Clinical Infectious Diseases

MAJOR ARTICLE

Risk Factors for Hepatitis C Virus Reinfection After Sustained Virologic Response in Patients Coinfected With HIV

Jim Young,[1,2] Carmine Rossi,[1] John Gill,[3] Sharon Walmsley,[4,5] Curtis Cooper,[5,6] Joseph Cox,[1] Valerie Martel-Laferriere,[7] Brian Conway,[8] Neora Pick,[9] Marie-Louise Vachon,[10] and Marina B. Klein[1,5]; for the Canadian Co-infection Cohort Investigators

[1]Department of Medicine, Division of Infectious Diseases, McGill University Health Centre, Montreal, Canada; [2]Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland; and [3]Southern Alberta HIV Clinic, Calgary, [4]University Health Network, University of Toronto, [5]CIHR Canadian HIV Trials Network, Vancouver, [6]Department of Medicine, University of Ottawa, [7]Department of Microbiology and Infectious Diseases, Centre de Recherche du Centre Hospitalier de l'Université de Montréal, [8]Vancouver Infectious Diseases Centre, [9]Division of Infectious Diseases, Oak Tree Clinic, BC Women's Hospital, Vancouver, and [10]Division of Infectious Diseases, Laval University, Québec City, Canada

Background. Highly effective hepatitis C virus (HCV) therapies have spurred a scale-up of treatment to populations at greater risk of reinfection after sustained virologic response (SVR). Reinfection may be higher in HIV–HCV coinfection, but prior studies have considered small selected populations. We assessed risk factors for reinfection after SVR in a representative cohort of Canadian coinfected patients in clinical care.

Methods. All patients achieving SVR after HCV treatment were followed with HCV RNA measurements every 6 months in a prospective cohort study. We used Bayesian Cox regression to estimate reinfection rates according to patient reported injection drug use (IDU) and sexual activity among men who have sex with men (MSM).

Results. Of 497 patients treated for HCV, 257 achieved SVR and had at least 1 subsequent RNA measurement. During 589 person-years of follow-up (PYFU) after SVR, 18 (7%) became HCV RNA positive. The adjusted reinfection rate (per 1000 PYFU) in the first year after SVR was highest in those who reported high-frequency IDU (58; 95% credible interval [CrI], 18–134) followed by MSM reporting high-risk sexual activity (26; 95% CrI, 6–66) and low-frequency IDU (22; 95% CrI, 4–68). The rate in low-risk MSM (16; 95% CrI, 4–38) was similar to that in reference patients (10; 95% CrI, 4–20). Reinfection rates did not diminish with time.

Conclusions. HCV reinfection rates varied according to risk. Measures are needed to reduce risk behaviors and increase monitoring in high-risk IDU and MSM if HCV elimination targets are to be realized.

Keywords. HIV; hepatitis C virus; reinfection; sustained virologic response; hepatitis C treatment.

Hepatitis C virus (HCV) coinfection is common among human immunodeficiency virus (HIV)-infected individuals and is associated with higher HCV RNA and more rapid liver disease progression compared with HCV infection alone [1]. HCV treatment is now highly effective in coinfected patients and can lead to marked reductions in liver disease and all-cause mortality [2]. Regardless, HCV treatment uptake in coinfected patients currently remains low as many providers are concerned about ongoing substance use and risk behaviors that could impact adherence and lead to reinfection after successful treatment [3].

In a recent metaanalysis, the rate of HCV reinfection after sustained virologic response (SVR) was higher among HIV-coinfected (32 per 1000 person-years of follow-up [PYFU]; 95% confidence interval [CI], 0–123) than among monoinfected patients (22 per 1000 PYFU; 95% CI, 13–33) [4], raising concerns about the long-term impact of treating HCV in coinfected patients. However, only 4 studies with coinfected patients were included in the analysis and reinfection rates were highly variable, ranging from zero in 2 clinical trials where people who inject drugs (PWID) were excluded [5, 6] to 96 per 1000 PYFU in high-risk men who have sex with men (MSM) [7] and 134 reinfections per 1000 PYFU in prisoners [8]. The variability in reinfection rates may be explained by the disparate clinical populations studied and the few reinfections in each study. Similar variability in reinfection rates has been reported in small studies of PWID with [9] and without HIV coinfection [10]. Therefore, there remains considerable uncertainty as to the true risk of reinfection in coinfected patients following SVR and the relative importance of various risk factors for reinfection.

New direct-acting antivirals (DAAs) for HCV are highly effective but expensive. Reinfections come at a cost to individuals

Received 22 August 2016; editorial decision 18 January 2017; accepted 9 February 2017; published online February 12, 2017.

Correspondence: M. B. Klein, Department of Medicine, Division of Infectious Diseases, McGill University Health Centre, 1001 Decarie Boulevard, D02.4110 Montreal, Quebec H4A 3J1, Canada (marina.klein@mcgill.ca).

Clinical Infectious Diseases® 2017;64(9):1154–62

© The Author 2017. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com.
DOI: 10.1093/cid/cix126

Downloaded from academic.oup.com/cid/article/64/9/1154/2990211 by guest on 24 September 2026

who may not be able to access retreatment in many jurisdictions [11, 12]; to public health, through increased transmissions; and to the healthcare system. Identifying patients at greatest risk of reinfection who would benefit most from monitoring and targeted counseling is important when making HCV treatment decisions. Therefore, using statistical methods appropriate for small samples, we assessed rates and risk factors for HCV reinfection after SVR in a broadly representative cohort of Canadian HIV-coinfected patients in clinical care.

METHODS

Study Population

Data from the Canadian Co-infection Cohort, an ongoing prospective study with visits scheduled every 6 months, were analyzed [13]. The cohort includes more than 1600 patients recruited from HIV clinic populations at 18 centers across 6 Canadian provinces. We followed all coinfected patients who achieved SVR with HCV treatment between January 2003 and July 2016 having at least 1 post-SVR study visit with an available HCV RNA measurement. SVR was defined as a negative HCV RNA at least 12 weeks after the end-of-treatment date (because >95% of late relapses occur within this period [14]). The study was approved by the community advisory committee of the Canadian Institutes of Health Research–Canadian HIV Trials Network and by all institutional ethics boards of participating centers.

Outcome

Patients were followed post-SVR with HCV RNA measurements every 6 months until reinfection or their last study visit prior to July 2016. We defined reinfection as a single detectable HCV RNA measurement post-SVR measured in local laboratories using either a qualitative assay (COBAS Ampliprep/TaqMan HCV Test, v2.0, Roche Molecular Systems) or a quantitative assay (Abbott RealTime PCR; Abbott Molecular Inc.).

Risk Factors

We categorized patients according to principal risk factors for incident HCV infection in HIV-coinfected persons (injection drug use [IDU] and high-risk sexual activity in MSM [15, 16]) using information that could be readily obtained by clinicians. Recent high-frequency IDU was defined as any self-reported use of injection cocaine or methamphetamines in the last 6 months because these drugs are associated with multiple injections per day and a high degree of risk-taking behavior [17]. Low-frequency IDU was defined as the self-report of any other injection drug (mainly opiates; Supplementary Table 1). Shared IDU equipment was defined as the reported sharing of needles or other paraphernalia such as containers and spoons. Recent high-risk sexual behavior among MSM was defined as reporting both more than 1 sexual partner and less than 100% condom use in the preceding 6 months. In a sensitivity analysis, we alternatively defined high-risk behavior among men as reporting a sexually transmitted infection (STI) in the previous 6 months.

Statistical Analyses

Regression methods are valid when large samples are used; small samples can lead to biased results. The consequence of too few events is a "sparse-data" bias away from the null [18]. Bayesian analyses with informative priors offer a solution to this problem [18] because appropriate informative priors anchor each parameter estimate to a range of values that is clinically sensible and reduce the possibility of extreme values that no knowledgeable clinician would find credible [19, 20].

We used Bayesian methods to fit an adjusted Cox regression model appropriate for interval censored data with an offset that allows for any variation in the time between follow-up visits [21]. To allow some variation in the baseline hazard over time, we estimated the rate of reinfection in each of the following 3 periods: within the first year, between 1 and 3 years, and beyond 3 years. For each parameter we asserted "weakly" informative priors. These are defined as distributions where "the percentiles of the prior distribution would be viewed as at least reasonable if not liberally inclusive by all those working in the research topic" [22]. We categorized potential risk factors as possibly or probably harmful, possibly or probably protective, or of uncertain direction. We then assigned wide log-normal distributions to each category such that these distributions reduced the probability of extreme hazard ratios (HRs; Supplementary Table 2). We used a prior HR of 1.5 (95% credible interval [CrI], 0.38–6.0) for possibly harmful risk factors, 2.0 (95% CrI, 0.5–8.0) for probably harmful risk factors, 1.0 (95% CrI, 0.25–4.0) for factors of uncertain direction, and 0.69 (95% CrI, 0.17–2.7) for possibly protective risk factors [20, 23]. We used R 3.1.0, R2WinBUGS 2.1–20 and WinBUGS 1.4.3 for our analysis.

Covariates that represent potential risk factors for reinfection were time-varying, taking the value measured at the visit prior to each measurement of HCV RNA. We considered that MSM, high-risk sexual behavior among MSM, and low-frequency IDU were all possibly harmful, while high-frequency IDU and shared equipment were both probably harmful. We also included covariates for sex, Aboriginal ethnicity, age (per 10 years), and CD4 cell count (per 100 cells/μL) as a measure of patient health. We considered sex and ethnicity to be risk factors of uncertain direction and increasing age and increasing CD4 cell count to be possibly protective.

We defined reference patients as males of other than Aboriginal ethnicity who reported neither male sexual partners nor IDU in the past 6 months and achieving SVR at age 45 with a CD4 cell count of 400 cells/μL. Our prior for the reinfection rate in reference patients was, however, based on an estimate from an earlier study that was similar to ours, rather than "weakly" informative. In this hospital-based Spanish coinfection cohort, 4

Downloaded from academic.oup.com/cid/article/64/9/1154/2990211 by guest on 24 September 2026

of 84 patients were reinfected in a mean follow-up of 34 months after an SVR [9]. Our prior for the reinfection rate (10 per 1000 PYFU; 95% CrI, 3–32) is as close to the estimate from this study (12; 95% CI, 3–31) as we could get with a log-normal prior.

With Bayesian methods, results should be interpreted with reference to the priors [19]. The shift from prior estimate to posterior estimate ("the results") reflects the information in the data. We therefore present both prior and posterior estimates and, in sensitivity analyses, we considered posterior estimates under different priors and under alternative assumptions.

Sensitivity Analysis

In a first sensitivity analysis, we replaced our prior for the rein-fection rate with a "weakly" informative prior (7 per 1000 PYFU; 95% CrI, 1–50). As an example, this distribution is far wider than the pooled estimate for high-risk HCV-monoinfected patients in a recent metaanalysis (22 per 1000 PYFU; 95% CI, 13–33) [4]. In a second sensitivity analysis, we made different assumptions about the date of reinfection for 3 patients for whom the date was uncertain because of missed follow-up visits. In a third sensitivity analysis, we used an alternative measure of high-risk MSM, that is, a male reporting an STI in the previous 6 months.

RESULTS

As of July 2016, 497 coinfected patients initiated HCV treatment, of whom 319 achieved SVR. Of these, 257 had at least 1 post-SVR HCV RNA measurement available and were included in the analysis (31 had recently completed follow-up and 31 had no available measures; Figure 1). Most of the patients were male (82%) with a history of IDU (74%); 14% were actively using injection drugs and 33% reported being MSM (Table 1). Fifty-one patients were treated with interferon-free regimens. The majority were receiving antiretrovirals (92%) and had undetectable HIV RNA (87%) with median CD4 cell count of 450 cells/μL. The median total post-SVR follow-up time was 1.5 years (interquartile range [IQR], 0.6, 3.2). All patients had more than 1 post-SVR HCV measurement (median, 3; IQR, 2, 6), with a median time between measurements of 6 months (IQR, 6, 8). Of the 239 who were censored without reinfection, 183 were administratively censored, 11 died, and 45 were lost to follow-up post-SVR (Supplementary Table 3).

During 589 PYFU after achieving SVR, 18 patients (7%) became HCV RNA positive (Table 2), with a median time to reinfection of 2.5 years (IQR, 1.6, 3.2) and an unadjusted reinfection rate of 31 per 1000 PYFU. Of 18 reinfections, 5 (28%) spontaneously cleared and 13 became chronically infected, 9 of whom had a genotype switch. The adjusted reinfection rate per 1000 PYFU was 10 (95% CrI, 4–20) for reference patients in the first year after SVR, 20 (95% CrI, 8–38) in the first 1 to 3 years, and 18 (95% CrI, 8–36) after 3 years (Supplementary Table 4). In our second sensitivity analysis these rates (per 1000 PYFU) were 12 (95% CrI, 6–24) in the first year after SVR, 18 (95% CrI, 8–32) in the first 1 to 3 years, and 16 (95% CrI, 6–32) after 3 years. Thus, the estimated rate of reinfection was lower in the first year than in later years regardless of when reinfection was assumed to have occurred for the 3 patients with an uncertain reinfection date (Supplementary Figure 1).

Patients who became reinfected were 3 times more likely to report having engaged in high-frequency IDU at the visit before reinfection compared to those who were censored (Table 1). Patients who became reinfected were also somewhat more likely to report being MSM in the last 6 months. Among the 6 MSM who became reinfected, none reported low-frequency IDU and only 1 reported high-frequency IDU; 3 reported recent high-risk sexual behavior and 2 reported a recent STI. At the time of reinfection, median CD4 cell count was lower and more patients were off antiretroviral therapy with a detectable HIV RNA compared to those not reinfected at the end of follow-up.

Comparison of posterior with prior HRs (Table 3) showed that high-frequency IDU was even more detrimental than we anticipated. There was no information in the data about the risk of sharing IDU equipment; none of the reinfected patients reported sharing IDU equipment at the visit prior to reinfection. Estimates for other risk factors were broadly in line with our expectations in that posterior intervals were contained within prior intervals. Estimates for high-risk sexual activity in MSM were similar regardless of how this was defined (posterior HR, 1.8; 95% CrI, 0.56–4.4, and posterior HR, 2.0; 95% CrI, 0.57–5.1 in the main and third sensitivity analysis, respectively).

The reinfection rate in those reporting high-frequency IDU was therefore potentially much higher than in reference patients; 58 per 1000 PYFU (95% CrI, 18–134) during the first year after SVR (Figure 2). By comparison, rates for high-risk MSM and for low-frequency IDU were intermediate (26; 95% CrI, 6–66 and 22; 95% CrI, 4–68 per 1000 PYFU, respectively). The rate for MSM reporting low-risk sexual activity (16; 95% CrI, 4–38 per 1000 PYFU) was lower and similar to that of reference patients.

DISCUSSION

Safe and simple short-course DAAs have spurred a rapid scale-up of HCV treatment to populations at greater risk of reinfection. Given the costly consequences of reinfection, it is essential to have reasonable estimates of the risk of reinfection and to understand which subgroups need risk reduction measures. In a large and diverse cohort representative of the Canadian coinfection population in care [13], we found that those engaging in high-frequency IDU (cocaine and methamphetamines) were at greatest risk of becoming reinfected at a rate roughly 6 times that of low-risk reference patients. This rate was higher than we had anticipated. We estimated intermediate, and comparable, risk for high-risk MSM and low-frequency IDU. Reinfections among MSM appear to have been sexually transmitted with one

Downloaded from academic.oup.com/cid/article/64/9/1154/2990211 by guest on 24 September 2026

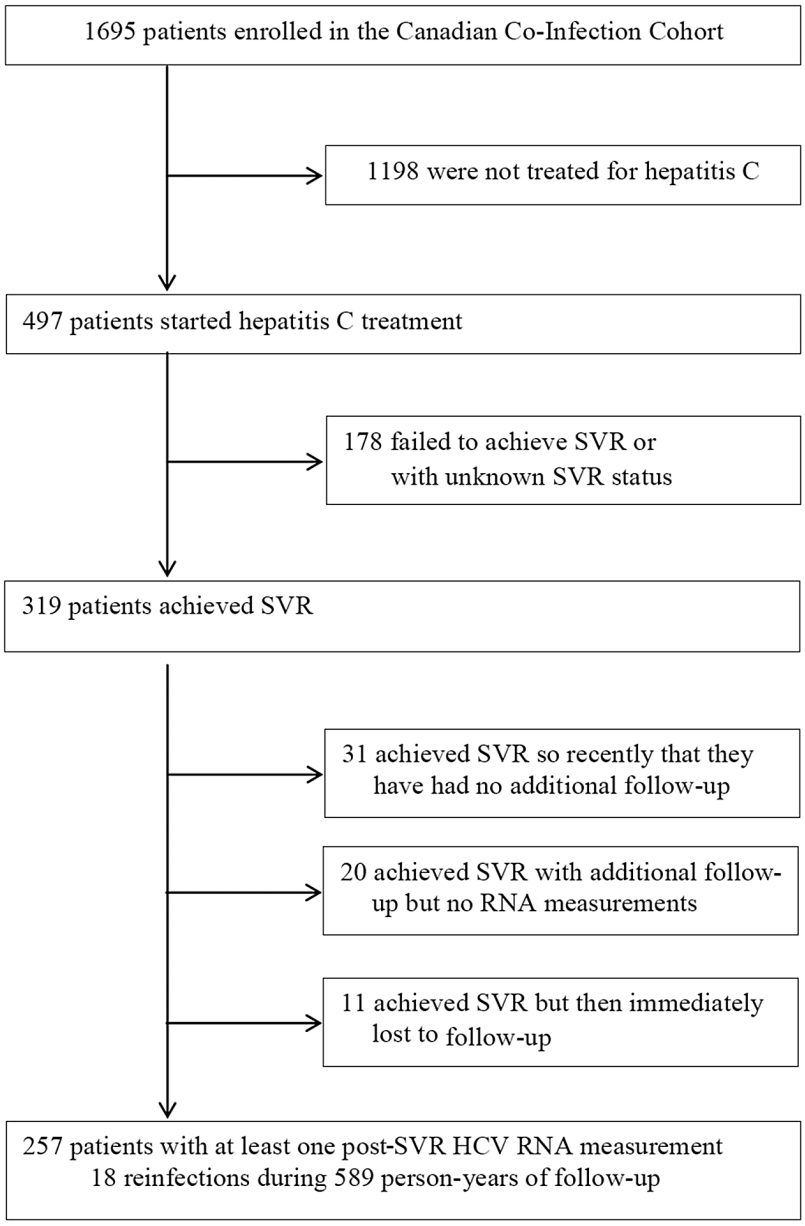

Figure 1. Patient flow diagram. As of July 2016, 497 coinfected patients initiated hepatitis C virus (HCV) treatment, of whom 319 achieved sustained virologic response (SVR). Of these, 257 patients had at least 1 post-SVR HCV RNA measurement available and were included in the analysis. Patients excluded from the analysis (n = 62) were older (median age 52 years), more likely to be Aboriginal (15%), and less likely to be former (65%) or current (8%) injection drug users than those included. Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

exception. Reinfection rates were low in low-risk MSM and in reference patients, the majority of whom were former PWID, emphasizing the safety of treating HCV in this subgroup.

By having a more broadly representative population than in past studies and evaluating reinfection in specific subgroups, we were able to put previous estimates of reinfection rates into context. For example, we estimated higher rates of reinfection than seen in several other studies of coinfected patients. Studies from clinical trials have reported no reinfections [5, 6]. This is not unexpected given stringent inclusion criteria that led to exclusion of active substance users and short post-trial follow-up [24]. In the study by Pineda et al (on which we based our prior distribution for the rate of reinfection) [9], the overall reinfection rate was 12 per 1000 PYFU (95% CI, 3–31), similar to the rate we estimated for our reference patients in the first year after SVR (Supplementary Table 4). However, while 86% acquired HCV through IDU in their study, the vast majority were no longer using injection drugs. Most of our reference patients were also former PWID. However, these rates are substantially higher than those estimated for HCV monoinfected patients with no reported risk factors (1.9 per 1000 PYFU; 95% CI, 0.7–3.4 [4]) although less than rates in high-risk HCV-monoinfected

Downloaded from academic.oup.com/cid/article/64/9/1154/2990211 by guest on 24 September 2026

Table 1. Patient Characteristics and Recent (in the Previous 6 Months) Risk Behavior Reported at the Time of Sustained Virologic Response (Baseline) and at the End of Follow-up

		At the End of Follow-up	
	At Sustained Virologic Response	At Visit Prior to Reinfection	At Visit Prior to Censoring (Without Reinfection)
Characteristic	(n = 257)	(n = 18)	(n = 239)
Follow-up in years, median (IQR)	–	2.5 (1.6, 3.2)	1.4 (0.6, 3.2)
Demographics and risk behaviors			
Age in years, median (IQR)	49 (43, 53)	48 (42, 54)	51 (45, 56)
Male sex, %	82	89	82
Aboriginal ethnicity, %	8	11	8
Ever IDU, %	74	72	74
Type of recent IDU, % [a,b]			
No IDU	86	50	86
Low frequency	3	6	2
High frequency	11	44	12
Recent shared IDU equipment, % [a]	0	0	1
Recent men who have sex with men activity, % [a,c,d]	33	40	29
Recent condom use, % [a,d]			
Not sexually active	43	50	47
Always	32	25	28
Sometimes or never	25	25	25
Recent sexually transmitted infection diagnosis, % [a,d]	3	11	4
Clinic type, %			
Tertiary care	79	72	80
Community based	17	28	16
Rural	4	0	4
HIV characteristics			
Time since HIV diagnosis in years, median (IQR)	15 (9, 22)	19 (12, 24)	17 (12, 23)
CD4 cell count in cells/μL, median (IQR) [d]	450 (310, 640)	465 (350, 590)	540 (390, 750)
HIV viral load >50 copies/mL, % [d]	13	28	8
On antiretroviral therapy, %	92	72	95
HCV characteristics			
Duration of HCV infection in years, median (IQR)	21 (12, 29)	21 (13, 28)	24 (15, 31)
HCV genotype at initial infection, % [e]			
1	62	44	63
2	8	17	7
3	20	28	20
4	2	0	2
Unknown	8	11	8
IL-28B haplotype, %			
CC	41	56	40
CT	27	22	27
TT	9	5	9
Unknown	23	17	24
Median AST to platelet ratio index (IQR)	0.42 (0.31, 0.71)	0.38 (0.25, 0.51)	0.40 (0.30, 0.55)
Cirrhosis, %	21	28	23
HCV treatment, %			
Interferon-free	20	0	21

Canadian Co-infection Cohort, n = 257.

Abbreviations: AST, aspartate aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range.

[a]Patient reported behavior for the previous 6 months.

[b]High frequency: patient reported injecting cocaine or methamphetamines. Low frequency: patient reported injecting some other drug.

[c]Among males only (n = 212).

[d]Notes on missing data: Recent men who have sex with men: at baseline, 3; at end of follow-up, 1 of those reinfected, 2 of those censored. Recent condom use: at baseline, 9; at end of follow-up, 2 of those reinfected, 5 of those censored. Recent sexually transmitted infection: at baseline, 6; at end of follow-up, 5 of those censored. CD4 cell count: at baseline, 4; at end of follow-up, 6 of those censored. HIV viral load: at baseline, 8; at end of follow-up, 7 of those censored.

[e]Prior to HCV treatment.

Downloaded from academic.oup.com/cid/article/64/9/1154/2990211 by guest on 24 September 2026

Table 2. Characteristics of the 18 Hepatitis C Virus Reinfections seen in the Canadian Co-infection Cohort

	Sex	Risk Factor Reported 6 Months Prior to Reinfection	First Positive HCV RNA Value After SVR	Genotype at Baseline	Genotype at Reinfection	Time from SVR to Reinfection (days)	Number of RNA Measures Before/ After Reinfection	Average Time Between Measures (days)	HCV RNA (copies/ mL) Values Post- Reinfection
1	Male	Low-risk MSM, high-frequency IDU	90 000	1	Not tested	1281	7/1	183	Subsequent visit undetectable
2	Male	None reported	Detectable (qualitative)	2b	3a	259	2/4	259	All subsequent visits detectable >3 000 000
3	Male	High-frequency IDU	126 000	2	1a	925	4/5	308	All subsequent visits detectable > 1 000 000
4	Male	High-risk MSM	Detectable (qualitative)	1a	3a	573	4/12	191	All subsequent visits detectable (qualitative)
5	Male	High-risk MSM	Detectable (qualitative)	1a	3a	370	3/1	185	Subsequent visit detectable (qualitative)
6	Male	Low-risk MSM	Detectable (qualitative)	3a	1	698	2/2	698	All subsequent visits detectable > 900 000
7	Female	High-frequency IDU	Detectable (qualitative)	1a	3a	1297	8/2	185	All subsequent visits detectable (qualitative)
8	Male	High-frequency IDU	Detectable (qualitative)	2b	1a	1309	6/4	262	All subsequent visits detectable (qualitative)
9	Male	High-frequency IDU	Detectable (qualitative)	3a	Not tested	1115	4/1	372	Subsequent visit undetectable
10	Male	High-risk MSM	Detectable (qualitative)	1a	Not tested	1088	7/4	181	All subsequent visits undetectable
11	Male	High-frequency IDU	26 000	3a	1a	548	2/2	274	Subsequent visits detectable > 26 100
12	Female	None reported	1 400 000	3a	1	719	3/1	360	Subsequent visit detectable at 5 000 000
13	Male	None reported	Detectable (qualitative)	3	3a	350	3/1	175	Subsequent visit detectable at 9000
14	Male	Low-risk MSM	27 000	1a	1a	1167	6/2	233	All subsequent visits detectable > 242 000
15	Male	None reported	Detectable (qualitative)	3a	Not tested	169	2/1	169	Subsequent visit undetectable
16	Male	Low-frequency IDU	178	Unknown	3a	1063	6/1	213	Subsequent visit undetectable
17	Male	High-frequency IDU	412 000	1a	1a	1396	5/1	349	Subsequent visit detectable at 1500
18	Male	High-frequency IDU	531 000	1a	1a	549	2/1	549	Subsequent visit detectable at 322 000

Abbreviations: HCV, hepatitis C virus; IDU, injection drug use; MSM, men who have sex with men; SVR, sustained virologic response.

patients (22 per 1000 PYFU; 95% CI, 13–33 [4]) and patients actively injecting drugs (24 per 1000 PYFU; 95% CI, 9–61 [25]). Previously it has been difficult to estimate the risk of reinfection after SVR according to recency, frequency, or type of IDU as we have done here because of lack of data [10].

Martin et al reported high reinfection rates after SVR among HIV-positive MSM attending a London clinic (96 per 1000 PYFU; 95% CI, 58–105) [7], nearly twice our estimate in high-risk MSM. Their population was clearly at elevated risk, with many patients having second and even third reinfections. High rates of reinfections have also been observed among MSM in Amsterdam after treatment of acute HCV (152 per 1000 PYFU; 95% CI, 80–265) [26]. The recent epidemic of sexually transmitted HCV infection among MSM has underscored the

Downloaded from academic.oup.com/cid/article/64/9/1154/2990211 by guest on 24 September 2026

Table 3. Prior and Posterior Estimates of Risk Factors for Reinfection With Hepatitis C in Patients With a Sustained Virologic Response After Treatment

Risk Factor	Prior HR (95% CrI)	Posterior HR (95% CrI)
MSM (vs heterosexual male) [a]	1.5 (0.38–6.0)	1.7 (0.62–3.4)
High-risk sexual behavior in MSM [a,b]	1.5 (0.38–6.0)	1.8 (0.56–4.4)
Low frequency IDU [a,c]	1.5 (0.38–6.0)	2.3 (0.53–6.3)
High frequency IDU [a,d]	2.0 (0.50–8.0)	6.1 (2.5–12)
Shared IDU equipment [a,e]	2.0 (0.50–8.0)	2.0 (0.44–5.6)
Female (vs heterosexual male)	1.0 (0.25–4.0)	1.0 (0.32–2.5)
Aboriginal ethnicity	1.0 (0.25–4.0)	1.6 (0.42–4.1)
Age at sustained virologic response (per 10-year increase)	0.67 (0.17–2.7)	0.90 (0.48–1.5)
Latest $CD4^+$ cell count (per 100 cells/μL increase)	0.67 (0.17–2.7)	0.82 (0.62–1.0)

Canadian Co-infection Cohort, n = 257.

Abbreviations: CrI, credible interval; HR, hazard ratio; IDU, injection drug use; MSM, men who have sex with men.

[a]Patient report of behavior in the previous 6 months.

[b]Patient reports more than 1 male sexual partner and less-than-perfect condom use.

[c]Patient reports injecting drugs other than cocaine or methamphetamines (mainly opiates).

[d]Patient reports injecting cocaine or methamphetamines.

[e]Patient reports shared use of needles or of other paraphernalia, such as containers and spoons.

importance of sexual networks [27, 28], and thus reinfection rates may be regionally specific. Lower rates of HCV infection among MSM have been seen in Canada than in Europe [29, 30]. Higher rates of HCV seroconversion have been reported among MSM with a recent STI, especially syphilis [30–32]. A recent STI in our study was suggestive of a higher risk of reinfection and likely serves as a marker of unprotected high-risk sexual activity that should prompt more frequent HCV testing.

In our study, the rate of reinfection did not diminish over time. This ongoing risk underlines that regular monitoring for reinfection is important following SVR, particularly in persons who continue to engage in IDU and for high-risk MSM. In a recent study from Scotland where concerted efforts to treat PWID for HCV have been made, the frequency of HCV RNA testing after SVR was low [33]. Only 61% were tested at least once in 4.5 years of follow-up post-SVR and only 31% received at least 2 tests. The reinfection rate was estimated to be 17 per 1000 PYFU (95% CI, 7–35), but this is likely an underestimate given the low rate of testing. In order to gauge the success of HCV treatment scale-up, it will be essential to routinely monitor for reinfection.

Strengths of our study include a relatively large number of reinfections from a widely generalizable population, although within the cohort fewer women, Aboriginals, and PWID received HCV treatment [3]. While we used methods to minimize small sample bias, we were still limited by a small number of reinfections, which led to imprecision in estimates. Risk behaviors were self-reported; however, we were interested in using reported risk behavior to identify patient subgroups at risk of reinfection. Not all risky behaviors appear to be useful for this purpose. For example, none of those who were reinfected reported sharing injection equipment at the visit 6 months prior to reinfection. While the majority of patients acquired a different HCV genotype at the time of reinfection, we were not able to distinguish reinfection from late relapse in 4 patients with similar genotypes at baseline and in 5 patients who spontaneously cleared following reinfection. The median time to reinfection for those who did not switch genotypes was, however, more than 2.5 years after SVR. There is no evidence thus far that HCV can reemerge from reservoirs after such a

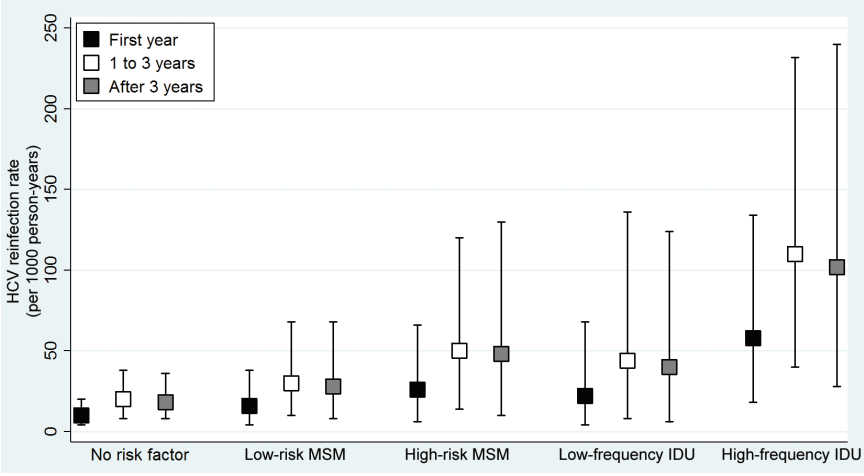

Figure 2. Hepatitis C reinfection rates and 95% credible intervals per 1000 person-years for up to 1 year, 1 to 3 years, and more than 3 years after a sustained virologic response (Canadian Co-infection Cohort, n = 257). Reference patients are those with no risk factors. Abbreviations: HCV, hepatitis C virus; IDU, injection drug use; MSM, men who have sex with men.

Downloaded from academic.oup.com/cid/article/64/9/1154/2990211 by guest on 24 September 2026

long period. While our results are generalizable to coinfected patients who receive care in a Canadian context, there may be very different geographical realities (concentrated epidemics) where infection rates could be considerably higher or lower. It is therefore important to understand local epidemiology when assessing the risk in a given community and in marginalized groups [34, 35]. Finally, the observed rates may be an underestimate of the potential reinfection risk in the era of DAAs, as most patients received interferon-based regimens that arguably could act as a disincentive to becoming reinfected given their poor tolerability.

While we report high rates of reinfection in some subgroups, the majority of patients did not become reinfected after achieving SVR. Our results should not serve to discriminate against offering HCV therapy to coinfected persons but rather should guide clinicians and policy makers on how best to intervene in order to reduce risk and identify subgroups that need more frequent monitoring. Indeed, information obtained from patients about their drug use and sexual activity was useful in determining the risk of reinfection. Patient education, harm reduction measures including substitution therapy [36, 37], enhanced social supports for PWID [38], and behavioral interventions for high-risk MSM [39, 40], while important, have met with mixed success. In particular, there are few therapeutic options to treat the high-frequency cocaine and methamphetamine users at highest risk of reinfection [41, 42]. Given the negative health consequences of HCV and the paucity of options for addressing high-risk behaviors, treatment needs to be rapidly expanded to all high-risk HCV transmitters from whom reinfections occur. Only in this way will the ambitious World Health Organization targets of reducing HCV infections by 90% by 2030 be realized [43].

Supplementary Data

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

Notes

Acknowledgments. We thank all study coordinators and nurses for their assistance with study coordination, participant recruitment, and care.

Financial support. The Canadian Co-infection Cohort is funded by the Canadian Institutes of Health Research (CIHR; FDN-143270), the CIHR-Canadian HIV Trials Network (CTN-222) and the Fonds de recherche Québec- Santé, Réseau SIDA/maladies infectieuses (FRQ-S). M. B. K. is supported by a Chercheur National career award from the FRQ-S.

Potential conflicts of interest. J. G. received personal fees for being a member of the national advisory boards of AbbVie, Gilead, Merck, Janssen, and ViiV Healthcare. S. W. received grants, consulting fees, lecture fees, nonfinancial support, and fees for the development of educational presentations from Merck, ViiV Healthcare, GlaxoSmithKline, Pfizer, Gilead, AbbVie, Bristol-Myers Squibb, and Janssen. C. C. reports receipt of consulting fees from AbbVie, Gilead, and Merck and grants from AbbVie and Gilead. J. C. received consulting fees from Bristol-Meyers Squibb, grants from ViiV Healthcare and Gilead, and payment for lectures from Merck. V. M.-L. reports receipt of consulting fees from Merck and Gilead, a grant from Gilead, and lecture fees from AbbVie, Merck, and Gilead. B. C. reports receipt of grants, travel support, personal fees for speakers bureau and advisory board participation from AbbVie, Gilead, and Merck. N. P. received personal fees for being a member of advisory boards from Gilead, ViiV Healthcare, and Merck. M.-L. V. has received consulting fees from Boehringer Ingelheim and Merck; consulting fees and lecture honoraria from Janssen Pharmaceuticals, Gilead, Hoffman–La Roche, and Vertex Pharmaceuticals; and speaker fees from Gilead. M. B. K. has received research grants for investigator-initiated trials from Merck and ViiV Healthcare; consulting fees from ViiV Healthcare, Bristol-Meyers Squibb, Merck, Gilead, and AbbVie. All other authors: No potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Peters L, Klein MB. Epidemiology of hepatitis C virus in HIV-infected patients. Curr Opin HIV AIDS **2015**; 10:297–302.
2. Limketkai BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. JAMA **2012**; 308:370–8.
3. Young J, Potter M, Cox J, et al. Variation between Canadian centres in the uptake of treatment for hepatitis C by patients coinfected with HIV: a prospective cohort study. CMAJ Open **2013**; 1:E106–14.
4. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. Clin Infect Dis **2016**; 62:683–94.
5. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology **2010**; 139:1593–601.
6. Soriano V, Núñez M, Camino N, et al. Hepatitis C virus-RNA clearance in HIV-coinfected patients with chronic hepatitis C treated with pegylated interferon plus ribavirin. Antivir Ther **2004**; 9:505–9.
7. Martin TC, Martin NK, Hickman M, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. AIDS **2013**; 27:2551–7.
8. Marco A, Esteban JI, Solé C, et al. Hepatitis C virus reinfection among prisoners with sustained virological response after treatment for chronic hepatitis C. J Hepatol **2013**; 59:45–51.
9. Pineda JA, Núñez-Torres R, Téllez F, et al; HEPAVIR Group of the Andalusian Society of Infectious Diseases. Hepatitis C virus reinfection after sustained virological response in HIV-infected patients with chronic hepatitis C. J Infect **2015**; 71:571–7.
10. Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. Clin Infect Dis **2013**; 57 Suppl 2:S105–10.
11. Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE. Restrictions for Medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States. Ann Intern Med **2015**; 163:215–23.
12. Marshall AD, Saeed S, Barrett L, et al; Canadian Network on Hepatitis C. Restrictions for reimbursement of direct-acting antiviral treatment for hepatitis C virus infection in Canada: a descriptive study. CMAJ Open **2016**; 4:E605–14.
13. Klein MB, Saeed S, Yang H, et al. Cohort profile: the Canadian HIV-hepatitis C co-infection cohort study. Int J Epidemiol **2010**; 39:1162–9.
14. Medrano J, Barreiro P, Resino S, et al. Rate and timing of hepatitis C virus relapse after a successful course of pegylated interferon plus ribavirin in HIV-infected and HIV-uninfected patients. Clin Infect Dis **2009**; 49:1397–401.
15. Kim AY, Onofrey S, Church DR. An epidemiologic update on hepatitis C infection in persons living with or at risk of HIV infection. J Infect Dis **2013**; 207 Suppl 1:S1–6.
16. Marcellin F, Lorente N, Demoulin B, et al; ANRS VESPA2 Study Group. Comparison of risk factors in HIV-infected men who have sex with men, coinfected or not with hepatitis C virus (ANRS VESPA2 French cross-sectional national survey). Sex Transm Infect **2015**; 91:21–3.
17. Leri F, Stewart J, Tremblay A, Bruneau J. Heroin and cocaine co-use in a group of injection drug users in Montréal. J Psychiatry Neurosci **2004**; 29:40–7.
18. Greenland S, Schwartzbaum JA, Finkle WD. Problems due to small samples and sparse data in conditional logistic regression analysis. Am J Epidemiol **2000**; 151:531–9.
19. Greenland S. Bayesian perspectives for epidemiological research: I. Foundations and basic methods. Int J Epidemiol **2006**; 35:765–75.

Downloaded from academic.oup.com/cid/article/64/9/1154/2990211 by guest on 24 September 2026

20. Greenland S. Bayesian perspectives for epidemiological research. II. Regression analysis. Int J Epidemiol **2007**; 36:195–202.
21. Carlin JB, Wolfe R, Coffey C, Patton GC. Analysis of binary outcomes in longitudinal studies using weighted estimating equations and discrete-time survival methods: prevalence and incidence of smoking in an adolescent cohort. Stat Med **1999**; 18:2655–79.
22. Greenland S. Prior data for non-normal priors. Stat Med **2007**; 26:3578–90.
23. Young J, Scherrer AU, Günthard HF, et al; Swiss HIV Cohort Study. Efficacy, tolerability and risk factors for virological failure of darunavir-based therapy for treatment-experienced HIV-infected patients: the Swiss HIV Cohort Study. HIV Med **2011**; 12:299–307.
24. Saeed S, Strumpf EC, Walmsley SL, et al; Canadian Co-Infection Cohort Study. How generalizable are the results from trials of direct antiviral agents to people coinfected with HIV/HCV in the real world? Clin Infect Dis **2016**; 62:919–26.
25. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis **2013**; 57 Suppl 2:S80–9.
26. Lambers FA, Prins M, Thomas X, et al; MSM Observational Study of Acute Infection With Hepatitis C Study Group. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. AIDS **2011**; 25:F21–7.
27. van de Laar T, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology **2009**; 136:1609–17.
28. Matthews GV, Hellard M, Haber P, et al; Australian Trial in Acute Hepatitis C Study Group. Characteristics and treatment outcomes among HIV-infected individuals in the Australian Trial in Acute Hepatitis C. Clin Infect Dis **2009**; 48:650–8.
29. Boesecke C, Grint D, Soriano V, et al; EuroSIDA in EuroCoord. Hepatitis C seroconversions in HIV infection across Europe: which regions and patient groups are affected? Liver Int **2015**; 35:2384–91.
30. Burchell AN, Gardner SL, Mazzulli T, et al. Hepatitis C virus seroconversion among HIV-positive men who have sex with men with no history of injection drug use: results from a clinical HIV cohort. Can J Infect Dis Med Microbiol **2015**; 26:17–22.
31. Bottieau E, Apers L, Van Esbroeck M, Vandenbruaene M, Florence E. Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001–2009. Euro Surveill **2010**; 15:19673.
32. Wandeler G, Gsponer T, Bregenzer A, et al; Swiss HIV Cohort Study. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. Clin Infect Dis **2012**; 55:1408–16.
33. Weir A, McLeod A, Innes H, et al. Hepatitis C reinfection following treatment induced viral clearance among people who have injected drugs. Drug Alcohol Depend **2016**; 165:53–60.
34. Centers for Disease Control and Prevention. Hepatitis C virus infection among adolescents and young adults: Massachusetts, 2002–2009. Morb Mortal Wkly Rep **2011**; 60:537–41.
35. Public Health Agency of Canada. Hepatitis C in Canada: 2005–2010 surveillance report. **2011**. Available at: http://publications.gc.ca/collections/collection_2012/aspc-phac/HP40-70-2012-eng.pdf. Accessed June 30, 2016.
36. Vickerman P, Page K, Maher L, Hickman M. Commentary on Nolan et al. (2014): opiate substitution treatment and hepatitis C virus prevention: building an evidence base? Addiction **2014**; 109:2060–1.
37. MacArthur GJ, Minozzi S, Martin N, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. BMJ **2012**; 345:e5945.
38. Raycraft T, Hakobyan S, Vafadary S, et al. Retrospective analysis of recurrent HCV viremia in high-risk HIV co-infected people who inject drugs (PWID). J Viral Hepat **2016**; 2:2. Available at: http://hepatitis.imedpub.com/. Accessed March 7, 2017.
39. Melendez-Torres GJ, Bonell C. Systematic review of cognitive behavioural interventions for HIV risk reduction in substance-using men who have sex with men. Int J STD AIDS **2014**; 25:627–35.
40. Berg R. The effectiveness of behavioural and psychosocial HIV/STI prevention interventions for MSM in Europe: a systematic review. Euro Surveill **2009**; 14.
41. Andraka-Christou B. A pressing need for pharmacotherapy development to treat drug addiction: an editorial from a legal perspective. Int Rev Neurobiol **2016**; 126:15–38.
42. Ling W, Hillhouse MP, Saxon AJ, et al. Buprenorphine + naloxone plus naltrexone for the treatment of cocaine dependence: the Cocaine Use Reduction with Buprenorphine (CURB) study. Addiction **2016**; In Press.
43. World Health Organization. Combating hepatitis B and C to reach elimination by 2030. Advocacy brief. **2016**. Available at: http://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/. Accessed June 29, 2016.

APPENDIX

The Canadian Co-infection Cohort investigators (CTN222) include Lisa Barrett, QEII Health Science Center for Clinical Research, Halifax, Nova Scotia; Jeff Cohen, Windsor Regional Hospital Metropolitan Campus, Ontario; Brian Conway, Vancouver Infectious Diseases Research and Care Centre, British Columbia; Curtis Cooper, the Ottawa Hospital Research Institute, Ontario; Pierre Côté, Clinique du Quartier Latin, Montréal, Quebec; Joseph Cox, MUHC IDTC-Montréal General Hospital, Quebec; John Gill, Southern Alberta HIV Clinic, Calgary; Shariq Haider, McMaster University, Hamilton, Ontario; Mark Hull, British Columbia Centre for Excellence in HIV/AIDS, Vancouver ; Marina Klein, McGill University Health Centre, Division of Infectious Diseases and Chronic Viral Illness Service, Montreal, Quebec; Julio Montaner, St. Paul's Hospital, Vancouver, British Columbia; Erica Moodie, McGill University, Montreal, Quebec; Neora Pick, Oak Tree Clinic, Children's and Women's Health Centre of British Columbia, University of British Columbia, Vancouver; Anita Rachlis, Sunnybrook & Women's College Health Sciences Centre, Toronto, Ontario; Danielle Rouleau, Centre Hospitalier de l'Université de Montréal, Quebec; Roger Sandre, HAVEN Program, Sudbury, Ontario; Mark Tyndall, Department of Medicine, Infectious Diseases Division, University of Ottawa, Ontario; Steve Sanche, SHARE University of Saskatchewan, Saskatoon; Marie-Louise Vachon, Centre Hospitalier Universitaire de Québec; Sharon Walmsley, University Health Network, Toronto, Ontario; Alex Wong, Regina Qu'Appelle Health Region, Regina General Hospital, Saskatchewan; and David Wong, University Health Network, Toronto, Ontario. We thank all study coordinators and nurses for their assistance with study coordination, participant recruitment, and care.

Downloaded from academic.oup.com/cid/article/64/9/1154/2990211 by guest on 24 September 2026