Benefits of DAA treatment on mortality related to extrahepatic manifestations among people who inject drugs: a population-based study in British Columbia, Canada

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BC Centre for Disease Control
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British Columbia Ministry of Health

BC HTC British Columbia Hepatitis Testers Cohort

UBC

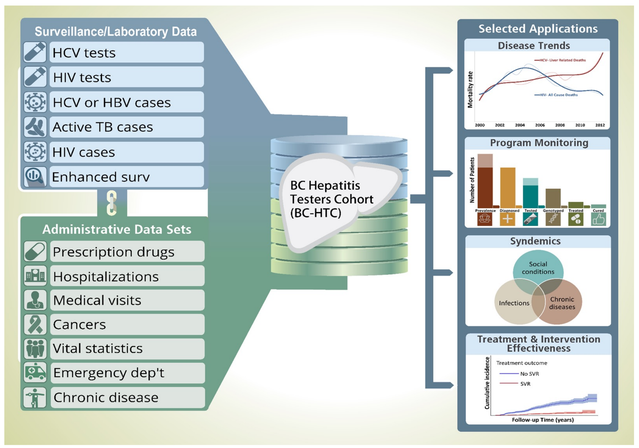
Background

- Infection with hepatitis C virus (HCV) increases the risk of extrahepatic manifestations (EHMs) and mortality related to EHMs.[1,2]
- Direct-acting antivirals (DAA) are highly effective and well tolerated treatment for HCV infection, and have been publicly funded in British Columbia (BC) since 2015 through Pharmacare.
- Treatment with DAA results in high sustained virologic response (SVR) rates, even among populations with lower adherence such as people who inject drugs (PWID). PWID have an increased risk for chronic HCV infection and EHM-related mortality. SVR from DAA treatment has been linked with decreased all-cause mortality.[3] DAA treatment is also expected to have a protective effect against EHMs and therefore decrease mortality related to EHMs.[4]

Purpose

- To assess the benefits of DAA treatment and SVR on mortality related to extrahepatic manifestations among people who inject drugs, using a large population-based linked laboratory and administrative data in British Columbia, Canada.

Methods



- This study used data from the BC Hepatitis Testers Cohort (BC-HTC), which includes ~1.3 million individuals tested for HCV at the BC Centre for Disease Control or reported as a case of HCV in BC since 1990. The BC-HTC is linked to BC Ministry of Health administrative databases (medical visits, hospitalizations, prescription drugs), cancer diagnoses and vital statistics.
- **Study population:** We included individuals who were identified to have a chronic HCV infection by December 31, 2018. PWID were identified using a previously validated algorithm[5] based on ICD-9/10 and physician billing codes related to injection drug use and related complications.
- **Exposure:** Individuals who received at least one DAA treatment were considered as 'Treated'. Those who never received treatment were considered 'Untreated'. Each treated person was matched to an untreated person, by the year of their first HCV RNA diagnosis date, within a 12-month timeframe, without replacement. Treatment outcome was assessed with SVR, determined with post-treatment HCV RNA testing with an undetectable serum HCV RNA obtained at at ≥10 weeks post treatment, with most SVR assessments ≥12 weeks after treatment.
- We compared three groups: **'Treated & SVR'**, **'Treated & no-SVR'** and **'Untreated'**.
- **Baseline** for treated persons was the date of first DAA treatment dispensation of the last treatment course; for untreated persons, the baseline of the matched treated person was used.
- **Outcome:** Deaths due to EHMs included deaths related to diabetes, cardiovascular, cerebrovascular and chronic kidney diseases, rheumatoid arthritis and neurocognitive disorders.
- We followed the study population from the baseline to the earliest of 1) EHM-related death; 2) other death; or 3) end of study (2019/12/31).
- We computed the crude EHM-related mortality rates and generated survival and cumulative incidence curves.
- To adjust for differences in baseline characteristics that exist between treated and untreated individuals, we estimated the inverse probability of treatment weights (IPTW) for the average treatment effect (ATE). Weights were assigned to induce balance between the three groups.
- We used a multivariable Fine-Gray subdistributional hazards model with IPTW, adjusting for competing mortality risk and confounders including socio-demographic and clinical characteristics assessed at baseline.

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Results

Table 1. Baseline characteristics of PWID and non-PWID by HCV treatment status

	PWID			non-PWID		
Covariate	**SVR (n=3,424)**	**no-SVR (n=224)**	**Untreated (n=4,744)**	**SVR (n=6,830)**	**no-SVR (n=216)**	**Untreated (n=5,950)**
Male sex (%)	2189 (63.9)	156 (69.6)	3092 (65.2)	4441 (65.0)	166 (76.9)	4101 (68.9)
Age category (%)						
<35	231 (6.7)	18 (8.0)	516 (10.9)	190 (2.8)	12 (5.6)	369 (6.2)
35 to 44	500 (14.6)	48 (21.4)	1008 (21.2)	333 (4.9)	14 (6.5)	593 (10.0)
45 to 54	1118 (32.7)	73 (32.6)	1559 (32.9)	1190 (17.4)	38 (17.6)	1362 (22.9)
55 to 64	1303 (38.1)	69 (30.8)	1349 (28.4)	3467 (50.8)	95 (44.0)	2123 (35.7)
≥65	272 (7.9)	16 (7.1)	312 (6.6)	1650 (24.2)	57 (26.4)	1503 (25.3)
Follow-up, mean years (SD)	2.23 (1.37)	1.61 (1.30)	1.96 (1.38)	2.70 (1.47)	2.35 (1.59)	2.11 (1.41)
Material deprivation (%)						
Q1 (most privileged)	538 (15.7)	33 (14.7)	642 (13.5)	1063 (15.6)	41 (19.0)	821 (13.8)
Q5 (most deprived)	1062 (31.0)	83 (37.1)	1792 (37.8)	1473 (21.6)	52 (24.1)	1583 (26.6)
Social deprivation (%)						
Q1 (most privileged)	242 (7.1)	13 (5.8)	332 (7.0)	847 (12.4)	27 (12.5)	689 (11.6)
Q5 (most deprived)	1672 (48.8)	125 (55.8)	2533 (53.4)	2108 (30.9)	67 (31.0)	2167 (36.4)
Genotype 1 (%)	2105 (61.5)	134 (59.8)	2063 (43.5)	4679 (68.5)	129 (59.7)	2572 (43.2)
HBV infection (%)	350 (10.2)	18 (8.0)	367 (7.7)	276 (4.0)	<5	184 (3.1)
HIV infection (%)	520 (15.2)	43 (19.2)	398 (8.4)	256 (3.7)	5 (2.3)	106 (1.8)
Hypertension (%)	739 (21.6)	26 (11.6)	750 (15.8)	2178 (31.9)	81 (37.5)	1389 (23.3)
Diabetes mellitus (%)	439 (12.8)	23 (10.3)	431 (9.1)	1052 (15.4)	43 (19.9)	742 (12.5)
Mood & anxiety disorder (%)	3031 (88.5)	192 (85.7)	4044 (85.2)	3939 (57.7)	114 (52.8)	3049 (51.2)
Cirrhosis (%)	271 (7.9)	17 (7.6)	267 (5.6)	600 (8.8)	47 (21.8)	299 (5.0)
Alcohol use disorder (%)	1904 (55.6)	124 (55.4)	2546 (53.7)	974 (14.3)	37 (17.1)	1019 (17.1)
Opioid agonist therapy (%)	2012 (58.8)	156 (69.6)	2801 (59.0)	580 (8.5)	33 (15.3)	900 (15.1)
Elixhauser Index ≥2 (%)	2391 (69.8)	158 (70.5)	3177 (67.0)	1548 (22.7)	75 (34.7)	1308 (22.0)

Table 2. EHM-related mortality rates among PWID and non-PWID per 1,000 person-years of follow-up

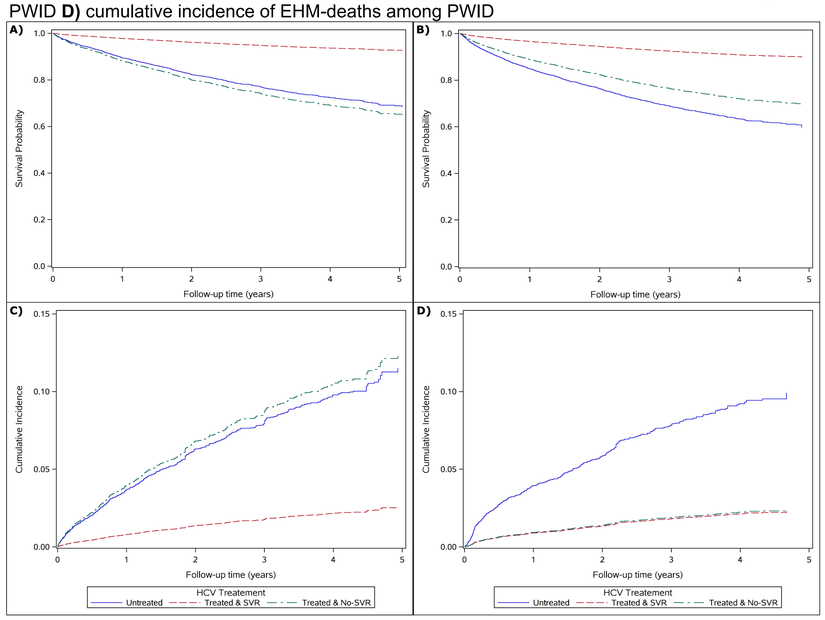
	PWID (95% CI)	Non-PWID (95% CI)	Overall (95% CI)
Treated & SVR	6.8 (5.2-9.0)	5.5 (4.5-6.6)	5.9 (5.0-6.9)
Treated & no-SVR	11.1 (4.2-29.5)	35.5 (22.3-56.3)	25.3 (16.7-38.5)
Untreated	29.0 (25.7-32.7)	29.7 (26.8-32.9)	29.4 (27.2-31.8)

Table 3. Adjusted hazard ratios for the effect of DAA treatment on EHM-related mortality, from Fine-Gray multivariable model*

	PWID aHR (95% CI)	Non-PWID aHR (95% CI)	Overall aHR (95% CI)
Untreated	Ref	Ref	Ref
No-SVR	0.20 (0.07-0.57)	0.95 (0.35-2.56)	0.72 (0.30-1.76)
SVR	0.17 (0.12-0.25)	0.16 (0.12-0.20)	0.16 (0.13-0.20)

*Adjusted for sex, categorical age, ethnicity, material and social deprivation quintiles, HCV genotype, HBV infection, HIV infection, ischemic stroke, heart failure, hypertension, statin use, diabetes mellitus, obesity, mood and anxiety disorder, cirrhosis, alcohol use disorder, opioid agonist therapy and Elixhauser comorbidity index

Figure 1. Survival probabilities and cumulative incidences of deaths due to extrahepatic manifestations among PWID and non-PWID by HCV treatment in BC **A)** survival probability among non-PWID **B)** survival probability among PWID **C)** cumulative incidence of EHM-deaths among non-PWID **D)** cumulative incidence of EHM-deaths among PWID



Key Findings

- Successful treatment of HCV infection with DAA was associated with **a significantly reduced risk of EHM-related mortality** compared to not ever receiving treatment
- Achieving SVR from DAA treatment provided benefits for **both PWID and non-PWID** in this population
- Among PWID, even without SVR, receiving treatment was associated with reduced EHM-related mortality. These results may be influenced by the small number of observed events, but still warrant **further assessment to explore the potential benefits** associated with providing treatment and engaging in care among PWID

Implications

Direct-acting antiviral treatment for HCV

84% Reduction in Mortality related to extrahepatic manifestations

For healthcare providers

- DAA treatment results in a significant reduction in EHM-related mortality in the overall population and among PWID
- Engagement in care may provide additional benefits
- Can be motivating for both providers and patients to treat hepatitis C infection

For patients

- HCV treatment can not only cure them of HCV but also provides non-liver related benefits; reducing mortality risk from heart, kidney, metabolic and neurologic disorders
- Being aware of all these benefits of treating hepatitis C can increase their motivation to start and finish treatment

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CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

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