MAJOR ARTICLE

A Systematic Review and Meta-Analysis of Interventions to Prevent Hepatitis C Virus Infection in People Who Inject Drugs

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Introduction. High rates of hepatitis C virus (HCV) transmission are found in samples of people who inject drugs (PWID) throughout the world. The objective of this paper was to meta-analyze the effects of risk-reduction interventions on HCV seroconversion and identify the most effective intervention types.

Methods. We performed a systematic review and meta-analysis of published and unpublished studies. Eligible studies reported on the association between participation in interventions intended to reduce unsafe drug injection and HCV seroconversion in samples of PWID.

Results. The meta-analysis included 26 eligible studies of behavioral interventions, substance-use treatment, syringe access, syringe disinfection, and multicomponent interventions. Interventions using multiple combined strategies reduced risk of seroconversion by 75% (pooled relative risk, .25; 95% confidence interval, .07–.83). Effects of single-method interventions ranged from .6 to 1.6.

Conclusions. Interventions using strategies that combined substance-use treatment and support for safe injection were most effective at reducing HCV seroconversion. Determining the effective dose and combination of interventions for specific subgroups of PWID is a research priority. However, our meta-analysis shows that HCV infection can be prevented in PWID.

Preventing hepatitis C virus (HCV) infection in people who inject drugs (PWID) is a tremendous public health challenge. HCV is highly efficiently transmitted via parenteral exposure to infectious blood, and the prevalence of HCV infection in PWID typically ranges between 40% and 90%, depending on geographic location and duration of exposure to injection drug use [1, 2]. Extremely high HCV prevalence rates—between 85% and 98%—have been reported [3–5]. Most reports of HCV incidence in PWID fall into the range of 20–40 infections per 100 PY [6–10]. However, incidence rates above and below this range have been recorded, with some of the highest rates observed in recent-onset drug injectors and in low- and middle-income countries [2, 11–14].

Acute HCV infection results in chronic carriage in 70%–80% of cases, and 20%–25% of those with persistent infection will develop liver disease that may manifest as cirrhosis, liver failure, or hepatocellular carcinoma [15]. In the United States, it is expected that HCV-related mortality will surpass HIV-related mortality in the coming years [16]. No vaccine exists to prevent HCV infection [17]. Treatment for HCV infection is costly, and PWID are less likely to receive medical monitoring and treatment of the infection than other patient groups [17, 18]. Thus, the prevention of primary HCV infection among PWID is a public health issue of major importance, and behavioral and structural interventions are needed to prevent HCV transmission among PWID. This paper describes the systematic review and meta-analysis of the association between HCV seroconversion and interventions that are intended to reduce injection-related acquisition of HCV among individuals.

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METHODS

We collected the data for these analyses as part of the HCV Synthesis Project, a systematic review and meta-analysis of HCV epidemiology and prevention in drug users [19]. The scope of the HCV Synthesis Project includes published and unpublished reports describing the epidemiology of HCV infection in PWID and in non–injection drug users who sniff or smoke heroin, cocaine, or amphetamine. These 2 groups of drug users have been identified as having a biologically plausible risk of exposure to HCV infection via drug-use practices, either through percutaneous or mucous membrane exposure to blood via sharing of straws or through pipes used to administer drugs [1, 20]. To be eligible for inclusion in the HCV Synthesis Project, studies must have reported HCV prevalence or incidence rates, measures of association with prevalence or incidence, HIV-HCV coinfection rates, or HCV genotype distributions in samples of eligible drug users. In addition, HCV status must have been determined by serologic testing of either sera or oral fluids; oral fluid tests have been shown to have high sensitivity (92%) and specificity (99%) [21].

Data collection and abstraction methods have been described in detail elsewhere [19]. We performed automated searches on electronic databases of the published medical literature, the proceedings of scientific conferences, and government and other Web sites related to public health, HIV, hepatitis, and drug use or control. Manual search methods included footnote chasing and searching of related journals and abstract books. We also sought unpublished studies by contacting investigators who were conducting or who had completed studies of HCV epidemiology or prevention. Reports published or released between January 1989 and December 2006 were included in an initial search that identified a total of 2375 reports that we screened for eligibility. Of these, 628 were determined to be eligible and were included in the HCV Synthesis Project sample. To update the systematic review of literature related to the effectiveness of interventions to reduce HCV seroconversion, we reperformed the automated searches and manually searched proceedings from scientific conferences in April 2010 to encompass the period after December 2006. We also examined bibliographies of qualitative reviews of HCV prevention to identify any additional studies [22–25]. Overlapping reports (ie, duplicate data from a single study) were identified based on matching study names, settings, and authors; this was followed by comparing sample sizes, years of data collection, and other study characteristics to select the most complete and informative report for our research question of interest. Eighteen reports from the pre-2007 set of studies and an additional 7 studies from the updated search were eligible for this analysis. All reports were in English, although the search included studies written in other languages.

We included studies in the current analysis if they reported HCV seroconversion rates or associations with HCV seroconversion (odds ratio [OR], relative risk [RR], hazard ratio) in PWID in relation to interventions that could, in theory, prevent HCV infection by reducing unsafe injections. Thus, the scope of this analysis included studies of the association between HCV seroconversion and participation in drug-treatment programs, syringe-access programs (syringe exchange or distribution, or pharmacy sales), supervised injection facilities, syringe disinfection with bleach, individual behavioral interventions, or combinations of any of these services, all measured at the individual level. Studies conducted at the population level (eg, comparison of HCV infection rates pre- and postimplementation of syringe-exchange programs) were not included, principally because none used seroconversion as the outcome measure. To our knowledge, no study has directly measured risk of sexual transmission of HCV in PWID or the effect of sexual risk reduction on HCV transmission. Given this and the much lower transmission efficiency via this route of exposure in other populations, prevention of sexual HCV transmission in PWID is currently of lesser importance, and thus this paper was restricted to prevention of injection-related transmission [26, 27].

Adjusted effect measures were used in the analysis where they were included in the source studies, under the assumption that adjustment was performed to remove bias in the estimate of the association between the intervention and risk of HCV seroconversion. Several cohort studies used ORs, including adjusted ORs, as their estimators; it has been shown that when the disease is common (incidence above 10 infections/100 PY), the OR will be biased away from the null value [28]. To correct for this bias, the ORs (crude or adjusted) and their 95% confidence intervals (CIs) were transformed into relative risks and their respective CIs [28]. When ORs were calculated in case-control studies and incidence density sampling was used to select controls, no transformation was necessary [29]. In studies that did not report ORs, rate ratios, hazard ratios, relative risks, or risk ratios as a measure of the effect of the intervention on HCV seroconversion, an unadjusted relative risk was calculated using the incidence data provided. If the study reported cumulative incidence of HCV seroconversion in a cohort, the effect measure was calculated [28] and labeled a risk ratio; if the study reported incidence density of HCV seroconversion, the effect measure was labeled an incidence rate ratio. For 1 study [30] that reported only hazard ratios and *P* values, CIs were calculated using standard methods [31]. Table 1 includes a column to show that risk measure was used in the analysis.

We evaluated heterogeneity of effects using Q and I^2 statistics. We tested Q values for significance using the χ^2 distribution; we considered I^2 values $>50\%$ to reflect meaningful heterogeneity [53]. We calculated summary estimates of the effects of similar interventions using Comprehensive Meta-Analysis software [54]. We also performed meta-analysis for subsets within intervention

Table 1. Studies That Have Examined the Effect of an Intervention on Hepatitis C Virus Seroconversion Among Injection Drug Users

1st author, publication year	Location and study years	Design	Sample size and HCV incidence rate (95% CI)	Intervention	Published association with HCV seroconversion	Risk measure used in analysis (95% CI)
1a. Behavioral interventions						
Garfein, 2007 [32]	Multisite, United States 1999–2004	RCT, Cohort	*N*= 854 18.4/100 PY (14.4–23.0)	Peer education (PEI) vs equal-attention controls (6 sessions each)	OR PEI vs controls 1.15 (95% CI, .72–1.82)	Published unadjusted odds ratio (PEI vs controls): OR = 1.15 (.72–1.82)
Stein, 2009 [33]	Providence, RI, United States 2001–2004	RCT, Cohort	*N* = 89 15.7/2 y	MI vs equal-attention controls (4 sessions)	Cumulative incidence 18% (95% CI, 5.9–30%) in MI vs 14% in controls (95% CI, 4.3–23.6%)	Calculated unadjusted risk ratio (MI vs controls): RR = 1.28 (.49–3.35)
1b. Substance-use treatment: Not specified						
Brunton, 2000 [34]	Multisite, New Zealand 1994–1996	OBS, Cohort	*N* = 39 23%/2 y (11%–30%)	In treatment at follow-up	Cumulative incidence 50% in treatment (7/14) vs 8% not in treatment (2/25)	Calculated unadjusted risk ratio: RR = 6.25 (1.3–30.09)
Lamothe, 1997 [35]	Montreal, Canada 1992	OBS, Cohort	*N* = 63 27.1/100 PY (18.0–29.1)	In treatment at follow-up	Incidence rate 30.5/100 PY in treatment vs 25.2/100 PY not in treatment	Published unadjusted hazard ratio: HR = 1.02 (.48–2.02)
Maher, 2006 [8]	New South Wales, Australia 1999–2002	OBS, Cohort	*N* = 368 30.8/100 PY (24.3–39.0)	In treatment at enrollment	Incidence rate 28.9/100 PY in treatment vs 34.3/100 PY not in treatment	Calculated unadjusted incidence rate ratio: IRR = .84 (.52–1.37)
Patrick, 2001 [36]	Vancouver, Canada 1996–1999	OBS, Cohort	*N* = 155 29.1/100 PY (22.3–37.3)	Nonmethadone addiction treatment during follow-up	Cumulative incidence 66.7% in those in addiction therapy vs 35.8% in those not in treatment	Calculated unadjusted risk ratio: RR = 1.86 (1.20–2.35)
Smyth, 2003 [14]	Dublin, Ireland 1992–1998	OBS, Cohort	*N* = 100 66/100 PY (51–84)	Addiction treatment > 3 mo vs less during follow-up	Incidence rate 52/100 PY among those in treatment > 3 mo vs 75/100 PY for others, *P* = .16	Calculated unadjusted incidence rate ratio: IRR = .69 (.42–1.1)
1c. Substance-use treatment: opiate-replacement therapy						
Craine, 2009 [37]	South Wales, United Kingdom 2004–2006	OBS, Cohort	*N* = 286 5.9/100 PY (3.4–9.5)	In ORT at follow-up	Incidence rate 2.9/100 PY in those in ORT vs 10.6/100 PY in others	Published adjusted incidence rate ratio: AIRR = .34 (.12–.99)
Crofts, 1997 [38]	Victoria, Australia 1991–1995	OBS, Retrospective cohort	*N* = 73 22.2/100 PY (14.2–34.8)	Continuous vs interrupted or no ORT during follow-up	Cumulative incidence 36.9% continuous ORT vs 14.2% interrupted vs 21.4% no ORT	Calculated unadjusted risk ratio (Continuous ORT vs interrupted or no ORT): RR = 2.25 (.91–5.54)
Dolan, 2005 [39]	New South Wales, Australia 1998–2002	RCT, Retrospective cohort	*N* = 39 21.3/100 PY (15.6–29.2)	Random assignment to ORT vs control while in prison	Incidence rate 16/100 PY in ORT treatment group vs 27/100 PY in controls	Published adjusted hazard ratio: AHR = .5 (.24–1.11)
Hallinan, 2004 [40]	Sydney, Australia 1996–2003	OBS, Retrospective cohort	N=54 3.8/100 PY (1.2–8.9)	Continuous vs interrupted ORT	Incidence rate 1.3/100 PY continuous ORT vs 7.4/100 PY interrupted ORT	Calculated unadjusted incidence rate ratio (continuous vs interrupted ORT): IRR = .18 (.02–1.59)
Lucidarme, 2004 [7]	Multisite, France 1999–2000	OBS, Cohort	*N* = 165 9/100 PY (4.6–13.4)	Substitution treatment at enrollment	Incidence rate 7.7/100 PY those in treatment vs 14.1/100 PY not in treatment	Published adjusted hazard rate: AHR = .41 (.12–1.40)
Rezza, 1996 [41]	Naples, Italy 1991–1993	OBS, Nested case-control	*N* = 106 28.6/100 PY (17.8–43.4)	ORT during follow-up	21.2% of seroconverters vs 28.2% of controls in ORT during follow-up	Calculated adjusted relative risk: ARR = .42 (.14–1.08)

Table 1. (*Continued*)

1st author, publication year	Location and study years	Design	Sample size and HCV incidence rate (95% CI)	Intervention	Published association with HCV seroconversion	Risk measure used in analysis (95% CI)
Thiede, 2000 [42]	Seattle, WA, United States 1994–1998	OBS, Cohort	*N* = 78 9.0%/y (5.7–12.2)	Continued vs disrupted or left ORT during follow-up	Cumulative incidence 4.6%/year in those who continued ORT vs 10.7% in disrupted or left ORT	Calculated unadjusted risk ratio (continued vs disrupted or left ORT): RR = .42 (.05–2.76)
van Beek, 1998 [43]	Sydney, Australia 1992–1995	OBS, Retrospective cohort	*N* = 152 20.9/100 PY (13.5–28.3)	Ever in ORT vs never in ORT	Incidence rate 18.0/100 PY both groups	Calculated unadjusted incidence rate ratio: IRR = 1.0 (.40–2.49)
1d. Syringe/injecting equipment access programs						
Hagan, 1995 [44]	Tacoma, WA, United States 1991–93	OBS, Case-control	*N* = 46 Incidence not applicable	Ever vs never participate in SEP	AOR .14 (95% CI .03–.62) SEP users vs nonusers	Published adjusted OR: AOR = .14 (.03–.62)
Hagan, 2004 [45]	Seattle, WA, United States 1994–2001	OBS, Cohort	*N* = 484 11.6/100 PY (9.8–13.5)	Any use of SEP during follow-up	HR 1.4 SEP users vs nonusers.	Published unadjusted hazard ratio: HR = 1.4 (.9–1.9)
Holtzman, 2009 [46]	Multisite, United States 1994–2004	OBS, Cohort	*N* = 1288 Incidence not given	Any use of SEP during follow-up	AOR 1.49 (95% CI .96–2.29) SEP users vs nonusers	Calculated adjusted relative risk: ARR = 1.41 (.96–2.01)
Lamothe, 1997 [35]	Montreal, Canada 1992	OBS, Cohort	*N* = 63 27.1/100 PY (18.0–29.1)	Obtained any needles from SEP during follow-up	55.9/100 PY SEP users vs 31.0/100 PY in nonusers.	Published unadjusted hazard ratio: HR = 2.24 (1.01–4.98)
Patrick, 2001 [36]	Vancouver, Canada 1996–1999	OBS, Cohort	*N* = 155 29.1/100 PY (22.3–37.3)	Frequent SEP attendance (> 1 time/week) during follow-up	Cumulative incidence 54.7%/year frequent attenders vs 26.3% others	Published adjusted hazard ratio: AHR = 2.56 (1.37–4.79)
Roy, 2007 [30]	Montreal, Canada 1997–2003	OBS, Cohort	*N* = 543 27.1/100 PY (23.4–30.9)	Any use of SEP during follow-up	HR 3.02 SEP users vs nonusers, *P* = .18.	Calculated[a] unadjusted hazard ratio: HR = 3.02 (2.32–3.72)
Thorpe, 2002 [47]	Chicago, IL, United States 1997–1999	OBS, Cohort	*N* = 353 10/100 PY (6.7–14.4)	Any use of SEP during follow-up	HR 1.29 SEP users vs nonusers.	Published unadjusted hazard ratio: HR = 1.29 (.6–2.79)
1e. Syringe disinfection with bleach						
Hagan, 2003 [48]	Seattle, WA, United States 1994–2001	OBS, Nested Case-control	*N* = 195 23.1% (17.1–28.9)	Always vs <always used bleach to disinfect used syringes during follow-up	Cumulative incidence 26%/year among those who always bleached vs 22% in those who did not AOR 1.4 (95% CI .7–3.0) always used bleach vs others.	Calculated adjusted relative risk: ARR = 1.21 (.68–1.95)
Hagan, 2010 [49]	Multisite, United States 1995–2000	OBS, Cohort	*N* = 483 17.2/100 PY (13.2–22.4)	Always vs did not always bleach shared syringes during follow-up	AOR 1.14 (95% CI .62–5.88) shared but always bleached vs others	Calculated[b] adjusted hazard ratio: AHR = 1.97 (.29–2.45)
Hahn, 2002 [50]	San Francisco, WA, United States 2000–2001	OBS, Cohort	*N* = 195 25/1/100 PY (18.7–32.9)	Bleached all borrowed syringes during follow-up	Incidence rate 38.5/100 PY bleached all syringes vs 46.5/100 PY in others.	Published unadjusted hazard ratio: HR = .8 (.3–2.2)
Kapadia, 2002 [51]	Multisite, United States 1997–1999	OBS, Nested case-control	*N* = 468 Incidence not given	Always vs not always bleach syringes during follow-up	AOR .45 shared but always bleached vs <all the time	Published adjusted odds ratio: AOR = .45 (.11–1.55)
1f. Multicomponent interventions						

Table 1. (*Continued*)

1st author, publication year	Location and study years	Design	Sample size and HCV incidence rate (95% CI)	Intervention	Published association with HCV seroconversion	Risk measure used in analysis (95% CI)
Abou-Saleh, 2008 [52]	London and Surrey, United Kingdom No dates given	RCT, Cohort	*N* = 95 12.9/100 PY	Participants entering drug treatment were assigned to: Enhanced prevention counseling (EPC, 4 sessions) vs standard counseling (SC, 1 session)	Incidence rate EPC 9.1/100 PY vs 17.2/100 PY SC	Calculated unadjusted incidence rate ratio: IRR = .53 (.13–2.21)
van den Berg, 2007 [12]	Amsterdam, Netherlands 1995–2005	OBS, Cohort	*N* = 168 6.8/100 PY (5.1–8.4)	Full harm reduction (HR) (> 60 mg/day methadone and no injection or always use SEP) vs incomplete HR (any methadone and irregular/no use of SEP, or 0–59 mg/day and always use SEP) vs no HR (no methadone, no SEP)	Incidence rate 3.5/100 PY full HR vs 24.1/100 PY incomplete HR vs 23.2/100 PY no HR. AIRR .36 (95% CI .13–1.03) full HR vs 1.17 (.6–2.3) incomplete vs no HR (reference)	Calculated unadjusted incidence rate ratio (Full harm reduction vs incomplete or no harm reduction): IRR = .15 (.06–.34)

NOTE. A(OR/HR/IRR/RR), Adjusted (risk measure); CI, Confidence interval; HCV, hepatitis C virus; HR, Hazard ratio; IRR, Incidence rate ratio; MI, Motivational interviewing; OBS, Observational study; OR, Odds ratio; ORT, Opiate replacement therapy; PY, Person-years; RCT, Randomized controlled trial; RR, Relative risk (incidence density) or Risk ratio (cumulative incidence); SEP, Syringe-exchange program.

[a] calculated CI from *P* value.

[b] calculated from raw data.

type defined by similarity in dose or comparison group. We used random effects models throughout to more accurately account for unmeasured sources of variation among studies [55]. We examined asymmetry in funnel plots of treatment effects against standard errors to assess potential publication bias [56].

RESULTS

A total of 26 studies were eligible for inclusion in this analysis [7, 8, 12, 14, 30, 32–52]. Of these, 1 study was unpublished [35], and 2 studies [35, 36] reported on >1 intervention. The studies included 4 randomized controlled trials (RCTs) [32, 33, 39, 52]; the remainder were observational studies. The RCTs examined the effects of single interventions [32, 33, 39] or those provided in combination [52]. There were 4 case-control studies, 3 of which were nested in longitudinal designs [41, 44, 49, 51]. All other studies used longitudinal cohort designs.

As shown in Table 1, most studies ($n = 13$) reported on the relation between substance-use treatment and HCV seroconversion; 5 of these studies did not specify the type of drug treatment measured, and 8 studies examined the effects of opiate-replacement therapy (ORT). In all, 7 studies reported on the association between syringe-access programs and HCV incidence; each of these examined needle-exchange programs. There were 4 reports on the effect of bleach disinfectant on HCV acquisition; 2 studies examined the association between multicomponent interventions and HCV seroconversion [12, 52]. No study reported on HCV seroconversion in relation to supervised injection facilities or pharmacy sales of syringes. All studies were from high-income countries in North America, Western Europe, or Asia. Most studies were completed before 2000. Funnel plots of effects by intervention type showed little evidence of publication bias (data not shown).

Behavioral Interventions

Of all the studies analyzed, 2 studies examined the effect of a behavioral intervention on the incidence of HCV infection in PWID (Tables 1a, 2a). The OR for the association between participation in a 6-session peer education training and HCV seroconversion was 1.15 (95% CI, .72–1.82) indicating no difference between the intervention arm and attention-matched controls [32]. A different study assigned 89 individuals enrolled in drug treatment to 4 sessions of motivational interviewing or to an equal-attention control condition; 2-year cumulative HCV incidence was 18% in the motivational-interviewing group vs 14% in controls ($P = .6$) [33]. The pooled relative risk was 1.18 (95% CI, .76–1.81). The Q statistic was not statistically significant, and I^2 was 0%.

Substance-Use Treatment: Not Specified

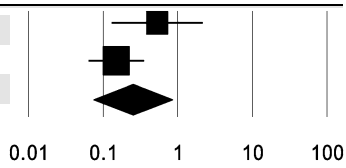
In these studies, substance-use treatment could conceivably have represented a range of modalities, including attending self-help

Table 2. Meta-Analyses of the Effect of Interventions on HCV Seroconversion in PWID.

1st author, publication year random effects estimate & heterogeneity statistics	Relative risk (95% CI[1])	Forest plot
2a. Behavioral interventions		
Garfein, 2007 (32)	1.15 (0.72, 1.82)[2]	
Stein, 2009 (33)	1.34 (0.43, 4.20)[2]	
Random effects estimate	1.18 (0.77, 1.81)[2]	
Q, I^2	0.6, 0%	
		0.01 0.1 1 10 100
2b. Substance-use treatment, not specified		
Brunton 2000 (34)	6.25 (1.30, 30.09)	
Lamothe 1997 (35)	1.02 (0.48, 2.02)	
Maher 2006 (8)	0.84 (0.52, 1.37)	
Patrick 2001 (36)	1.86 (1.20, 2.35)	
Smyth 2003 (14)	0.69 (0.42, 1.15)	
Random effects estimate	1.21 (0.71, 2.08)	
Q, I^2	17.6**, 77%	
		0.01 0.1 1 10 100
2c. Substance-use treatment, Opiate-Replacement Therapy (ORT)		
Craine 2009 (37)	0.34 (0.12, 0.99)	
Crofts 1997 (38)	2.25 (0.91, 5.54)	
Dolan 2005 (39)	0.50 (0.24, 1.11)	
Hallinan 2004 (40)	0.18 (0.02, 1.59)	
Lucidarme 2004 (7)	0.41 (0.12, 1.40)	
Rezza 1996 (41)	0.42 (0.14, 1.08)	
Theide 2000 (42)	0.42 (0.05, 2.76)	
van Beek 1998 (43)	1.00 (0.40, 2.49)	
Random effects estimate	0.60 (0.35, 1.03)	
Q, I^2	12.8, 45%	
		0.01 0.1 1 10 100
2d. Syringe access program, syringe exchange		
Hagan 1995 (44)	0.14 (0.03, 0.62)	
Hagan 2004 (45)	1.40 (0.90, 1.90)	
Holtzman 2009 (46)	1.41 (0.96, 2.01)	
Lamothe 1997 (35)	2.24 (1.01, 4.98)	
Patrick 2001 (36)	2.56 (1.37, 4.79)	
Roy 2007 (30)	3.02 (2.32, 3.72)	
Thorpe 2002 (47)	1.29 (0.60, 2.79)	
Random effects estimate	1.62 (1.04, 2.52)	
Q, I^2	32.3**, 81%	
		0.01 0.1 1 10 100
2e. Syringe disinfection, bleach		
Hagan 2003 (48)	1.21 (0.68, 1.95)	
Hagan 2010 (49)	1.97 (0.54, 7.14)	
Hahn 2002 (50)	0.80 (0.30, 2.20)	
Kapadia 2002 (51)	0.45 (0.11, 1.55)	
Random effects estimate	1.07 (0.70, 1.63)	
Q, I^2	3.0, 1%	
		0.01 0.1 1 10 100
2f. Multicomponent interventions		

Table 2. (*Continued*)

1st author, publication year random effects estimate & heterogeneity statistics	Relative risk (95% CI[1])	Forest plot
Abou-Saleh 2008 (52)	0.53 (0.13, 2.21)	
van den Berg 2007 (12)	0.15 (0.06, 0.34)	
Random effects estimate	0.25 (0.07, 0.83)	
Q, I^2	2.2, 55%	



* $p < 0.05$

** $p < 0.01$

[1] CI = Confidence Interval

[2] Odds Ratio

groups, outpatient drug-free programs, or inpatient residential programs. Timing and duration of exposure to substance-use treatment was measured in a number of ways, including whether participants were in treatment at study enrollment, were in treatment at the end of the follow-up period, or received treatment throughout follow-up or for a specified length of time (Table 1b). As shown in Table 2b, there was substantial heterogeneity in the association between participation in these programs and HCV seroconversion, with 2 studies showing lower rates of HCV infection among those exposed to drug treatment [8, 14] and 2 showing statistically significant higher rates [34, 36]. HCV incidence rates in the studies ranged from cumulative incidence of 23% over a 2-year period [34] to 66 infections per 100 PY [14]. The *Q* value was statistically significant and I^2 was 77%, so the pooled relative risk (1.21; 95% CI, .71–2.08) should be interpreted with caution. Excluding the study that compared substance-use treatment to a comparison group of individuals who received treatment for a shorter period of time [14], the pooled relative risk was 1.43, (95% CI, .79–2.58); the *Q* value was not significant ($P = .24$) and $I^2 = 73\%$.

Substance-Use Treatment: Opiate-Replacement Therapy

In the 8 studies evaluating the effect of ORT on HCV incidence, degree of exposure was measured for whether participants were in ORT at study enrollment or at the end of the follow-up period, or had remained in treatment throughout the follow-up period (Table 1c). In the RCT that evaluated the effect of ORT started when participants were incarcerated, incidence was measured 1–5 years after the end of trial, when some participants were still in prison and others had been released [39].

In several of these studies, HCV incidence rates among participants in treatment were rather low, including 2.9/100 PY among PWID in the United Kingdom who were in ORT at the end of follow-up [37]; 1.3/100 PY among Sydney PWID who remained in treatment throughout [40]; and cumulative incidence of 4.6% at the end of 1 year in PWID who remained in treatment in Seattle [42]. In 1 early study, HCV incidence was higher among those who remained in ORT as compared with that among those who left or had no ORT during follow-up [38].

As shown in Table 2c, the pooled relative risk of HCV seroconversion in relation to ORT was .60 (95% CI, .35–1.03). Heterogeneity was not significant and I^2 was 45%. A pooled relative risk was also calculated for studies where the comparison group excluded "interrupted" ORT [7, 37, 39, 41, 43]; the pooled RR estimate was similar to that for the full set of ORT studies (RR, .52; 95% CI, .34–.79), but there was much less heterogeneity, with $Q = 2.9$ ($P = .57$) and $I^2 = 0\%$. When the analysis was restricted to studies that compared continuous enrollment in ORT (throughout follow-up) to those who disrupted or left ORT [38, 40, 42], the pooled RR was .70, (95% CI, .14–3.60), the *Q* was 5.8 ($P = .056$), and I^2 was 65%.

Syringe-Access Programs

All 7 studies that examined participation in syringe-access programs (syringe-exchange programs [SEP]) in relation to HCV seroconversion were from North America (Table 1d). Sample sizes ranged from 46 to 1288 participants, and median sample size was 353 participants. All but 1 study [36] examined SEP exposure as any use compared with no use during the period of susceptibility to HCV infection.

Only 1 study, which used a case-control design [44], found that participation in an SEP was associated with a significantly lower risk of HCV seroconversion. A Canadian study [36] showed significantly elevated risk of HCV infection in frequent exchange-program attendees compared with the risk in other PWID. All other studies reported no significant association. The resulting pooled effect (RR, 1.62; 95% CI, 1.04–2.52) showed substantial heterogeneity ($Q = 32.3$; $P < .01$; $I^2 = 81\%$).

Syringe Disinfection

The effect on risk of HCV infection of disinfecting syringes with bleach was evaluated in 4 studies in the United States [Table 1e].

All studies defined bleach use as either always using bleach or disinfecting all syringes with bleach. The estimates of the association ranged between .42 and 1.97, and the pooled estimate was 1.08 (95% CI, .66–1.75). Heterogeneity was not significant.

Multicomponent Programs

In 2 studies, investigators examined the effect of participation in multicomponent interventions [Table 1f]. In the United Kingdom study, ORT combined with enhanced HCV prevention counseling was compared with ORT alone; HCV seroconversion was lower among those in the combined intervention group (9.1/100 PY vs 17.2/100 PY in the ORT alone group; $P > .05$) [52]. In the Amsterdam study, ''full participation in harm reduction''—defined as >60 mg methadone per day and always using SEP—was compared with ''less than full harm reduction'' or no harm reduction [12]. HCV incidence was 3.5/100 PY in the full–harm-reduction group compared with 23.9/100 PY in other study participants. As shown in Table 2f, the pooled RR was .25 (95% CI, .07–.83). Although the Q value was not significant, I^2 was 55%.

DISCUSSION

The meta-analysis found a substantial and statistically significant reduction in HCV incidence in PWID—of approximately 75%—when combination prevention strategies were applied. This finding is consistent with an understanding that an array of factors facilitate HCV transmission among PWID, including the large disease reservoir of HCV-infectious injectors, the efficiency with which HCV may be transmitted via a number of different drug injection–related practices, and the chaotic and rushed atmosphere of the injection setting [9, 10, 47, 50, 57]. Thus, multicomponent interventions that support a range of strategies (reduction or elimination of drug injection, adoption of safe injection practices through the provision of sterile syringes and drug-preparation equipment, or behavior-change counseling) would be expected to achieve greater success than those offering fewer options for lowering risk.

Both of the multicomponent interventions examined here included ORT; in the Abou-Saleh study, reduced HCV incidence was observed when enhanced prevention counseling was administered to PWID while in substitution treatment, and in the van den Berg study, lowest HCV incidence was among those receiving ≥60 mg of methadone per day and obtaining all their syringes from an SEP [12, 52]. However, the meta-analysis of ORT alone showed a less substantial, inconsistent impact on HCV seroconversion risk. Therefore, one cannot conclude that the large-magnitude effect of multicomponent programming on HCV infection rates is wholly attributable to ORT. In several studies of ORT, remaining in treatment was associated with significant reductions in injection frequency, but not elimination [12, 37, 40]. Thus, maintaining control over one's drug intake via injection may be a key element in reducing HCV risk.

A strength of this analysis is its restriction to studies that used HCV seroconversion as an outcome measure, as opposed to HCV prevalence or injection risk behavior. Although scientifically defensible, this restriction left a relatively small number of studies. The results of the meta-analysis are also consistent with the conclusion of qualitative reviews of HCV prevention in PWID, that packages of harm reduction programs may be effective [22–25]. Another meta-analysis from the HCV Synthesis Project showed that the expansion of syringe access and ORT programs in high-income countries was associated with a lengthening in the time from onset of drug injection to acquisition of HCV [2]. The results shown here are also consistent with the findings of a qualitative study of long-term HCV-seronegative PWID who reported that they used a combination of strategies to avoid withdrawal symptoms and practice safe injection [58].

The study has limitations that must be kept in mind in interpreting the results. As with all meta-analyses, we were restricted to the data that could be obtained from written reports. In some cases, information bias may have been introduced by the use of antibody tests to detect seroconversion or the use of self-report to assess intervention participation; such error (if nondifferential) would have biased results toward a null association. Null and weak effects in some studies may also have been observed as a result of low dose of exposure to the intervention in question. Indeed, hypothesis testing should be led by an assertion of the degree of exposure to the intervention that is likely to prevent transmission. For example, being in substance-use treatment on the date of study enrollment or on the follow-up visit may represent sporadic treatment. However, focusing on studies where ORT was received throughout follow-up (RR = .71) did not reveal a larger-magnitude effect (RR = .60 for the full set of ORT studies). In contrast, measurement of syringe disinfection with bleach was consistent across the 4 studies (bleached all syringes during follow-up), so the finding of a distribution of RRs around the null value of the pooled estimate (RR = 1.07, $P > 0.05$) rather strongly supports a conclusion of no effect on HCV transmission.

Removal of confounding cannot be assumed in the analysis shown here. Even adjusted RRs may not have been calculated following data-based approaches [59], and multivariate models may have included only statistically significant terms and thus omitted important confounding factors [29, 60]. Further, structural interventions such as expanded syringe access are designed to reduce risk of infection for a *population* of PWID; research has shown that individual-level comparisons of SEP users to nonusers may be particularly prone to volunteer bias (a form of confounding) in that exchange programs attract and retain higher-risk PWID [61, 62] Consequently, the positive *individual* association between HCV acquisition and SEP

participation found in this meta-analysis should not be interpreted as suggesting that SEP participation increases risk of HCV acquisition. Less biased evaluations of SEPs would require random assignment of communities; ethical considerations, research cost, and possible community resistance to being assigned to a non-SEP control condition all make such community-level evaluations unlikely in the foreseeable future. The variation in HCV incidence rates among PWID noted in the introduction also suggests that many communities would be needed in a community-level controlled trial. A final comment on the limitations is that the small number of studies by intervention type limited our ability to detect publication bias; pooled effect estimates in this study may thus overestimate or underestimate the true effects. The small sample size also precluded subgroup analyses in relation to PWID characteristics.

There are several implications for future research on HCV prevention for PWID, both for content and design. Foremost is that multicomponent interventions that include methods to reduce drug-use frequency and to support safe injection should be developed and tested in a variety of settings and subsets of PWID (eg, young, racial or ethnic minority PWID, and low- and middle-income countries). Design of an evaluation should be based on an a priori conceptualization of what constitutes an adequate dose of the intervention and assuring that measurement of exposure reflects dosage. Reporting of the results of future evaluations should include detailed descriptions of the intervention for dose and duration, and examine the effects of participation in multiple intervention types. In the meantime, the currently available research indicates that HCV can be prevented among PWID.

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