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Impact of direct-acting antiviral treatment on mortality related to extrahepatic manifestations: findings from a large population-based cohort in British Columbia, Canada

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UBC

Acknowledgements

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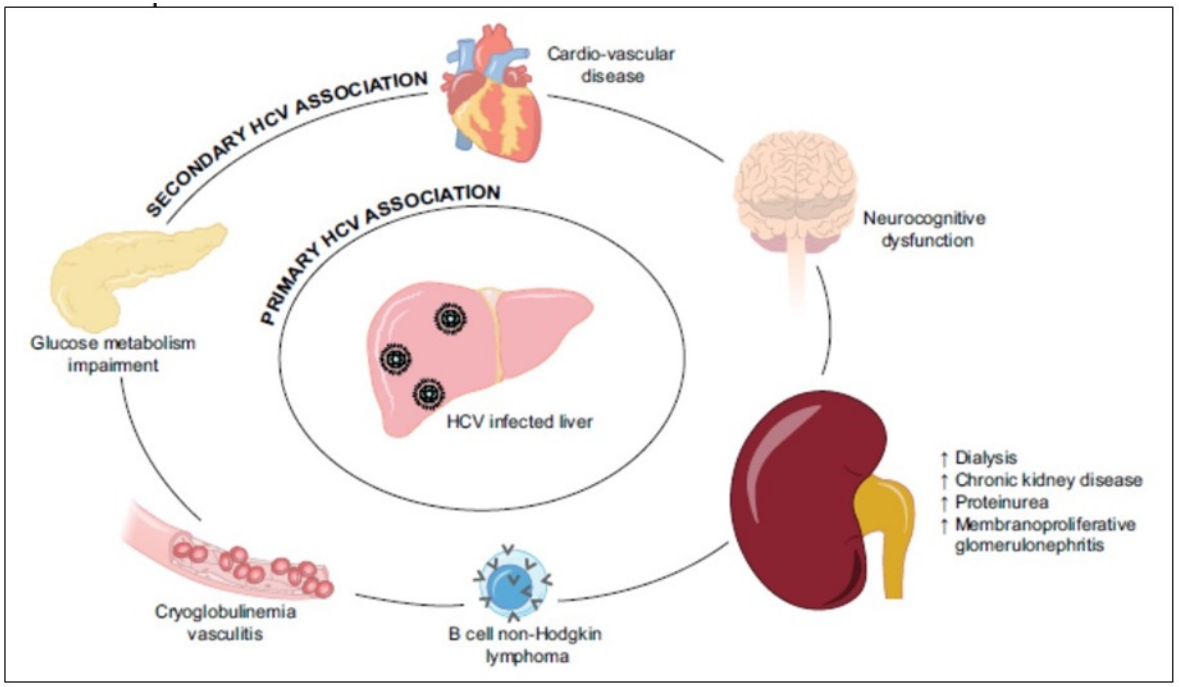
Disclosure of Interest

I have no conflict of interest to disclose

Extrahepatic manifestations (EHMs) of chronic HCV infection

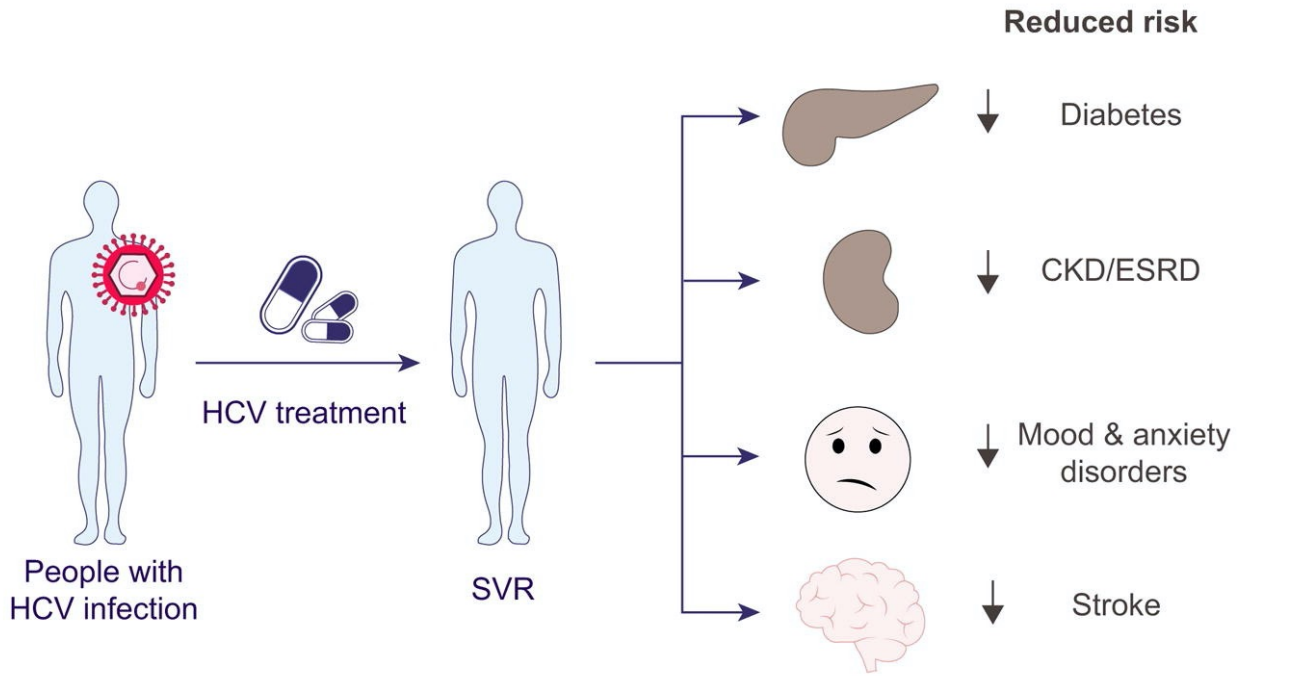


Cacoub P, et al. *J Hepatol.* 2016;65(1 Suppl):S82-S94.

What's known?:

- Extrahepatic manifestations (EHMs) caused by chronic HCV infection
- EHMs can amplify harmful effects of HCV infection and disease sequelae including deaths

Effect of direct-acting antivirals on EHMs



Rossi C *et al* J Hepatol 2019. https://doi.org/10.1016/j.jhep.2019.07.021

What's known?:

- DAAs associated with reduced risk of EHMs
- DAAs associated with decreased all-cause and liver-related mortality

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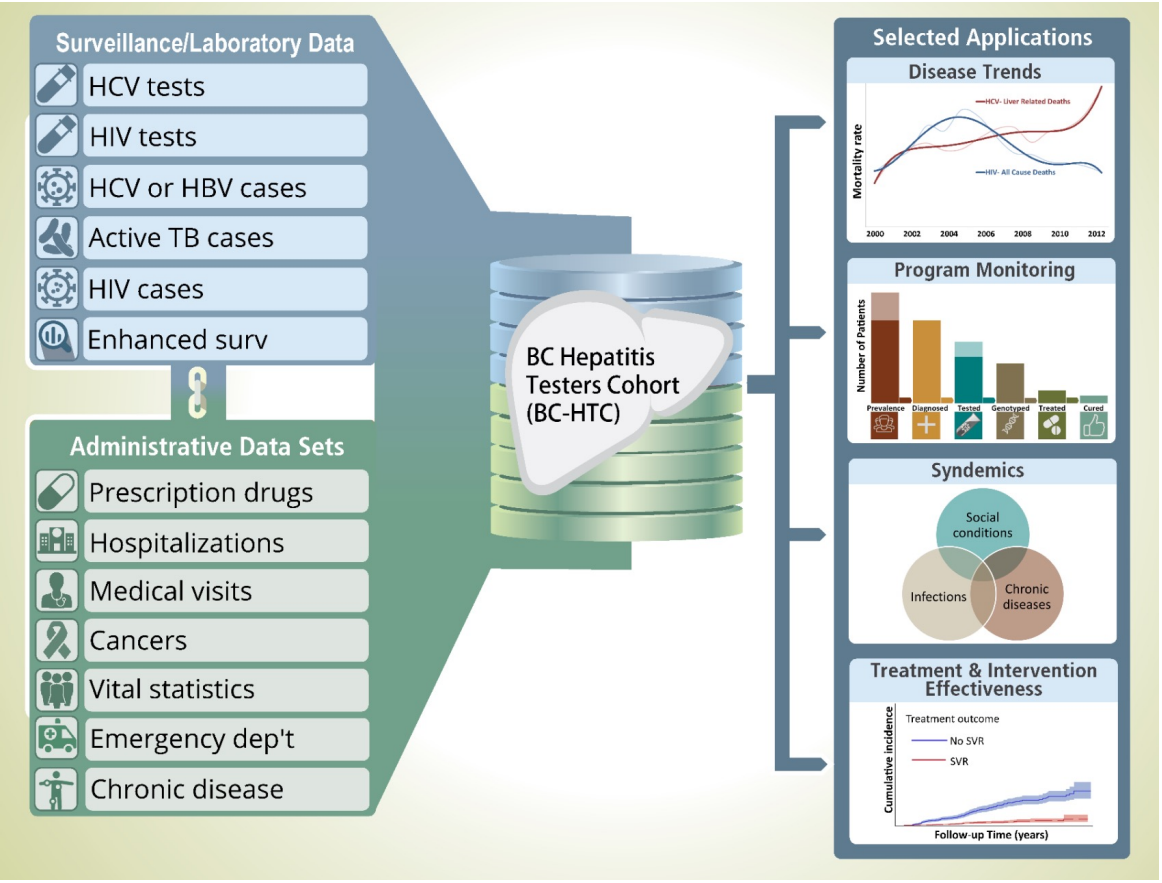
What is the impact of DAA treatment and SVR on reducing mortality related to extrahepatic manifestations?

Data source



- A large population-based linked administrative data
- Includes ~1.3 million people tested for HCV at BCCDC Public Health Laboratory or reported as a confirmed case since 1990
- Linked to BC Ministry of health administrative databases, including all prescription medications dispensations, hospital or ambulatory visits, primary care visits and chronic disease registry

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Study population

Individuals who were identified to have a chronic HCV infection by December 31, 2018:

- Those who received at least one DAA treatment were matched to those who never received treatment by the year of their HCV diagnosis date, within a 12-month timeframe.
- The *index date (baseline)* for treated individuals was the treatment start date, and this date was assigned to the matched untreated individual as their index date.

Study participants were followed from the index date to the earliest of:

1) Death related to EHMs
2) Any other death
3) End of study (December 31, 2019)

Study variables

Exposure: we compared three groups, ***treated & SVR***, ***treated & no-SVR***, and ***untreated***

- SVR was determined through post-treatment HCV RNA testing, with an undetectable HCV RNA obtained ≥ 12 weeks after treatment.
- People with missing information on SVR was excluded.

Outcome: EHM-related deaths included deaths related to six types of EHMs (diabetes, cardiovascular diseases, cerebrovascular diseases, chronic kidney diseases, rheumatoid arthritis and neurocognitive disorders)

Covariates: socio-demographic and clinical characteristics (e.g. age at HCV diagnosis, sex, social and material deprivation, comorbidities at baseline)

Stratified analysis

- People who use injection drugs (PWID) have an increased risk of chronic HCV infection and therefore EHM-related mortality as well
- Previous studies have shown differences in risk of mortality among PWID compared to overall population; by stratifying, we tried to assess if there was any disparity in EHM-related mortality among PWID
- PWID were identified using a previously validated algorithm based on ICD 9/10 and physician billing codes related to injection drug use (IDU) and complications related to IDU
  - Definition of IDU: the occurrence of at least 1 MSP (physician billing code), 1 hospitalization, or 1 PharmaNet code for major drug-related diagnoses involving addiction, dependence, and drug-induced mental disorders; illicit drug use most likely to be injecting (e.g. excluding cannabis), or illicit use of prescribed drugs including: hallucinogens, barbiturates/tranquillizers, sedatives, hypnotics, anxiolytics, opioids, cocaine, amphetamine, volatile solvents; or discharge to drug rehabilitation, counselling, and surveillance ($11 \leq$ diagnosis age ≤ 65).

Analytical steps

To assess the impact of DAA treatment on mortality related to EHMs:

1) We computed crude EHM mortality rates
2) Generated survival curves and cumulative incidence curves
3) Estimated the inverse probability of treatment weights (IPTW) for the average treatment effect (ATE) to adjust for differences in baseline characteristics that exist between treated and untreated individuals
4) Used Fine-Gray multivariable subdistributional hazards model with IPTW to adjust for competing mortality risk and confounders

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Results

Study participants' characteristics

- Study population included:
  - 10,694 untreated individuals
  - 10,694 treated individuals
    - 10,254 achieved SVR (95.9%)
    - 440 did not achieve SVR (4.1%).
- In the study population, there were 8,392 persons with history of IDU (39.2%)
- Among PWID, majority (56.5%) had never received treatment, compared to non-PWID that majority (54.2%) had received treatment.
- Overall, 3.9% of PWID and 3.8% of non-PWID had died due to EHMs. For deaths unrelated to EHMs, 12.2% of PWID in the study population had died compared to 7.0% of non-PWID.

EHM-related mortality rates among PWID and non-PWID

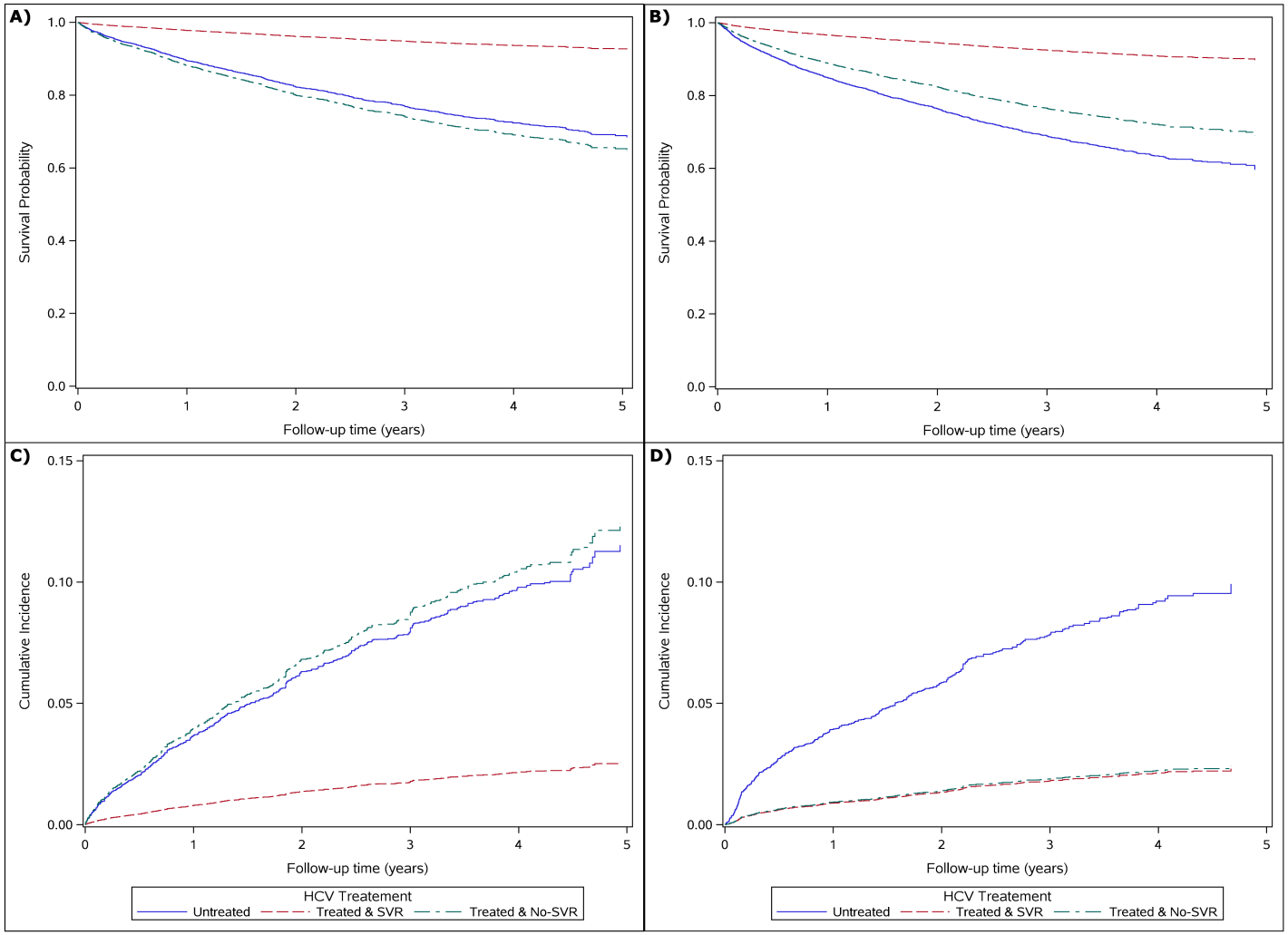
EHM-related mortality rate (per 1,000 person-years of follow-up)

	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)

Survival and cumulative incidence curves

Non-PWID

PWID



Impact of DAA treatment on EHM-related mortality

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

Covariate	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

Sensitivity analyses

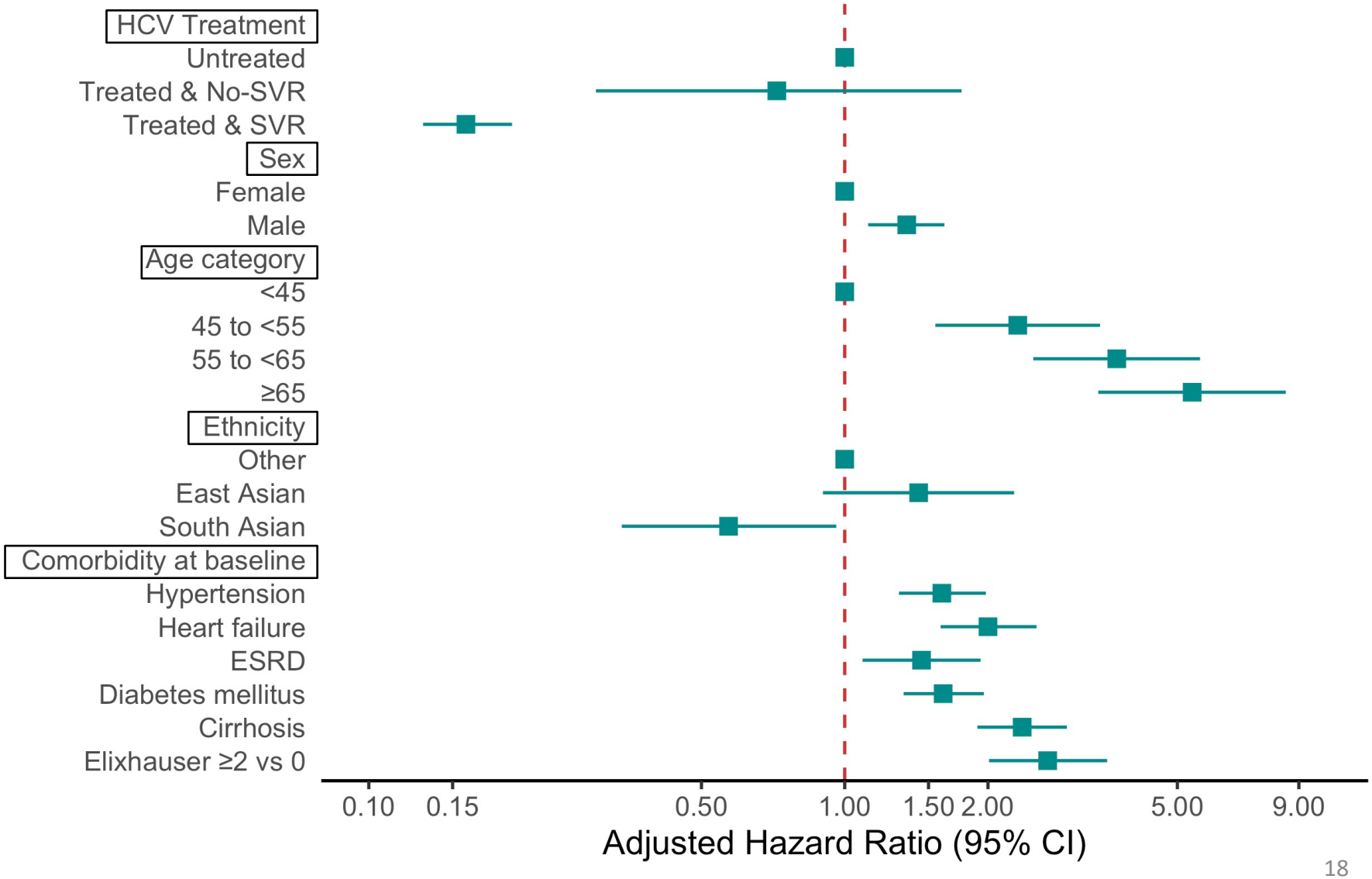
Adjusted hazard ratios for the effect of SVR compared to untreated on EHM-related mortality, from Fine-Gray multivariable model (excluding no-SVR)

Covariate	PWID aHR (95% CI)	Non-PWID aHR (95% CI)	Overall aHR (95% CI)
Untreated	Ref	Ref	Ref
SVR	0.17 (0.12-0.24)	0.16 (0.12-0.20)	0.16 (0.13-0.20)

Adjusted hazard ratios for the effect of SVR compared to no-SVR on EHM-related mortality, from Fine-Gray multivariable model (excluding untreated)

Covariate	PWID aHR (95% CI)	Non-PWID aHR (95% CI)	Overall aHR (95% CI)
No-SVR	Ref	Ref	Ref
SVR	0.49 (0.14-1.67)	0.21 (0.11-0.40)	0.21 (0.12-0.37)

Impact of DAA treatment on EHM-related mortality



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Key findings & Implications

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.
- SVR from DAA provided benefits for both PWID and non-PWID.
- 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

Disclaimer

All inferences, opinions, and conclusions drawn in this presentation are those of the author(s), and do not reflect the opinions or policies of the BC Ministry of Health or Data Steward(s).

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Questions? Comments?

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