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Incidence, Risk Factors, and Prevention of Hepatitis C Virus Reinfection

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Outline

- Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study
- Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort
- HCV reinfection rates after cure or spontaneous clearance among HIV-infected and uninfected MSM

Background

- Most of new hepatitis C infections in developed countries occur in people who inject drugs (PWID) and other high risk groups
- Historically less likely to be treated with interferon based regimens
- Direct acting antiviral agents (DAAs) have mitigated concerns related to compliance and adherence among high-risk populations such as people who inject drugs (PWID)
 - Treatment uptake among PWID increasing
- High re-infection rate an indication of treatment reach to high risk people but sustained high rates could also impede HCV elimination efforts
- Need systems to monitor re-infection and evaluate interventions



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Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study

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Summary

Background People remain at risk of reinfection with hepatitis C virus (HCV), even after clearance of the primary infection. We identified factors associated with HCV reinfection risk in a large population-based cohort study in British Columbia, Canada, and examined the association of opioid substitution therapy and mental health counselling with reinfection.

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Objective

- To estimate incidence rate of re-infection and
- Identify factors associated with reinfection risk, and examine the role of opioid substitution therapy (OST) and psychotherapy on HCV reinfection among PWID

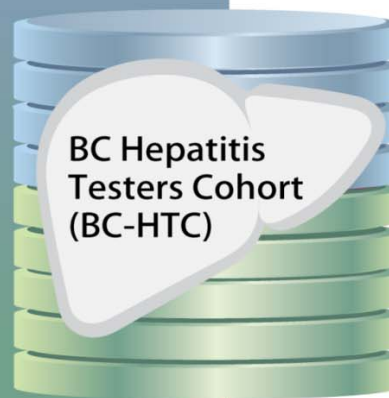
The BC Hepatitis Testers Cohort (BC-HTC)

Surveillance/Laboratory Data

-  HCV tests
-  HIV tests
-  HCV or HBV cases
-  Active TB cases
-  HIV cases
-  Enhanced surv

Administrative Data Sets

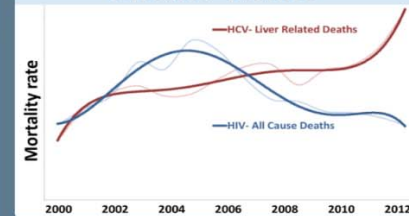
-  Prescription drugs
-  Hospitalizations
-  Medical visits
-  Cancers
-  Vital statistics
-  Emergency dep't
-  Chronic disease



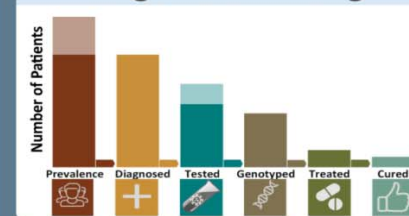
~ 1.7 million people
HCV+: ~ 73,000

Selected Applications

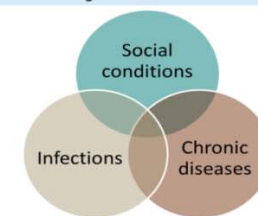
Disease Trends



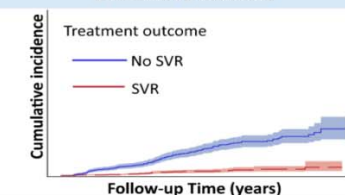
Program Monitoring



Syndemics

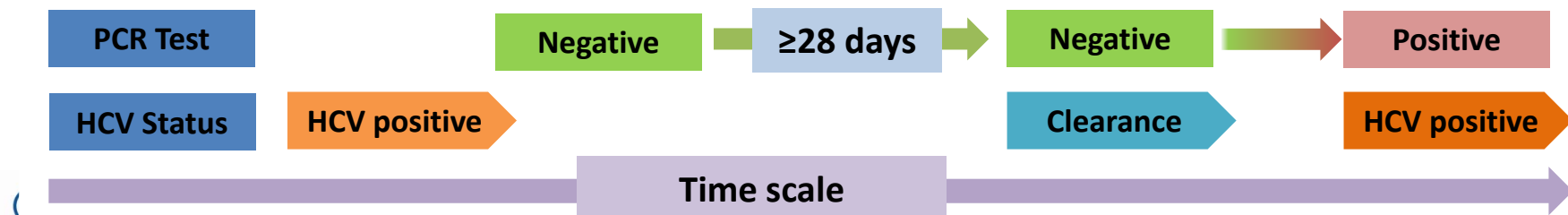


Treatment & Intervention Effectiveness



Methods

- **Context:** Centralized testing for 95% serology, all confirmation, HCV-RNA and genotype
 - All dispensed prescriptions recorded in a centralized system
- **Eligibility:** At least one valid HCV-PCR after primary clearance (either spontaneous or treatment-induced sustained virologic response) to Dec 31, 2013.
- **HCV Reinfection:** positive RNA test after two consecutive negative PCR tests ≥ 28 days apart. Sensitivity analysis: one negative PCR for clearance



Analysis

- The incidence rates of HCV reinfection / 100 person-years [PY, and 95% confidence intervals (CI), assuming a Poisson distribution
- Multivariable Cox proportional hazards (PH) models
 - Stratified by spontaneous clearance vs SVR group.
 - Effects of mental health counseling, and OST in PWIDs.
 - OST based on prescription, as time varying variable

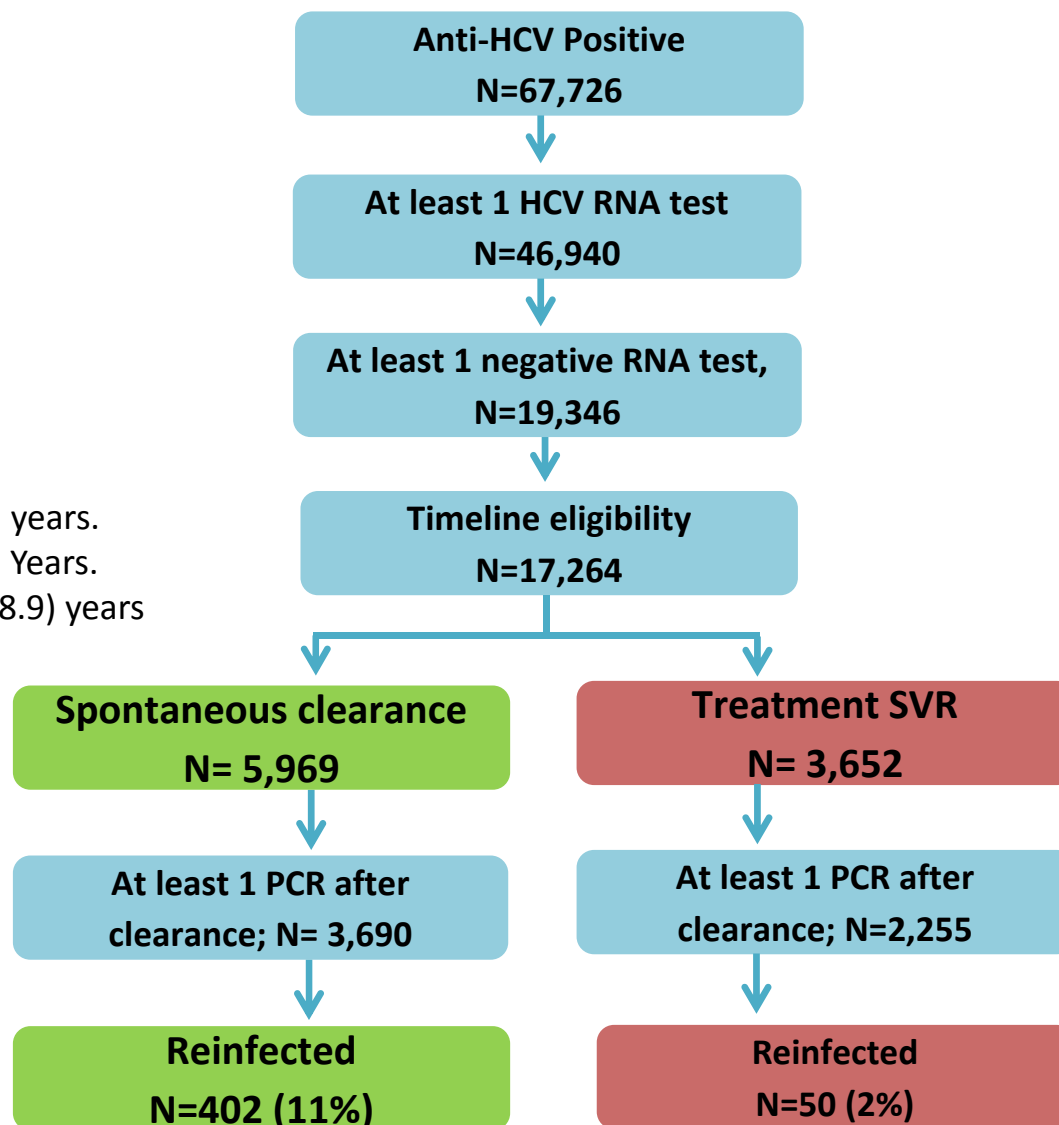
Selection of participants for HCV reinfection analysis in British Columbia, Canada

Median Follow up time:

Full cohort: 5.4 (IQR: 2.9-8.7) years.

Reinfected: 3.0 (IQR: 1.5-5.4) Years.

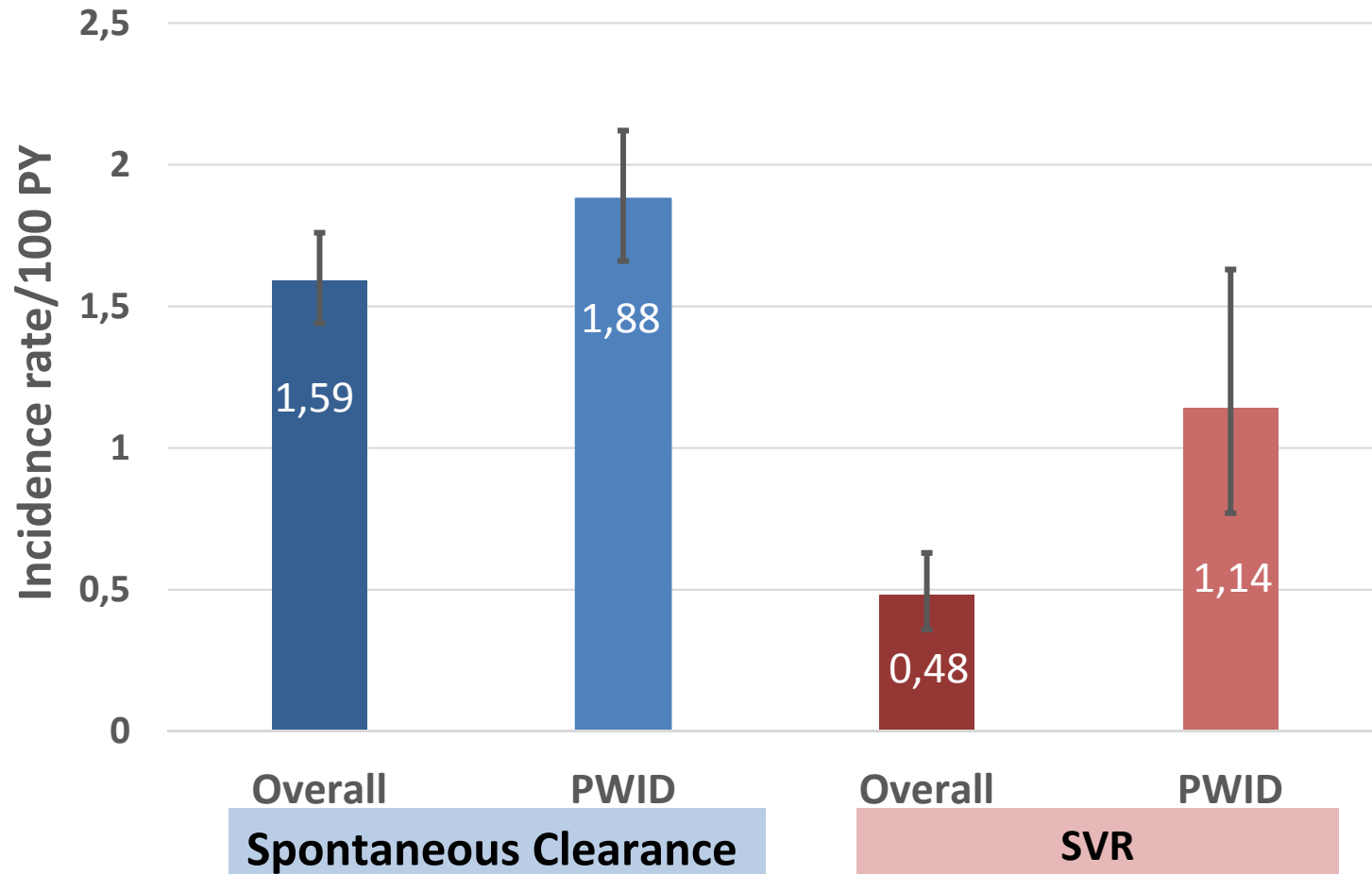
No reinfection: 5.7 (IQR: 3.1-8.9) years



Participant profile

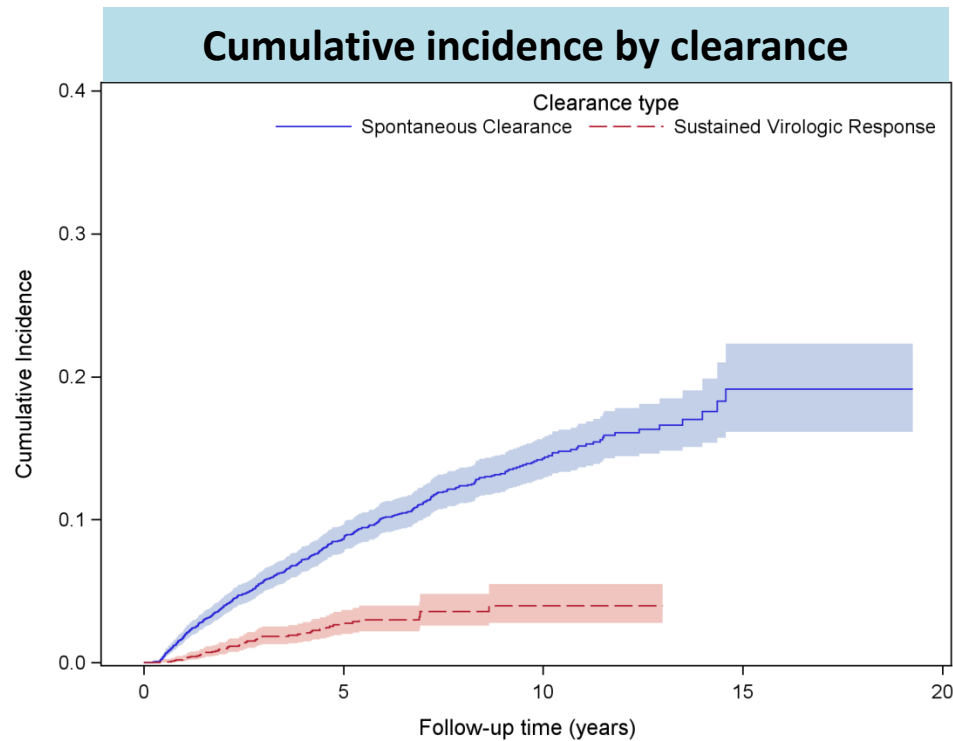
	Spontaneous clearance		SVR		Total	
	Overall	Reinfection	Overall	Reinfection	Overall	Reinfection
Age at clearance (years)	(n=3690)	(n=402)	(n=2225)	(n=50)	(n=5915)	(n=452)
< 35	1216(33)	180 (44.8)	248(11.1)	9 (18)	1464(24.8)	189 (41.8)
35-44	1224(33.2)	151 (37.6)	443(19.9)	16 (32)	1667(28.2)	167 (37)
≥ 45	1250(33.9)	71 (17.7)	1534(68.9)	25 (50)	2784(47.1)	96 (21.2)
Median [IQR]	40[32-47]	36[28-42]	50[42-55]	45[36-53]	43[35-51]	37 [30-43]
Male	2068(56)	248 (61.7)	1403(63.1)	40 (80)	3471(58.7)	288 (63.7)
HIV co-infection	407(11)	79 (19.7)	126(5.7)	12 (24)	533(9.0)	91 (20.1)
≥1 mental health counseling visit	1168(31.7)	119 (29.6)	414(18.6)	16 (32)	1582(26.7)	135 (29.9)
Injection drug use	1928(52.2)	268 (66.7)	565(25.4)	30 (60)	2493(42.1)	298 (65.9)
Problematic alcohol use	1615(43.8)	210 (52.2)	586(26.3)	19 (38)	2201(37.2)	229 (50.7)
Material deprivation quintile						
Q1 (most privileged)	492(13.3)	42 (10.5)	321(14.4)	11 (22)	813(13.7)	53 (11.7)
Q5 (most deprived)	1183(32.1)	132 (32.8)	577(25.9)	13 (26)	1760(29.8)	145 (32.1)
Genotype						
G1	400 (10.8)	109 (27.1)	846 (38)	17 (34)	1246 (21.1)	126 (27.9)
G3	280 (7.6)	73 (18.2)	616 (27.7)	20 (40)	896 (15.1)	93 (20.6)

Reinfection incidence rate

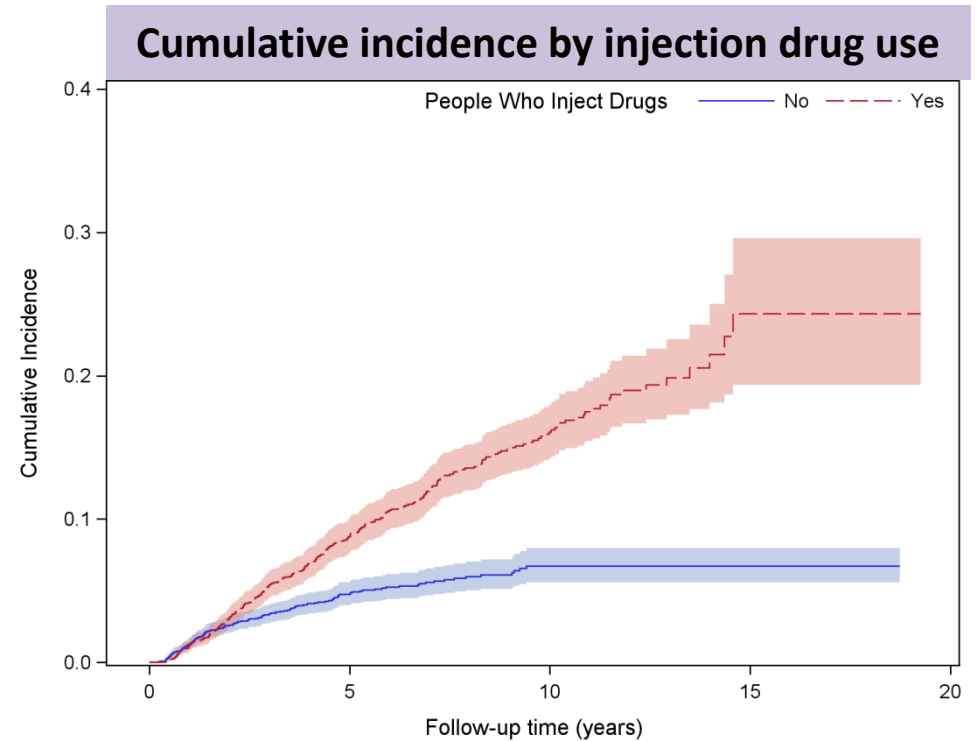


Incidence Rate Single PCR	
Spontaneous Clearance	SVR
Overall	1.00 (0.83-1.18)
PWID	2.11 (1.66-2.65)

Cumulative incidence of HCV reinfection by clearance type of previous episode, and by injection drug use status



Timeline	Spontaneous Clearance	SVR
5 years	9% (8-10)	3% (2-4)
10 years	14% (13-16)	4% (3-5)
15 years	19% (16-22)	-



Timeline	PWID	Not PWID
5 years	9% (8-10)	5% (4-6)
10 years	16% (14-18)	7% (6-8)
15 years	24% (19-30)	7% (6-8)

Cox proportional hazards model for time to HCV reinfection in British Columbia, Canada

Characteristics	Unadjusted HR (95% CI)	Adjusted HR (95%CI)
Age at clearance (years) (Ref: ≥ 45)		
< 35	3.18 (2.49-4.07)	
35-44	2.39 (1.86-3.08)	
Birth cohort (Ref: ≥1975)		
< 1965	0.35 (0.27-0.44)	0.48 (0.37-0.63)
1965-1974	0.79 (0.62-1.01)	0.87 (0.68-1.13)
Female	0.71 (0.59-0.86)	0.57 (0.47-0.7)
Spontaneous clearance	3.63 (2.7-4.89)	2.71 (2.0-3.68)
HIV co-infection	2.77 (2.20-3.49)	2.25 (1.78-2.85)
At least one mental health counseling visit	0.9 (0.74-1.1)	
Injection drug use	2.21 (1.82-2.69)	1.53 (1.21-1.92)
Problematic alcohol use	1.45 (1.21-1.75)	1.04 (0.84-1.28)

Factors associated with reinfection among PWIDs

Characteristics	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Age at clearance (years) (Ref: ≥ 45)		
< 35	2.47 (1.58-3.86)	
35-44	1.8 (1.13-2.87)	
Birth cohort (Ref: ≥1975)		
< 1965	0.39 (0.28-0.55)	0.47 (0.33-0.69)
1965-1974	0.71 (0.52-0.98)	0.89 (0.63-1.25)
Female	0.82 (0.63-1.07)	0.71 (0.54-0.93)
Spontaneous clearance	1.52 (0.9-2.58)	
HIV co-infection	2.11 (1.59-2.81)	2.39 (1.79-3.19)
≥ 1 mental health counseling visit	0.72 (0.55-0.94)	0.71 (0.54-0.92)
Problematic alcohol use	0.92 (0.69-1.22)	
Opioid substitution therapy	0.74 (0.55-1)	0.73 (0.54-0.98)

HCV Reinfection Rate and Cox Proportional Hazards models for Factors Associated with reinfection Overall and among PWIDs

Characteristics	Main analysis ¹	Sensitivity analysis ²
Total sample	5,915	10,408
Reinfection; N(%)	452 (7.6%)	1,231 (11.8%)
Reinfection Incidence Rate (95% CI)/100 person-years		
Overall	1.27 (1.15-1.39)	2.42 (2.29-2.56)
Spontaneous clearance ³	1.59 (1.44-1.76)	2.88 (2.71-3.05)
SVR ⁴	0.48 (0.36-0.63)	1.00 (0.83-1.18)
PWID	1.77 (1.57-1.98)	3.34 (3.12-3.56)
Factors associated with HCV reinfection; aHR (95% CI)		
Female	0.57 (0.47-0.7)	0.77 (0.68-0.86)
Spontaneous clearance ³	2.71 (2.0-3.68)	2.62 (2.16-3.17)
HIV co-infection	2.25 (1.78-2.85)	2.03 (1.74-2.38)
Injection drug use	1.53 (1.21-1.92)	1.72 (1.49-1.98)
Effect of OST on HCV reinfection among PWID; aHR (95% CI) ⁵	0.73 (0.54-0.98)	0.80 (0.69-0.94)

¹ Clearance was defined as two consecutive negative PCR ≥ 28 days apart; ² Clearance was defined as single negative PCR; ³ Clearance type of previous episode; aHR= Adjusted Hazard Ratios; CI= Confidence Interval; ⁴SVR= Sustained Virologic Response; PWID= People Who Inject Drugs; OST= Opioid Substitution Therapy; ⁵ adjusted for birth cohort, gender, psychotherapy, HIV & yr.

Summary

- Overall incidence of reinfection during interferon era higher among those who spontaneously cleared (1.6 or 2.9 /100 PY), HIV coinfecting (2.56 or 4.17/100 PY) and PWID (1.77 or 3.34/100 PY)
 - More PWIDs especially those with ongoing high risk injecting behavior being treated with DAAs, reinfection rate expected to increase
- OST and mental health counselling reduced risk of re-infection.
 - Requires further investigations to assess impact of OST, needle distribution and other support services



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Research Article
Viral Hepatitis



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Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort

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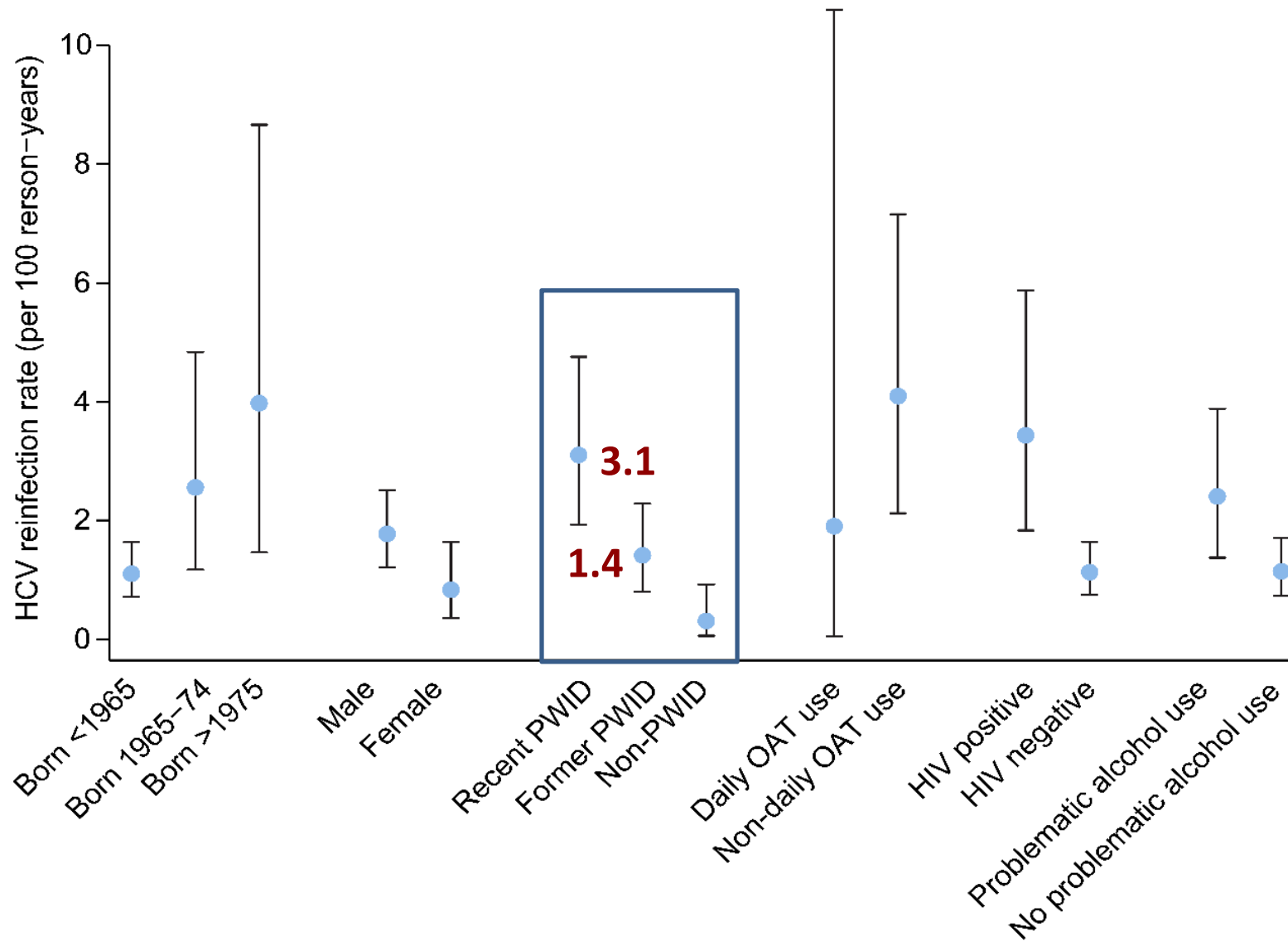
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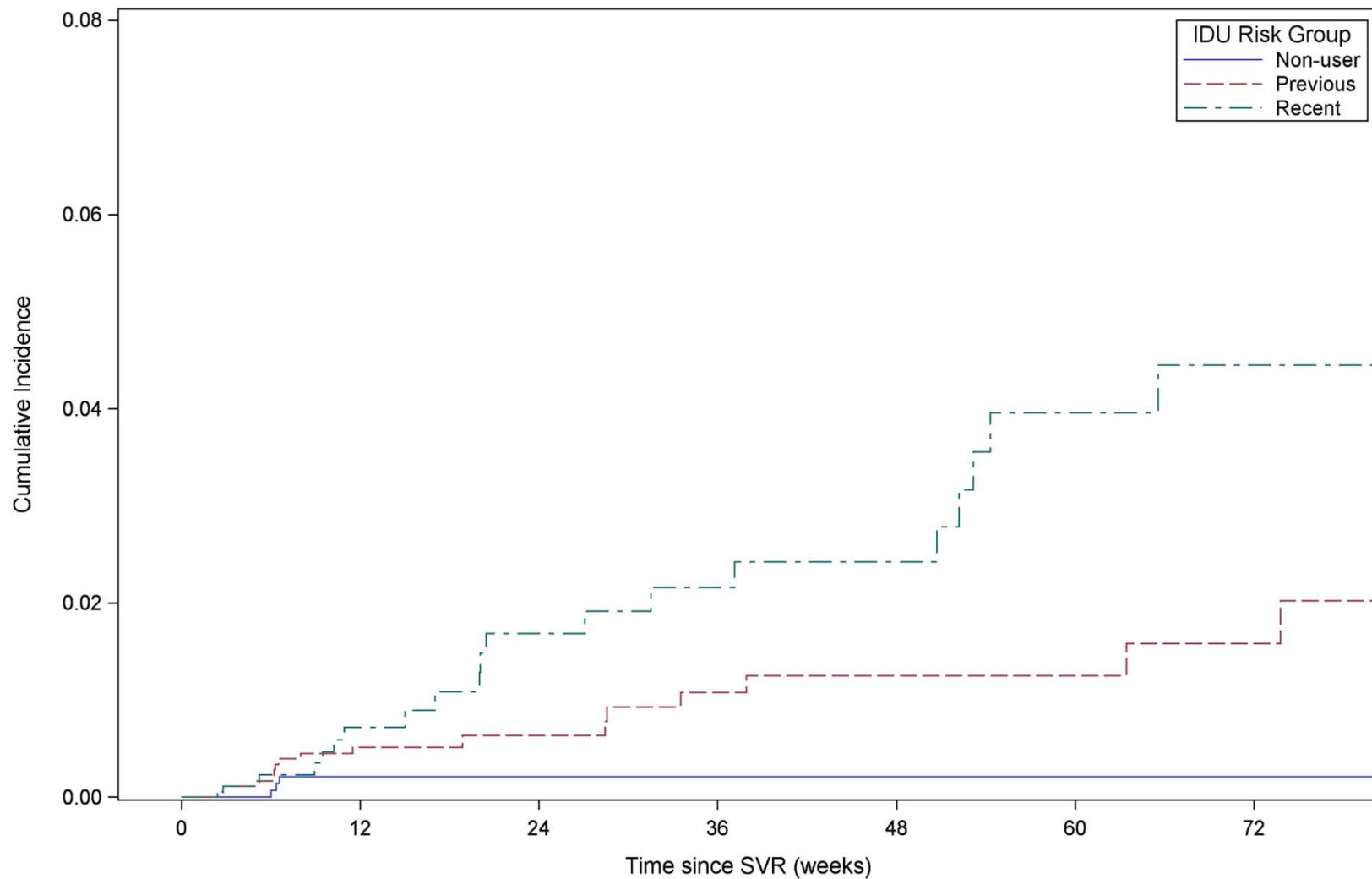
Methods

- **The BC Hepatitis Testers Cohort:** Integration of HCV testing data with prescription, mortality and other administrative data
- DAA initiators (n = 4,114) were followed from date of sustained virologic response (SVR) until the earliest of reinfection, death, or last HCV RNA measurement before 2017/12/31.
- HCV reinfection was defined as a single positive HCV RNA measurement after ascertainment of SVR status.
- We assessed factors associated with reinfection: age, sex, birth cohort, HIV co-infection, recent and former IDU, opioid-agonist therapy (OAT) use, alcohol use, and major mental illness.
- Poisson regression was used to model incidence rate ratios (IRRs), overall, and among PWIDs, adjusted for the variables listed above.

HCV reinfection rates (per 100 person-years)



Cumulative incidence curves for reinfection by IDU history



1446	1194	621	526	375	290	212
1793	1495	743	610	440	335	234
875	747	459	379	287	215	165

HCV reinfections rates (per 100 person-years) and adjusted IRRs (95% CIs), overall and among PWIDs

	Overall (n = 4,114)		Recent PWIDs (n = 875)	
	Crude Incidence Rate/100 PY	Adjusted IRR (95% CI)	Crude Incidence Rate/100 PY	Adjusted IRR (95% CI)
Age group				
< 45 years	4.16 (1.90, 7.90)	5.8 (1.4, 9.1)	10.4 (4.74, 19.7)	1.5 (1.3, 1.6) per year increase
45 to 64 years	1.43 (0.96, 2.06)	3.0 (0.7, 7.1)	2.26 (1.17, 3.94)	
≥ 65 years	0.38 (0.05, 1.38)	Reference	0 (0, 6.58)	
Gender				
Male	1.77 (1.21, 2.50)	3.0 (1.1, 7.8)	3.82 (2.23, 6.12)	2.3 (0.8, 6.8)
Female	0.83 (0.36, 1.64)	Reference	1.74 (0.47, 4.46)	Reference
PWID				
Recent	3.11 (1.93, 4.76)	6.7 (1.9, 23.5)		
Former	1.41 (0.80, 2.28)	3.7 (1.1, 12.9)		
No	0.31 (0.06, 0.92)	Reference		
OAT in previous 12 weeks				
Daily use		N/A	1.90 (0.05, 10.6)	0.7 (0.4, 2.4)
Non-daily use		N/A	4.10 (2.12, 7.16)	Reference
Major mental illness				
Yes	2.11 (1.27, 3.29)	1.1 (0.5, 2.1)	3.02 (1.45, 5.56)	0.5 (0.2, 1.3)
No	1.13 (0.70, 1.72)	Reference	3.20 (1.60, 5.73)	Reference
Problematic alcohol use				
Yes	2.40 (1.37, 3.89)	1.2 (0.6, 2.4)	4.55 (2.35, 7.94)	2.1 (0.8, 5.2)
No	1.14 (0.73, 1.70)	Reference	2.19 (1.00, 4.16)	Reference
HIV Co-Infection				
Yes	3.44 (1.83, 5.87)	1.6 (0.8, 3.3)	5.67 (2.59, 10.8)	1.8 (0.7, 4.5)
No	1.13 (0.75, 1.64)	Reference	2.33 (1.20, 4.07)	Reference

Summary

- In DAA era, re-infection rates among PWID treated with DAAs similar to SC during interferon era.
 - Rates similar to other settings.
- Risk factors are similar: younger age, HIV co-infection, problematic alcohol use.
- Data show trend towards prevention of reinfection by OST but would require further monitoring as characteristics of those being treated are changing.
- Among MSM, HIV co-infection, IDU, problematic alcohol use associated with higher risk while psychotherapy associated with lower risk.

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Thank you!

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