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https://escholarship.org/uc/item/1d62c2nc

Journal

Clinical Infectious Diseases, 64(7)

ISSN

1058-4838

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Publication Date

2017-04-01

DOI

10.1093/cid/ciw869

Peer reviewed

IDSA — Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Geographic Differences in Temporal Incidence Trends of Hepatitis C Virus Infection Among People Who Inject Drugs: The InC3 Collaboration

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Background. We determined temporal trends (1985–2011) in hepatitis C virus (HCV) incidence and associated behavioral exposures for people who inject drugs (PWID) from the United States (Boston, Baltimore, and San Francisco), Canada (Montreal), the Netherlands (Amsterdam), and Australia (Sydney and Melbourne).

Methods. Using population-based cohort data from HCV-negative PWID, we calculated overall and within-city HCV incidence trends, HCV rates by study enrollment period (1985–2011), and temporal trends in exposure behaviors. Poisson regression models estimated trends in HCV incidence over calendar-time. Survival models identified risk factors for HCV incidence across cities and estimated independent effects of city and calendar period on HCV infection risk.

Results. Among 1391 initially HCV-negative participants followed prospectively (1644.5 person-years of observation [PYO]), 371 HCV incident infections resulted in an overall incidence of 22.6 per 100 PYO (95% confidence interval [CI], 20.4–25.0). Incidence was highest and remained elevated in Baltimore (32.6/100 PYO), San Francisco (24.7/100 PYO), and Montreal (23.5/100 PYO), lowest in Melbourne and Amsterdam (7.5/100 PYO and 13.1/100 PYO, respectively), and moderate (21.4/100 PYO) in Sydney. Higher rates of syringe and equipment sharing and lower prevalence of opioid agonist therapy were associated with HCV incidence in cities with the highest incidence. Risk for infection dropped by 18% for every 3-year increase in calendar-time (adjusted hazard ratio, 0.8 [95% CI, .8–.9]) in the multivariable model.

Conclusions. Differences in prevention strategies and injecting contexts may explain the ongoing high HCV incidence in these North American cities and emphasize the need for scale-up of opioid agonist therapy and increased coverage of needle and syringe programs in North America.

Keywords. hepatitis C virus (HCV); incidence trends; epidemiology; people who inject drugs; harm reduction strategies.

More than 10 million people who inject drugs (PWID) live with chronic hepatitis C virus (HCV) infection globally, and HCV prevalence is estimated to be between 10% and 90% in this population [1, 2]. Injection drug use continues to be the major mode of HCV transmission in high- and middle-income countries since the implementation of effective blood supply screening in the early 1990s [3]. To date, meta-analyses and systematic reviews of HCV have focused on prevalence, with analyses of data from the same studies [1, 4, 5]. Only 2

meta-studies included HCV incidence estimates, and no prior studies compared HCV incidence across geographic regions or time periods [6, 7]. Robust data on HCV incidence are essential for describing disease etiology and developing effective public health responses, including prevention and treatment.

Longitudinal studies enable the observation and analysis of HCV transmission trends over time and produce insights into drivers of the epidemic. The International Collaboration of Incident HIV and HCV in Injecting Cohorts (InC3) study brings together well-characterized longitudinal cohorts of PWID in the United States (Boston, Baltimore, and San Francisco), Canada (Montreal), the Netherlands (Amsterdam), and Australia (Sydney and Melbourne) [8] (https://ctsc.health.unm.edu/apps/inc3/). Each cohort systematically collected prospective serologic and behavioral data from HCV antibody–negative PWID recruited from the community, and together, span >2 decades (1985–2011). City-level differences in harm reduction policies and intervention coverage are difficult to directly measure. We leveraged epidemiological data collected at

the individual level to (1) estimate overall incidence of HCV infection and temporal (1985–2011) trends in incidence; (2) examine behavioral predictors of HCV infection; and (3) describe and compare temporal trends in injecting exposures within a subset of InC3 cities (Baltimore, San Francisco, Montreal, Sydney, Amsterdam, and Melbourne). This study provides findings on HCV etiology and inferences about drivers of infection trends within a high-income country context, globally.

METHODS

Study Population

Participants were selected from pooled epidemiological data collected from prospective cohort studies in Baltimore [9], San Francisco [10], Montreal [11], Sydney [12, 13], Amsterdam [14], and Melbourne [15]. Study eligibility criteria required PWID to be HCV antibody (anti-HCV) negative and HCV RNA negative at enrollment, with at least 1 follow-up serologic visit, and to self-report recent injection drug use (Table 1). Two InC3 cohorts (Boston Boston Acute HCV Study: Transmission, Immunity, and Outcome Network (BAHSTION) cohort and the Sydney Australian Trial in Acute Hepatitis C (ATAHC) cohort) were excluded because only participants with acute or early (within 2 years of exposure) HCV infection were enrolled. A third InC3 cohort (Australian HITS-p cohort) recruited from prisons, rather than community samples, and thus was excluded [8].

Table 1. Summary of Inclusion and Study Procedures Applicable to Study Analysis

Cohort Name	City	Sample Size	Inclusion Criteria	No. of Sites	Recruitment Method(s)	Enrollment Period[a]	Follow-up Interval for Serology[b]
Amsterdam Cohort Studies (ACS)	Amsterdam	48	Active drug users (both PWID and non-PWID) using hard drugs at least 3 times/wk; ≥18 y of age; HIV negative and anti-HCV negative	1	Community-based outreach; open enrollment	1984–present	4-mo intervals (until 2003) then 6-mo intervals
Baltimore Before and After Acute Study in Hepatitis (BBAASH)[c]	Baltimore	288	Active PWID aged 18–65 y; anti-HCV negative	1	Community-based outreach; open enrollment	1996–present	Monthly
Networks Study (N2)	Melbourne	199	Injection drug use in past 6 mo; ≥18 years of age; anti-HCV negative	6	Community-based outreach and respondent-driven sampling; open enrollment	2005–2012	3-mo intervals
St Luc Cohort (HEPCO)	Montreal	244	Injection drug use in past 6 mo; ≥14 y of age; anti-HCV negative	1	Community-based outreach; open enrollment	2004–present	3–6-mo intervals
The UFO Study (UFO)	San Francisco	398	Injection drug use in past mo; <30 y of age at enrollment; anti-HCV negative	1	Community-based outreach; open enrollment	2000–present	Monthly
Hepatitis C Virus Cohort (CU)	Sydney	257	Injection drug use within the past 6 mo; anti-HCV negative	3	Community-based outreach; open enrollment	1999–2002	3–6-mo intervals
Hepatitis C Incidence and Transmission Study- Community (HITS-c)	Sydney	134	Injection drug use within past 12 mo; ≥16 y of age; anti-HCV negative	5	Community-based outreach; open enrollment	2008–2012	3-, 6-, 9-, 12-, 15-, 18-, 24-mo intervals

All cohorts enrolled participants prospectively.

Abbreviations: anti-HCV, hepatitis C virus antibody; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PWID, people who inject drugs.

[a]As of March 2015.

[b]Antibody and RNA testing were performed at the time of acute HCV detection. Anti-HCV testing was performed using the following assays: HCV enzyme immunoassay (EIA) 2.0 (Abbott Laboratories, Abbott Park, Illinois), EIA-3 (Ortho Clinical Diagnostics, Raritan, New Jersey), or Abbott Architect anti-HCV. Very little difference in antibody detection has been demonstrated between HCV EIA 2.0 and 3.0 [18]. Qualitative HCV RNA testing was performed using the following assays: Versant TMA (Bayer, Australia; <10 IU/mL), COBAS AmpliPrep/COBAS TaqMan (Roche, Branchburg, New Jersey; <15 IU/mL), COBAS Amplicor HCV Test v2.0 (Roche Diagnostics, Mannheim, Germany; <50 IU/mL), or discriminatory HCV transcription-mediated amplification component of the Procleix HIV-1/HCV (Gen-Probe, San Diego, California; <12 copies/mL). Quantitative HCV RNA testing was performed using the Versant HCV RNA 3.0 (Bayer; <615 IU/mL), COBAS Amplicor HCV Monitor 2.0 (Roche Diagnostics; <600 IU/mL), COBAS AmpliPrep/COBAS TaqMan (Roche; <15 IU/mL), or an in-house polymerase chain reaction (<1000 IU/mL).

[c]BBAASH recruits and monitors young PWID for HCV infection, with a focus on serological data to assess the clinical characteristics of acute infection and reinfection. Because research goals focus on understanding questions related to immunology and virology, behavioral data were not systematically collected between 2000 and 2012. The BBAASH data server was compromised in 2005, leading to the loss of data on age and biological sex for some participants. Investigators preformed genome-wide association studies to obtain sex for participants who acquired HCV infection, but because age is not a genetic trait, age information was not recovered.

Data Collection and Procedures

Cohorts systematically collected self-reported data on sociodemographic characteristics, injecting behaviors, and serological data on anti-HCV and HCV RNA. All cohorts also provided loss-to-follow-up data.

HCV Testing

HCV testing methods varied by cohort, including anti-HCV, HCV RNA, and genotype testing, but were consistent within each site (Figure 1). The majority of HCV tests occurred during regular study data collection periods, with some retrospective testing on frozen serum or plasma specimens to fill in data gaps.

HCV Infection Outcome

In this analysis, primary HCV incident infection (hereafter referred to as HCV incident infection) was defined as either (1) positive anti-HCV *and* HCV RNA positive, or (2) positive HCV RNA test following a previously documented negative anti-HCV and HCV RNA test (Figure 1). Because a few cohorts stopped following participants at the 24-month mark (Baltimore and Sydney), we censored the follow-up period of all participants eligible for this analysis at 24 months.

The date of HCV infection was estimated as either (1) the midpoint between the last negative and first positive anti-HCV test dates for those defined as having anti-HCV seroconversion, or (2) the date of the first HCV RNA–positive visit minus 28 days for those whose infection was identified via an RNA-positive/anti-HCV–negative test [16]. The median duration of observed time to incident HCV was 12 months (interquartile range [IQR], 6–20).

Figure 1. Participant inclusion flowchart. Abbreviations: HCV, hepatitis C virus; InC3, International Collaboration of Incident HIV and HCV in Injecting Cohorts.

Statistical Analyses

To examine potential bias due to differential loss to follow-up, we used Pearson χ^2 or Kruskal-Wallis tests to compare distributions of selected demographic and injecting risk behavior variables between participants with follow-up visits and those with only baseline visits.

We used descriptive analyses to characterize the study population overall and by city (Baltimore, San Francisco, Montreal, Sydney, Amsterdam, and Melbourne). Primary analyses employed life-table methods to construct HCV incidence curves by city and calculate HCV infection rates within the first 24 months of follow-up (presented as rates per 100 person-years of observation [PYO] with 95% confidence intervals [CIs]). Next, we conducted analyses to describe overall and within-city HCV incidence trends. To compare HCV infection rates across cities, we used Kaplan-Meier estimates and log-rank tests (see Supplementary Figure 1). The same approach was used to compare HCV rates by period of study enrollment (1985–1990 and in 3-year intervals from 1991 to 2011) across cities. We used Poisson regression to test for the trend in HCV incidence over calendar-time (presented as incidence rate ratios [IRRs] per 3-year intervals and 95% CIs).

We fit bivariate Poisson regression models to examine possible explanations for differences in HCV incidence trends across cities. Next, using self-reported data collected at enrollment, we plotted temporal trends in the proportion of persons reporting the following *recent* injecting behaviors: (1) main or most frequent/often illicit drug injected (heroin, methamphetamine/amphetamine, cocaine, other opiates (ie, prescription opioids), *or* heroin and cocaine in combination); (2) receptive syringe sharing (RSS) (yes/no); (3) opioid agonist therapy (OAT), including methadone and buprenorphine (yes/no); and (4) access to sterile syringes through safe sources (needle syringe program, chemist/pharmacist, vending machine, mobile outreach) (yes/no). Supplementary Table 1 provides details on time frames for risk factor measures by cohort. Proportions were calculated for 1985–1990 and 3-year intervals from 1991 to 2011. Analyses did not include time-varying covariates due to variability in follow-up intervals and data availability. Last, we fit a stratified multivariable Cox propositional hazards model, allowing unique baseline hazards by city, to assess the independent relationship between recent RSS, OAT, and calendar-time with risk for HCV incidence, while controlling for biological sex, age, and city. Sensitivity analyses assessed multivariable model fit and main effects when Baltimore was included (Supplementary Table 2). All analyses were performed using Stata software version 13.0 (College Station, Texas).
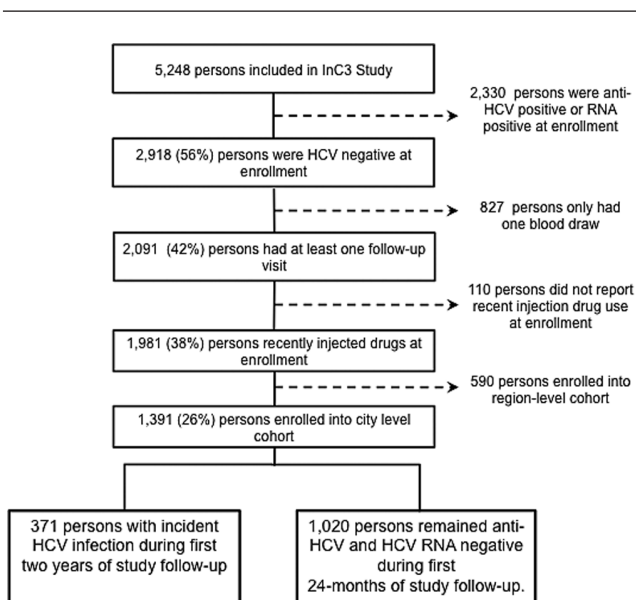
RESULTS

General Characteristics

In total, 827 HCV-negative participants did not complete follow-up visits. These participants were not significantly different from those with at least 1 follow-up visit with respect to biological

sex, ethnicity, main or most frequent drug injected, frequency of injection, recent OAT, and history of incarceration. However, participants lost to follow-up were significantly younger (mean age, 23 vs 26 years; $P \leq .001$), more educated (53% vs 41% completed secondary school; $P \leq. 001$), and more likely to report RSS (40% vs 19%; $P \leq. 001$) than those who were retained. Supplementary Table 3 details loss to follow-up rates by city.

Of the 1391 persons included in this study, 49% were in the United States, 18% in Canada, 30% in Australia, and 3% in the Netherlands. Overall, 64% were male, and the median age at enrollment was 25 years (IQR, 21–29 years). The most frequently injected drug at baseline was heroin (53%), followed by meth/amphetamine (21%), cocaine (13%), other opiates (8%), and heroin and cocaine in combination (4%); Baltimore did not collect data on drug use. Table 2 shows all participant characteristics, including loss to follow-up, at enrollment by city.

HCV Incidence: Overall, Geographic, and Temporal Trends
Overall Incidence
Over 1644.5 PYO, 371 persons had a HCV incident infection for an overall estimated incidence of 22.6/100 PYO (95% CI, 20.4–25.0). Approximately one-half (n = 187) of incident infections were identified via an RNA-positive test. Overall, incidence decreased from 24.6/100 PYO (95% CI, 21.8–27.8) in the first year of observation to 18.8/100 PYO (95% CI, 15.5–22.7) during the second study year. Compared with Melbourne, which had the lowest incidence rate of HCV (7.5/100 PYO [95% CI, 4.6–12.3/100 PYO]), IRRs were significantly elevated for Baltimore (IRR, 1.89 [95% CI, 1.1–3.14]), San Francisco (IRR, 2.6 [95% CI, 1.5–4.4]), Montreal (IRR, 2.6 [95% CI, 1.5–4.4]), and Sydney (IRR, 2.2 [95% CI, 1.3–3.8]). Incidence in Amsterdam was not significantly elevated compared with Melbourne (IRR, 1.6 [95% CI, .7–3.6]). Table 2 describes overall HCV incidence rates by city.

Temporal Trends in HCV Incidence
We observed differences in the magnitude and direction of HCV incidence trends across cities (Figure 2). In Baltimore, HCV incidence was initially very high at 45.1/100 PYO during 1997–1999, but then significantly declined to 20.1/100 PYO during 2009–2011 (IRR, 0.7 per 3 years [95% CI, .6–.9]) (Figure 2A). In San Francisco, incidence was 23.4/100 PYO during 2000–2002, remaining high and relatively constant across calendar-time with an increase to 30.8/100 PYO during 2009–2011 (IRR, 1.0 [95% CI, .8–1.2]). In Montreal, incidence remained high (range, 20.9–26.6) across 2003–2011 (IRR, 1.1 [95% CI, .8–1.6]). In Sydney, incidence was high during the early 2000s (33.4/100 PYO) with a statistically significant decline in 2009–2011 (9.9/100 PYO) (IRR, 0.7 [95% CI, .6–.8]). In Amsterdam, incidence was initially high during 1986–1993, but quickly declined to 9.0/100 PYO during 1994–1996 with no new infections identified in subsequent years (IRR, 0.4 [95% CI,

.3–.8]). Last, in Melbourne, incidence was low and remained low across all years (IRR, 0.8 [95% CI, .4–1.5]).

Geographical Differences in Behaviors/Characteristics
Table 2 displays HCV incidence estimates by demographic and behavioral variables for each city.

Temporal Trends in Injection-Related Exposures
To further contextualize observed differences in HCV incidence trends across cities, Figure 3 illustrates temporal trends in the most frequent drug injected, recent RSS, recent OAT use, and recent access to sterile syringes through safe sources reported at enrollment. For San Francisco, where the majority of persons were injecting heroin, levels of RSS remained between 35% and 43%, with few (8%–12%) reporting recent OAT across all time periods. In Montreal, cocaine was the most frequently injected drug in the 2003–2005 period, but by 2009–2011 had declined and was primarily superseded by "other opiates." Additionally, consistent levels (36%–38%) of RSS and OAT (19%–37%) were observed. In Sydney, reports of heroin as the most frequent drug injected were varying (53%–95%) over time, with methamphetamine injecting increasing from 4% to 40% from 2000 to 2008; a sharp decline in the prevalence of RSS from 39% in 2000–2002 to 7% in 2009–2011 was coupled with increasing levels (34%–60%) of OAT. In Amsterdam, levels of heroin injection fluctuated across 1994–2008, with levels of methamphetamine injection steadily increasing from 5% during 1994–1999 to 38% in 2006–2008; RSS declined as OAT levels increased from 3% in 1994–1996 to almost 100% in 2009–2011. In Melbourne, during 2003–2011, the majority of individuals reported injecting heroin, and RSS levels decreased from 20% to 11%; levels of OAT were consistent (42%–58%). Obtaining sterile syringes from needle syringe provision (NSP), pharmacies, vending machines, or through outreach was high (>80%) across all time periods and in all cities, with the exception of Sydney, where access levels increased from 50% in 2000–2002 to 90% in 2009–2011.

Independent Differences in Risk for HCV Incidence
After adjusting for age, biological sex, and city, recent RSS was independently associated with an elevated risk for HCV infection (adjusted hazard ratio [aHR], 1.5 [95% CI, 1.2–2.0]), whereas recent OAT use reduced risk (aHR, 0.5 [95% CI, .4–.7]). Risk of infection dropped by approximately 18% for every 3-year increase in calendar-time (aHR, 0.7 [95% CI, .6–.8]). No significant effect was observed for biological sex or age at enrollment (Table 3).

DISCUSSION

To our knowledge, this is the first multicity study of trends in HCV incidence and injecting behavior over the past 25 years. Overall HCV incidence was high (21.5/100 PYO), and the risk

Table 2. Frequencies and Hepatitis C Virus Incidence Estimates for Baseline Characteristics by City (N = 1391)

Characteristic	Baltimore (n = 288)		San Francisco (n = 398)		Montreal (n = 244)		Sydney (n = 294)		Amsterdam (n = 48)		Melbourne (n = 119)	
	No. (%)	IR	No. (%)	IR	No. (%)	IR	No. (%)	IR	No. (%)	IR	No. (%)	IR
Overall HCV incidence	108 (37)	32.6 (26.8–39.8)	137 (34)	24.7 (20.4–29.9)	94 (38)	23.5 (18.8–29.4)	66 (22)	21.4 (16.7–27.3)	17 (35)	13.1 (7.0–24.3)	32 (27)	7.5 (4.6–12.3)
Median No. of study visits (IQR)	13 (5–23)	…	4 (3–7)	…	8 (4–15)	…	4 (2–5)	…	17 (5–29)	…	4 (3–8)	…
Loss to follow-up before 24 mo (n = 1020)	112 (59)	…	201 (68)	…	61 (36)	…	181 (78)	…	9 (24)	…	39 (38)	…
Biological sex												
Male	141 (49)	41.5 (32.0–54.0)	265 (67)	22.2 (17.5–29.3)	197 (81)	24.6 (19.3–31.3)	200 (68)	24.6 (19.3–31.3)	35 (73)	14.6 (7.3–29.3)	78 (66)	9.2 (5.3–15.8)
Female	78 (27)	60.0 (44.3–81.0)	133 (33)	30.4 (22.2–41.6)	47 (19)	19.0 (10.8–33.4)	94 (32)	19.0 (10.8–33.4)	13 (27)	9.2 (2.3–36.6)	41 (35)	4.2 (1.4–13.0)
Unknown[a]	69 (24)	1.0 (0.1–7.2)	0	…	0 (0)		0 (0)		0 (0)	…	0 (0)	
Median age, y (IQR)	25 (23–29)		22 (20–26)		31 (26–39)		24 (20–28)		27 (24–31)		25 (22–28)	
Education level												
High school or below	0 (0)	…	173 (44)	25.7 (19.6–33.7)	64 (26)	29.0 (19.4–43.2)	117 (40)	29.0 (19.4–43.2)	3 (6)	…	31 (26)	3.1 (0.8–12.3)
Completed high school or above	0 (0)	…	219 (55)	22.4 (16.9–29.7)	180 (74)	21.7 (16.5–29.3)	177 (60)	21.7 (16.5–28.3)	0 (0)	…	16 (13)	5.8 (1.5–23.4)
Unknown[a]	288 (100)	…	6 (1)	…	0 (0)	…	0 (0)	…	45 (94)	…	72 (61)	10.6 (6.0–18.6)
Ethnicity												
White/Caucasian	147 (51)	…	298 (75)	25.7 (20.8–31.9)	220 (90)	24.1 (19.1–30.4)	218 (74)	24.1 (19.1–30.4)	39 (81)	12.6 (6.3–25.2)	94 (79)	5.9 (3.2–11.1)
Black/African	39 (14)	…	33 (8)	20.2 (9.6–42.3)	2 (1)	40.2 (5.7–285.6)	54 (18)	40.2 (5.7–285.6)	0 (0)	…	16 (13)	17.3 (7.2–41.1)
Indigenous/Native American	0 (0)	…	9 (2)	20.8 (5.2–83.3)	8 (3)	26.4 (6.6–105.6)	13 (4)	26.4 (5.6–105.6)	0 (0)	…	6 (5)	…
Mixed or other	2 (1)	…	52 (13)	24.0 (13.9–42.2)	6 (2)	23.5 (5.9–93.9)	7 (2)	23.5 (5.9–93.9)	5 (10)	13.2 (1.9–93.8)	0 (0)	…
Unknown[a]	100 (45)	…	6 (1)	…	8 (3)	7.0 (1.0–49.9)	2 (1)	…	4 (8)	18.5 (2.6–131.4)	3 (3)	21.7 (3.1–154.0)
History of prison sentence												
No	0 (0)	…	79 (20)	22.1 (14.1–34.6)	64 (26)	21.1 (13.3–33.5)	78 (27)	13.8 (8.0–23.8)	0 (0)	…	87 (73)	8.4 (4.9–14.5)
Yes	0 (0)	…	316 (80)	24.6 (19.8–30.5)	180 (73)	24.4 (18.9–31.4)	56 (19)	4.5 (1.5–13.9)	20 (42)	2.6 (0.4–18.6)	32 (27)	5.1 (1.6–15.8)
Unknown[a]	288 (100)	…	3 (<1)	…	0 (0)	…	160 (54)	34.7 (26.2–46.1)	28 (58)	23.5 (12.2–45.2)	0 (0)	…
Recent unstable housing												
No	0 (0)	…	59 (15)	17.6 (9.2–33.8)	91 (37)	18.6 (12.4–27.8)	100 (34)	9.0 (5.0–16.3)	26 (54)	7.0 (2.3–21.8)	76 (63.9)	7.93 (4.4–14.3)
Yes	0 (0)	…	329 (82.7)	24.9 (20.3–30.6)	153 (62.7)	26.7 (20.4–35.0)	194 (66)	**30.0 (22.9–39.2)**	17 (35.4)	6.7 (1.7–26.7)	43 (36.1)	6.6 (2.8–16.2)
Unknown[a]	288 (100)	…	10 (2)	…	0 (0)	…	0 (0)	…	5 (10)	…	0 (0)	…
Recent unemployment												
No	0 (0)	…	94 (24)	25.4 (16.9–38.2)	153 (63)	26.3 (20.0–34.5)	77 (26)	28.5 (18.2–44.6)	0 (0)	…	49 (41)	3.5 (1.1–10.7)
Yes	0 (0)	…	286 (72)	23.9 (19.1–30.0)	72 (30)	15.7 (9.8–25.3)	83 (28)	40.6 (28.2–58.4)	0 (0)	…	69 (58)	11.3 (6.6–19.5)
Unknown[a]	288 (100)	…	19 (5)	32.9 (15.7–69.0)	19 (8)	371 (18.5–74.1)	134 (46)	9.6 (6.1–16.2)	48 (0)	…	1 (<1)	…
HIV status												
Positive	0 (0)	…	7 (2)	20.4 (5.1–81.6)	1 (1)	…	0 (0)	…	0 (0)	…	0 (0)	…
Negative	0 (0)	…	265 (67)	23.7 (18.8–29.9)	241 (98)	23.3 (18.6–29.2)	134 (46)	10.0 (6.1–16.2)	35 (73)	5.0 (1.6–15.6)	67 (56)	8.4 (4.4–16.2)
Unknown[a]	288 (100)	…	126 (31)	27.5 (19.6–38.7)	2 (1)	84.4 (11.9–598.8)	160 (54)	24.9 (19.0–32.5)	13 (27)	41.5 (19.8–872)	52 (44)	6.6 (3.2–13.9)
Median (IQR) duration of injection drug use, y	0 (0)	…	4 (1–7)		7 (3–13)		4 (2–8)		4 (1–8)		6 (3–10)	
≤2 y	0 (0)	…	105 (26)	24.3 (16.7–35.5)	34 (14)	35.3 (20.9–59.5)	58 (20)	35.3 (20.9–59.5)	17 (35)	19.9 (8.3–47.7)	14 (12)	13.7 (4.4–42.5)

Table 2. Continued

Characteristic	Baltimore (n = 288)		San Francisco (n = 398)		Montreal (n = 244)		Sydney (n = 294)		Amsterdam (n = 48)		Melbourne (n = 119)	
	No. (%)	IR	No. (%)	IR	No. (%)	IR	No. (%)	IR	No. (%)	IR	No. (%)	IR
>2 y	0 (0)	…	293 (73)	24.8 (19.9–31.0)	210 (86)	21.9 (17.1–28.0)	236 (80)	21.9 (17.1–28.0)	31 (65)	9.7 (4.1–23.4)	104 (87)	7.2 (4.2–12.4)
Drug injected most often												
Heroin	0 (0)	…	214 (54)	27.4 (21.2–35.6)	68 (28)	12.4 (7.0–21.8)	203 (69)	**25.3 (18.7–34.1)**	18 (38)	17.9 (7.5–43.1)	76 (64)	8.3 (4.6–15.0)
Amphetamine/ methamphetamine	0 (0)	…	126 (32)	17.5 (11.8–25.9)	1 (1)	…	70 (24)	**7.8 (3.4–17.3)**	5 (10)	…	19 (16)	10.4 (3.4–32.0)
Cocaine	0 (0)	…	9 (2)	16.4 (4.1–65.5)	121 (49)	**19.3 (13.5–27.6)**	6 (2)	56.9 (31.5–102.8)	5 (10)	12.0 (1.7–85.5)	1 (1)	…
Other opiates	0 (0)	…	3 (1)	32.7 (4.6–232.1)	50 (21)	**51.3 (34.4–76.6)**	14 (5)	6.6 (0.9–46.8)	0 (0)	…	20 (17)	5.5 (1.4–22.0)
Heroin + cocaine (combined)	0 (0)	…	28 (7)	35.3 (19.6–63.8)	5 (2)	…	0 (0)	…	17 (35)	16.1 (6.1–43.0)	0 (0)	…
Unknown[a]	288 (100)	…	18 (4)	…	6 (2)	38.7 (21.4–69.8)	1 (<1)	12.6 (7.4–21.2)	3 (6)	…	3 (2)	…
Recent receptive syringe sharing												
No	0 (0)	…	231 (58)	**18.4 (14.0–24.3)**	166 (68)	22.5 (17.1–29.5)	226 (77)	22.5 (17.1–29.5)	28 (58)	9.3 (3.9–22.4)	97 (82)	6.3 (2.5–11.4)
Yes	0 (0)	…	147 (37)	**34.6 (26.1–45.8)**	76 (31)	26.0 (17.6–38.5)	68 (23)	26.0 (17.6–38.5)	7 (15)	39.0 (16.2–93.7)	22 (18)	13.7 (5.7–33.0)
Unknown[a]	288 (100)	…	20 (5)	71.6 (29.8–171.9)	2 (1)	…	0 (0)	…	13 (27)	…	0 (0)	…
Recent equipment sharing												
No	0 (0)	…	67 (17)	**15.8 (9.2–22.0)**	139 (57)	22.5 (16.7–30.4)	233 (79)	22.5 (16.7–30.4)	0 (0)	…	47 (40)	4.8 (2.0–11.5)
Yes	0 (0)	…	257 (65)	**28.1 (22.6–34.9)**	103 (42)	24.9 (17.8–34.8)	61 (21)	24.9 (17.8–34.8)	0 (0)	…	1 (1)	…
Unknown[a]	288 (100)	…	74 (19)	19.6 (10.6–36.5)	2 (1)	…	0 (0)	…	48 (100)	13.1 (7.0–24.3)	71 (60)	11.2 (6.2–20.3)
Recent opioid agonist therapy, including methadone and buprenorphine												
No	0 (0)	…	342 (86)	24.2 (18.7–31.3)	168 (69)	26.4 (20.7–33.7)	157 (53)	26.4 (20.7–33.7)	23 (48)	19.9 (9.5–41.6)	44 (37)	8.4 (4.5–15.6)
Yes	0 (0)	…	50 (13)	11.8 (3.8–36.6)	75 (31)	15.3 (8.9–26.3)	137 (46)	15.3 (8.9–26.3)	25 (52)	7.3 (2.3–22.6)	75 (63)	5.4 (2.2–12.9)
Unknown[a]	288 (100)	…	6 (2)	…	1 (1)	…	0 (0)	…	0 (0)	…	0 (0)	…
Recently obtained any needles/syringes from safe source[b]												
No	0 (0)	…	47 (12)	**6.9 (2.3–18.4)**	21 (8)	8.6 (2.8–26.8)	14 (5)	…	0 (0)	…	3 (3)	…
Yes	0 (0)	…	350 (88)	**27.7 (22.8–33.6)**	223 (92)	25.3 (20.1–31.7)	115 (39)	10.8 (6.5–18.0)	44 (92)	13.0 (6.8–25.0)	53 (45)	4.5 (1.9–10.9)
Unknown[a]	287 (100)	…	1 (<1)	…	0 (0)	…	165 (56)	24.9 (19.1–32.5)	4 (8)	13.7 (1.9–97.4)	63 (53)	11.3 (6.3–20.5)

Incidence rates are shown as IR per 100 person-years (95% confidence interval), calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter. Boldface values indicate significant difference at *P* < .05.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; IR, incidence rate; PY, person-years.

[a] Data not collected by cohort or not reported by participant; the Baltimore cohort recruits and monitors young people who inject drugs for HCV infection, with a focus on serological data to assess the clinical characteristics of acute infection and reinfection. Because research goals focus on understanding questions related to immunology and virology, behavioral data were not systematically collected between 2000 and 2012. The Baltimore data server was compromised in 2005, leading to the loss of data on age and sex for some participants. Investigators preformed genome-wide association studies to obtain sex for participants who acquired HCV infection, but because age is not a genetic trait, age information was not recovered.

[b] Safe source defined as needle syringe program, needle exchange program, chemist/pharmacist, vending machine, mobile outreach.
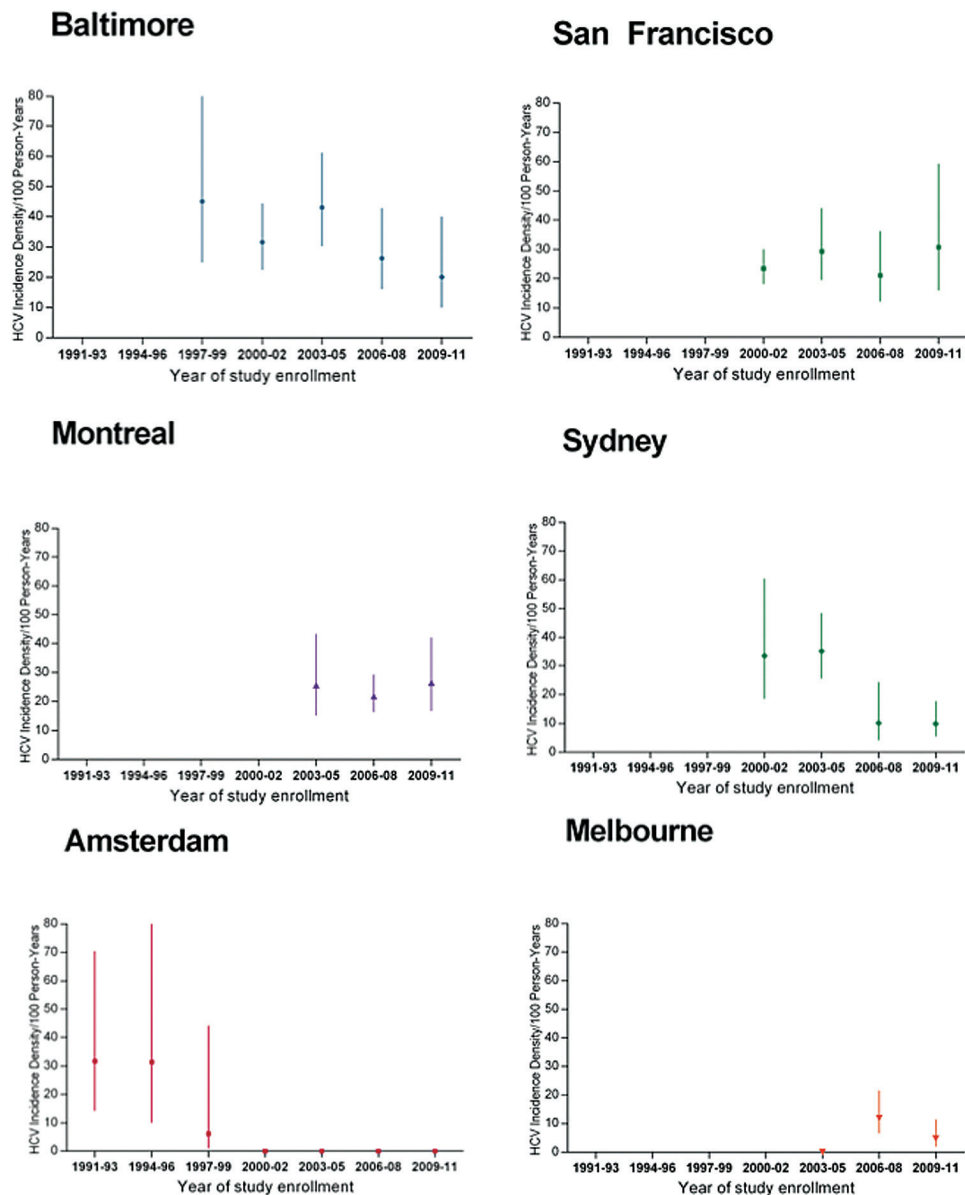
Figure 2. Trends in hepatitis C virus (HCV) incidence density (per 100 person-years) across calendar period, by city. Vertical lines represent 95% confidence intervals. Abbreviation: HCV, hepatitis C virus.

for HCV infection decreased an average of 18% per 3 years from a high of 31.3/100 PYO in 1994–1997, independent of city, OAT, RSS, age, and biological sex. While overall HCV incidence was high, we identified differences in infection trends across continents and cities. High infection rates persisted in the North American cities of Baltimore, San Francisco, and Montreal. In contrast, incidence was lower in Australian cities (Sydney and Melbourne), with Sydney showing a significant reduction in the HCV incidence over time. The most significant change was observed in Amsterdam, where a sharp decline in HCV incidence was experienced early in the epidemic (1985–1996).

The lower HCV incidence in Amsterdam and Melbourne, and the downward trend in Sydney, likely reflect an early and sustained implementation of harm reduction services. The

Netherlands and Australia were global leaders in scaling up harm reduction programs to include NSP services. NSP services first became available in the Netherlands in 1981; they were expanded by the Dutch government in 1984 to include the provision of sterile injecting equipment, healthcare, and health information and were available at pharmacies and community centers and through outreach [17, 18]. Similarly, Australia established free and legal government-funded NSP programs in the late 1980s. By 1991, 6.3 million syringes were being distributed annually to an estimated 62 000 regular injectors across Australia [19]. Our data show a high (≥80%) level of NSP program access across cities. Given the equivalent NSP access levels across cities, observed differences in HCV trends likely reflect city-specific receptive RSS behaviors. HCV incidence
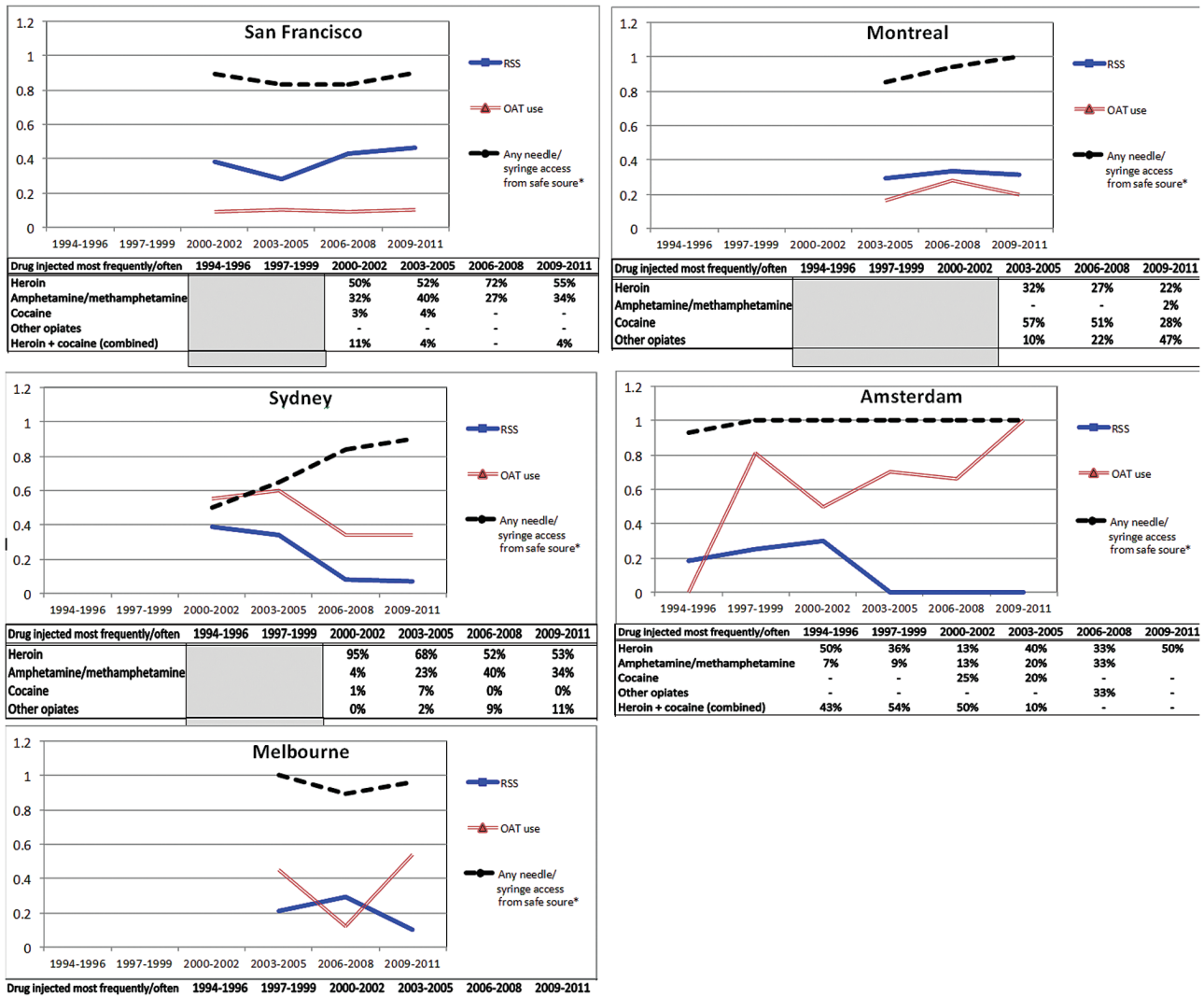
Figure 3. Trends in proportions of self-reported exposures across calendar period, by city. Measurement of selected exposure behaviors collected at enrollment. Proportions were calculated for 1985–1990 and 3-year intervals from 1991 to 2011. Note that the Baltimore (Maryland) cohort does not collect survey data. Abbreviations: OAT, opioid agonist therapy; RSS, receptive syringe sharing.

San Francisco

Drug injected most frequently/often	1994-1996	1997-1999	2000-2002	2003-2005	2006-2008	2009-2011
Heroin			50%	52%	72%	55%
Amphetamine/methamphetamine			32%	40%	27%	34%
Cocaine			3%	4%	-	-
Other opiates			-	-	-	-
Heroin + cocaine (combined)			11%	4%	-	4%

Montreal

Drug injected most frequently/often	1994-1996	1997-1999	2000-2002	2003-2005	2006-2008	2009-2011
Heroin				32%	27%	22%
Amphetamine/methamphetamine				-	-	2%
Cocaine				57%	51%	28%
Other opiates				10%	22%	47%

Sydney

Drug injected most frequently/often	1994-1996	1997-1999	2000-2002	2003-2005	2006-2008	2009-2011
Heroin			95%	68%	52%	53%
Amphetamine/methamphetamine			4%	23%	40%	34%
Cocaine			1%	7%	0%	0%
Other opiates			0%	2%	9%	11%

Amsterdam

Drug injected most frequently/often	1994-1996	1997-1999	2000-2002	2003-2005	2006-2008	2009-2011
Heroin	50%	36%	13%	40%	33%	50%
Amphetamine/methamphetamine	7%	9%	13%	20%	33%	
Cocaine	-	-	25%	20%	-	-
Other opiates	-	-	-	-	33%	-
Heroin + cocaine (combined)	43%	54%	50%	10%	-	-

Melbourne

Drug injected most frequently/often	1994-1996	1997-1999	2000-2002	2003-2005	2006-2008	2009-2011

was highest within the North American cities of Baltimore, San Francisco, and Montreal, where the prevalence of RSS was consistently >40%. In contrast, the epidemic remained relatively stable in cities like Melbourne, where RSS levels were substantially lower. Our findings expand on the results of other studies showing the relationship between high RSS on increased HCV incidence [20–23]. Similar to previous individual human immunodeficiency virus (HIV) and HCV incidence studies among PWID, we found a relationship between NSP access and HCV infection [22–27], which is understandable considering that persons seeking NSP services are more likely to experience homelessness and inject drugs more frequently than those not accessing NSP services.

Overall, HCV incidence rates were lower in Sydney, Melbourne, and Amsterdam where OAT uptake was higher than in San Francisco. This finding is consistent with recent evidence from the United States, Canada, and Australia demonstrating the strong protective effect of OAT against HCV infection [13, 28, 29]. Important differences in OAT policies and subsequent OAT availability exist across cities. Compared to the long waiting periods for entry and high-threshold restrictions associated with OAT service access in the United States, Australia and the Netherlands have lower thresholds for participation and higher coverage rates [30, 31]. Our results are consistent with other, usually single-site, studies showing the synergistic effect of both NSP and OAT on reducing HCV infection among PWID [32], an approach that, if sustained with high coverage, has the potential to also reduce HCV prevalence [33, 34]. Studies show that full participation in methadone maintenance therapy (a form of OAT) combined with obtaining 100% coverage of syringes from sterile distribution sources reduces HCV infection risk by 80% compared with no participation [7, 31].

Table 3. Association Between Recent Receptive Syringe Sharing, Opioid Agonist Therapy, and Enrollment Year After Adjusting for Biological Sex, Age, and City (n = 1137)

Variable	Adjusted HR (95% CI)
City	
Amsterdam	…
Sydney	…
Montreal	…
San Francisco	…
Baltimore	…
Biological sex	
Female	1.15 (.88–1.50)
Unknown	…
Age at enrollment (per 1-y increase)	0.98 (.96–1.00)
Recent receptive syringe sharing	
Yes	**1.53 (1.19–1.97)**
Unknown	1.17 (.43–3.23)
Recent OAT, including methadone and buprenorphine	
Yes	**0.50 (.36–.70)**
Unknown	**2.18 (1.40–3.42)**
Enrollment year (per 3-y increase)	**0.72 (.62–.83)**

Boldface text indicates $P \le .05$. Stratified Cox models satisfied proportional hazards assumptions. Model stratified by city to allow a unique baseline hazard by city.

Abbreviations: CI, confidence interval; HR, hazard ratio; OAT, opioid agonist therapy.

In Montreal, HCV incidence rates remained high (approximately 20/100 PYO) even though NSP, OAT, and RSS levels were comparable to the lower-HCV-incidence settings of Sydney and Melbourne. Montreal's high prevalence of cocaine injection suggests limited impact of OAT on HCV incidence in settings where opioids are not the primary drug. When analyses are restricted to Montreal (participants who mainly injected heroin/opiates), HCV incidence was significantly lower among those reporting recent OAT compared with no recent OAT (IRR, 0.4 [95% CI, .2–.8]; data not shown). Given that opioids are not the only drug injected, expanded prevention strategies to meet the needs of non–opioid users are needed. For example, cocaine injectors have larger injecting networks, inject more frequently, and engage in riskier injecting practices than do opioid injectors [35, 36], and therefore, require increased coverage of sterile injecting equipment. Last, given the efficacy of OAT in reducing HCV incidence by decreasing injection frequency [13, 28, 32], a need remains for efficacious pharmacotherapies for cocaine and methamphetamine dependence.

Our study is distinguished from previous work by its international scope and its use of participant-level data collected from well-characterized cohorts of PWID. However, several limitations exist. First, heterogeneity in cohort protocols for behavioral data collection resulted in an inability to assess time-varying predictors of HCV infection. Although this lack of harmonization is challenging, we were able to map behavioral trends over time by using baseline data on key exposure measures. Differing cohort start dates limited our ability to compare cities prior to

1990. Last, the lack of city-level measures for overall and individual harm reduction intervention coverage limited our ability to assess participant-level differences while controlling for city-level variability. Subsequent studies leveraging city-level measures of harm reduction and health service access on city-level HCV infection rates are vital to better understanding how structural-level factors, such as changes in access to sterile injecting equipment, interact with individual-level factors to drive HCV epidemics.

CONCLUSIONS

Contextual differences in the timing and level of harm reduction programs reflect observed city heterogeneity in behavioral patterns and HCV incidence trends. A sustained commitment to fund evidence-based harm reduction programs is necessary to maintain low incidence in Amsterdam, Sydney, and Melbourne; in contrast, in San Francisco, Baltimore, and Montreal, where HCV incidence remains high, an aggressive public health approach is urgently needed. In December 2015, the US Congress approved the Consolidated Appropriations Act 2016, which allows the use of government funds for NSP services [37]. For this decision to result in a tangible impact, an expanded budget dedicated to NSP services is imperative. NSP programs provide a window of opportunity to engage with populations who are often underserved by traditional healthcare services. Capitalizing on the high (>80%) level of NSP engagement among PWID across cities, scaling up resources for NSP services can offer long-term impact. For example, new HCV direct-acting antiviral (DAA) therapies offer a highly effective tool for controlling the HCV epidemic [38]. Expanding current NSP services to inform and introduce DAA treatment both for cure and as prevention has the potential to drive down incidence [39] while also improving health by resolving infection [40].

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