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Research Paper

Drug-related deaths in a population-level cohort of people living with and without hepatitis C virus in British Columbia, Canada

Hasina Samji[a,b,*], Amanda Yu[b], Stanley Wong[b], James Wilton[b], Mawuena Binka[b], Maria Alvarez[b], Sofia Bartlett[b,e], Margo Pearce[b,c], Prince Adu[b,c], Dahn Jeong[b,c], Emilia Clementi[b,c], Zahid Butt[d], Jane Buxton[b,c], Mark Gilbert[b,c], Mel Krajden[b,e], Naveed Z. Janjua[b,c]

[a] Faculty of Health Sciences, Simon Fraser University, 8888 University Dr, Burnaby, British Columbia, Canada, V5A 1S6
[b] British Columbia Centre for Disease Control, 655 West 12th Avenue, Vancouver, British Columbia, Canada, V5Z 4R4
[c] School of Population and Public Health, University of British Columbia, 2206 E Mall, Vancouver, British Columbia, Canada, V6T 1Z3
[d] School of Public Health and Health Systems, University of Waterloo, 200 University Avenue West, Waterloo, Ontario, Canada, N2L 3G1
[e] Department of Pathology and Laboratory Medicine, University of British Columbia, 2211 Wesbrook Mall, Vancouver, British Columbia, Canada, BC V6T 2B5

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ABSTRACT

Background: The majority of new HCV infections in Canada occur in people who inject drugs. Thus, while curative direct antiviral agents (DAAs) herald a promising new era in hepatitis C virus (HCV) treatment, improving the lives and wellbeing of people living with HCV (PLHCV) must be considered in the context of reducing overdose-related harms and with a syndemic lens. We measure drug-related deaths (DRDs) among HCV-negative people and PLHCV in British Columbia (BC), Canada, and the impact of potent contaminants like fentanyl on deaths.

Methods: We identified DRDs among PLHCV and HCV-negative individuals from 2010 to 2018 in the BC Hepatitis Testers Cohort, a population-based dataset of ~1.7 million British Columbians comprising comprehensive administrative and clinical data. We estimated annual standardized liver- and drug-related mortality rates per 100,000 person-years (PY) and described the contribution of specific drugs, including fentanyl and its analogues, implicated in DRDs over time.

Results: DRDs constituted 20.1% of deaths among PLHCV and 4.7% of deaths among HCV-negative individuals; a 4.3-fold (95% confidence interval: 4.0-4.5) difference. Drug-related mortality overtook liver-related mortality for PLHCV in 2015 and HCV-negative individuals in 2016 and rose from 241.7 to 436.5 per 100,000 PY from 2010 to 2018 amongPLHCV and from 20.0 to 57.1 per 100,000 PY for HCV-negative individuals over the same period. The proportion of deaths attributable to drugs among PLHCV and HCV-negative individuals increased from 15.1% to 26.1% and 3.1% to 8.0%, in 2010 and 2018, respectively. The proportion of DRDs attributed solely to synthetic opioids such as fentanyl averaged across both groups increased from 2.1% in 2010 to 69.6% in 2017.

Conclusion: Steep drug-related mortality increases among PLHCV and HCV-negative individuals over the last decade highlight the urgent need to address overdose-related drivers and harms in these populations using an integrated care approach.

Introduction

The advent of direct acting antiviral (DAA) short-course, well-tolerated therapy has dramatically altered the hepatitis C virus (HCV) treatment landscape. Response rates over 95% are leading to dramatic reductions in liver-related mortality as well as new global targets to eliminate HCV as a public health threat by 2030 (N. Janjua et al., 2018; World Health Organization, 2019). However, increasing injecting drug use and the epidemic of drug overdose-related deaths in North America threaten to arrest or even reverse the progress heralded by the DAA era among people who use drugs with HCV and the morbidity, mortality and well-being of all people who use drugs, regardless of HCV status.

In Canada, new HCV infections occur mainly among people who inject drugs (PWID) (N. Z. Janjua, Yu, et al., 2016). Moreover, syndemic conditions of co-occurring mental illness, HIV co-infection and higher material deprivation are more common among people living with HCV

* Corresponding author.
E-mail address: Hasina.Samji@bccdc.ca (H. Samji).

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(PLHCV) compared to HCV-negative individuals (McKee et al., 2018), prompting a need to examine data by HCV status. In British Columbia (BC), an estimated 1.2 to 1.5% of the population injects drugs and more than 65% of those will have a lifetime exposure to HCV (Jacka et al., 2020; N. Z. Janjua et al., 2018; Public Health Agency of Canada, 2014). Increasing rates of injecting drug use have been observed in Canada and the US since 2010, likely exacerbated by policies to reduce prescription opioid overprescribing, diversion and misuse (Powell et al., 2019). Other policies (e.g. prescription drug monitoring programs, more stringent guidelines) have also been implicated (Martins et al., 2019). A national US study observed a 76% increase in drug treatment admissions (from 13% to 22%) due to injecting drug use between 2004 and 2014; these increases were particularly pronounced among individuals 20 to 39 years of age (Zibbell et al., 2018). Acute HCV infections subsequently tripled in the US between 2011 and 2015 (Centers for Disease Control and Prevention, 2017; Gonzalez & Trotter, 2018; Zibbell et al., 2018), representing a reversal in progress towards reducing rates of acute HCV in the US, which declined by almost 50% between 2001 and 2010. Similarly, HCV incidence in BC decreased between 2001 and 2012 and then began rising thereafter (Li Y et al., 2019).

In both Canada and the US, these "dual epidemics" of injecting drug use and HCV transmission have the potential to derail years of sustained progress in reversing the HCV epidemic, as PWID are at high risk of drug overdose-related mortality. While the rate of drug-related deaths (DRDs) in Canada has nearly doubled from 5.8 deaths per 100,000 population in 2015 to 11.5 deaths per 100,000 population in 2017, the situation in BC is particularly concerning with 60% of Canadian DRDs recorded in that province (Statistics Canada, 2019a). In 2018, more than 1,500 people died of a drug overdose in BC - approximately 4.5 times the number of deaths due to motor vehicle accidents within the province (BC Coroners Service, 2020a). The proportion of DRDs in which synthetic opioids such as fentanyl and its analogs have been detected increased more than six fold between 2012 and 2015, prompting the BC Provincial Health Officer to declare a state of emergency under the Public Health Act in April, 2016 for the first time (BC Gov News, 2016). National and provincial gains in life expectancy have also been halted and reversed for the first time in four decades due to the overdose epidemic; men in BC were the most affected, losing 0.28 years between 2016 and 2017 (Statistics Canada, 2019b; Ye et al., 2018).

As noted above, PLHCV have a higher proportion of injecting drug use in Canada and PLHCV who inject drugs also have higher proportion of co-occurring mental illness, HIV co-infection, HBV co-infection and material and social deprivation (McKee et al., 2018). It is hypothesized that as PLHCV have higher drug use and are more marginalized, DRDs will be higher among them. However, there is no data assessing if the rate of DRDs is higher among PLHCV compared to HCV-negative individuals. We use a population-based database of all individuals tested for HCV in BC to compare rates and trends over time in DRD and liver-related deaths (LRDs) and identify whether there are differences in DRDs among PLHCV and HCV-negative individuals. We also quantify the impact of fentanyl on DRDs in our study population over the last decade.

Methods

Study population

The BC Hepatitis Testers Cohort (BC-HTC) includes more than 1.7 million individuals tested for HCV or HIV at the BC Centre for Disease Control Public Health Laboratory and all confirmed cases of HBV, HCV, HIV, and active TB reported by the public health system in BC from 1990 to 2015. Individuals in BC are generally tested due to HCV risk, investigation of liver disease, routine screening in pregnancy and if they are undergoing procedures such as renal dialysis, and those tested during the mid-1990s as part of blood system lookbacks (Krajden et al., 2019). These data were integrated with data on prescription drug dispensations, physician diagnostic and billing data, hospitalization records, emergency department visits, cancers, and deaths and are described in more detail in Supplemental Table S1. Additional information about the BC-HTC, including methodology, data linkages, and population characteristics by HCV status has been published previously (N. Z. Janjua, Kuo, et al., 2016; McKee et al., 2018). The dynamic, retrospective cohort was formed under a public health mandate of the BC Centre for Disease Control. All residents in BC are registered in the publicly funded insurance plan that acts as a single payer system and covers services provided by fee-for-service practitioners, allowing for comprehensive population-level monitoring. Eligible individuals for this study had at least one HCV test (i.e., anti-HCV or HCV RNA) performed or were a reported HCV case from April 1992 to December 2015. Characterization of DRD was restricted to 2010 onwards to highlight the surge of DRDs among people with HCV over the last decade.

Drug-related deaths (DRDs)

DRDs were identified using BC Vital Statistics Agency (BCVSA) death registry, which includes all deaths registered in the province of BC, underlying and/or contributing cause of death mortality data, and categorized using the International Classification of Diseases, Tenth Revision (ICD-10) codes (Supplemental Table S2). Any deaths not deemed "natural" (a death primarily resulting from a disease or progressive fatigue of the bodily systems) are investigated by the BC Coroners Service (BCCS). The finalization of the medical certificates of death can take anywhere from several months to several years from date of death. BCVSA processes information received from the BCCS on the finalized Medical Certificate of Death and applies these ICD-10 codes using an internationally standardized coding software provided by Statistics Canada. A broad definition specifying both acute and chronic poisonings was adapted from consensus recommendations for national and state poisoning surveillance developed by the Safe States Alliance (The Safe States Alliance, 2012) and which has also been used by the US Centres for Disease Control and Prevention.

Specific drug categorization

In addition, ICD-10 multiple-cause codes provide information on the types of drugs or drug classes involved in the death ("T-codes"); of these, heroin (T40.1); natural/semisynthetic opioids (T40.2); methadone (T40.3); synthetic opioids other than methadone (including fentanyl and fentanyl analogues) (T40.4); cocaine (T40.5); other and unspecified narcotics (40.6); and psychostimulants with abuse potential (T43.6) were used. Deaths involving methadone (T40.3) and natural/semisynthetic opioids such as hydrocodone and oxycodone (T40.2) are grouped together as prescription opioid deaths (Jalal et al., 2018; Jones et al., 2018), a category which includes opioids prescribed to the deceased person or prescribed to someone else (diverted). In 2016, in response to the DRD public health emergency, supplementary codes to identify deaths where fentanyl ("Z7221") or carfetanil ("Z7222") were specifically implicated in finalized death investigations were added to the "lifestyle / environmental" field in BCVSA mortality data files; thus, we also included these codes in our categorization of "synthetic opioids other than methadone."

Drug-related T-codes are attached to a parent "external cause" ICD code that signals the circumstances or intent under which the substance was used (accidental, intentional / suicide, homicide, undetermined intent or adverse reaction in therapeutic use) and is assigned during DRDs investigations. BCCS investigations include toxicology results, scene evidence and death investigation information (such as existing prescription information). These investigations also help determine drug origin; for instance, whether a drug is pharmaceutically-derived (including prescribed to the deceased or diverted), non-pharmaceutical,

or undetermined (e.g. fentanyl identified through toxicology but without prescription or evidence suggesting non-pharmaceutical fentanyl use) (Onatrio Agency for Health Protection and Promotion (Public Health Ontario) 2017). Similarly, illicit fentanyl is differentiated from prescribed fentanyl through investigation of evidence of prescription/patch versussuggestion of a non-pharmaceutical origin (e.g., other illicit substances detected on toxicology or drug paraphernalia on the scene). Heroin (6-monoacetyl morphine), which is rapidly metabolized into morphine and therefore may be underestimated, also relies on investigation to finalize classification(Onatrio Agency for Health Protection and Promotion (Public Health Ontario) 2017). Most deaths involved more than one type of drug; thus, categories are not mutually exclusive.

Lastly, if an underlying cause of death code was recorded as ICD-10 R99 (other ill-defined and unspecified causes, usually assigned when cause of death is still under investigation), and manner of death was listed as "pending," "accident," or "undetermined," we re-categorized the death as drug-related if the death met the following criteria: attributable to a person aged 20 to 64 years who also injects drugs (defined as any drug-related diagnoses, use of injection drugs, record of opioid agonist therapy dispensation or injection related infection using physician diagnostic and billing data, hospitalizations, prescription data, vital statistics and emergency room data), based on validation studies in the US and in the BC-HTC (Centers for Disease Control and Prevention, 2004; Janjua et al., 2018) to mitigate the impact of missing data on the analysis. As the majority of R99 codes are resolved within a few years as the BCCS completes investigations of sudden deaths prior to death categorization, we excluded deaths occurring after December 31st, 2018 to reduce the impact of open investigations and the need to impute missing data by re-categorizing deaths. While we were able include many DRDs with R99 codes in the analysis through application of our algorithm described above, it was not possible to assign T-codes to these deaths as these codes are only assigned in concluded investigations (Janjua et al., 2018; BC Coroners Service, 2020). As such, analyses involving T-codes were limited to data collected on or before December 31st, 2017.

Additional variables

We used deidentified linked databases to identify other important variables for analyses. LRDs included deaths due to decompensated liver disease, liver cancer, HCV, other types of viral hepatitis, and alcoholic or non-alcoholic liver disease. We assessed baseline participant characteristics such as age, sex and material and social deprivation (Québec Index of Material and Social Deprivation) (Pampalon et al., 2012). We also evaluated concurrent conditions including HIV and HBV co-infection, major mental illness (hospitalization or at least two visits to a psychiatrist for disorders including schizophrenia, bipolar, major depressive and personality), and psychosis diagnosis as well as access to opioid agonist therapy (OAT) and HCV treatment. Diagnostic codes and variable definitions are presented in more detail in Supplemental Table S3.

Statistical analysis

We compared PLHCV and HCV-negative individuals who died of DRDs, estimated annual age and sex-adjusted drug-related mortality rates per 100,000 person-years (PY) for these groups and examined trends over time by sex. Rates are age and sex-standardized to the 1991 Canadian population. PY were calculated from either first HCV negative or first HCV positive date, censored at death or HCV sero-conversion. Secondly, we compared demographic and risk factor characteristics of people who died of liver- vs. drug-related causes and estimated annual age and sex-adjusted liver- and drug-related mortality rates per 100,000 PY for these groups. Lastly, we described the contribution or "co-involvement" of specific drugs, including fentanyl and its analogues, implicated in DRDs overall and stratified by HCV status over time. For instance, for deaths involving heroin, we identify what proportion also included fentanyl involvement each year using the T-codes described above assigned through coroner's investigation of each drug-related death. As more than one drug can contribute to a DRD, categories representing specific drug involvement in a DRD are not mutually exclusive. For descriptive analyses comparing groups, we used Wilcoxon's rank sum test for continuous variables and the chi^2 test for categorical data. SAS version 9.4 was used for all analyses.

Ethical approval

The study was approved by the University of British Columbia Clinical Research Ethics Board (H14-01649).

Results

There were 1,355,952 people who were HCV tested or reported as an HCV case in the cohort as of December 31, 2015, of whom 71,715 (5.3%) were PLHCV and 1,284,237 (94.7%) were HCV-negative individuals. A total of 85,899 deaths were recorded from 2000 to 2018 of which 11.7% were among PLHCV. DRDs constituted 20.1% (2,018/10,024) of deaths among PLHCV and 4.7% (3,598 /75,875) of deaths among HCV-negative individuals; a 4.3-fold (95% confidence interval [CI]: 4.0-4.5) difference.

Drug-related deaths among PLHCV and HCV-negative individuals

The majority of DRDs among PLHCV occurred among those with a history of injecting drug use (95.4%). Similarly, a majority of HCV-negative individuals individuals dying of a DRD had a history of injection drug use (85.6%) (Tables 1 and 2). The population of PLHCV dying of DRDs was also older (born prior to 1965: 52.0% vs. 27.9%), more likely to have co-infections such as HIV (13.6% vs. 1.6%), and HBV (10.5% vs. 1.1%), to have a record of OAT (54.9% vs. 26.0%), and be more materially (most deprived quintile: 36.8% vs. 27.9%) and socially (most deprived quintile: 55.9% vs. 39.2%) deprived compared to the HCV-negative individuals (Table 2). More than half of PLHCV and HCV-negative groups had a major mental illness diagnosis and more than 20% in each group reported a diagnosis of psychosis.

Annual drug-related standardized mortality rates among PLHCV and HCV-negative individuals by sex are presented in Fig. 1. Drug-related mortality was 1.3 (95% CI: 1.2-1.3) to 1.5 (95% CI: 1.5-1.6) times higher in men compared to women living with HCV and from 1.8 (95% CI: 1.5-2.3) to 3.3 (95% CI: 3.2-3.5) times higher among HCV negative men compared to women. Increases over time were observed for all groups, with rates among men without HCV increasing the most dramatically, from 27.1 per 100,000 PY in 2010 to 96.0 per 100,000 PY in 2018; a 3.5-fold increase (95% CI: 3.1-4.1). Increases over the same time period were also observed for men living with HCV (283.4 to 490.0 per 100,000 PY; 1.7 fold increase [95% CI: 1.7-1.8]) and women without HCV (14.8 to 29.0 per 100,000 PY; 2.0-fold increase [95% CI: 1.6-2.4]) and women living with HCV (184.4 to 372.2 per 100,000 PY; 2.0-fold increase [95% CI: 1.9-2.1]).

The proportion of deaths attributable to drugs among PLHCV increased from 15.1% (135/896) in 2010 to 26.1% (322/1274) in 2018. Similarly, the proportion of deaths attributable to drugs among HCV-negative individuals more than doubled from 2010 to 2018, increasing from 3.1% (202/6540) to 8.0% (748/9361).

Drug vs. liver-related deaths among PLHCV and HCV-negative individuals

Table 1 describes characteristics of PLHCV and HCV-negative individuals who died of drug-related (5,616) vs. liver-related (6,884) causes during the study period. Notably, the median age at death was 45 (interquartile range [IQR]: 35, 54) vs. 64 (IQR: 57, 72) years for DRDs and LRDs, respectively; a difference of 19 years. Individuals

Table 1
Comparison of characteristics of individuals dying of liver and drug-related deaths in the British Columbia Hepatitis Testers Cohort (2010-2018).

	Drug-related deaths (N = 5616) n (%)	Liver-related Deaths (N = 6884) n (%)	p-value
Median age at death [IQR]	45 [35, 54]	64 [57, 72]	<.0001
Male sex	3941 (70.2)	4533 (65.8)	<.0001
Birth year			
<1945	67 (1.2)	2229 (32.4)	<.0001
1945-1964	1987 (35.4)	4028 (58.5)	
1965+	3562 (63.4)	627 (9.1)	
HCV infection*	2018 (35.9)	2533 (36.8)	0.319
Ever HCV treatment (all types) (n = 4551)	316 (15.7)	775 (30.6)	<.0001
DAA treatment (ever) (n = 4551)	104 (5.2)	194 (7.7)	<.0001
Median age at HCV diagnosis [IQR]	37 [30, 43]	49 [42, 56]	<.0001
HBV infection*	251 (4.5)	618 (9.0)	<.0001
HIV infection*	331 (5.9)	149 (2.2)	<.0001
Injecting drug use (ever)^	5006 (89.1)	4158 (60.4)	<.0001
Opioid agonist therapy (ever)^	2042 (36.4)	460 (6.7)	<.0001
Major mental illness (ever)*	3136 (55.8)	1739 (25.3)	<.0001
Psychosis diagnosis*	1226 (21.8)	510 (7.4)	<.0001
Material deprivation quintile**			
1 (most privileged)	931 (16.6)	952 (13.8)	<.0001
2	806 (14.4)	1127 (16.4)	
3	876 (15.6)	1442 (20.9)	
4	1184 (21.1)	1533 (22.3)	
5 (Most deprived)	1747 (31.1)	1770 (25.7)	
Missing	72 (1.3)	60 (0.9)	
Social deprivation quintile**			
1 (most privileged)	600 (10.7)	905 (13.1)	<.0001
2	623 (11.1)	909 (13.2)	
3	758 (13.5)	1071 (15.6)	
4	1024 (18.8)	1532 (22.3)	
5 (Most deprived)	2539 (45.2)	2407 (35.0)	
Missing	72 (1.3)	60 (0.9)	

*Ever as of December 31st, 2015.
^Physician visits, hospitalizations and emergency room visits until December 31st, 2015 and prescription data until December 31st, 2019.
**At time of death.

whose deaths were drug-related were more likely to be male (70.2% vs. 65.8%), younger (born after 1964: 63.4% vs. 9.1%), living with HIV (5.9% vs. 2.2%), have a history of injecting drug use (89.1% vs. 60.4%), a record of OAT (36.4% vs. 6.7%), major mental illness (55.8% vs. 25.3%) and diagnosis of psychosis (21.8% vs. 7.4%) compared to those who died of LRD. They were also more likely to rank in the most materially (31.1% vs. 25.7%) and socially (45.2% vs. 35.0%) deprived quintiles of the Québec Index of Material and Social Deprivation and less likely to have ever accessed HCV treatment (15.7% vs. 30.6%) or have HBV infection (4.5% vs. 9.0%).

Annual liver- and drug-related standardized mortality rates among PLHCV and HCV-negative individuals and overall deaths are presented in Fig. 2. Drug-related mortality rate rose from 241.7 per 100,000 PY in 2010 to 436.5 per 100,000 PY (IRR: 1.8; 95% CI: 1.7-1.9) in 2018 for PLHCV and from 20.0 to 57.1 per 100,000 PY (IRR: 2.9; 95% CI: 2.4-3.4) for HCV-negative individuals with the majority of the increase after 2014. From 2010 to 2018, liver-related mortality rates among PLHCV almost halved from 313.7 to 183.2 per 100,000 PY (IRR: 1.7; 95% CI: 1.6-1.8); similarly, liver-related mortality rates among HCV-negative individuals decreased from 42.7 to 22.6 per 100,000 PY (IRR: 1.9; 95% CI: 1.6-2.2) over the same period. Drug-related mortality overtook liver-related mortality for PLHCV in 2015 and HCV-negative individuals in 2016.

Table 2
Characteristics of people living with and without HCV who died of drug-related causes (N = 5616) in the BC-HTC (2010-2018).

	Drug-related deaths among HCV+ (N = 2018) n (%)	Drug-related deaths among HCV- (N = 3598) n (%)	p-value
Median age at death [IQR]	50 [42, 56]	37 [30, 47]	<.0001
Male sex	1423 (70.5)	2518 (70.0)	0.676
Birth year			
<1945	8 (0.4)	59 (1.6)	<.0001
1945-1964	1042 (51.6)	945 (26.3)	
1965+	968 (48.0)	2594 (72.1)	
HBV infection*	211 (10.5)	40 (1.1)	<.0001
HIV infection*	275 (13.6)	56 (1.6)	<.0001
Injecting drug use (ever)^	1925 (95.4)	3081 (85.6)	<.0001
Opioid agonist therapy (ever)^	1108 (54.9)	934 (26.0)	<.0001
Major mental illness (ever)*	1116 (55.3)	2020 (56.1)	0.543
Psychosis diagnosis*	461 (22.8)	765 (21.3)	0.168
Material deprivation quintile**			
1 (most privileged)	324 (16.1)	607 (16.9)	<.0001
2	224 (11.1)	582 (16.2)	
3	259 (12.8)	617 (17.1)	
4	439 (21.8)	745 (20.7)	
5 (Most deprived)	742 (36.8)	1005 (27.9)	
Missing	30 (1.5)	42 (1.2)	
Social deprivation quintile**			
1 (most privileged)	132 (6.5)	468 (13.0)	<.0001
2	153 (7.6)	470 (13.1)	
3	225 (11.1)	533 (14.8)	
4	350 (17.3)	674 (18.7)	
5 (Most deprived)	1128 (55.9)	1411 (39.2)	
Missing	30 (1.5)	42 (1.2)	

*Ever as of December 31st, 2015.
^Physician visits, hospitalizations and emergency room visits until December 31st, 2015 and prescription data until December 31st, 2019.
**At time of death.

Specific drugs (2010-2017)

From 2010 to 2017, DRDs increased from 337 to 1,184, totaling 4,546 over that period. 73.7% (3,352/4,546) of DRDs had an assigned T-code specifying at least one drug, and 61.3% of these had more than one drug recorded. Since 2010, the proportion of DRDs attributed solely to synthetic opioids such as fentanyl has increased in our cohort from 2.1% in 2010 to 69.6% in 2017 (Fig. 3). In 2017, synthetic opioids were co-involved in 93.3% of all opioid-related deaths, 68.9% of prescription opioid deaths, 88.5% of heroin-related deaths, 79.1% of cocaine-related deaths, and 85.8% of deaths involving psychostimulants. Results stratified by HCV status are included in Supplemental Table S4.

Discussion

We examined DRDs in a population-based cohort of HCV testers in BC. We found that DRDs were higher among PLHCV compared to HCV-negative individuals. Drug-related causes have overtaken liver-related causes of death among PLHCV, accounting for more than a quarter of deaths in this population in 2018, with similar trends observed among HCV-negative individuals. Drug-related mortality has increased among men and women living with and without HCV since 2014; the steepness of the curves for each group has increased every year, indicating a worsening problem, with absolute rates several fold higher for PLHCV compared to HCV-negative individuals. Our data suggest that synthetic opioids such as fentanyl are ubiquitous in the drug supply, contributing to more than three quarters of deaths involving opioids in 2017.

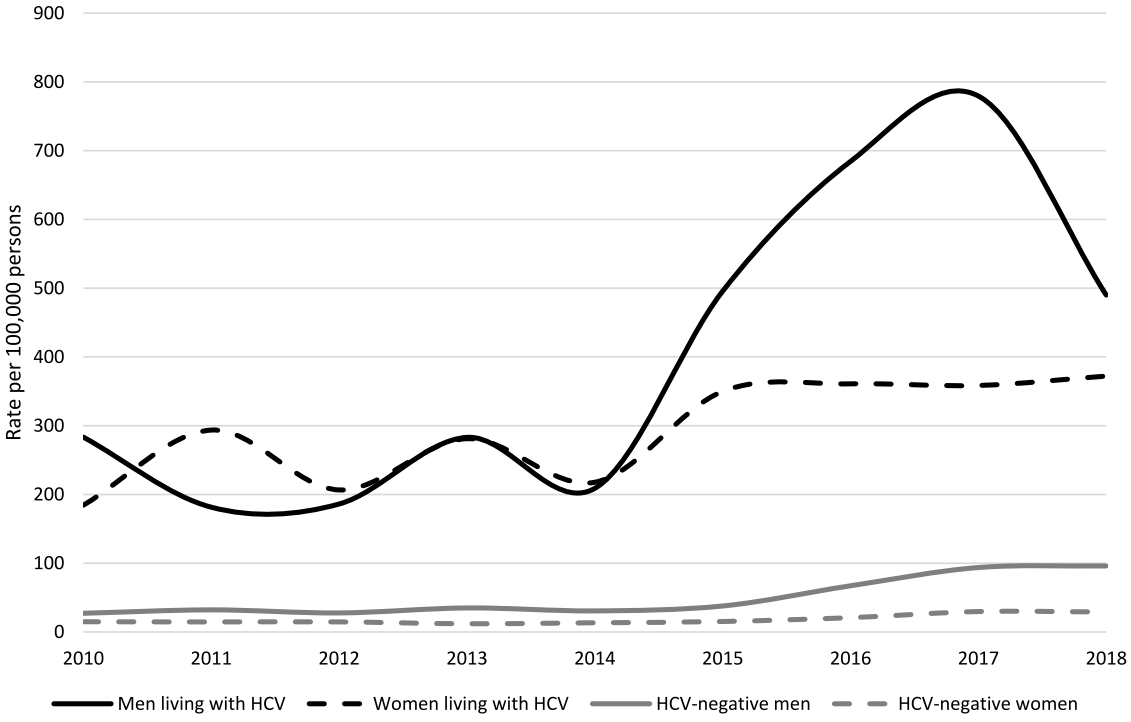

Fig. 1. Annual age and sex-adjusted drug-related mortality rates by HCV status and sex, BC Hepatitis Testers Cohort (2010-2018).

While injecting drug use was pervasive among both PLHCV and HCV-negative individuals dying of drug-related causes in BC, we found differences in group characteristics. PLHCV were older, had a higher proportion of co-occurring HIV, HBV infections and social and material deprivation and may therefore represent PWID with a longer duration of drug use. The median age of DRD in our study among HCV-negative individuals was 37 years (vs. 49 years among PLHCV); similarly, provincial data on overdose deaths illustrates that people between the ages of 30 and 39 years had the highest rate of illicit drug overdose deaths (57.4 per 100,000 person years) in 2018 (BC Coroners Service, 2020a). These younger HCV-negative individuals could represent PWID with shorter duration of drug use who are dying before they have a chance to access drug-related treatment services or to acquire a blood-borne pathogen. Another explanation is that practices protecting people from acquiring blood-borne pathogens such as using drugs through non-injecting pathways do not protect against fentanyl exposure. More than half of overdose deaths in BC were not injecting-related in 2018 (BC Coroners Service, 2018). These data underscore the need to prevent initiation of injecting drug use, to promote reversal to non-injecting use, and to minimize exposure to fentanyl to reduce DRDs (Des Jarlais et al., 2018).

Indeed, increasing rates of injecting drug use, acute HCV infection, and overdose deaths signal a crisis for public health in North America and elsewhere. Recent outbreaks of HIV following changing drug use

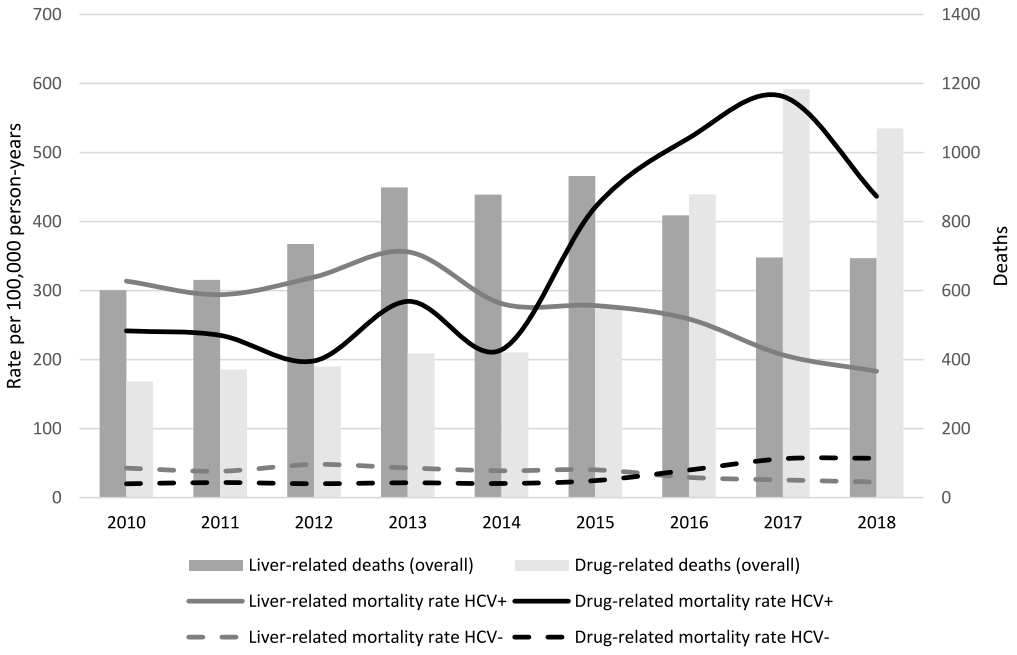

Fig. 2. Annual age and sex-adjusted liver- and drug-related mortality rates by HCV status, BC Hepatitis Testers Cohort (2010-2018).

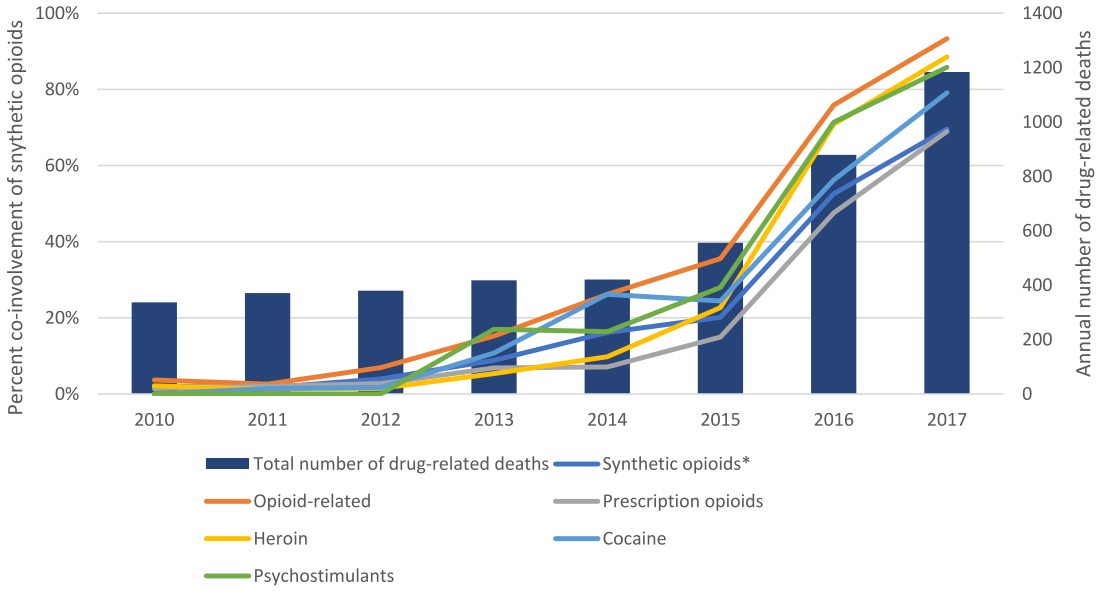

Fig. 3. Synthetic opioid co-involvement in drug-related deaths among individuals in the BC Hepatitis Testers Cohort, 2010-2017^ (N = 4546) ^Categories are not mutually exclusive; many deaths involve multiple drugs *Proportion of total drug-related deaths with synthetic opioid co-involvement.

practices and trends have been observed among PWID in both rural and urban settings. A rapid increase in new cases of HIV infection among PWID in Indiana (Peters et al., 2016) led the US Centers for Disease Control to identify regions at high risk of HIV transmission due to the opioid epidemic (Van Handel et al., 2016); subsequent HIV outbreaks in Washington, Massachusetts and Ontario among PWID have also been described (Alpren et al., 2020; Ball et al., 2019; Golden et al., 2019). Structural inequalities such as poor economic prospects, unaddressed trauma, stigma, and unequal access to healthcare are driving this syndemic and must be addressed to reduce drug-related harms (Parker et al., 2019). Overdose deaths and sequalae from drug use such as infectious disease acquisition are preventable; developing a comprehensive suite of services, such as integrating HIV pre-exposure prophylaxis services for PWID at risk of acquiring HIV as well as infectious disease treatment (antiretroviral treatment for HIV and DAA therapy for HCV) and medication-assisted treatment for opioid use disorder (Singer, 2020) should be explored in these contexts.

Our results indicate that potent synthetic opioids such as fentanyl have increasingly contaminated the illicit drug supply in BC, with the proportion of deaths with co-involvement of synthetic opioids increasing sharply across all drug categories including cocaine and stimulant-related deaths since 2015. Substantiating these findings are drug testing results in BC, which found that 80% of drugs tested positive for fentanyl, including 84% of heroin samples, and 65% of non-opiate drugs such as crystal meth, ecstasy/MDMA, and cocaine (Vancouver Coast Health, 2017). The strong association between the number of fentanyl-positive samples seized by Canadian law enforcement agencies and overdose deaths in BC (Karamouzian et al., 2020) also supports fentanyl's direct impact on mortality rates. While there was a decrease in overdose deaths in BC in 2019, the number of deaths and non-fatal overdoses remain at epidemic levels. Moreover, the COVID-19 pandemic era appears to have precipitated a striking spike in deaths, with June 2020 recording the highest number of illicit drug toxicity deaths observed in BC to date (BC Coroners Service, 2020b). There is thus renewed urgency to develop and implement strategies to reduce overdose deaths in BC and elsewhere.

Novel proximal level interventions such as take-home drug checking test strips may be explored to reduce the impact of the toxic drug supply on PWID. Existing harm reduction interventions such as supervised consumption sites and take-home naloxone kits are operational in BC and have averted an estimated 3000 deaths over a 20-month period during which 2,177 deaths were observed (Irvine et al., 2019) but can be expanded and implemented elsewhere. Furthermore, distal interventions should address the underlying motives propelling the syndemic of mental health, blood-borne infections, and injecting drug use and other "diseases of despair" such as suicide and problematic alcohol use including unaddressed antecedent physical and psychological trauma, economic disadvantage, social isolation, and hopelessness (Dasgupta et al., 2018) to create a durable impact on drug-related mortality. For instance, using "life projects" approaches that de-stigmatize and humanize PWID engaging in HCV treatment as well as culturally-safe, healing-centered approaches that acknowledge histories of trauma (E. Williams et al., 2019; Pearce et al., 2019) are paramount for addressing barriers to care and treatment and promoting long term wellness beyond HCV or drug treatment.

Notably, we found that more than half of PLHCV and HCV-negative individuals were diagnosed with a major mental illness and more than a fifth of each group with psychosis. Severe and persistent mental illness has been associated with an increased risk of acquiring sexually transmitted and blood-borne infections (STBBIs); a recent meta-analysis observed an HCV prevalence of 17.4% among individuals with severe and persistent mental illness compared to 1% of those in the general population (Hughes et al., 2016). This increased risk is primarily due to co-morbid substance use, though a national U.S. study of veterans found a 50% increased odds of having an HCV diagnosis among veterans with severe and persistent mental illness even after controlling for substance use (Himelhoch et al., 2009). As such, strategies to improve screening for individuals with severe and persistent mental illness for HCV, drug use and other STBBIs and providing risk reduction counseling in this population are warranted.

There are several limitations to consider in our study. Recent deaths of undetermined intent (ICD-10 code R99) pending a coroner's investigation, with manner of death reported "pending," "accident," or "undetermined," and classified as DRDs in our study based on age and PWID criteria may be misclassified, possibly leading to an over-estimation of DRD, though age restriction and history of IDU decreases

likelihood of misclassification. An estimated 1.2% (1004/85,899) of all deaths in 2018 were assigned an ICD-10 R99 code. However, not including any of these deaths as drug-related would certainly under-estimate DRDs; we chose to be inclusive. Similarly, using administrative data to identify PWID, while a useful strategy for large population-level datasets, may also lead to misclassification. Another important consideration is that there may be temporal trends in the classification of deaths whereby investigation practices and therefore classification of deaths differed; for instance, as the overdose epidemic grew, it is possible that more deaths were investigated as drug-related. Next, although our inclusion criteria specify that everyone is tested for HCV on entry, DRDs among undiagnosed HCV seroconverters who do not have a positive test will be misclassified. Lastly, we see a decline in drug related mortality among men living with HCV in 2018 which preceded a decline in overall DRDs in BC surveillance data (BC Coroners Service, 2020a) in 2019. This decline in men living with HCV may be real, related to improvements in healthcare and HCV treatment access, or could be a data artifact which may become clear as additional data become available.

In summary, fentanyl has significantly impacted mortality rates among PWID with and without HCV; widespread interventions to reduce harms and address the toxic drug supply are urgently needed. For PLHCV, DRDs represent a failure of engagement in care and a missed opportunity to deliver highly effective DAA treatment and resulting quality of life improvements. Thus, integration of overdose prevention and HCV services is necessary to improve survivability as well as quality of life of these populations and to realize the benefit of curative HCV therapy.

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Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

Declarations of Interests

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Supplementary materials

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