Treatment of HCV with direct-acting antivirals on reducing mortality related to extrahepatic manifestations: a large population-based study in British Columbia, Canada

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Summary

Background HCV infection is associated with mortality due to extrahepatic manifestations (EHM). Sustained virologic response (SVR) following direct-acting antiviral (DAA) therapy has been linked to decreased all-cause and liver-related mortality. However, evidence regarding the impact of DAA on EHM-related deaths is lacking. This study aimed to assess the impact of DAA and SVR on EHM-related mortality.

Methods The British Columbia Hepatitis Testers Cohort comprises ~1.7 million people tested for HCV between 1990 and 2015 and is linked with administrative health data. Among individuals diagnosed with HCV by 12/31/2020, those who received at least one DAA treatment were matched to those who never received treatment by the year of their first HCV RNA positive date. We compared three groups: treated & SVR, treated & no-SVR, and untreated; and generated EHM mortality rates and incidence curves. To account for differences in baseline characteristics, we used inverse probability of treatment weights (IPTW). IPTW-weighted multivariable cause-specific Cox regression models were adjusted for competing risk and confounders.

Findings Study population included 12,815 treated (12,287 SVR, 528 no-SVR) and 12,815 untreated individuals (median follow-up 3.4 years, IQR 2.9). The untreated group had the highest EHM mortality rate (30.9 per 1000 person-years [PY], 95% CI 29.2–32.8), followed by the treated & no-SVR group (21.2 per 1000 PY, 95% CI 14.9–30.1), while the treated & SVR group had the lowest EHM mortality rate (7.9 per 1000 PY, 95% CI 7.1–8.7). In the multivariable model, EHM mortality in the treated & SVR group was significantly decreased (adjusted cause-specific hazard ratio [acsHR] 0.20, 95% CI 0.18–0.23). The treated & SVR group had significant reductions in mortality related to each of the EHMs (78–84%).

Interpretation Treatment of HCV with DAA was associated with significant reductions in EHM-related mortality. These findings emphasize the critical importance of timely diagnosis and treatment of HCV to prevent deaths associated with EHM, and have important implications for clinical practice and public health.

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Keywords: Population-based study; HCV infection; Extrahepatic manifestations; Mortality; Direct-acting antivirals; Inverse probability of treatment weighting

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Research in context

Evidence before this study

HCV infection is a chronic systemic disease that can cause liver damage as well as other health problems outside the liver known as extrahepatic manifestations (EHMs), such as cardiovascular and cerebrovascular diseases, chronic kidney diseases, diabetes, and mental health conditions. Previous studies showed that chronic HCV infection is associated with increased mortality related to these EHMs. We reviewed the existing evidence of the effectiveness of direct-acting antivirals (DAAs) in treating HCV infection and reducing all-cause and liver-related mortality indexed in PubMed. Search terms included "direct-acting antivirals" AND "extrahepatic manifestations" OR "non-liver related" AND "mortality". Additional searches included epidemiologic studies of direct-acting antivirals, extrahepatic manifestations and EHM-related mortality. While some studies have investigated the effectiveness of DAAs in reducing mortality related to EHMs, previous studies had limited sample sizes and focused on the effect of sustained virologic response (SVR) only among treated individuals, without an untreated comparison group. This lack of an untreated comparison group does not provide a proper baseline for assessing the impact of DAA treatment on outcomes.

Added value of this study

This study included a large population-based sample of over 25,000 people diagnosed with chronic HCV, comparing 12,815 persons with who received DAA treatment matched to 12,815 persons with who were never treated. By including both people who were treated and those who never received treatment, the study was able to assess the effect of successful HCV treatment on reducing mortality related to EHMs compared to those who never received treatment. Moreover, the large study sample size allowed for an examination of the impact of treatment on specific EHMs, including cardiovascular, cerebrovascular, chronic kidney diseases, diabetes and certain mental health conditions, providing detailed evidence on the effectiveness of DAA therapy in reducing EHM-related deaths. To address the challenges of comparing treated and untreated individuals, we used a prescription time-distribution matching technique to equalize the follow-up time between treated and untreated individuals to adjust for immortal time bias. In addition, recognizing that individuals who received treatment and those who were never treated may differ in many baseline clinical and sociodemographic characteristics, we estimated the inverse probability of treatment weights with propensity scores to induce balance in the baseline characteristics between the treated and untreated individuals. Furthermore, we used multivariable cause-specific Cox regression models to account for competing risk of mortality related to non-EHM causes.

Implications of all the available evidence

This study showed that treating HCV with direct-acting antivirals greatly reduced deaths related to extrahepatic manifestations, including cardiovascular, cerebrovascular, chronic kidney diseases, diabetes, mood and anxiety disorders, and mental health conditions, with the reduction in mortality risk ranging from 78 to 84%. These findings highlight the significant benefits of successful HCV treatment in preventing deaths associated with extrahepatic manifestations among people living with HCV, emphasizing the importance of early diagnosis and treatment of HCV and the need to scale up global HCV treatment. Informing treatment providers and patients about these benefits is critical in promoting timely HCV treatment.

Introduction

Chronic hepatitis C virus (HCV) infection continues to be a major public health concern. In 2020, it was estimated that approximately 57 million people were living with HCV infection globally.[1] Mortality due to viral hepatitis, including HCV, increased by 22% between 2000 and 2015, and it was expected to further increase as the majority of people living with hepatitis age and have high risk of developing end-stage liver disease and cancer.[2] Mortality due to complications of chronic HCV infection is also expected to rise, as many people living with HCV around the globe remain undiagnosed or untreated.[3] Complications of chronic HCV infection are not limited to liver-related morbidity and mortality, but also include extrahepatic manifestations (EHMs).[4] Chronic HCV infection causes inflammation of various systems in affected individuals, and combined with endocrine effects, viral replication in extrahepatic cells, heightened immune response and systemic effects, can lead to development of EHMs, including metabolic, cardiovascular, cerebrovascular, renal and mental health conditions.[5–7] HCV infection has been associated with higher mortality from these extrahepatic diseases.[4,8,9]

Direct-acting antivirals (DAA) are a highly effective treatment for HCV, curing about 95% of all infections. Successful treatment is characterised by achieving a sustained virologic response (SVR), which has been shown to decrease all-cause and liver-related mortality.[10–12] Several studies have documented that treatment of HCV with DAA could be protective against EHMs.[13–15] A systematic review by Cacoub et al.[16] found that SVR was associated with reduced extrahepatic mortality, however, the studies investigating

extrahepatic mortality[17–19] included a small number of patients who received interferon-based treatment, and only included treated persons, comparing those who achieved SVR and those who did not achieve SVR. The extent of the protective effect of HCV treatment with DAA on extrahepatic mortality has not been fully studied, especially in large, population-based cohorts comparing people who received treatment and people who did not. People living with HCV infection can have multiple EHMs at the same time and are at a high risk of mortality.[16] Globally, only 21% of people with HCV infection are diagnosed, and 62% of those receive treatment.[20] A comprehensive evidence base evaluating the benefits associated with HCV treatment with DAA could serve as additional support for the goal of global HCV elimination.

In this analysis, we aimed to assess the effect of HCV treatment with DAA and SVR on extrahepatic mortality, using a large, population-based linked administrative dataset from British Columbia, Canada.

Methods

Data source

The British Columbia Hepatitis Testers Cohort (BC-HTC) is a longitudinal population-based cohort which includes ~1.7 million people tested for HCV, HIV or hepatitis B virus (HBV) at the BC Centre for Disease Control Public Health Laboratory (BCCDC-PHL), or reported by public health as a confirmed case of HCV, HBV, HIV/AIDS, syphilis, gonorrhoea, chlamydia or active tuberculosis (TB), from 1990 to 2015. Over 95% of HCV serology and all HCV RNA testing in British Columbia are performed at the BCCDC-PHL. Through a unique personal health number assigned to each resident by the BC Ministry of Health Client Roster, the BC-HTC integrates cases and testing data with various administrative health datasets, such as medical visits, hospitalisations and chronic disease registry (Supplementary Table S1). The cohort also integrates data from PharmaNet, a central system that records all prescription medication dispensed in the province including all DAA prescriptions, regardless of the payer. All deaths in BC are registered with BC Vital Statistics Agency, and the records on mortality are linked with the BC-HTC. More detail on the creation of the BC-HTC are available elsewhere.[21,22] The creation of BC-HTC and integration of data were performed under the auspices of the BC Centre for Disease Control's public health mandate, which was reviewed and approved by the Behavioural Research Ethics Board at the University of British Columbia (H14-01649).

Study population, design and exposure

From the BC-HTC, we included individuals who were identified as having a chronic HCV infection, either from a positive HCV RNA test or based on treatment data, before December 31, 2020. Individuals were considered as treated if they received at least 1 prescription of DAA. Untreated individuals had never received HCV treatment. To better understand the effect of direct-acting antivirals on extrahepatic mortality, we excluded people who only received interferon-based treatment, and those for whom the information on SVR status wasn't available. Fig. 1 shows the flowchart of the creation of study population. Treated individuals were further classified as achieving SVR or not. SVR was determined with post-treatment HCV RNA testing, where an undetectable serum HCV RNA test obtained at ≥10 weeks after treatment completion was defined as an SVR. We compared three groups: 'Treated & SVR', 'Treated & no-SVR' and 'Untreated'.

Outcome assessment

The main outcome of interest was deaths related to extrahepatic manifestations, which included deaths associated with cardiovascular diseases, cerebrovascular diseases, chronic kidney disease, diabetes mellitus, mood and anxiety disorders and other mental health-related conditions. All deaths in BC are registered with the Vital Statistics Agency, and the coroner or physician records the causes of deaths as: antecedent cause of death (acod), contributing cause of death (ccod), immediate cause of death (icod), natural cause of death (ncod), underlying cause of death (ucod) and life style factor (lsf), which can include environmental/occupational exposures and lifestyle risk factors such as asbestos, substance and tobacco use. Deaths related to EHMs were determined based on having an EHM-related ICD-10-CA diagnostic code (Supplementary Table S2) in any of the causes of death in the death certificate.[23] Mortality was assessed until December 31, 2021. A summary of causes of deaths by participant treatment status is presented in Supplementary Table S3.

Variable selection

We selected the following clinical and socio-demographic variables as potential risk factors for extrahepatic mortality based on previous literature[4,5,24]: sex, age, ethnicity, material and social deprivation quintiles, HCV genotype, HBV infection, HIV infection, hypertension, cirrhosis, alcohol use disorder, history of receiving opioid agonist therapy and history of injection drug use. Ethnicity was determined with a validated name recognition algorithm, Onomap.[25,26] Material and social deprivation quintiles were based on the Québec Index of Material and Social Deprivation which combines indicators related to health and welfare that represent material and social deprivation based on Canadian Census data.[27] HBV and HIV diagnoses were based on laboratory testing data or as reported as a confirmed case in the reportable diseases database. Elixhauser Comorbidity Index was based on a modified

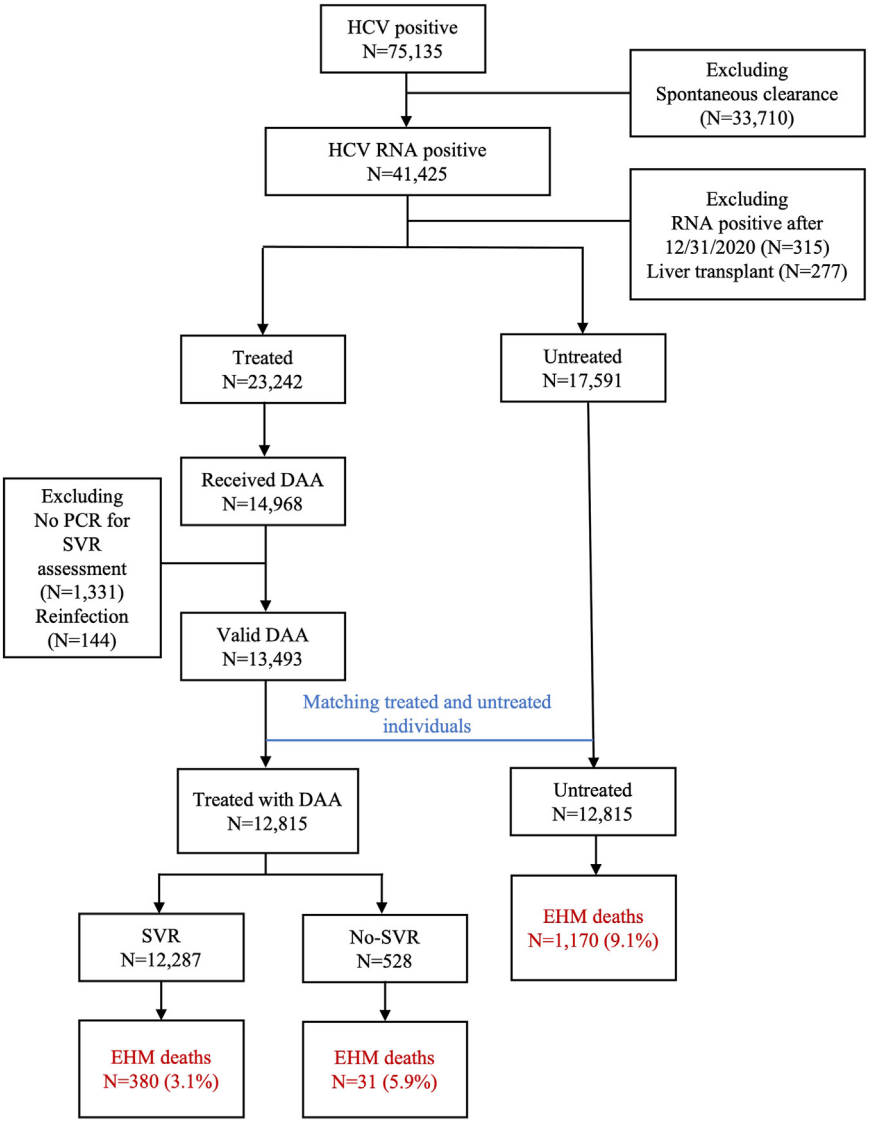


***Fig. 1:* Study population flowchart.** Abbreviations: DAA, direct-acting antivirals; EHM, extrahepatic manifestations; HCV, hepatitis C virus; SVR, sustained virologic response.

score calculated for each individual, where any hospitalization for one of the 31 Elixhauser diagnostic groups was scored as 1.[28] Clinical conditions were determined based on validated algorithms using ICD-9/10 diagnostic, procedural codes, and prescription dispensation data. More details of variable definitions can be found in Supplementary Table S2.

Statistical analysis

To assess the impact of HCV treatment with DAA and SVR on extrahepatic mortality, we followed the study participants from the baseline to the earliest of 1) death related to EHMs, 2) other death or 3) end of study (2021/12/31). To mitigate immortal time bias between treated and untreated individuals, prescription-time distribution matching approach was employed.[29] Each treated person was randomly matched to an untreated person, by the year of their first HCV RNA diagnosis date, within a 12-month timeframe, without replacement. Those who weren't matched (n = 678) were excluded (Fig. 1). For study participants who received DAA treatment, follow-up started on the date of first DAA dispensation of the last treatment course, and the same date was assigned to the matched untreated persons as the start of follow-up to avoid the imbalance of the prescription-time distribution and to equalize the period of outcome observation between treated and untreated individuals.

In addition, prior to 2018, there were restrictions for DAA reimbursement in BC based on fibrosis stage of patients, requiring a stage F2 or greater.[30,31] As such, individuals with chronic HCV infection who received DAA treatment are likely to be different from those who never received treatment, as well as those who achieve SVR and those who do not. To adjust for the imbalance in the baseline characteristics, we employed inverse probability of treatment weighting (IPTW) to estimate the average treatment effect (ATE) by inducing balance between 'Treated & SVR', 'Treated & no-SVR' and 'Untreated' groups.[32,33] Propensity scores (PS) were estimated with generalized linear models for multinomial treatment groups with the estimand ATE, and used to produce stabilized inverse probability of treatment weights. PS model included variables that are risk factors of extrahepatic mortality, or confounders in the relationship between DAA treatment and extrahepatic mortality: sex, age (in categories of <45, 45–54, 55–64, ≥65), ethnicity, material deprivation quintiles, social deprivation quintiles, HCV genotype, history of hypertension, HBV infection, HIV infection, alcohol use disorder, cirrhosis, major mental illness, opioid agonist therapy, injection drug use, hepatocellular carcinoma, statin use and Elixhauser Comorbidity Index (in categories of 0, 1, ≥2). We assessed the balance between the three groups using the standardized mean difference (SMD) approach and an SMD <0.1 was used to indicate a balanced distribution.[34]

We computed the crude extrahepatic mortality rates and generated survival and cumulative incidence curves for the three groups. Then, we used multivariable cause-specific Cox regression model to account for competing risk of other non-EHM related deaths, weighted with IPTW.[35] Covariates for the multivariable model were selected a priori based on literature as confounders of EHM-related deaths[6,8] and included sex, age (in categories of <45, 45–54, 55–64, ≥65), ethnicity, material and social deprivation, HCV genotype, HBV infection, HIV infection, history of hypertension, cirrhosis, alcohol use disorder, opioid agonist therapy and injection drug use. Finally, we looked at the effect of achieving SVR on mortality related to six specific EHMs: cardiovascular diseases, cerebrovascular diseases, chronic kidney diseases, diabetes mellitus, mood and anxiety disorders, and other mental health-related conditions. In the analyses investigating each of the EHMs, individuals who were treated but did not achieve SVR were excluded due to the small number of outcomes in some of the groups (less than 5). In addition, models for mortality related to cardiovascular and cerebrovascular diseases were also adjusted for baseline diagnosis of diabetes and statin use; model for mortality related to CKD was adjusted for baseline diagnosis of diabetes; and model for mortality related to diabetes was adjusted for baseline diagnosis of CKD.

As sensitivity analysis, we performed the regression analyses while excluding individuals with HIV or HBV co-infection. The multivariable regression models for sensitivity analyses did not include baseline diagnosis of HIV and HBV infection as covariates. We created the analytic dataset and produced plots using SAS/STAT software version 9.4[36] and performed statistical analyses in SAS and R, version 4.1.2.[37] We estimated propensity scores with 'WeightIt' package in R version 0.13.1.[38]

Role of the funding source

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Study participant characteristics

Overall, the study population included 12,815 persons who received DAA treatment and had a valid PCR test result for SVR assessment post-treatment, matched to 12,815 persons who never received treatment (Fig. 1). There were more males in the untreated group compared to treated (8657 [67.6%] vs 8352 [65.2%]). The untreated group tended to be slightly younger compared to the treated group (median age 55 vs 58 years), and they were more materially and socially deprived. Overall, the treated group had a longer follow-up compared to the untreated group (median follow-up of 3.7 vs 2.9 years, respectively). A greater proportion of the treated group had a diagnosed HBV (922 [7.2%] vs 701 [5.5%]) or HIV infection (1046 [8.2%] vs 634 [4.9%]). The treated group also presented greater proportions of hypertension (3382 [26.4%] vs 2630 [20.5%]), diabetes (1924 [15.0%] vs 1510 [11.8%]) and cirrhosis (1642 [12.8%] vs 1005 [7.8%]) at baseline. However, the treated group was less likely to have history of alcohol use disorder (4145 [32.3%] vs 4674 [36.5%]), opioid agonist therapy (3753 [29.3%] vs 4487 [35.0%]), or injection drug use (5097 [39.8%] vs 6149 [48.0%]). Among those who received DAA treatment, 528 (4.1%) did not achieve SVR. Compared to the majority of the treated individuals who achieved SVR, those who didn't achieve SVR were slightly younger (median age 56 vs 58 years). They were also more likely to have been diagnosed with HIV infection (60 [11.4%] vs 986 [8.0%]), cirrhosis (91 [17.2%] vs 1551 [12.6%]), alcohol use disorder (216 [40.9%] vs 3929 [32.0%]), opioid agonist therapy (242 [45.8%] vs 3511 [28.6%]) and injection drug use (303 [57.4%] vs 4794 [39.0%]) at baseline (Table 1). After PS weighting to create balance in the baseline characteristics between 'Treated & SVR', 'Treated & no-SVR' and 'Untreated' groups, the SMDs for all covariates were <0.05, indicating a balanced distribution (Supplementary Table S4).

Covariate	SVR (n = 12,287)	No-SVR (n = 528)	p-value[a]	All treated (n = 12,815)	Untreated (n = 12,815)	p-value[b]
Sex (%)			<0.0001			<0.0001
Female	4321 (35.2)	142 (26.9)		4463 (34.8)	4158 (32.4)	
Male	7966 (64.8)	386 (73.1)		8352 (65.2)	8657 (67.6)	
Age category (%)			<0.0001			<0.0001
<45	1722 (14.0)	129 (24.4)		1851 (14.4)	2945 (23.0)	
45–54	2826 (23.0)	122 (23.1)		2948 (23.0)	3322 (25.9)	
55–64	5430 (44.2)	181 (34.3)		5611 (43.8)	4101 (32.0)	
≥65	2309 (18.8)	96 (18.2)		2405 (18.8)	2447 (19.1)	
Median age, years [Q1–Q3]	58 [50–63]	56 [45–62]	<0.0001	58 [50–63]	55 [45–62]	<0.0001
Median follow-up, years [Q1–Q3]	3.8 [2.6–5.5]	2.4 [1.2–3.9]	<0.0001	3.7 [2.6–5.4]	2.9 [1.3–4.3]	<0.0001
Ethnicity (%)			0.27			0.98
Other[c]	11,631 (94.7)	506 (95.8)		12,137 (94.7)	12,144 (94.8)	
East Asian	265 (2.2)	6 (1.1)		271 (2.1)	267 (2.1)	
South Asian	391 (3.2)	16 (3.0)		407 (3.2)	404 (3.2)	
Material deprivation (%)			0.25			<0.0001
Q1 (most privileged)	1807 (14.7)	71 (13.4)		1878 (14.7)	1702 (13.3)	
Q2	1909 (15.5)	70 (13.3)		1979 (15.4)	1586 (12.4)	
Q3	2128 (17.3)	87 (16.5)		2215 (17.3)	1801 (14.1)	
Q4	2633 (21.4)	110 (20.8)		2743 (21.4)	2588 (20.2)	
Q5 (most deprived)	3703 (30.1)	185 (35.0)		3888 (30.3)	4989 (38.9)	
Unknown	107 (0.9)	5 (0.9)		112 (0.9)	149 (1.2)	
Social deprivation (%)			0.011			<0.0001
Q1 (most privileged)	1094 (8.9)	34 (6.4)		1128 (8.8)	953 (7.4)	
Q2	1497 (12.2)	68 (12.9)		1565 (12.2)	1297 (10.1)	
Q3	1927 (15.7)	70 (13.3)		1997 (15.6)	1630 (12.7)	
Q4	2265 (18.4)	80 (15.2)		2345 (18.3)	2172 (16.9)	
Q5 (most deprived)	5397 (43.9)	271 (51.3)		5668 (44.2)	6614 (51.6)	
Unknown	107 (0.9)	5 (0.9)		112 (0.9)	149 (1.2)	
HCV genotype (%)			<0.0001			<0.0001
1	5617 (45.7)	187 (35.4)		5804 (45.3)	4227 (33.0)	
2	772 (6.3)	23 (4.4)		795 (6.2)	784 (6.1)	
3	1471 (12.0)	91 (17.2)		1562 (12.2)	1626 (12.7)	
Other/unknown	4427 (36.0)	227 (43.0)		4654 (36.3)	6178 (48.2)	
HBV infection (%)	884 (7.2)	38 (7.2)	1.0	922 (7.2)	701 (5.5)	<0.0001
HIV infection (%)	986 (8.0)	60 (11.4)	0.0090	1046 (8.2)	634 (4.9)	<0.0001
Ischemic heart disease (%)	956 (7.8)	36 (6.8)	0.46	992 (7.7)	977 (7.6)	0.74
Hypertension (%)	3272 (26.6)	110 (20.8)	0.0030	3382 (26.4)	2630 (20.5)	<0.0001
Statin use (%)	1568 (12.8)	53 (10.0)	0.071	1621 (12.6)	1306 (10.2)	<0.0001
ESRD (%)	421 (3.4)	21 (4.0)	0.47	442 (3.4)	480 (3.7)	0.22
Diabetes mellitus (%)	1848 (15.0)	76 (14.4)	0.76	1924 (15.0)	1510 (11.8)	<0.0001
Mood & anxiety disorder (%)	8381 (68.2)	374 (70.8)	0.21	8755 (68.3)	8444 (65.9)	<0.0001
Cirrhosis (%)	1551 (12.6)	91 (17.2)	0.0030	1642 (12.8)	1005 (7.8)	<0.0001
Alcohol use disorder (%)	3929 (32.0)	216 (40.9)	<0.0001	4145 (32.3)	4674 (36.5)	<0.0001
Opioid agonist therapy (%)	3511 (28.6)	242 (45.8)	<0.0001	3753 (29.3)	4487 (35.0)	<0.0001
Injection drug use (%)	4794 (39.0)	303 (57.4)	<0.0001	5097 (39.8)	6149 (48.0)	<0.0001
Elixhauser Comorbidity Index (%)			<0.0001			<0.0001
0	5005 (40.7)	155 (29.4)		5160 (40.3)	5154 (40.2)	
1	2580 (21.0)	104 (19.7)		2684 (20.9)	2259 (17.6)	
≥2	4702 (38.3)	269 (50.9)		4971 (38.8)	5402 (42.2)	

Abbreviations: DAA, direct-acting antivirals; ESRD, end-stage renal disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; Q, quintiles; SVR, sustained virologic response. [a]Wilcoxon rank sum test for continuous variables, Chi-square test for categorical variables were used for comparison between study participants with SVR and those with No-SVR. [b]Wilcoxon rank sum test for continuous variables, Chi-square test for categorical variables were used for comparison between treated and untreated study participants. [c]Other included White, Indigenous, Black, Latin American, Pacific Islander, Central/West Asian, Filipino, Southeast Asian and other residents of British Columbia.

Table 1: **Baseline characteristics of study participants treated with DAA (SVR, No-SVR) and untreated study participants.**

	Treated & SVR	Treated & No-SVR	Untreated
Overall EHM mortality	7.86 (7.11–8.69)	21.19 (14.91–30.14)	30.93 (29.21–32.76)
Mortality related to cardiovascular diseases	5.13 (4.53–5.81)	11.62 (7.23–18.7)	20.01 (18.64–21.49)
Mortality related to cerebrovascular diseases	1.12 (0.86–1.46)	2.73 (1.03–7.29)	5.68 (4.97–6.5)
Mortality related to chronic kidney diseases	2.19 (1.81–2.65)	6.15 (3.2–11.83)	7.06 (6.26–7.96)
Mortality related to diabetes mellitus	1.82 (1.48–2.24)	4.1 (1.84–9.13)	5.76 (5.05–6.58)
Mortality related to mood and anxiety disorders	0.41 (0.27–0.64)	1.37 (0.34–5.47)	1.77 (1.39–2.25)
Mortality related to other mental health conditions[a]	0.43 (0.28–0.67)	1.37 (0.34–5.47)	2.17 (1.75–2.69)

Abbreviations: DAA, direct-acting antivirals; EHM, extrahepatic manifestations; SVR, sustained virologic response. [a]Other mental health related conditions included delirium, other mental disorders due to brain damage and dysfunction and to physical disease, personality and behavioural disorders due to brain disease, damage and dysfunction, schizophrenia, persistent delusional disorders, schizoaffective disorders, unspecified nonorganic psychosis and non-specified mental disorders.

Table 2: **Extrahepatic mortality rates per 1000 person-years of follow-up (95% confidence interval) among study participants by DAA treatment.**

Deaths related to extrahepatic manifestations

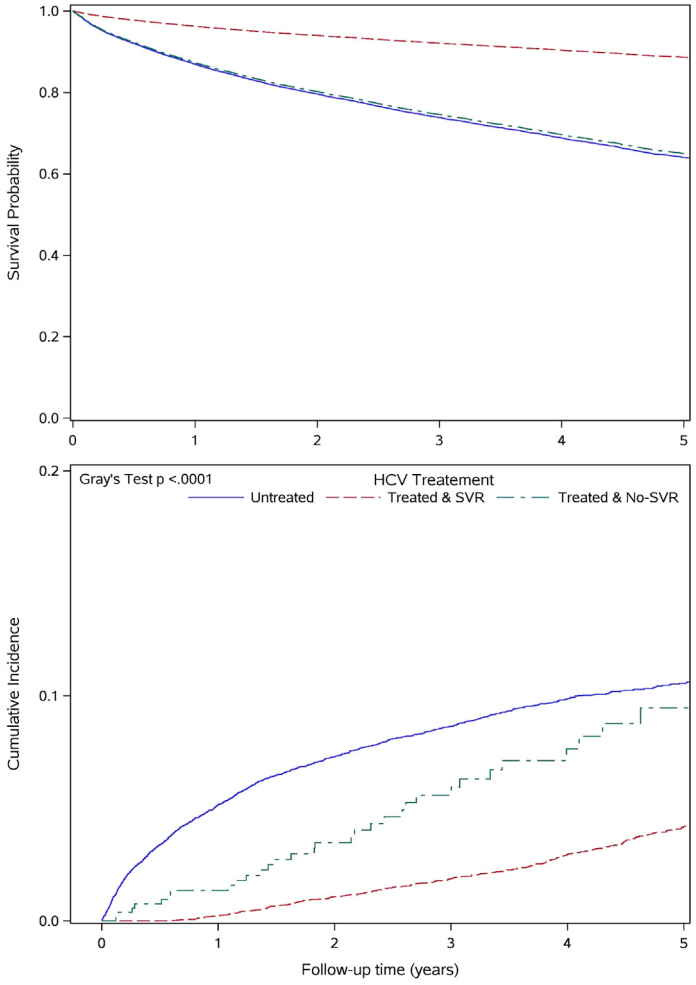
During the study period, there were 1170 deaths related to EHMs among people who never received treatment over 37,824 person-years of follow-up (PY), resulting in an extrahepatic mortality rate of 30.93 per 1000 PY (95% CI 29.21–32.76) (Table 2). In those who were treated with DAA and achieved SVR, there were 380 deaths related to EHMs over 48,357 PY, resulting in extrahepatic mortality rate of 7.86 per 1000 PY (95% CI 7.11–8.69). Finally, among those who were treated but did not achieve SVR, there were 31 deaths over 1463 PY, resulting in extrahepatic mortality rate of 21.19 per 1000 PY (95% CI 14.91–30.14). Kaplan Meier survival curves showed lower mortality among people who were treated and achieved SVR compared to those who were never treated or had no-SVR; cumulative incidence curves for death related to EHMs showed that extrahepatic mortality was highest among individuals who never received treatment (Fig. 2). Furthermore, mortality related to specific EHMs were assessed among individuals who were treated and achieved SVR and those who were never treated. Between the specific EHMs evaluated, mortality rate for cardiovascular diseases was the highest, especially in those who were never treated, with 20.01 per 1000 PY (95% CI 18.64–21.49). Mortality rates for each of the EHMs were higher among individuals who never received treatment compared to those who were treated and achieved SVR (Table 2). Fig. 3 shows the cumulative incidence curves for each of the EHMs, comparing people who were treated & SVR and people who were untreated (Fig. 3).

Effect of DAA and SVR on extrahepatic mortality

In the cause-specific Cox regression multivariable model weighted with IPTW, accounting for confounding and competing risks, the overall extrahepatic mortality risk was significantly lower among the treated & SVR group compared to people who never received treatment (adjusted cause-specific hazard ratio [acsHR] 0.20, 95% CI 0.18–0.23) (Table 3). We also looked at the impact of DAA treatment on deaths related to specific EHMs by treating these as individual outcomes and comparing those who were treated and achieved SVR with those who were never treated. From the multivariable models, mortality risks related to each individual EHMs were reduced for those who were treated & SVR compared to those who never received treatment, with relative risk reductions varying from 78% to 84% (Table 3). Other factors associated with higher risk of extrahepatic mortality based on unadjusted regression models included history of HBV and HIV infection, baseline history of hypertension, cirrhosis and alcohol use disorder (Supplementary Table S5). When excluding individuals with HIV or HBV co-infection, the hazard ratios were similar for overall and individual EHMs, showing reduced risk of mortality related to EHMs for people who were treated and had SVR compared to those who were never treated (Supplementary Table S6).

Discussion

This analysis was based on a large population-based cohort, including 12,815 people with HCV infection who received at least one DAA treatment and 12,815 people with HCV infection who never received treatment. Overall, we observed 1581 deaths associated with EHMs in this cohort. Successful treatment of HCV with DAA was associated with a significant reduction in extrahepatic mortality. The cumulative incidence of deaths related to EHMs, including cardiovascular diseases, cerebrovascular diseases, chronic kidney diseases, diabetes mellitus, mood and anxiety disorders and other mental health conditions, was significantly lower among people who were treated and attained virologic cure compared to those who never received treatment. After accounting for the differences in baseline characteristics between those treated and those never treated, as well as potential confounders and competing risk of mortality unrelated to EHMs, the effect of successful DAA treatment on reduced extrahepatic mortality remained significant. Overall, these findings show the benefits of successful HCV treatment with DAA in greatly reducing mortality related to EHMs.

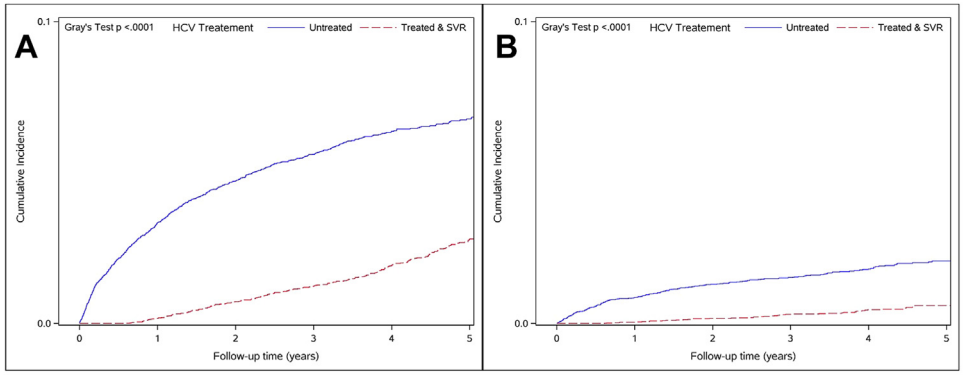


Number of individuals at risk (cumulative number of EHM-related deaths)

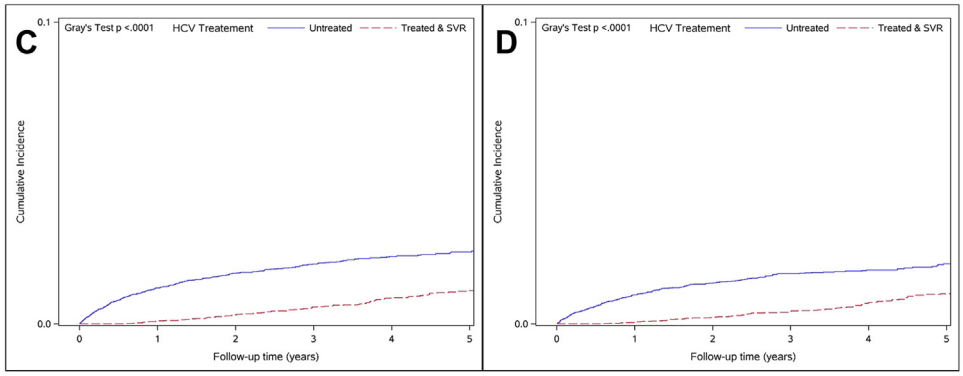
Time	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Untreated	12815 (0)	10205 (654)	8370 (900)	6221 (1034)	3785 (1122)	2107 (1151)
SVR	12287 (0)	11617 (26)	10318 (122)	8350 (201)	5709 (281)	3732 (345)
no-SVR	528 (0)	422 (7)	315 (16)	209 (23)	127 (28)	76 (31)

***Fig. 2:* The survival curves and cumulative incidence curves of extrahepatic mortality by treatment status.** Abbreviations: EHM, extrahepatic manifestations; HCV, hepatitis C virus; SVR, sustained virologic response.

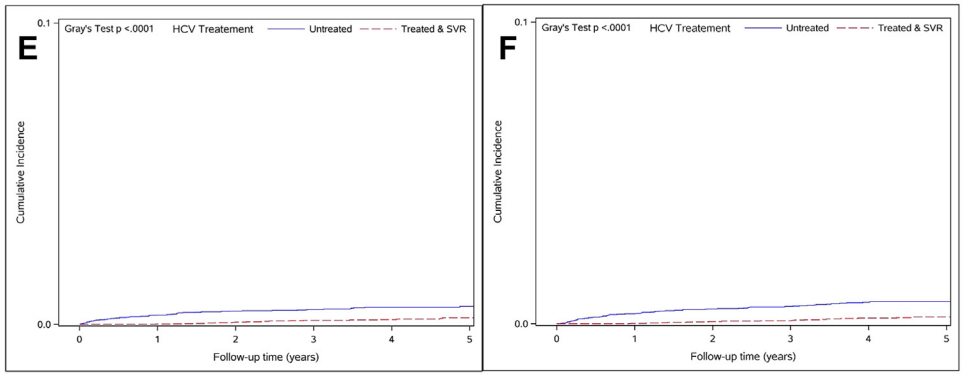
To date, there is limited evidence on the impact of HCV treatment with DAA on mortality related to EHMs. A meta-analysis from Cacoub et al.[16] estimated that SVR was correlated with 56% reduction in extrahepatic mortality among individuals who received treatment and achieved SVR compared to those who had received treatment and did not achieve SVR. Lin et al.[19] evaluated extrahepatic mortality in a cohort of patients treated with interferon (IFN)-based regimens in Taiwan, comparing those who achieved SVR and those who did not achieve SVR and found a 54% reduction of extrahepatic mortality. In a prospective cohort for research on HIV, viral hepatitis, and viral cirrhosis in France,[18] SVR achieved from IFN- or DAA-based regimens was associated with reduced extrahepatic mortality, which included deaths from bacterial infection, extrahepatic cancers, and cardiovascular diseases. Two other studies included in this meta-analysis[17,39] had very small sample sizes (n = 13 and n = 74) and consequently found very large confidence intervals for the estimated hazard ratios looking at the effect of SVR on extrahepatic mortality. Our study compared the mortality risk associated with EHMs among those who were treated with DAA and those who were never treated, and found significant reduction in mortality associated with DAA therapy. In addition, a larger prospective cohort in France including around



	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Untreated	12815 (0)	10205 (423)	8370 (582)	6221 (671)	3785 (726)	2107 (743)	12815 (0)	10205 (109)	8370 (160)	6221 (182)	3785 (202)	2107 (214)
SVR	12287 (0)	11617 (20)	10318 (83)	8350 (133)	5709 (184)	3732 (229)	12287 (0)	11617 (5)	10318 (19)	8350 (32)	5709 (43)	3732 (50)



	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Untreated	12815 (0)	10205 (151)	8370 (207)	6221 (237)	3785 (255)	2107 (261)	12815 (0)	10205 (122)	8370 (167)	6221 (198)	3785 (206)	2107 (214)
SVR	12287 (0)	11617 (10)	10318 (35)	8350 (60)	5709 (82)	3732 (94)	12287 (0)	11617 (6)	10318 (24)	8350 (45)	5709 (65)	3732 (81)



	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Untreated	12815 (0)	10205 (39)	8370 (55)	6221 (60)	3785 (65)	2107 (66)	12815 (0)	10205 (42)	8370 (61)	6221 (69)	3785 (79)	2107 (80)
SVR	12287 (0)	11617 (1)	10318 (8)	8350 (14)	5709 (16)	3732 (19)	12287 (0)	11617 (2)	10318 (9)	8350 (11)	5709 (18)	3732 (20)

Fig. 3: **Cumulative incidence of mortality related to each EHM by treatment status.** (A) Deaths related to cardiovascular diseases. (B) Deaths related to cerebrovascular diseases. (C) Deaths related to chronic kidney diseases. (D) Deaths related to diabetes mellitus. (E) Deaths related to mood and anxiety disorders. (F) Deaths related to other mental health illnesses. Tables under figures show the number of individuals at risk and cumulative number of deaths related to each EHM at timepoints (Yrs 1–5). Abbreviations: EHM, extrahepatic manifestations; HCV, hepatitis C virus; SVR, sustained virologic response.

	Crude csHR (95% CI)	Adjusted csHR (95% CI)
Overall extrahepatic mortality[a]		
Untreated	Ref	Ref
Treated & No-SVR	0.53 (0.37–0.78)	0.49 (0.33–0.71)
Treated & SVR	0.23 (0.21–0.26)	0.20 (0.18–0.23)
Mortality related to cardiovascular diseases[b]		
Untreated	Ref	Ref
Treated & SVR	0.24 (0.21–0.28)	0.21 (0.18–0.24)
Mortality related to cerebrovascular diseases[b]		
Untreated	Ref	Ref
Treated & SVR	0.18 (0.13–0.25)	0.16 (0.12–0.22)
Mortality related to chronic kidney diseases[c]		
Untreated	Ref	Ref
Treated & SVR	0.26 (0.21–0.33)	0.20 (0.16–0.25)
Mortality related to diabetes mellitus[d]		
Untreated	Ref	Ref
Treated & SVR	0.27 (0.21–0.34)	0.23 (0.18–0.30)
Mortality related to mood and anxiety disorders		
Untreated	Ref	Ref
Treated & SVR	0.23 (0.14–0.38)	0.21 (0.13–0.35)
Mortality related to other mental health conditions[e]		
Untreated	Ref	Ref
Treated & SVR	0.24 (0.15–0.38)	0.21 (0.13–0.33)

Abbreviations: csHR, cause-specific hazard ratio; CI, confidence interval; DAA, direct-acting antivirals; SVR, sustained virologic response. [a]Adjusted cause-specific hazard ratios were obtained from IPTW for ATE weighted cause-specific Cox regression models adjusted for sex (Male, Female), age at baseline (<45, 45–54, 55–64, ≥65), ethnicity (East Asian, South Asian, Other), material deprivation quintiles, social deprivation quintiles, HCV genotype, baseline diagnosis of HBV infection, HIV infection, hypertension, cirrhosis, alcohol use disorder, opioid agonist therapy and injection drug use. [b]Models for mortality related to cardiovascular diseases and cerebrovascular diseases were adjusted for sex, age at baseline, ethnicity, material deprivation quintiles, social deprivation quintiles, HCV genotype, baseline diagnosis of HBV infection, HIV infection, hypertension, diabetes, statin use, cirrhosis, alcohol use disorder, opioid agonist therapy and injection drug use. [c]Model for mortality related to chronic kidney diseases was adjusted for sex, age at baseline, ethnicity, material deprivation quintiles, social deprivation quintiles, HCV genotype, baseline diagnosis of HBV infection, HIV infection, hypertension, diabetes, cirrhosis, alcohol use disorder, opioid agonist therapy and injection drug use. [d]Model for mortality related to diabetes was adjusted for sex, age at baseline, ethnicity, material deprivation quintiles, social deprivation quintiles, HCV genotype, baseline diagnosis of HBV infection, HIV infection, hypertension, chronic kidney disease, cirrhosis, alcohol use disorder, opioid agonist therapy and injection drug use. [e]Other mental health related conditions included delirium, other mental disorders due to brain damage and dysfunction and to physical disease, personality and behavioural disorders due to brain disease, damage and dysfunction, schizophrenia, persistent delusional disorders, schizoaffective disorders, unspecified nonorganic psychosis and non-specified mental disorders.

Table 3: **Unadjusted and adjusted cause-specific hazard ratios for the effect of HCV treatment with DAAs on overall and specific extrahepatic mortality.**

3000 patients with baseline cirrhosis, DAA treatment was associated with a 60% decrease in non-liver-related mortality.[10] The causes for non-liver-related deaths in Carrat et al.[10] included non-liver cancers, cardiac, gastrointestinal, immune system, nervous system, respiratory, vascular, renal and urinary disorders, infections, injuries and poisoning, and unknown causes, however, the authors only reported the estimate for overall extrahepatic mortality, without assessing estimates related to specific EHM, likely due to the small number of outcomes. In our study, we included over 12,000 individuals who were treated with interferon-free, direct-acting antivirals, matched to people with HCV who had never received treatment, and assessed the impact of successful HCV treatment with DAA on deaths related to EHMs, overall and specific to each EHM. When compared to those who never received treatment, SVR achieved from DAA treatment was associated with a greatly reduced risk of mortality from all extrahepatic causes.

An analysis based on US Census and the National Center for Health Statistics reported a decreasing trend of liver-related mortality among patients with HCV infection during the DAA era (2007–2017), while an increasing trend of mortality from cardiovascular disease or diabetes were seen among patients with HCV infection.[40] The authors suggested that the improved longevity in individuals with HCV due to highly effective DAA treatment might be marred by increasing extrahepatic mortality. Our findings show that DAA treatment can in fact greatly reduce the risk of death from extrahepatic complications among individuals with HCV, and the scale-up of treatment may prevent extrahepatic mortality, especially if HCV treatment is started without delay. A cost-effectiveness analysis in 2017 also found that adopting immediate HCV treatment compared to delayed treatment provides substantial economic benefits due to reduction of extrahepatic mortality associated with successful treatment.[41]

A major limitation in previous studies assessing the impact of successful DAA treatment on clinical outcomes was the very high SVR rate of the DAA treatment; as most studies were based solely on individuals who received treatment, the comparison groups (people who do not achieve SVR) were small and made assessing the effect of DAA treatment difficult.[16] In this study, the analysis was based on a large general population-based cohort including individuals who never received treatment, therefore, the assessment of the treatment effect was possible. The large sample size of this study also allowed for multivariable analysis adjusting for important confounders such as sociodemographic characteristics and pre-existing clinical characteristics. The median follow-up time close to 3 years or more allowed for longer follow-up for outcome assessment. However, this study is not without limitations. The mortality was assessed from underlying causes of deaths based on ICD-10 codes as recorded in vital statistics and may be subject to misclassification bias. This is likely to be non-differential for people who received treatment and who did not receive treatment, and would have biased the estimate towards the null. It is also important to note that people who received HCV treatment and those who never received treatment may be very different. To account for these baseline confounding factors and to ensure exchangeability between treated and untreated persons, we employed IPTW and doubly robust methods.[42,43] However, as this analysis is based on administrative data, there are some unmeasured variables that may be important for extrahepatic outcomes, such as body mass index (BMI) or LDL levels, which were not directly captured in this study. In addition, the retrospective design of the study is subject to potential residual confounding that still remains, although we tried to address confounding with IPTW and double adjustment in regression models. The results of this study should be considered within this context and corroborated with other large-scale prospective studies assessing the effect of DAA treatment on non-liver related outcomes. Furthermore, due to the nature of the administrative data, it was not possible to assess the outcomes for individuals who moved out of the province. We opted to include them and censor at the study end date as this approach provided more conservative estimates of hazard ratios, but these may have biased the results towards the null. Given the substantial size of our study population, comprising over 25,000 individuals, we anticipate such bias to have minimal impact on the overall study conclusions. Finally, to account for immortal time bias, we used prescription-time distribution matching, where we assigned the person-times of the treated individuals to those who never received treatment, by randomly matching them based on the year of their first HCV RNA diagnosis date, within a 12-month timeframe. This approach has been shown to validly estimate the treatment effect when confounders at baseline are measured and adjusted for[44]; other methods such as sequential Cox and sequential stratification methods have been suggested to improve precision with narrower confidence intervals when time distribution matching may exclude some eligible study participants.[29,45] As this analysis included over 12,000 individuals in each of the treated and untreated groups, we expect the difference in analysis approaches to be minimal. However, future studies using observational data, especially when looking at mortality related to a specific EHM with smaller sample sizes, or when including individuals with re-infection, should consider these different strategies to account for immortal time bias.

In summary, the findings of this large population-based cohort study demonstrated important benefits of successful HCV treatment with DAA in reducing mortality related to extrahepatic manifestations. These results highlight the importance of early treatment and the need to scale-up global HCV treatment to prevent EHM-related deaths. It is critical to inform treatment providers and patients of the benefits of starting HCV treatment without delay on preventing deaths related to extrahepatic manifestations.

Contributors

DJ: Conceptualization, Methodology, Analysis, Writing—Original Draft; SW: Analysis, Data Curation; MEK, ARM: Methodology, Writing—Review & Editing, Supervision; JDM, SRB, HAVG, DL, PA, MB: Writing—Review & Editing; AY, MK: Data Curation, Project Administration; NZJ: Conceptualization, Methodology, Resources, Data Curation, Writing—Review & Editing, Supervision.

Data sharing statement

The data analysed in this study is subject to the following licenses/restrictions: the data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declaration of interests

MK has received grant/research support from Roche, Merck, Siemens, Boeringer Ingelheim and Hologic. SRB has consulted for Cepheid, Gilead, and Abbvie, but no personal payments accepted, and has received investigator-initiated grants from Gilead and Abbvie through her institution. NZJ participated in advisory boards and has spoken for AbbVie and Gilead, not related to current work. DJ, SW, MEK, ARM, JDM, HAVG, DL, PA, MB and AY have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100658.

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