Risk factors for hepatitis C virus reinfection after sustained virologic response in patients co-infected with HIV

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Supplementary Material – Table of Contents

Supplementary Table 1.

Self-reported use of injection drugs at sustained virologic response and at the end of follow-up.

Note: The categories are not mutually exclusive. For example, a crack/cocaine user may have reported using heroin at the same visit.

Injection drug	**At sustained virologic response (n=257)**	**At visit prior to re-infection (n=18)**	**At visit prior to censoring (without reinfection) (n=239)**
Crack/cocaine	24 (9%)	7 (39%)	24 (10%)
Methamphetamines	4 (2%)	1 (6%)	5 (2%)
Any opiate, including heroin	14 (5%)	5 (28%)	11 (5%)
Heroin	10 (4%)	5 (28%)	9 (4%)
Other, besides heroin	7 (3%)	0 (0%)	6 (3%)
All other illicit drugs	2 (1%)	0 (0%)	1 (< 1%)

Supplementary Table 2.

Posterior hazard ratios for risk factors of reinfection under weakly informative or uninformative priors.

Note: Weakly informative prior distributions were used in the main analysis. These distributions are shown in Table 3. The uninformative prior distributions were all flat log normal distributions with mean zero and variance 100. Using weakly informative priors restricts posterior estimates to a more plausible range – for example, interval estimates for high and low frequency injection drug use (IDU) and aboriginal ethnicity – ruling out values that a knowledgeable clinician would not find credible.

	Posterior hazard ratios (95% CrI) given:	
Risk factor (n=257)	Weakly informative prior distributions	Uninformative prior distributions
MSM (versus heterosexual male) [1]	1.7 (0.62–3.4)	1.3 (0.24–3.9)
High risk sexual behavior in MSM [1,2]	1.8 (0.56–4.4)	2.8 (0.27–11)
Low frequency IDU [1,3]	2.3 (0.53–6.3)	4.6 (0.10–19)
High frequency IDU [1,4]	6.1 (2.5–12)	8.8 (2.8–21)
Shared IDU equipment [1,5]	2.0 (0.44–5.6)	0.31 (0.00–2.8)
Female (versus heterosexual male)	1.0 (0.32–2.5)	0.69 (0.06–2.4)
Aboriginal ethnicity	1.6 (0.42–4.1)	2.6 (0.06–8.9)
Age at SVR (per 10 year increase)	0.90 (0.48–1.5)	0.92 (0.48–1.6)
Latest $CD4^+$ cell count (per 100 cells/µL increase)	0.82 (0.62–1.0)	0.81 (0.62–1.0)

SVR, sustained virologic response; CrI, credible interval; MSM, men who have sex with men; IDU, injection drug use.

[1] Patient report of behaviour in the previous six months.

[2] Patient reports more than one male sexual partner and less than perfect condom use.

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

[4] Patient reports injecting cocaine or methamphetamines.

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

Supplementary Table 3.

Characteristics of patients censored without reinfection at their last visit prior to censoring.

Characteristic at last visit prior to censoring	**Administrative censoring (n=183)**	**No visit in the last year** [1] **(n=45)**	**Died (n=11)**
Age in years, median (IQR)	51 (46, 56)	45 (40, 51)	55 (44, 64)
Male sex, %	80	87	100
Aboriginal ethnicity, %	7	11	0
Ever IDU, %	75	71	73
Type of recent IDU, % [2,3]			
No recent IDU	88	82	64
Low frequency	3	0	9
High frequency	9	18	27
Recent MSM activity (among males only), % [2]	28	38	18
Recent condom use, % [2]			
Not sexually active	47	41	70
Always	28	30	10
Sometimes or never	25	29	20
Time since HIV diagnosis in years, median (IQR)	19 (13, 25)	13 (8, 19)	17 (13, 20)
CD4 cell count in cells/μL, median (IQR)	560 (420, 780)	490 (360, 650)	560 (320, 730)
HIV viral load >50 copies/mL, %	8	5	22
On antiretroviral therapy, %	95	98	91

IQR, inter-quartile range; IDU, injection drug use; MSM, men who have sex with men.

[1] Loss to follow-up: no study visits after July 2015, one year before the end of the study.

[2] Patient reported behaviour for the previous six months.

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

Supplementary Table 4.

Observed and estimated reinfection rates over time.

Note: Estimated reinfection rates are lower in reference patients because risk factors are absent.

	Within the first year	1 to 3 years	Beyond three years
Observed			
Patients at the start of the period	257	146	63
Reinfections during the period	4	9	5
Cumulative risk [1]	0.02	0.08	0.15
Person-years of follow-up	219	214	156
Rate per 1000 PYFU	18	42	32
Estimated rate per 1000 PYFU (95% credible interval)			
Unadjusted with an uninformative prior [2]	19 (5 – 40)	42 (19 – 73)	32 (11 – 65)
In reference patients and with:			
uninformative priors [3]	10 (2 – 26)	24 (6 – 56)	26 (6 – 62)
weakly informative priors [4]	10 (2 – 20)	22 (8 – 44)	20 (6 – 46)
in the main analysis [5]	10 (4 – 20)	20 (8 – 38)	18 (8 – 36)

PYFU, person-years of follow-up.

[1] One minus the probability of reinfection-free survival calculated using the Kaplan-Meier method.

[2] A flat prior for the reinfection rate – a log normal distribution with mean zero and variance 100.

[3] Flat priors for all covariates and for the reinfection rate.

[4] Weakly informative priors for all covariates and for the reinfection rate (first sensitivity analysis).

[5] Weakly informative priors for all covariates and an informative prior for the reinfection rate.

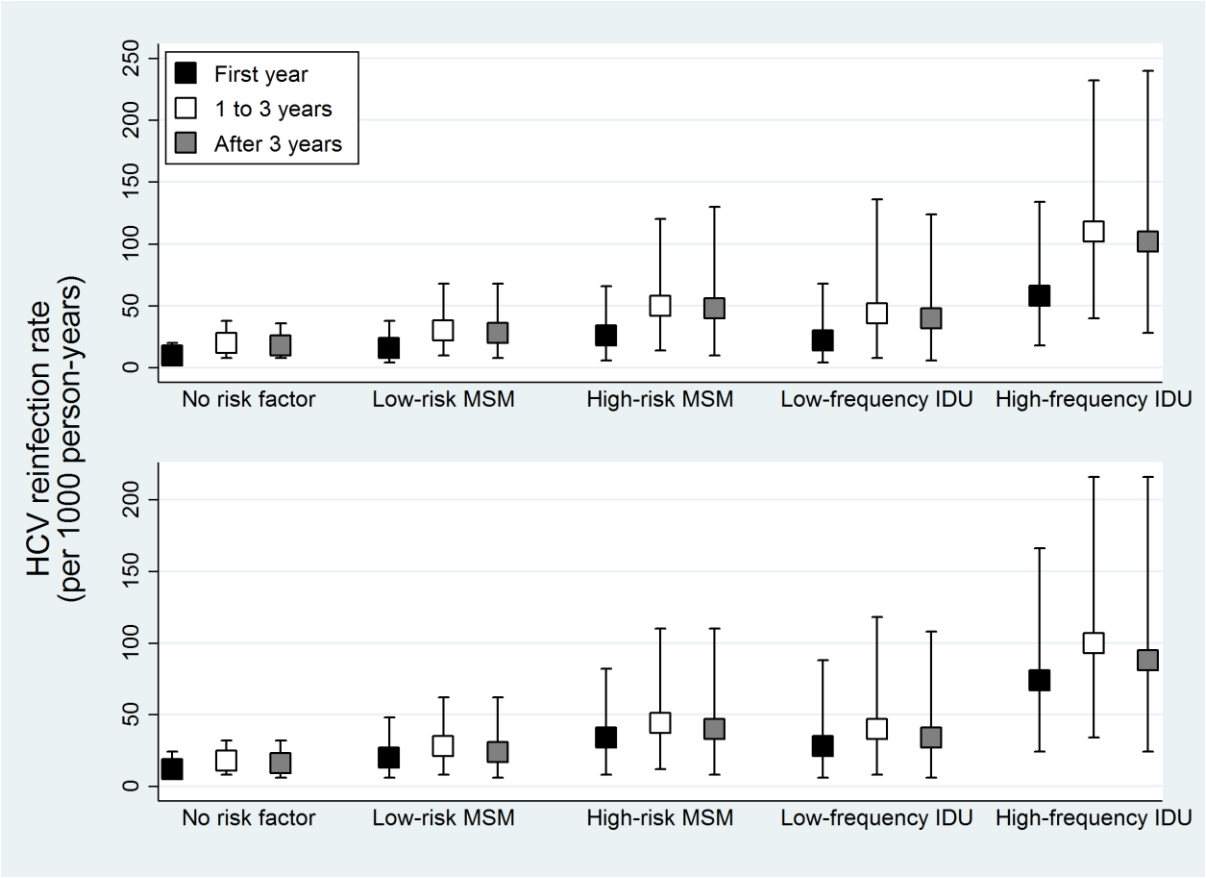
Supplementary Figure 1.

Rates of reinfection over time in the main analysis and in the second sensitivity analysis.

Note: RNA measurements were missing when either the patient did not attend a scheduled visit or the patient attended a scheduled visit but a measurement was not made. In many cases, patients then tested negative at a subsequent visit, so it was safe to assume the patient was not reinfected at the time of the missing measurement. There were seven patients who had a missing measurement followed by a positive test when a next measurement was made. For these seven patients, we went back to site investigators to ask whether there was other information that would allow us to determine when re-infection occurred (such as ALT and AST values). This process left only three patients where we were uncertain about the date when re-infection would have been seen at a scheduled visit.

This figure shows estimated Hepatitis C reinfection rates and 95% credible intervals per 1000 person years in the first year, one to three years and more than three years after a sustained virologic response (n=257). The top panel shows results of the main analysis – for three patients, reinfection was assumed to have been first detectable only when it was first measured after a sequence of missed visits. The bottom panel shows results for the second sensitivity analysis – for those three patients, reinfection was assumed to have first detectable at the first missed visit in their sequence of missed visits (three, six and nine months earlier respectively).

Comparing these two sets of estimates suggests that the rate of reinfection was lower in the first year than in later years (see also Supplementary Table 4) regardless of when reinfection was assumed to have occurred for these three patients.


HCV reinfection rate
(per 1000 person-years)
First year
1 to 3 years
After 3 years
0
50
100
150
200
250
No risk factor
Low-risk MSM
High-risk MSM
Low-frequency IDU
High-frequency IDU
0
50
100
150
200
No risk factor
Low-risk MSM
High-risk MSM
Low-frequency IDU
High-frequency IDU