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Research paper

Hepatitis C virus (HCV) disease progression in people who inject drugs (PWID): A systematic review and meta-analysis

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ABSTRACT

Background: Understanding HCV disease progression rates among people who inject drugs (PWID) is important to setting policy to expand access to detection, diagnosis and treatment, and in forecasting the burden of disease. In this paper we synthesize existing data on the natural history of HCV among PWID, including fibrosis progression rates (FPR) and the incidence of compensated cirrhosis (CC), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC).

Methods: We conducted electronic and manual searches for published and unpublished literature. Reports were eligible if they (i) included participants who were chronically infected with HCV and reported current or previous injection drug use; (ii) presented original data on disease progression in a study sample comprised of at least 90% PWID; (iii) published between January 1, 1990, and December 31, 2013; and (iv) included data from upper-middle- or high-income countries. Quality ratings were assigned using an adaptation of the Quality In Prognosis Studies (QUIPS) tool. We estimated pooled FPRs using the stage-constant and stage-specific methods, and pooled incidence rates of CC, DC, and HCC.

Results: Twenty-one reports met the study inclusion criteria. Based on random-effect models, the pooled stage-constant FPR was 0.117 METAVIR units per year (95% CI, 0.099–0.135), and the stage-specific FPRs were F0 → F1, 0.128 (95% CI 0.080, 0.176); F1 → F2, 0.059 (95% CI 0.035, 0.082); F2 → F3, 0.078 (95% CI 0.056, 0.100); and F3 → F4, 0.116 (95% CI 0.070, 0.161). The pooled incidence rates of CC, DC, and HCC were 6.6 (95% CI 4.8, 8.4), 1.1 (95% CI 0.8, 1.4), and 0.3 (95% CI −0.1, 0.6) events per 1000 person-years, respectively. Following the stage-constant estimate, average time to cirrhosis is 34 years post-infection, and time to METAVIR stage F3 is 26 years; using the stage-specific estimates, time to cirrhosis is 46 years and time to F3 is 38 years.

Conclusion: Left untreated, PWID with chronic HCV infection will develop liver sequelae (including HCC) in mid- to late-adulthood. Delaying treatment with the new drug regimens until advanced fibrosis develops prolongs the period of infectiousness to perhaps thirty years. Scaling up of effective HCV prevention and early engagement in care and treatment will facilitate the elimination HCV as a source of serious disease in PWID.

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Introduction

Hepatitis C virus (HCV) infection is a chronic blood-borne viral infection that is of global importance (Averhoff, Glass, & Holtzman, 2012; Nelson et al., 2011). Approximately 160 million people, or 2–3% of the world's population, have chronic HCV; chronic HCV accounts for one-quarter of cases of cirrhosis and hepatocellular carcinoma (HCC) (Averhoff et al., 2012; Lavanchy, 2011; Nelson et al., 2011; World Health Organization, 2014). The vast majority of incident and prevalent HCV infections in the world are related to unsafe medical and illicit drug injections (Colvin & Mitchell, 2010). In most high-income countries, the primary route of HCV transmission is due to drug injection. HCV is concentrated in people who inject drugs (PWID) in these countries (Aceijas & Rhodes, 2007; Nelson et al., 2011), and approximately 50–80% of PWID are chronically infected (Nelson et al., 2011; Wiessing et al., 2014).

Viral and host factors hinder the detection, diagnosis and treatment of HCV in PWID (Hagan, 2011). Acute infection is typically asymptomatic and chronically infected individuals may not develop significant sequelae for decades after initial infection

(Grebely et al., 2012). If left untreated, chronic liver disease will occur in 60–70%, cirrhosis in 5–20%, and 1–5% will die from decompensated cirrhosis or HCC (Rein et al., 2011). It has been estimated that fewer than 5% of PWID have received treatment for chronic HCV (Adeyemi et al., 2004; Grebely et al., 2009).

New HCV treatments feature shorter drug regimens with manageable side effects, and are highly likely to result in cure (Kohli, Shaffer, Sherman, & Kottilil, 2014). However these options are expensive and treatment eligibility guidelines may explicitly exclude active drug users (Fralick, 2014; Harris & Rhodes, 2013; Robaeys et al., 2013; World Health Organization, 2014). Many US states' public insurance programs (e.g., Medicaid) have restricted coverage of these new treatments to those with more advanced disease, i.e., METAVIR fibrosis stages 3 or 4, which may delay treatment for years; this restriction will disproportionately affect PWID and other low-income patients (Viohl & Associates, 2014). These restrictions also are in conflict with new HCV treatment guidelines from the American Association for the Study of Liver Disease (2015), which state explicitly that active injection drug users should be prioritized for treatment in part because of the risk of transmission to susceptible injection partners.

Understanding HCV disease progression rates among PWID is important to setting policy to expand access to detection, diagnosis and treatment, and in forecasting the burden of disease. In this paper we synthesize existing data on the natural history of HCV among PWID, including fibrosis progression rates and the incidence of compensated cirrhosis (CC), decompensated cirrhosis (DC), and HCC. Prior systematic reviews of HCV disease progression in PWID did not explicitly exclude studies of HIV-HCV co-infected patients. Because the majority of PWID with HCV are mono-infected, it is important to characterize this group separately. Estimates from the analysis will be used to inform simulations of the impact and cost-effectiveness of HCV management among PWID. This systematic review and meta-analysis and related simulations are conducted as part of the HCV Synthesis Project (see Hagan et al., 2014; Jordan, Des Jarlais, & Hagan, 2014), which is funded to develop guidance and recommendations for HCV control strategies for the US.

Methods

Search strategy

A combination of manual and electronic searches for published literature, including scientific conference websites and abstract books, were conducted within the databases of Ovid, Proquest, PubMed, and Web of Science. Variations of the search string consisted of keywords such as "HCV," "hepatitis C," "PWID," "injection drug use," "intravenous drug use," "natural history," "disease progression," "survival," "fibrosis," "cirrhosis," "hepato-cellular carcinoma," and "end stage liver disease." The search filters applied included publication date, peer-reviewed journal, and human studies. Manual searches of the reference lists of eligible reports, pertinent reviews, and methodological papers also were conducted for additional literature. The conduct and reporting of this project was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009); the protocol was registered with PROSPERO (CRD42014008805).

Inclusion and exclusion criteria

Reports were eligible for inclusion if they met the following criteria: (i) included participants who were chronically infected with HCV and reported current or previous injection drug use (hereafter referred to as PWID); (ii) presented original data on disease progression in a study sample comprised of at least 90% PWID; (iii) published between January 1, 1990, and December 31, 2013; and (iv) included data from upper-middle- or high-income countries. (The restriction in (iv) was placed under the assumption that disease progression may be influenced by country-level factors including access to health services, which vary in relation to national income (Peters et al., 2008).) Reports were excluded if more than 50% of participants were co-infected with HIV or HBV, or were receiving or previously had received HCV treatment or liver transplantation. (Four reports included HIV+ PWID (range 2.2%, 33.4%).)

Exposure measure

The exposure of interest was chronic HCV infection, defined as HCV RNA positivity or based on a statement in the report that all participants were chronically infected (Chen & Morgan, 2006; Hoofnagle, 2002).

Outcome measures

Outcomes included the fibrosis progression rate (FPR) and the incidence and prevalence of CC, DC, and HCC. The *preferred criterion* for measuring fibrosis and cirrhosis was a liver biopsy in which the sample was staged according to the METAVIR, Ishak, Knodell, or Scheuer scoring systems. In addition to staging based on liver biopsy, diagnostic evidence from clinical examination (e.g., coagulation tests) or ultrasonographic evaluation served as *alternative criteria* for measuring CC. In the included reports, DC was determined based on the clinical presentation of symptoms, e.g., esophageal varices, ascites, hepatic encephalopathy, jaundice, and esophageal varices. (Reports did not always specify whether or not variceal bleeding was used to diagnosis DC). CC was detected through computed tomography, ultrasonography, liver biopsy, or, in one study, alpha-fetoprotein testing and radiography. We excluded reports in which noninvasive procedures were used to stage fibrosis (e.g., FibroSURE and FibroScan). A limitation of noninvasive methods is their difficulty to differentiate between intermediate METAVIR stages, which generates discordance with liver biopsy in staging results (de Lucca Schiavon, Narciso-Schiavon, & de Carvalho-Filho, 2014; Fallatah, 2014). The exclusion of data acquired from noninvasive procedures minimized bias due to measurement error.

Screening and data collection

Two research assistants (RAs) independently screened abstracts and extracted data. In the event that consensus between the RAs was not reached on the eligibility of a report, the project director and principal investigator were consulted for a final decision. From all included reports we collected data on the following domains: citation information; study cohort, period, and location; study design; sampling, recruitment, testing, and statistical methodology; incidence or prevalence of fibrosis, CC, DC, and HCC; rates of fibrosis progression; disease duration; and participant character-istics, particularly factors understood to be associated with accelerated liver disease progression (e.g., age, sex, alcohol consumption). In the case of missing or inconsistent data in a report, the corresponding author was contacted for additional information or clarification. Of seven authors contacted, two fulfilled our data request (29%).

Report quality

All reports included in the systematic review were assigned quality ratings using an adapted version of the Quality In Prognosis

Studies (QUIPS) tool for the assessment of bias in studies of prognostic factors (Hayden, Côté, & Bombardier, 2006; Hayden, van der Windt, Cartwright, Côté, & Bombardier, 2013). (The complete adapted instrument is available by request.) Each report was given an overall rating (and an associated numeric grade) of *high* (2), *moderate* (1), or *low* (0), which summarized the degree to which the design and analysis of the study controlled selection bias, misclassification, and confounding.

Data analysis

Time to event

For every report, time to event was recorded in person-years (PYs). In cases where total PYs were not provided, aggregate PYs were approximated by cumulative disease duration or time between biopsies, which were estimated by the product of the sample size and the sample mean of the duration of infection or interval separating paired biopsies.

Fibrosis progression

We estimated the progression of fibrosis using two methods: (i) the stage-constant method, wherein the rate of progression is assumed to be linear, and therefore constant, across person-time, and (ii) the stage-specific method, in which fibrosis progression is presumed to be nonlinear and thus advances unevenly over person-time. All fibrosis staging data were standardized by converting the original fibrosis scores graded by the Ishak, Knodell, or Scheuer system to METAVIR units (F0–F4) (Thein, Yi, Dore, & Krahn, 2008).

Linear estimation

An annual stage-constant FPR, which refers to a uniform rate of progression from METAVIR stage F0 → F1, was estimated for any report that did not directly report it but provided relevant data for its computation. The FPR was approximated using one of three methods depending on the amount of data included in the report. In general, a modified version of the indirect or direct method for estimating a stage-constant FPR, appropriate for single-biopsy or serial-biopsy data (Thein et al., 2008; Yi, Wang, & Krahn, 2004), respectively, was applied when the report provided the distribution of fibrosis stages.

1. *Standard direct method:* The FPR was the average of each participant's progression rate, which was calculated by dividing the difference in a participant's METAVIR scores between two biopsies by the time interval separating the biopsies.
2. *Modified direct method:* The estimated FPR was the quotient of the difference in cumulative METAVIR units between paired biopsies divided by the time elapsed between the biopsies.
3. *Modified indirect method:* The FPR was derived from the ratio of cumulative METAVIR units to total disease duration of the participants biopsied.

Nonlinear estimation

We also estimated annual stage-specific FPRs, which describe fibrosis progression as a function of METAVIR staging—that is, the rate at which an individual transitions from one given METAVIR stage to the next. For each report that provided the fibrosis staging distribution and person-time of the sample, four METAVIR-stage-specific transition rates were estimated: F0 → F1, F1 → F2, F2 → F3, and F3 → F4. The stage-specific FPRs were generated using the Markov maximum likelihood (MML) estimation method (Bochud et al., 2009; Sweeting et al., 2006; Thein et al., 2008; Yi et al., 2004).

Incidence of hepatic sequelae

Separate incidence rates of CC, DC, and HCC were estimated as the ratio of the event count for an outcome to the cumulative PYs of the subgroup under examination. When necessary, total PYs were estimated as described in the preceding section. All estimates of incidence were expressed as events per 1000 PYs.

Meta-analysis

Pooled estimates were generated from both fixed-effect and random-effects meta-analysis models. Heterogeneity was assessed using both Cochran's Q and I^2 (Higgins, Thompson, Deeks, & Altman, 2003) measures. Random-effects meta-regression of fibrosis progression and incidence of CC were performed. Statistical analysis was conducted using Stata 13.1 (StataCorp, 2013) and SAS 9.3 (SAS Institute Inc., 2012).

Results

Overview of included reports

As presented in Fig. 1, 21 unique reports were included in this review. Tables 1 and 2 present the pooled estimates and characteristics of the included reports for each of the four main outcomes of interest: FPR (10 reports), CC (15 reports), DC (4 reports), and HCC (5 reports). The geographic scope of the data focused largely on Europe where 11 reports (52%) originated; a smaller percentage represented data from the United States (5; 24%) and Australia (5; 24%). A total of 8502 unique PWID contributing 145,228.6 person-years (PYs) of observation for the study of four major HCV-related outcomes were included in this review. Among the 8495 PWID for which data on duration of infection was available, the estimated mean disease duration was 15.0 years (median 14.1; range 5.6, 26.0; 20 reports); in 7177 PWID, the estimated age of infection was 20.8 years (median 21.1; range 15.8, 23.0; 17 reports).

Across the included reports, very few participant characteristics were consistently measured and presented. Sex and age were described most frequently; 19 reports (90%) summarized the sex distribution, and 14 reports (67%) provided a mean or median estimate of age at enrollment. Despite its critical role in the progression of liver disease, alcohol consumption among participants was given in only 13 reports (62%), measurement of alcohol use varied widely, and few reports specifically assessed problem or excess drinking.

Pooled estimates

In Tables 1–5, both fixed-effect and random-effects meta-analysis results are presented. We discuss below only the random-effects estimates.

Fibrosis progression rate

A total of 2607 participants representing 41,119 PYs and 3775 cumulative METAVIR units contributed to the study of FPR in 10 reports. Among 2361 PWID in 9 of the remaining 10 reports, the estimated mean duration of infection was 15.2 years (median 14.6; range 5.6, 26.0) and the estimated mean age of infection was 20.7 years (median 21.0; range 15.8, 23.0).

Linear estimation

In the 10 reports, the pooled stage-constant estimate of fibrosis progression (F0 → F4), described in Table 1, was 0.117 units per year (range 0.070, 0.232). Using this estimate, time to CC was 34 years for an individual with chronic HCV.
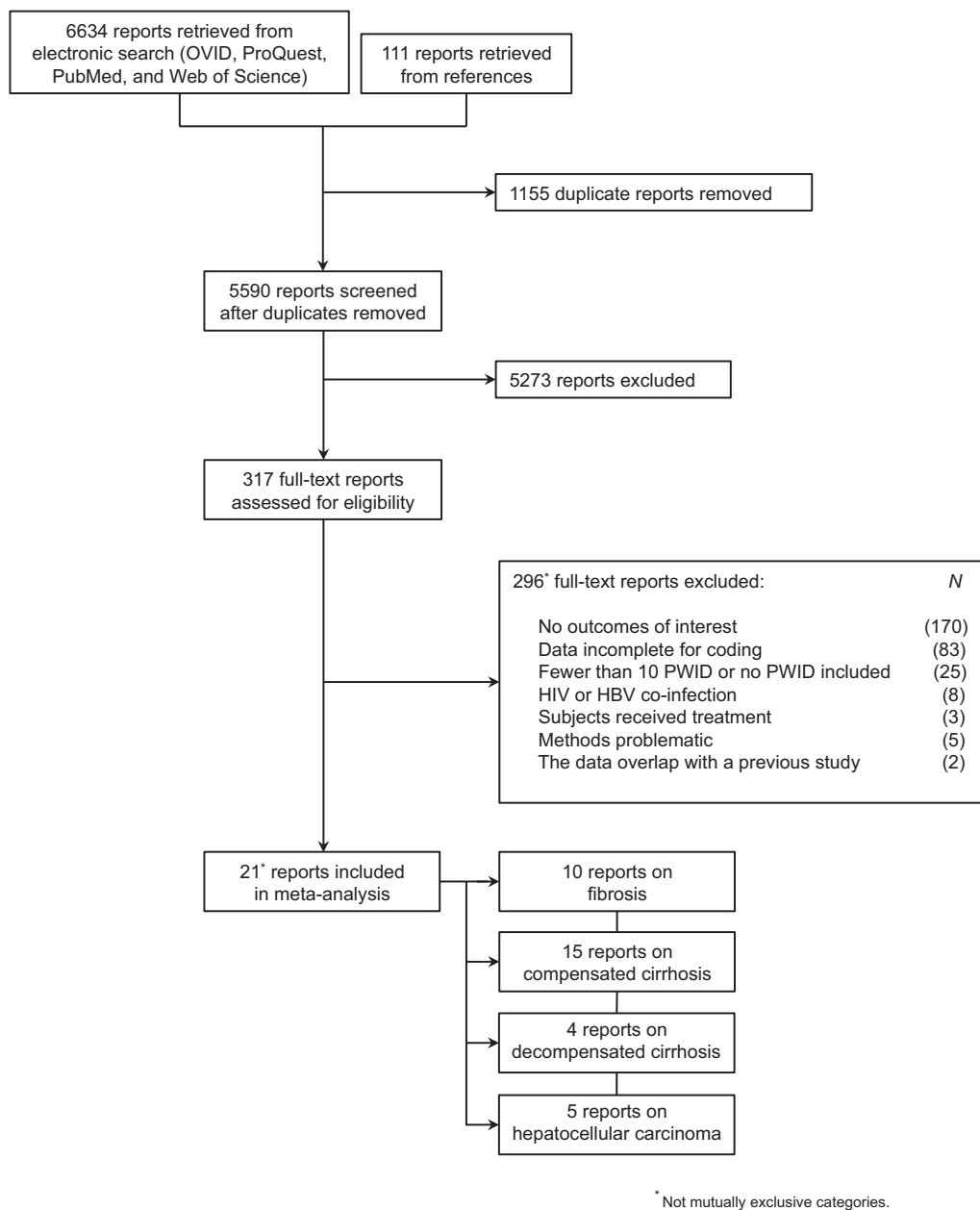
Fig. 1. PRISMA flow diagram of literature search and eligibility assessment.

Nonlinear estimation

MML estimation was performed for 6 of the 10 reports containing sufficient data on the fibrosis staging distribution and person-time of the sample. Table 3 presents the pooled stage-specific transition rates among this subset; the FPRs were the following: F0 → F1, 0.128 (CI 0.080, 0.176); F1 → F2, 0.059 (CI 0.035, 0.082); F2 → F3, 0.078 (CI 0.056, 0.100); and F3 → F4, 0.116 (CI 0.070, 0.161). Based on this progression sequence, time to CC was 46 years.

Cirrhosis

In aggregate, 4340 participants contributing 66,256 PYs were examined in the 15 reports characterizing CC. Among these participants the estimated mean disease duration was 15.4 years (median 14.6; range 7.8, 26.0); from 12 reports examining 3022 PWID, the estimated mean age of infection was 20.5 years (median 21.0; range 15.8, 22.0). The pooled incidence rate was 6.6 events per 1000 PYs (95% CI 4.8, 8.4).

Decompensated cirrhosis

Within the four reports investigating DC, there were 2003 participants who provided 41,311 PYs of observation. The estimated mean duration of infection was 18.3 years (median 17.7; range 12.0, 26.0; 4 reports), and the estimated mean age of infection was 19.9 years (median 20.9; range 15.8, 22.0; 4 reports). The pooled incidence was 1.1 events per 1000 PYs (95% CI 0.8, 1.4).

Hepatocellular carcinoma

HCC was examined in five reports representing 80,096 PYs and 4506 participants. In these reports, the estimated mean disease duration was 16.9 years (median 18.0; range 12.0, 19.0); from the four reports that assessed 4432 PWID, the estimated mean age of infection was 20.4 years (median 20.3; range 19.0, 22.0). Most of these reports presented data from cohorts prior to 2001. The pooled incidence rate was 0.3 events per 1000 PYs (95% CI −0.1, 0.6).

Table 1
Reports investigating the incidence, prevalence, or progression of fibrosis.

References (pub. yr)	Study characteristics					Quality rating	N	Cumulative METAVIR units	Total person-years	Progression rate (METAVIR units/year)	
	Study period	Location	Time-to-event origin	Recruitment method	Recruitment site					Reported mean	Calculated mean
Single-biopsy method											
Benhamou et al. (1999)	1995–1998	France	Date of first injection	Other systematic	Hospital (liver unit)	2	122	198	1647	0.135	–
Hallinan et al. (2007)	2002–2005	Australia	Date of first injection or last Ab-	Consecutive sampling	Drug treatment center	2	22	62	440	–	0.141
Harder et al. (2004)	1997–1998	Germany	Estimated date of infection not reported	Consecutive sampling	Drug treatment center	0	47	48	263	–	0.182
Kielland et al. (2014)	1970–2008	Norway	Date of two years post-first injection	Consecutive sampling	Drug treatment center	2	61	83	1079	0.097	
Larsen et al. (2010)	2001–2007	France	Date of first injection or last Ab-	Consecutive sampling	Hospital (liver unit)	2	1725	2988	31,050	–	0.096
Ostapowicz et al. (1999)	No dates given	Australia	Date of first injection	Unspecified	Hospital (liver unit)	2	130	205	1898	–	0.108
Romeo et al. (2000)	1991–1992	Italy	Estimated date of infection not reported	Consecutive sampling	Hospital (liver unit)	0	71	85	556	–	0.153
Wali et al. (1999)	1989–1997	United Kingdom	Date of first injection	Consecutive sampling	Hospital (liver unit)	2	64	64	896	0.070	–
Serial-biopsy method											
Wilson et al. (2006)	1996–2003	United States	Date of first biospy	Convenience sampling	Community-based organization	2	119	40	500	–	0.080
Yeh et al. (2005)	1972–1975	United States	Date of first biospy	Unspecified	Hospital (multiple units)	0	7	2	14	–	0.232

Pooled fixed-effect stage-constant FPR (10 studies): 0.101 METAVIR units per year (95% CI 0.098, 0.104).
Pooled random-effects stage-constant FPR (10 studies): 0.117 METAVIR units per year (95% CI 0.099, 0.135).
Heterogeneity: $Q = 105.95$, $p = 0.000$; $I^2 = 91.5\%$.

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Table 2
Reports investigating the incidence or prevalence of compensated cirrhosis (CC), decompensated cirrhosis (DC), or hepatocellular carcinoma (HCC).

Outcome	References	Study period	Study location	Study design	Time-to-event origin	Recruitment method	Recruitment site	Quality rating	N Subjects	Events	Total person-years	Incidence rate per 1000 person-years
CC	DiMartino et al. (2001)	1980–1997	France	Cohort	Date of first injection	Other systematic	Hospital (unspecified unit)	1	80	3	816	3.7
	Gordon et al. (1998)	1989–1997	United States	Cohort	Date of first injection	Unspecified	Hospital (unspecified unit)	2	195	40	3705	10.8
	Hallinan et al. (2007)	2002–2005	Australia	Cohort	Date of first injection or last Ab-	Consecutive sampling	Drug treatment center	2	22	7	440	15.9
	Khan et al. (1998)	1982–1994	Australia	Cross-sectional	Date of first injection	Consecutive sampling	Hospital (liver unit)	2	196	18	2352	7.7
	Kielland et al. (2014)	1970–2008	Norway	Cohort	Date of two years post-first injection	Consecutive sampling	Drug treatment center	2	61	7	1079	6.5
	Larsen et al. (2010)	2001–2007	France	Cross-sectional	Date of first injection or last Ab-	Consecutive sampling	Hospital (liver unit)	2	1725	177	31,050	5.7
	McGuinness et al. (1996)	No dates given	Australia	Cross-sectional	Estimated date of infection not reported	Unspecified	Unspecified	0	19	5	267	18.7
	Ostapowicz et al. (1999)	No dates given	Australia	Cross-sectional	Date of first injection	Unspecified	Hospital (liver unit)	2	346	41	5052	8.1
	Pol et al. (1998)	No dates given	France	Cross-sectional	Date of first injection	Consecutive sampling	Hospital (unspecified unit)	1	150	23	1770	13.0
	Poynard et al. (2001)	1993–1998	France	Cross-sectional	Date of first injection	Unspecified	Hospital (unspecified unit)	1	355	18	7100	2.5
	Romeo et al. (2000)	1991–1992	Italy	Cross-sectional	Estimated date of infection not reported	Consecutive sampling	Hospital (liver unit)	0	71	2	556	3.6
	Roudot-Thoraval et al. (1997)	1991–1993	France	Cross-sectional	Estimated date of infection not reported	Other systematic	Hospital (unspecified unit)	1	889	52	7112	7.3
	Serfaty et al. (2001)	1995–1996	France	Cross-sectional	Date of first injection	Other systematic	Hospital (multiple units)	2	38	1	532	1.9
	Tong and El-Farra (1996)	1981–1994	United States	Cohort	Date of first injection	Convenience sampling	Hospital (liver unit)	1	74	25	1332	18.8
	Wilson et al. (2006)	1996–2003	United States	Cohort	Date of first injection	Convenience sampling	Community-based organization	2	119	5	3094	1.6

Pooled fixed-effect incidence rate of CC (15 studies): 4.9 events per 1000 person-years (95% CI 4.4, 5.4).
Pooled random-effects incidence rate of CC (15 studies): 6.6 events per 1000 person-years (95% CI 4.8, 8.4).
Heterogeneity: $Q = 98.41$, $p = 0.000$; $I^2 = 85.8\%$.

Outcome	References	Study period	Study location	Study design	Time-to-event origin	Recruitment method	Recruitment site	Quality rating	N Subjects	Events	Total person-years	Incidence rate per 1000 person-years
DC	Khan et al. (2000)	1982–1996	Australia	Cohort	Date of first injection	Consecutive sampling	Hospital (liver unit)	2	198	2	2376	0.8
	McGuinness et al. (1996)	No dates given	Australia	Cross-sectional	Estimated date of infection not reported	Unspecified	Unspecified	1	19	2	267	7.5
	Thomas et al. (2000)	1988–1997	United States	Cohort	Date of first injection	Convenience sampling	Community-based organization	2	1667	40	35,574	1.1
	Wilson et al. (2006)	1996–2003	United States	Cohort	Date of first injection	Convenience sampling	Community-based organization	2	119	3	3094	1.0

Pooled fixed-effect incidence rate of DC (4 studies): 1.1 events per 1000 person-years (95% CI 0.8, 1.4).
Pooled random-effects incidence rate of DC (4 studies): 1.1 events per 1000 person-years (95% CI 0.8, 1.4).
Heterogeneity: $Q = 1.72$, $p = 0.633$; $I^2 = 0.0\%$.

Outcome	References	Study period	Study location	Study design	Time-to-event origin	Recruitment method	Recruitment site	Quality rating	N Subjects	Events	Total person-years	Incidence rate per 1000 person-years
HCC	Gordon et al. (1998)	1989–1997	United States	Cohort	Date of first injection	Unspecified	Hospital (unspecified unit)	2	195	2	3705	0.5
	Khan et al. (2000)	1982–1996	Australia	Cohort	Date of first injection	Consecutive sampling	Hospital (liver unit)	2	198	1	2376	0.4
	Kielland et al. (2014)	1970–2008	Norway	Cohort	Date of two years post-first injection	Consecutive sampling	Drug treatment center	2	61	1	1079	0.9

Table 2 (Continued)

Outcome	References	Study period	Study location	Study design	Time-to-event origin	Recruitment method	Recruitment site	Quality rating	N		Total person-years	Incidence rate per 1000 person-years
									Subjects	Events		
	Larsen et al. (2010)	2001–2007	France	Cross-sectional	Date of first injection or last Ab-	Consecutive sampling	Hospital (liver unit)	2	3978	8	71,604	0.1
	Tong and El-Farra (1996)	1981–1994	United States	Cohort	Date of first injection	Convenience sampling	Hospital (liver unit)	1	74	3	1332	2.3

Pooled fixed-effect incidence rate of HCC (5 studies): 0.1 events per 1000 person-years (95% CI 0.0, 0.2).
Pooled random-effects incidence rate of HCC (5 studies): 0.3 events per 1000 person-years (95% CI -0.1, 0.6).
Heterogeneity: $Q = 5.21$, $p = 0.267$; $I^2 = 23.2\%$.

Table 3
Pooled stage-specific transition rates.

METAVIR stage transition	Fixed-effect model		Random-effects model		Heterogeneity		
	Estimate	95% CI	Estimate	95% CI	Q	p	I^2
F0 → F1	0.113	0.102–0.124	0.128	0.080–0.176	57.11	0.000	91.2
F1 → F2	0.058	0.051–0.065	0.059	0.035–0.082	24.90	0.000	79.9
F2 → F3	0.079	0.064–0.093	0.078	0.056–0.100	5.76	0.331	13.2
F3 → F4	0.120	0.085–0.155	0.116	0.070–0.161	5.48	0.360	8.7

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Table 4
Comparison of pooled random-effects FPRs and time-to-CC by quality rating and recruitment from a liver speciality clinic.

Factor	Stage constant				Stage-specific									
	N reports	F0 → F4		Years to CC	N reports	F0 → F1		F1 → F2		F2 → F3		F3 → F4		Years to CC
		Estimate	95% CI			Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
Quality rating														
Low	3	0.164	0.136–0.191	24	1	0.139	0.067–0.210	0.160	0.032–0.287	0.322	−0.066–0.710	0.070	−0.105–0.246	34
Moderate	0	–	–	–	0	–	–	–	–	–	–	–	–	–
High	7	0.107	0.089–0.126	37	5	0.126	0.073–0.180	0.055	0.032–0.078	0.078	0.060–0.095	0.118	0.057–0.178	44
Recruited exclusively from a liver specialty clinic														
Yes	5	0.112	0.090–0.135	36	4	0.143	0.129–0.157	0.064	0.043–0.086	0.083	0.064–0.103	0.133	0.094–0.172	42
No	5	0.125	0.089–0.162	32	2	0.081	0.011–0.151	0.046	−0.009–0.101	0.052	0.010–0.093	0.065	−0.015–0.144	69

Table 5
Random-effects meta-regression results.

Factor	Stage-constant FPR			Stage-specific FPR												CC incidence rate (per 1000 PYs)		
	F0 → F4			F0 → F1			F1 → F2			F2 → F3			F3 → F4					
	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Age at infection	0.011	0.006	0.111	−0.012	0.024	0.704	0.017	0.028	0.654	−0.038	0.085	0.733	−0.182	0.192	0.517	1.487	1.526	0.362
Duration of infection	−0.003	0.002	0.114	−0.007	0.006	0.437	0.002	0.008	0.808	−0.021	0.020	0.485	−0.055	0.044	0.430	0.213	0.577	0.723
Males (%)	0.128	0.079	0.154	−0.398	0.321	0.432	0.626	0.407	0.367	0.172	1.170	0.907	−3.310	2.356	0.394	−4.003	23.012	0.867
Recruitment location																		
Non-clinical setting	(ref. cat.)			(ref. cat.)			(ref. cat.)			(ref. cat.)			(ref. cat.)			(ref. cat.)		
Clinical setting	−0.022	0.014	0.161	0.059	0.060	0.504	−0.004	0.059	0.959	0.056	0.330	0.894	0.280	0.490	0.670	−2.678	4.901	0.602
Constant	−0.140	0.150	0.386	0.755	0.763	0.503	−0.787	0.894	0.541	1.053	2.438	0.741	7.157	6.077	0.448	−21.622	46.591	0.657
No. of reports	11			6			6			6			6			12		

Quality ratings

Mean quality scores, ranging from 0 (low) to 2 (high), by outcome for the reports on FPR, CC, DC, and HCC were 1.5, 1.3, 1.8, and 1.8, respectively. Using random-effects modeling, we conducted subgroup analysis of the quality ratings for the reports examining fibrosis progression; reports were stratified by quality score and pooled stage-constant estimates were calculated. Referring to Table 4, the results suggest a negative correlation between report quality and fibrosis progression—that is, in higher quality reports, the FPR is slower (low 0.164, n studies = 3; moderate N/A, $n = 0$; high 0.107, $n = 7$). The variance across the pooled estimates translates to a range for time to cirrhosis of 24–37 years.

Of the study design issues accounted for in the quality ratings instrument, we were particularly interested in selection bias, defined for our purposes as the likelihood that observed disease progression was related to the setting or method for recruiting participants. The overall rating for selection bias was 1.4. This mean score corresponds to the lower rating applied to reports that sampled from liver or unidentified units in hospitals, wherein the population is believed to be composed disproportionately of individuals with more severe hepatic conditions.

Table 4 presents additional analysis of report-level data and fibrosis progression. The pooled stage-constant FPR was 0.112 for those reports in which recruitment exclusively occurred in liver clinics ($n = 5$) compared to 0.125 for reports that recruited across multiple clinics or non-clinical settings ($n = 5$); the difference in time to CC was approximately 4 years (36 vs. 32 years). In comparing the chain of stage-specific rates in Table 4, CC occurs at 42 years post-infection among samples exclusively drawn from liver clinics ($n = 4$) and at 69 years for samples recruited in all other settings ($n = 2$).

Heterogeneity

Tests for heterogeneity, detailed in Tables 1–3, revealed significant variability across the reports contributing to four of the eight outcomes. Among the meta-analysis estimates affected by heterogeneity, the Q-statistic was associated with a p-value less than 0.05, and the I^2 values suggested moderate to high inconsistency. However, there was no strong evidence to suggest the influence of heterogeneity in the estimation of four outcomes: the stage-specific progression from F2 → F3 and F3 → F4, and the incidence of DC and HCC. The p-values for all Q-statistics were greater than 0.10, and I^2 values were below 23%.

Meta-regression

We performed a random-effects meta-regression to examine the influence of report and participant characteristics on fibrosis progression and incidence of CC. Both stage-constant and stage-specific rates were used as dependent variables. In a univariate regression, quality rating (coeff. −0.029; 95% CI −0.055, −0.004; $p = 0.026$) was associated with a slower stage-constant FPR. However, there was no evidence of an effect of quality rating on stage-specific fibrosis progression or incidence of CC. (Results are not shown.) The results of a multivariate analysis are presented in Table 5. Across all three outcome variables, there was no evidence to suggest the influence of age at infection, duration of infection, male sex, or recruitment from clinical settings.

Discussion

This systematic review synthesized the available data on the progression of fibrosis and the incidence of severe hepatic sequelae in PWID with chronic HCV infection. Random-effects estimation generated a stage-constant FPR of 0.117 and stage-specific FPRs of 0.128 (F0 → F1), 0.059 (F1 → F2), 0.078 (F2 → F3), and 0.116 (F3 → F4). The stage-constant rate (0.117) is within the range (and near the midpoint) of other stage-constant estimates from samples of HIV-negative patients with HCV infection due to other exposures (range 0.07, 0.151) (Bochud et al., 2009; Bonacini, Groshen, Yu, Govindarajan, & Lindsay, 2001; Mathurin et al., 1998; Mohsen et al., 2003; Rodríguez-Torres et al., 2006; Souza, Tovo, Mattos, & Chaves, 2008).

Likewise, based on a progression rate of 0.117, the estimated time to cirrhosis of 34 years is near the midpoint of the time-to-event range (22, 57) in the other patient groups. Although there is wide variance in the estimates of fibrosis progression and the associated times to event, the stage-constant rate of the present meta-analysis lies near the centers of the distributions.

Similarly, the stage-specific rates we derived—0.128 (F0 → F1), 0.059 (F1 → F2), 0.078 (F2 → F3), and 0.116 (F3 → F4)—are consistent with the rates of Thein et al. (2008), who also examined fibrosis progression among PWID: 0.116 (F0 → F1), 0.085 (F1 → F2), 0.085 (F2 → F3), and 0.130 (F3 → F4). With the exception of the transition from F1 → F2, our estimates deviate slightly from Thein et al.; this is demonstrated in the comparison of between-stage duration and overall time to CC. We estimate the occurrence of compensated cirrhosis at 46 years post-infection, and Thein et al. provide an estimate of 40 years. One explanation for the difference in rates is the moderation effect of HIV co-infection, which was prevalent in higher proportions in the PWID samples of Thein et al.

Limitations

There are several limitations to our study. Our inclusion criteria restricted the size of the dataset and limited generalizability to upper-middle and high-income countries. Also, the study-level estimates for the included reports were calculated using estimators that rely on cohort-level data rather than participant-level data, which was generally unavailable. Furthermore, our linear FPR was based on the assumption of stage-constant disease progression, and recent literature suggests that the course of disease may actually vary across fibrosis stages (Bochud et al., 2009; Sweeting et al., 2006; Thein et al., 2008; Yi et al., 2004), as suggested by the MML estimates we provided. However, because the lack of required data in some of the reports precluded calculation of stage-specific rates for all included literature that examined fibrosis progression, our MML estimation must be viewed with caution.

This analysis is further limited by the shortcomings of the contributing reports. First, reports varied in methodology, particularly the definition of chronic infection, the approximation of date of infection, and recruitment location. The potential inclusion of RNA-negative participants and the use of date of first injection as a time point for infection would underestimate rates of fibrosis progression and incidence of severe liver outcomes. On the other hand, many of the included studies recruited participants from hospitals, especially liver units, and this may overestimate progression to serious sequelae. This concern arises from studies of other conditions showing that patients who are experiencing symptoms (and have more advanced disease) are more likely to be found in specialty clinics (Ness et al., 2009; Wilfley, Pike, Dohm, Striegel-Moore, & Fairburn, 2001).

Additionally, there was not enough information in the reports on factors that are known to influence the rate of progression (e.g., alcohol consumption), and thus we could not examine whether these factors explained variability. Furthermore, some extracted data, particularly those measuring

baseline covariates, introduced the possibility of misclassification, wherein the reported sample characteristics may not accurately represent PWID after losses to follow-up. More consistent characterization and improved reporting of participants with respect to these prognostic factors in future studies will allow for more informative syntheses of disease progression rates.

Policy and research implications

Based on our synthesis of fibrosis progression, PWID on average will reach METAVIR stage F3 26–38 years after HCV infection, and will develop cirrhosis within 34–46 years. As in other populations where carcinogenic viruses are endemic, PWID are infected at an early age and thus may develop HCC in mid- to late-adulthood, leading to losses of individuals in their most productive period of life (Yang & Roberts, 2010). The prognosis following diagnosis with HCC is extremely poor, and the median length of survival is 12–15 months (Yip et al., 2014).

It is clear that there is a need for more literature describing the impact of alcohol consumption and other factors on disease development in PWID, particularly in view of the likelihood that new HCV treatments will not be made available on a public health scale and that other measures to reduce disease development will remain important. Consistent reporting of excess or problem drinking using standard measures, such as the Alcohol Use Disorders Identification Test (AUDIT) (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001), will permit comparing and pooling of data across studies. Our review showed that the number of studies of the natural history of HCV in PWID is relatively small, so standard reporting of drinking and other patient characteristics is particularly important to advancing our understanding of the role of these factors.

Our results also demonstrate that attempts to manage HCV-related costs by delaying treatment with the new regimens until patients develop advanced disease will result in a period of infectiousness that persists for an average of three to four decades. The impact of such restrictions on any proposed HCV eradication efforts will certainly be deleterious, resulting in increased costs to care for ill patients and delaying the achievement of HCV control. A Markov model of treatment with new agents demonstrated that liver disease complications were three times higher post-treatment in patients with cirrhosis compared to those with less advanced disease (Younossi & Henry, 2014).

One of the main goals in synthesizing data on disease progression rates is to inform our (and others') modeling of the impact of various combinations of prevention and treatment interventions on HCV disease burden and its associated costs to society and individual patients, so as to influence policy decisions regarding the allocation of public health resources. Recent evidence shows that combination prevention (opiate substitution treatment and syringe access) may reduce HCV incidence in PWID by 75–80% (Hagan, Pouget, & Des Jarlais, 2011; Turner et al., 2011).

However, just as new HCV treatments may not be implemented at public health scale to control HCV in PWID, the implementation of HCV prevention strategies lags far behind knowledge. Policy decisions regarding HCV treatment for PWID historically have been influenced by the perception that these patients will not adhere to treatment and will become re-infected (again, despite knowledge to the contrary) (de Vos & Kretzschmar, 2014; Harris & Rhodes, 2013). Progress toward elimination of HCV infection as a source of cirrhosis, liver failure and cancer will certainly require directly addressing the persistent stigmatization of drug use and drug users.

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