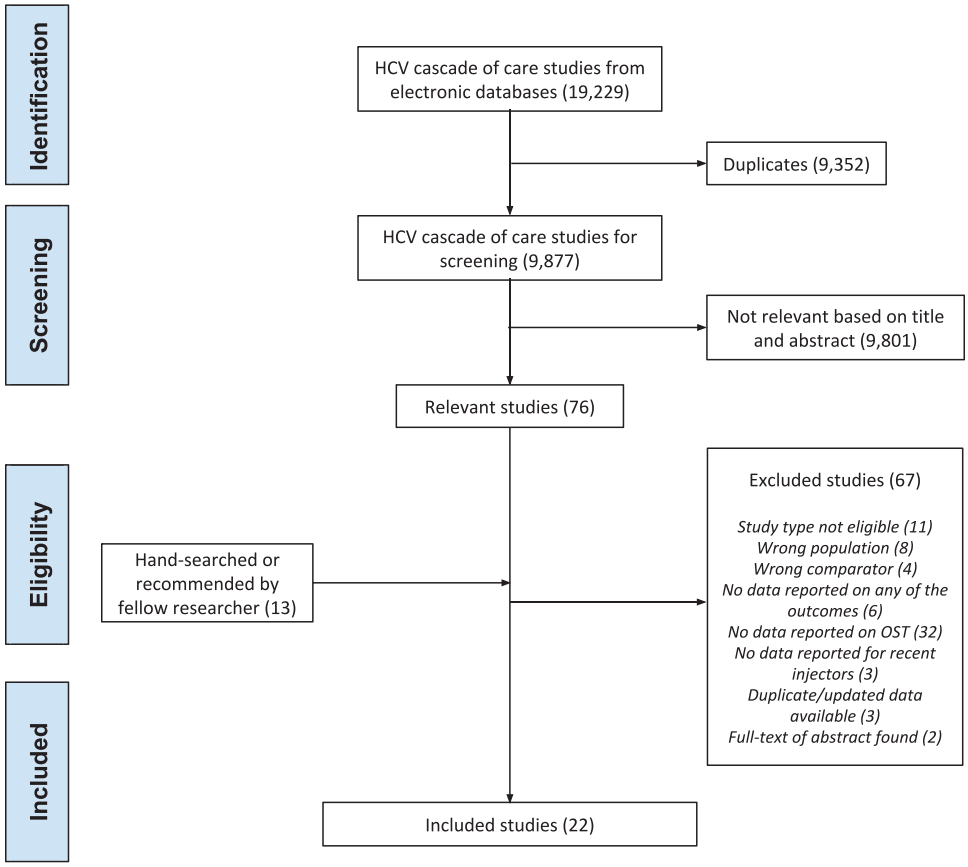

Figure 1. PRISMA flow chart. Abbreviations: HCV, hepatitis C virus; OAT, opioid agonist therapy.

Study characteristics are summarized in Tables 1, 2 and Supplementary Table 1. We identified 9 published studies that measured the impact of exposure to OAT on having ever received HCV antibody testing (ever OAT, 7 studies [14, 16–19, 28]; recent OAT, 7 studies [13, 14, 16–18, 20, 28]) or recently received HCV antibody testing (ever OAT, 3 studies [18, 28]; recent OAT, 4 studies [15, 18, 20, 28]; Table 2). We identified 5 published studies that measured the impact of exposure to OAT on having ever received HCV RNA testing (ever OAT, 5 studies [14, 16, 17, 28]; recent OAT, 5 studies [14, 16, 17, 20, 28]; Table 2) or recently received HCV RNA testing among those HCV antibody–positive (ever OAT, 2 studies [28]; recent OAT, 2 studies [20, 28]; Table 2). We identified 8 published studies that measured the impact of exposure to OAT on having ever received HCV treatment among those HCV RNA detectable (ever OAT, 6 studies [14, 16, 20–22, 28]; recent OAT, 7 studies [14, 16, 20, 21, 23, 24, 28]; Table 2). We identified 9 published studies that measured the impact of exposure to recent OAT on DAA treatment completion (9 studies) and SVR (9 studies; Supplementary Table 1) (none of these studies included data on ever OAT) [29–38]. There was insufficient data on adherence to include this outcome.

Description of Studies

Tables 1 and 2 and Supplementary Table 1 summarize the characteristics of the included studies undertaken in Australia (n = 10), Canada (n = 4), France (n = 1), Georgia (n = 1), Italy (n = 1), Thailand (n = 1), Ukraine (n = 1), and the United States (n = 2). Twenty studies were observational (12 cohort studies and 8 cross-sectional studies), 1 study was a clinical trial, and 1 study was an interventional trial (Table 1). Definition of recent injecting drug use, proportion ever receiving OAT (52%–88%), and proportion recently/currently receiving OAT (25%–73%) varied across studies.

Risk of Bias

Risk of bias was serious in 21 studies and moderate in 1 study (Supplementary Materials). The domains that were most often associated with serious risk of bias included bias due to confounding and bias in the selection of participants. For all other risk of bias domains, most studies were rated as being at low risk of bias. It was not appropriate to conduct sensitivity analyses (eg, excluding studies at serious/critical risk of bias) because all but 1 study met this criteria.

Table 1. Characteristics of the Studies Included in the Analysis

Characteristic	Number of Studies (N = 22) (%)	Number of Study Participants
Study design		
Observational, prospective	7 (32)	2016
Observational, retrospective	5 (23)	1539
Cross-sectional	8 (36)	14 236
Clinical trial	2 (10)	305
Study setting		
Community clinic	3 (14)	437
Tertiary care	3 (14)	431
Needle and syringe program	5 (23)	10 357
Mixed	6 (27)	3730
Other/not reported	5 (23)	2953
Number of centers		
Single-center	8 (35)	1359
Multicenter	14 (64)	16 549
Definition of recent drug use[a]		
During the past 1 month	3 (14)	1323
During the past 6 months	14 (64)	6223
During the past 12 months	2 (9)	301
Ongoing or active drug use	4 (18)	10 713
Definition of opioid agonist therapy[a]		
Current	20 (91)	8574
Past 6 months	1 (5)	345
Ever	8 (36)	10 867

[a]Total equals more than 100% due to 6 studies reporting multiple groups.

Impact of OAT on HCV Antibody Testing

Across 8 studies, the proportion of people who ever received HCV antibody testing was between 33% and 94% (Table 2). Studies were pooled measuring the impact of ever having received OAT (7 studies) and recently/currently receiving OAT (7 studies) on having ever received HCV antibody testing (Figure 2). Random-effect meta-analysis of estimates demonstrated that having ever received OAT was associated with an increased odds of having ever received HCV antibody testing (OR, 2.74; 95% CI, 1.70–4.40; I^2 = 86.0%). Recent exposure to OAT was associated with an increased odds of having ever received HCV antibody testing (OR, 2.26; 95% CI, 1.80–2.85; I^2 = 37.2%).

The proportion who recently received HCV antibody testing was between 48% and 71% (Table 2). We also pooled data from studies that measured the impact of ever having received OAT (3 studies) and recently/currently receiving OAT (4 studies) on having recently received HCV antibody testing (Figure 2). Having ever received OAT was associated with an increased odds of recent HCV antibody testing (OR, 2.12; 95% CI, 1.07–4.20; I^2 = 75.7%). Recent exposure to OAT was associated with an increased odds of recent HCV antibody testing (OR, 1.81; 95% CI, 1.40–2.34; I^2 = 12.6%).

Impact of OAT on HCV RNA Testing

The proportion of people who had ever received HCV RNA testing among those who were HCV antibody–positive was between 35% and 89% (Table 2). Studies were pooled measuring the impact of ever having received OAT (5 studies) and recently/currently receiving OAT (5 studies) on having ever received HCV RNA testing (Figure 2). Having ever received OAT was associated with an increased odds of having ever received HCV RNA testing (OR, 2.14; 95% CI, 1.55–2.95; I^2 = 69.3%). Recent OAT exposure was associated with an increased odds of having ever received HCV RNA testing (OR, 1.74; 95% CI, 1.29–2.35; I^2 = 71.4%).

The proportion who had recently received HCV RNA testing was 44% in 1 study and 45% in the other study (Table 2). We pooled data from studies that measured the impact of ever having received OAT (2 studies) and having recently/currently receiving OAT (2 studies) on having recently received HCV RNA testing (Figure 2). Having ever received OAT was not associated with an increased odds of having recently received HCV RNA testing (OR, 2.38; 95% CI, .94–6.07; I^2 = 90.5%). Having recently received OAT was associated with an increased odds of having received HCV RNA testing (OR, 1.83; 95% CI, 1.28–2.61; I^2 = 49.8%).

Impact of OAT on HCV Treatment Uptake

The proportion of people who had ever received HCV treatment among those who were HCV RNA detectable was between 6% and 72% (Table 2). Data from studies that measured the impact of ever having received OAT (6 studies; DAA: 4 studies) and recently/currently receiving OAT (7 studies; DAA: 5 studies) on having ever received HCV treatment were pooled (Figure 3). The association of having ever received OAT and having ever received HCV treatment was not statistically significant (OR, 1.53; 95% CI, .92–2.55; I^2 = 86.3%). Recent OAT exposure was associated with an increased odds of having ever received HCV treatment (OR, 1.56; 95% CI, 1.07–2.26; I^2 = 82.3%). The intervention association strengthened and heterogeneity decreased when only studies in the DAA era were considered (6 studies; OR, 1.83; 95% CI, 1.51–2.21; I^2 = 0.0%). Having ever received OAT was associated with an increased odds of having ever received DAA HCV treatment (4 studies; OR, 2.15; 95% CI, 1.67–2.76; I^2 = 0.0%).

Impact of OAT on HCV Treatment Completion and SVR

The proportion of people who had completed HCV treatment among those who initiated HCV treatment was between 65% and 100% and the proportion who had achieved SVR was between 64% and 94% (Supplementary Table 1). We pooled data from studies that measured the impact of recently/currently receiving OAT on having completed HCV treatment (9 studies) or having achieved an SVR (9 studies; Figure 4). There was no impact of having recently received OAT on treatment completion (OR, 1.25; 95% CI, .57–2.76; I^2 = 54.2%) or SVR (OR, 0.79; 95% CI, .42–1.51; I^2 = 62.1%).

Table 2. Characteristics of Included Studies and Reported Outcomes for Hepatitis C Virus (HCV) Antibody Testing, HCV RNA Testing, and HCV Treatment Uptake

HCV Antibody Testing

First Author, Year (Country)	Study Design	Definition of Recent Injecting Drug Use	Total n	Age Mean or Median, Y	Male (%)	Used Opioids Ever (%)	OAT Ever (%)	OAT Recently (%)	HCV Antibody Testing Ever (%)	HCV Antibody Testing Recently (%)	HCV Antibody Testing Ever				Recent HCV Antibody Testing			
											No OAT Ever	OAT Ever	No Recent OAT	OAT Recently	No OAT Ever	OAT Ever	No Recent OAT	OAT Recently
Bajis, 2019 (Australia) [13]	Observational cohort	Previous 6 months	605	42	67	NA	NA	65	72	NA	NA	NA	137/210 (65%)	297/395 (75%)	NA	NA	NA	NA
Butler, 2015 (Australia) [14]	Cross-sectional	Previous 6 months	854	40	64	98	74	44	94	NA	201/233 (90%)	601/630 (95%)	441/477 (92%)	362/377 (96%)	NA	NA	NA	NA
Butler, 2019 (Australia) [16]	Cross-sectional	Previous 6 months	887	43	67	97	64	38	92	NA	272/311 (87%)	540/571 (95%)	493/546 (90%)	323/341 (95%)	NA	NA	NA	NA
Day, 2008 (Australia) [15]	Cross-sectional	Previous 6 months	197	36	64	NA	NA	68	NA	71	NA	NA	NA	NA	NA	NA	37/63 (59%)	103/134 (77%)
Gibbs, 2019 (Australia) [28]	Cross-sectional	Previous 6 months	905	43*	66	95	66	38	88	57	252/308 (82%)	541/594 (91%)	482/564 (85%)	314/341 (92%)	151/308 (49%)	364/594 (61%)	297/564 (53%)	220/341 (65%)
Iakunchykova, 2018 (Ukraine) [17]	Cross-sectional	Ongoing/active	1002	36*	76	100	52	30	83	NA	215/481 (45%)	352/521 (68%)	215/481 (45%)	215/300 (72%)	NA	NA	NA	NA
Roux, 2016 (France) [18]	Intervention	Ongoing/active	202	30	77	98	87	71	82	48	16/57 (28%)	149/176 (85%)	27/57 (47%)	121/143 (85%)	7/57 (12%)	90/176 (51%)	16/57 (28%)	73/143 (51%)
Ti, 2013 (Thailand) [19]	Cross-sectional	Previous 6 months	427	38	81	NA	76	NA	33	NA	13/104 (13%)	128/323 (40%/)	NA	NA	NA	NA	NA	NA
Valerio, 2019 (Australia) [20]	Observational cohort	Previous 6 months	1147	43	65	96	82	67	85	51	139/205 (68%)	837/942 (89%)	284/373 (76%)	692/774 (89%)	84/205 (41%)	500/942 (53%)	159/373 (43%)	500/774 (65%)

HCV RNA Testing

First Author, Year (Country)	Study Design	Definition of Recent Injecting Drug Use	Total n	Age Mean or Median, Year	Male (%)	Used Opioids Ever (%)	OAT Ever (%)	OAT Recently (%)	HCV RNA Testing Ever (%)	HCV RNA Testing Recently (%)	HCV RNA Testing Ever				Recent HCV RNA Testing			
											No OAT Ever	OAT Ever	No Recent OAT	OAT Recently	No OAT Ever	OAT Ever	No Recent OAT	OAT Recently
Butler, 2015 (Australia) [14]	Cross-sectional	Previous 6 months	547	41	62	99	82	49	59	NA	48/96 (50%)	275/451 (61%)	155/277 (56%)	168/270 (62%)	NA	NA	NA	NA
Butler, 2019 (Australia) [16]	Cross-sectional	Previous 6 months	481	44	67	98	77	47	89	NA	97/113 (86%)	332/368 (90%)	225/257 (88%)	203/224 (91%)	NA	NA	NA	NA
Gibbs, 2019 (Australia) [28]	Cross-sectional	Previous 6 months	796	43*	66	95	68	39	68	45	132/252 (52%)	405/541 (75%)	301/482 (62%)	238/314 (76%)	84/252 (33%)	272/541 (50%)	199/482 (41%)	158/314 (50%)
Iakunchykova, 2018 (Ukraine) [17]	Cross-sectional	Ongoing/active	1002	37*	76	100	52	30	35	NA	126/481 (26%)	220/521 (42%)	126/481 (26%)	145/300 (48%)	NA	NA	NA	NA
Valerio, 2019 (Australia) [20]	Observational cohort	Previous 6 months	796	45	66	99	89	75	77	45	55/86 (64%)	559/710 (79%)	144/202 (71%)	470/594 (79%)	32/86 (37%)	329/710 (46%)	79/202 (39%)	282/594 (47%)

Table 2. Continued

										HCV Treatment Uptake			
First Author, Year (Country)	Study Design	Definition of Recent Injecting Drug Use	Total Number of Participants	Age Mean or Median, Year	Male (%)	Used Opioids Ever (%)	OAT Ever (%)	OAT Recently (%)	HCV Treatment Ever (%)	No OAT Ever	OAT Ever	No Recent OAT	OAT Recently
Butler, 2015 (Australia) [14]	Cross-sectional	Previous 6 months	179	41	61	98	88	57	20	6/21 (29%)	29/158 (18%)	13/77 (17%)	18/102 (18%)
Butler, 2019 (Australia) [16]	Cross-sectional	Previous 6 months	289	43	72	99	77	45	32	15/68 (22%)	77/223 (35%)	37/159 (23%)	55/130 (42%)
Gibbs, 2019 (Australia) [28]	Cross-sectional	Previous 6 months	334	44*	71	98	81	50	72	35/62 (56%)	204/271 (75%)	108/168 (64%)	131/166 (79%)
Iversen, 2014 (Australia) [21]	Cross-sectional	Ongoing/active	9478	35	64	NA	81	50	6	128/1767 (7%)	468/7683 (6%)	128/1767 (7%)	283/4743 (6%)
Iverson, 2019 (Australia) [22]	Cross-sectional	Previous 1 month	486	NA	66	NA	76	NA	41	32/117 (27%)	165/369 (45%)	NA	NA
Makarenko, 2019 (Canada) [23]	Observational cohort	Previous 6 months	308	42	85	NA	NA	33	26	NA	NA	46/206 (22%)	34/102 (33%)
Socías, 2019 (Canada) [24]	Observational cohort	Previous 6 months	611	47	60	NA	NA	56	13	NA	NA	25/266 (9%)	53/345 (15%)
Valerio, 2019 (Australia) [20]	Observational cohort	Previous 6 months	620	44	70	98	89	74	64	29/69 (42%)	364/551 (66%)	82/159 (52%)	311/461 (67%)

*Asterisk indicates median age.

Abbreviations: HCV, hepatitis C virus; OAT, opioid agonist therapy.

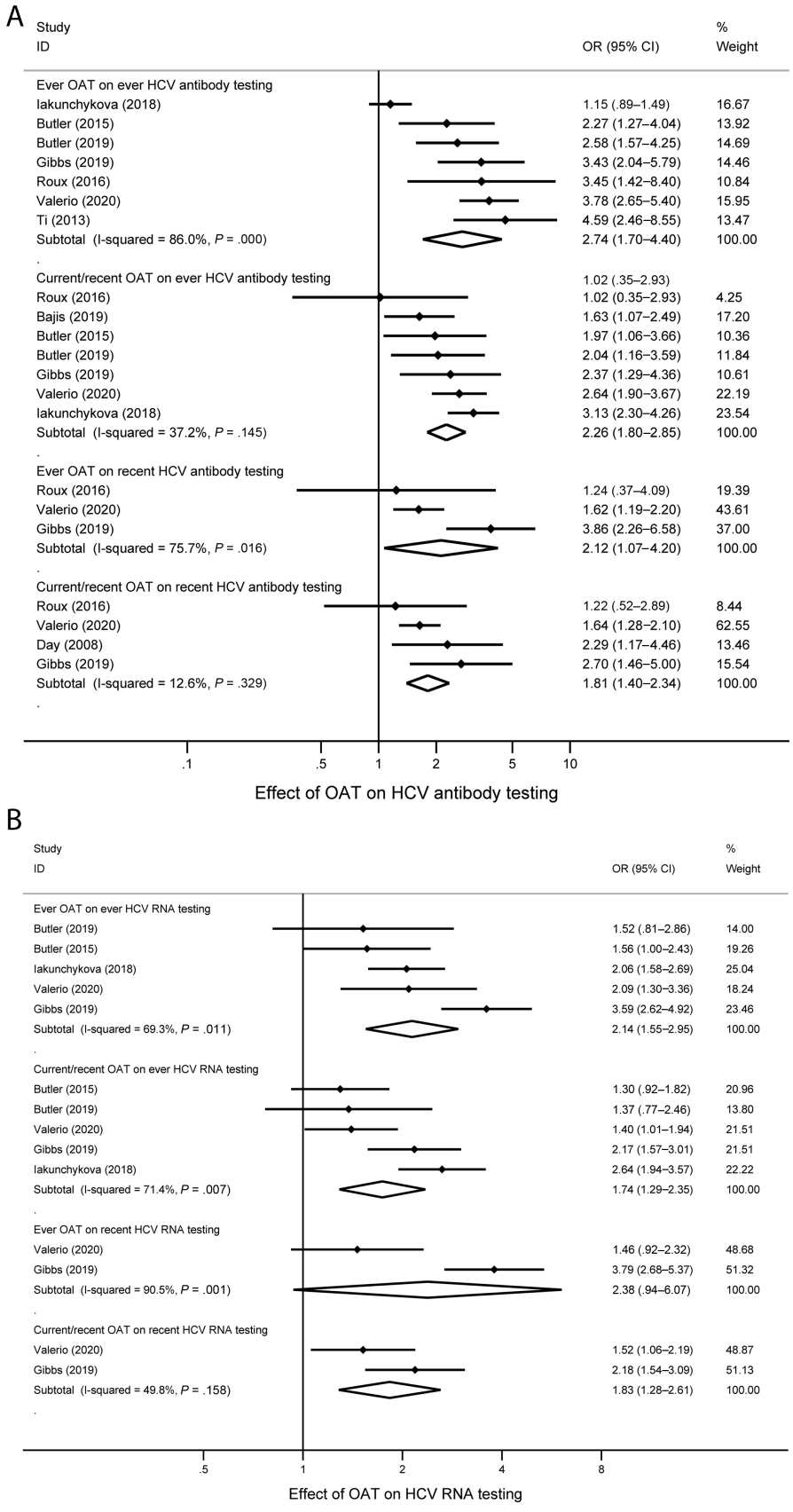

Figure 2. Forest plots examining the association between and (*A*) HCV antibody and (*B*) HCV RNA testing. Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OAT, opioid agonist therapy; OR, odds ratio.

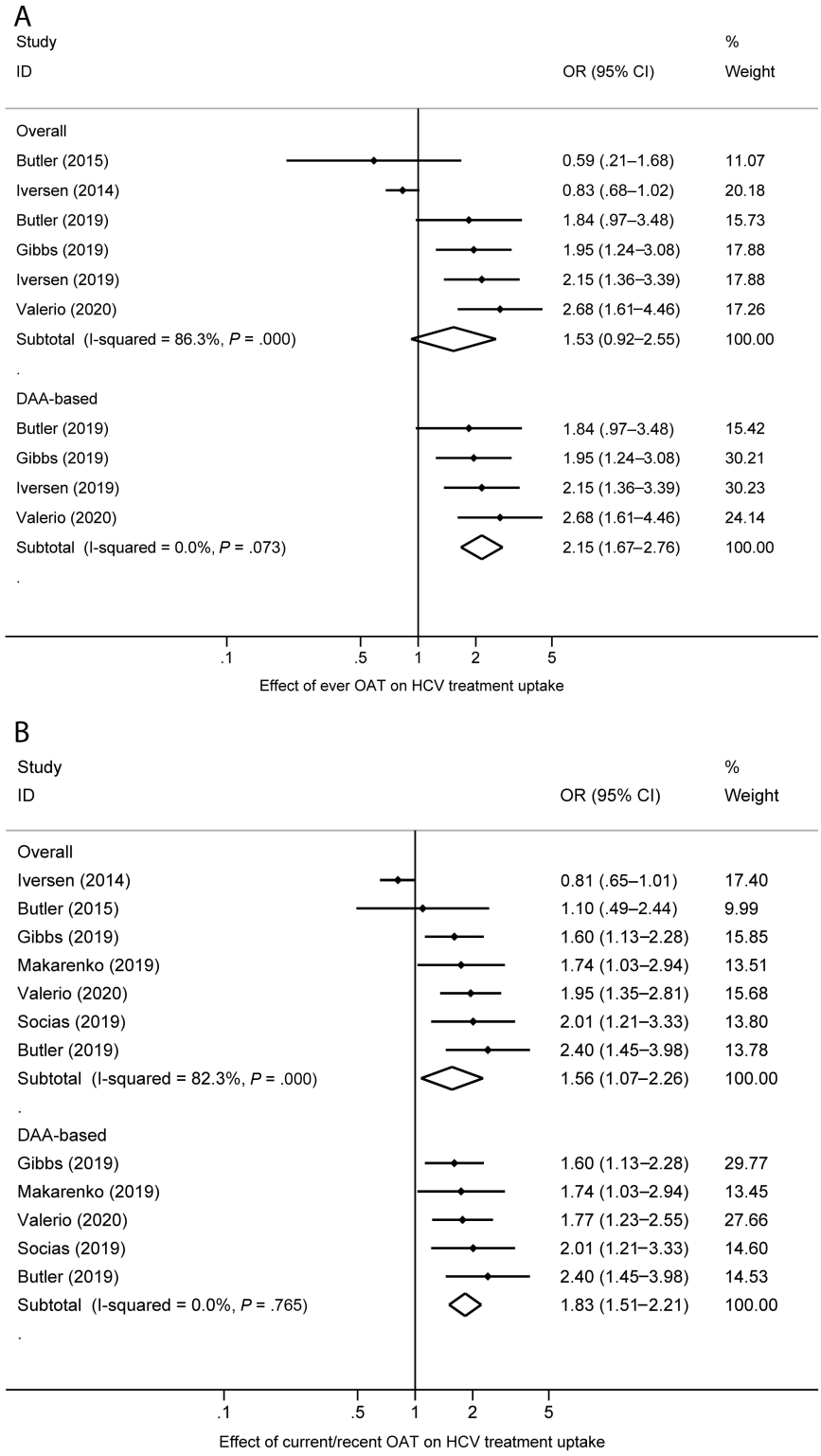

Figure 3. Forest plots examining the association between (*A*) ever OAT and (*B*) current/recent OAT and HCV treatment uptake. Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OAT, opioid agonist therapy; OR, odds ratio.

DISCUSSION

We found evidence of an association between recent OAT exposure and ever receiving OAT on HCV testing and treatment uptake among PWID. Recent OAT was not associated with DAA treatment completion or SVR. These data have important implications for clinical management and health policy,

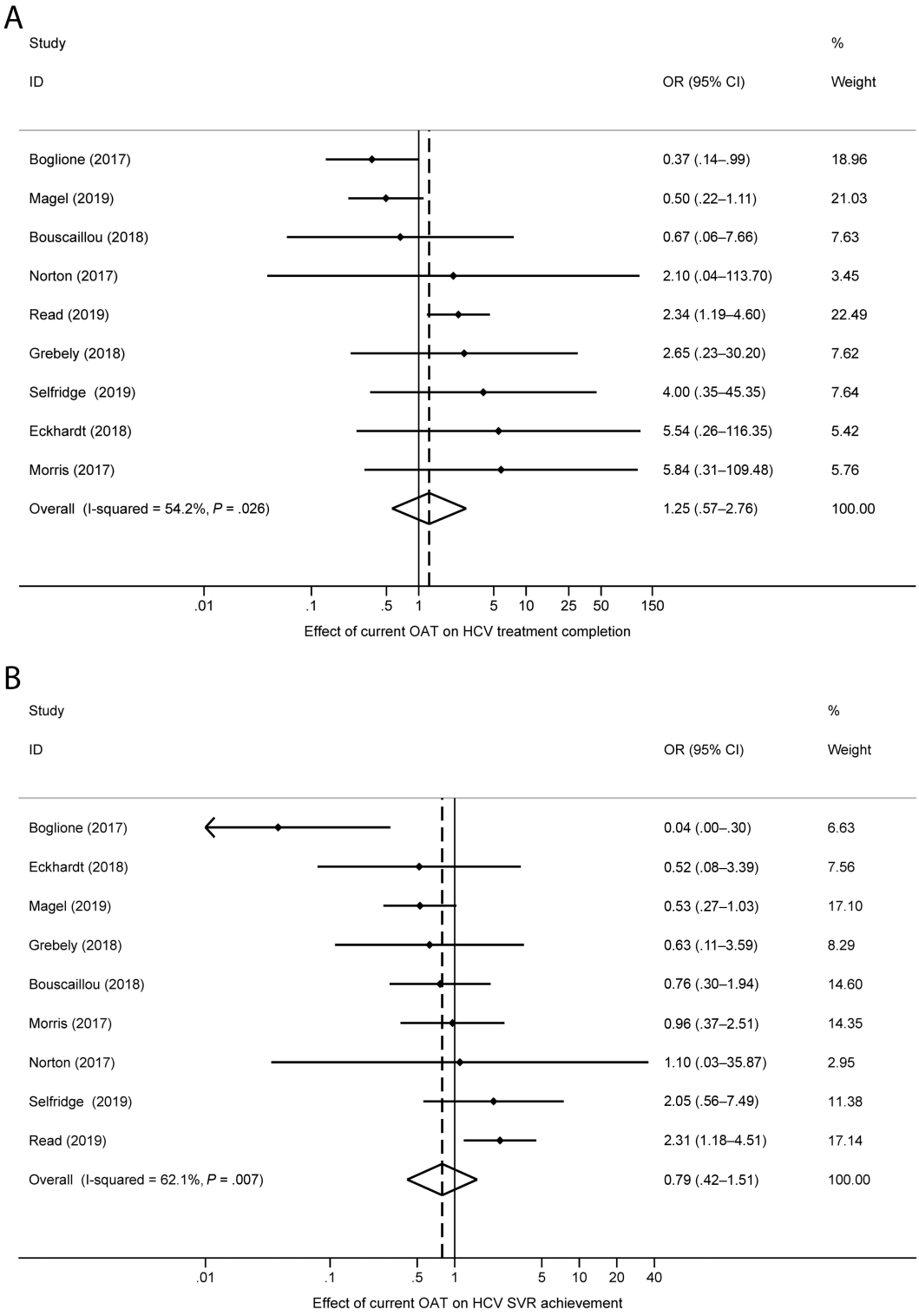

Figure 4. Forest plots examining the association between current OAT and (*A*) treatment completion and (*B*) SVR. Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OAT, opioid agonist therapy; OR, odds ratio; SVR, sustained virologic response.

supporting the integration of services for the treatment of opioid dependence and HCV care among PWID.

OAT was associated with improvements in HCV testing and treatment uptake, consistent with literature demonstrating that OAT reduces harms across multiple health outcomes for people who are opioid dependent [39]. OAT improves engagement in HIV treatment, adherence, and virologic suppression [10]. OAT is also associated with reductions in injecting risk behavior [40],

risk of HIV and HCV infections [11, 12], criminal activity [41], and all-cause [42] and overdose [42] mortality. It is unsurprising that current OAT was not associated with DAA treatment completion or SVR, given the high proportion of PWID who complete and respond to DAA therapy [43].

The mechanism behind the association between OAT and improvements in HCV testing and treatment is likely multifactorial, relating to the interplay between system-, provider-, social-, and patient-level factors. Most people receiving OAT attend drug treatment clinics or community health centers that provide services other than OAT, including other medical care (including HCV), mental health services, and vocational and other assistance. People receiving OAT often have regular contact with health services with persistent cues for engagement and education [44], offering increased opportunities for engaging in HCV education, testing and treatment, particularly when services are integrated and on-site [45].

Qualitative interviews with people receiving and providing services in drug treatment clinics have highlighted key facilitators for engagement in HCV care [44, 46–51]. In drug treatment settings, engagement in HCV care is facilitated by existing relationships of trust between people receiving OAT and their healthcare providers [46–50], with HCV care providing opportunities to strengthen therapeutic relationships [51]. People using drug treatment services report that the provision of HCV testing and treatment on-site allows more immediate and accessible care [49]. This eliminates the need for often problematic and unsuccessful referral from OAT to off-site hospital-based models of HCV care [49], which may be associated with negative, stigmatizing, or discriminatory experiences [44, 47]. People receiving OAT also highlight that drug treatment clinics offer the potential for greater familiarity [47, 48, 51], flexibility [47], and convenience through on-site care (including reduced travel time and costs) [44, 47–51].

Integration of OAT and HCV treatment has been shown to be highly acceptable to both clients and staff [52]. In a study of people with ongoing injecting drug use and opioid dependence offered HCV and buprenorphine treatment, 79% (53 of 67) not receiving OAT at baseline subsequently initiated buprenorphine during HCV therapy, with reductions in injecting risk observed among those receiving OAT [53]. Integration of OAT and HCV services can occur in a range of settings where people are already accessing health services (eg, drug treatment clinics, HIV clinics, harm reduction services) in combination with different interventions (eg, financial incentives, telemedicine, peer-based support) [13, 45]. No one size will fit all, with models of care requiring person-centric approaches [54]. However, key barriers to HCV treatment among PWID must be addressed, including stigma, housing, criminalization, and healthcare systems [55].

Major strengths of this study include synthesizing estimates for the association of OAT with components of the HCV cascade of care among PWID and the supplementary data included through contacting authors. Key limitations of the evidence include the small number of studies and that the majority of studies were from 1 country (Australia). Most studies were at serious risk of bias due to the potential for confounding and biases in the selection of participants into the studies. The control of confounders was limited and inconsistent across the studies. As such, unadjusted ORs had to be pooled and there were insufficient studies to perform a meta-regression to explore sources of heterogeneity. The majority of studies identified were cross-sectional, and the effect of residual confounding on OAT and components of the HCV cascade of care cannot be ruled out. People who accessed OAT may also have been more likely to have characteristics that may have led to increased HCV testing and treatment uptake. Since most studies were cross-sectional, it is possible that OAT use may not have preceded the outcome. This temporality of the association between the exposure (OAT) and outcome (HCV testing and treatment) is a limitation. We cannot, therefore, assume that OAT use commenced before, rather than after, HCV testing or treatment. The impact of OAT on HCV testing and treatment uptake at a population level will also be determined by the proportion of PWID within that population with opioid dependence. Although the majority of studies had a high proportion of participants with a history of opioid use, not all participants may have been opioid dependent and/or required OAT. This misclassification bias may have overestimated the observed association between OAT and HCV outcomes.

In conclusion, this study demonstrated that recent OAT was associated with improvements in HCV testing and treatment uptake, supporting the integration of HCV services in drug treatment settings. This study also provides important information to inform mathematical modeling of interventions to enhance HCV care among PWID. Further work is needed to understand strategies to optimize HCV testing and treatment within drug treatment settings and improve the overall health of people who use drugs.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. G., L. T., L. D., S. L., M. H., P. V., and B. H. conceived the scope of the review, which was critically revised by all coauthors. Screening, review, data extraction, and verification was done by J. G., L. T., L. D., A. D-D., T. S., H.V., and B. H. Data analysis was done by L. T. and T. S., which was reviewed by J. G. J. G., L. D., and B. H. drafted the first draft of the manuscript. All authors made substantial contributions to the critical review, editing, and revision of the manuscript. All authors approved the final version of the manuscript.

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