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MAJOR ARTICLE

Concurrent Hepatitis C and B Virus and Human Immunodeficiency Virus Infections Are Associated With Higher Mortality Risk Illustrating the Impact of Syndemics on Health Outcomes

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Background. Hepatitis C virus (HCV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV) infections are associated with significant mortality globally and in North America. However, data on impact of concurrent multiple infections on mortality risk are limited. We evaluated the effect of HCV, HBV, and HIV infections and coinfections and associated factors on all-cause mortality in British Columbia (BC), Canada.

Methods. The BC Hepatitis Testers Cohort includes ~1.7 million individuals tested for HCV or HIV, or reported as a case of HCV, HIV, or HBV from 1990 to 2015, linked to administrative databases. We followed people with HCV, HBV, or HIV monoinfection, coinfections, and triple infections from their negative status to date of death or December 31, 2016. Extended Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for factors associated with all-cause mortality.

Results. Of 658 704 individuals tested for HCV, HBV, and HIV, there were 33 804 (5.13%) deaths. In multivariable Cox regression analysis, individuals with HCV/HBV/HIV (HR, 8.9; 95% CI, 8.2–9.7) infections had the highest risk of mortality followed by HCV/HIV (HR, 4.8; 95% CI, 4.4–5.1), HBV/HIV (HR, 4.1; 95% CI, 3.5–4.8), HCV/HBV (HR, 3.9; 95% CI, 3.7–4.2), HCV (HR, 2.6; 95% CI, 2.6–2.7), HBV (HR, 2.2; 95% CI, 2.0–2.3), and HIV (HR, 1.6; 95% CI, 1.5–1.7). Additional factors associated with mortality included injection drug use, problematic alcohol use, material deprivation, diabetes, chronic kidney disease, heart failure, and hypertension.

Conclusions. Concurrent multiple infections are associated with high mortality risk. Substance use, comorbidities, and material disadvantage were significantly associated with mortality independent of coinfection. Preventive interventions, including harm reduction combined with coinfection treatments, can significantly reduce mortality.

Keywords. all-cause mortality; coinfections; observational cohort; syndemics.

Globally, hepatitis C virus (HCV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV) are major public health issues with approximately 71 million individuals with HCV, 257 million with HBV [1], and 36.9 million people with HIV [2]. In Canada, an estimated 230 000–450 000 individuals are infected with HCV [3], approximately 75 500 have HIV, and 285 000 have HBV [4, 5]. Independently, HCV, HIV, and HBV infections are associated with significant morbidity and mortality [6–8]. These viruses share common transmission routes and predisposing vulnerabilities to infection; therefore, co-occurrence of these infections is relatively high. Material and social deprivation, social vulnerabilities, and/or other conditions (eg, addictions, mental illness, tuberculosis [TB]) are common in those with HCV, HBV, and/or HIV [9, 10].

The interaction among HCV, HBV, and HIV infections is therefore likely driven by shared underlying socioeconomic, environmental, and political conditions, which increase the morbidity and mortality related to these infections. Population-level clustering of social and health conditions constitutes a "syndemic" [11], which enhances the adverse consequences of HIV, HCV, and HBV infections. Vulnerable and underserved populations, such as people who inject drugs (PWID) and gay, bisexual, and other men who have sex with men, immigrants, and indigenous populations, are disproportionately affected by HIV, HCV, and HBV [9, 12–14]. Estimating the

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population-level impact of HIV-, HCV-, and HBV-associated syndemics on mortality would help in designing and evaluating programs and interventions to prevent and reduce syndemic-related morbidity and mortality.

Previous research on mortality associated with HIV, HCV, and HBV coinfections has relied on smaller clinical cohorts [15] and individuals that are either HIV or HCV positive [16, 17]. Studies did not take into account important factors, such as ethnicity, alcohol use, socioeconomic status, and chronic conditions and their relation with all-cause mortality [16]. None of the studies evaluated the transition of infection status from no infection to coinfection and triple infection and its impact on all-cause mortality.

We aimed to address knowledge gaps and limitations identified in previous research by analyzing the British Columbia Hepatitis Testers Cohort, a large population-based cohort, with up-to-date information on HIV, HCV, and HCV infections, concomitant risk factors, and mortality. We have previously reported factors associated with HIV, HCV, and HBV syndemics [9, 10]. In this study, we document the impact of these syndemics, comorbid conditions, and substance use on mortality. We evaluated the effect of HIV, HCV, and HBV infections, coinfections, and associated factors on all-cause mortality among British Columbians since 1990.

METHODS

The British Columbia Hepatitis Testers Cohort (BC-HTC) includes all individuals (~1.7 million individuals) tested for HCV or HIV at the BCCDC Public Health Laboratory (BCCDC-PHL) or reported as a confirmed case of HCV, HBV, HIV, or acquired immunodeficiency syndrome (AIDS), or active TB, since 1990. This cohort is linked with provincial healthcare administrative databases and registries, including medical visits, hospitalizations, prescription drugs, cancers, and deaths (Supplementary Table 1). Almost all HIV and HCV testing in BC is performed at the BCCDC-PHL. All dispensed prescriptions in BC are recorded in a central system called PharmaNet, regardless of the payer. Detailed cohort characteristics and related data are presented elsewhere [18].

Definitions

An individual testing positive for HCV antibodies, HCV RNA, or genotype or who was reported as an HCV case to public health was considered as an HCV case [18]. Of the 42 187 cases of HCV that were tested for all 3 infections, there were 36 820 cases who were HCV antibody positive only (data not shown). An individual reported as a case of HIV/AIDS, or who had a positive HIV laboratory test result, was considered a case. Additional HIV cases were ascertained through a validated algorithm based on 2 medical visits or 1 hospitalization of a condition associated with HIV/AIDS [18]. Hepatitis B virus cases included individuals with positive laboratory tests for HBV deoxyribonucleic acid or hepatitis B surface antigen, those who received treatment for HBV, or individuals reported as HBV cases in the BC provincial registry (Supplementary Table 2). Active TB diagnoses were based on provincial and national guidelines [18]. Socioeconomic status was assessed using the Québec Index of Material and Social Deprivation, which is based on Canadian Census Data on small area units [9]. The deprivation index includes 6 indicators grouped along social and material dimensions and are produced from principal component analyses [19]. The material component consisted of indicators for education, employment, and income (persons without high school diploma, ratio employment-population ratio, and average personal income), whereas the social component comprised indicators related to marital status and family structure (persons living alone, persons separated, divorced or widowed, and single-parent families). Assessment of injection drug use (IDU) and problematic alcohol use was based on diagnostic codes (Supplementary Table 1) for medical visits and hospitalizations in respective databases. Ethnicity was classified on the basis of validated name recognition software Onomap, as reported previously [20]. The algorithm has high sensitivity and specificity for South Asian and East Asian peoples, with the exception of Filipinos. It may misclassify many ethnic groups, including people who would describe themselves as having mixed ethnicity, people whose surnames are not specific to an ethnic group, and people who adopt surnames of another ethnic group [21]. Onomap does not identify people with Indigenous ethnicity. Due to legislated forced assimilation in Canada during the 18th–20th centuries, Indigenous peoples' names were routinely changed to biblical or other European names [22]. Thus, people of European ancestry and those with similar names were classified as Other in our study. Ethnicity was categorized as South Asian (eg, Pakistani, Indians, Bangladeshis, Nepali, and Sri Lankans), East Asian (eg, Chinese, Filipinos, Japanese, Korean and people from other South-East Asian countries), and Other (including Caucasian, Black individuals and people from Central Asian, Latin American, Pacific Islander, people of European ancestry and those with similar names, and West Asian countries).

Diabetes, chronic kidney disease, heart failure, and hypertension were assessed using (1) a combination of *International Classification of Diseases* (ICD) diagnostic or procedure codes or (2) fee item codes from medical visits, hospital admissions, or prescription database, based on the British Columbia Chronic Disease Registry definitions (Supplementary Table 2). All-cause mortality was ascertained by using the ICD-10 codes (A00–R99; V01–Y99).

Statistical Analysis

For this analysis, study population included individuals that were tested for all 3 infections (HCV, HBV, and HIV). Individuals tested for 1 or 2 infections, but not all 3, were excluded from

the cohort. The study population (n = 658 704) was classified as those who tested negative for HCV, HBV, and HIV infections (negative group), tested positive for HCV, but negative for HBV and HIV (HCV monoinfected), tested positive for HBV, but negative for HCV and HIV (HBV monoinfected), tested positive for HIV, but negative for HCV and HBV (HIV monoinfected), tested positive for HCV and HBV, but negative for HIV (HCV/HBV coinfected), tested positive for HCV and HIV, but negative for HBV (HCV/HIV coinfected), tested positive for HBV and HIV, but negative for HCV (HBV/HIV coinfected), and tested positive for all 3 infections (HCV/HBV/HIV triple infection). A time updated variable for infection groups was created to account for transition from no infection (negative group) to first, second, and third infection, respectively. This enabled us to account for the time spent in each infection group (negative, monoinfected, coinfected, or with triple infections).

We followed people with HCV, HBV, or HIV monoinfection, coinfections, and triple infections from their first negative test status to date of death or December 31, 2016 to estimate mortality rates. The Kaplan-Meier method was used to construct survival curves for infection groups. For comparison of survival curves, the log-rank test was used. Extended Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for factors associated with all-cause mortality. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Patient Consent Statement

Data linkage to establish the BC-HTC was performed under the auspices of the BCCDC's public health mandate. The study was approved by Behavioral Research Ethics Board (H15-01776) at the University of British Columbia.

RESULTS

Of 658 704 individuals tested for HCV, HBV, HIV infections, there were 33 804 (5.13%) deaths during the study interval. Of these 658 704 individuals, 596 079 (90.5%) were negative for all infections, 34 807 (5.3%) were HCV monoinfected, 14 913 (2.3%) were HBV monoinfected, 4846 (0.8) were HIV monoinfected, 3472 (0.5%) were positive for both HCV and HBV (HCV/HBV coinfected), 2668 (0.4%) were positive for both HCV and HIV (HCV/HIV coinfected), 679 (0.1%) were positive for both HBV and HIV (HBV/HIV coinfected) and 1240 (0.2) were positive for all 3 infections (HCV/HBV/HIV triple infection). The majority of individuals in all infection groups were male, with the highest proportion among individuals with HBV/HIV coinfection (90.4%). Almost all infections and co-/triple infections were higher among Other ethnicity than other ethnicities, except HBV monoinfection, which was highest among East Asians (52.9%) (Table 1). Most of the infections were in individuals aged over 45 years, except HIV monoinfection (32.2%), HCV/HIV coinfection (38.4%), and HCV/HBV/HIV triple infection (38.8%), which were higher among the 35 to 44 age group. Among infection groups, IDU was highest among individuals with triple infection (84.0%), followed by HCV/HIV coinfection (68.7%), HCV/HBV coinfection (56.5%), and HCV monoinfection (41.6%). A similar trend was observed for problematic alcohol use (Table 1). Regarding chronic diseases, a higher proportion of type 2 diabetes was found among HCV/HBV-coinfected individuals (11.3%), followed by those with HBV/HIV coinfections (8.1%), and HCV monoinfection (7.9%). A higher proportion of chronic kidney disease was observed among individuals with triple infection (13.2%), HBV/HIV coinfection (11.5%), and HCV/HBV coinfection (9.8%), whereas hypertension was highest among individuals with HCV/HBV coinfections (26.4%), followed by HCV monoinfection (25.2%) and HBV/HIV coinfections (23.4%). Almost all groups had higher proportions living in socially and materially deprived areas (Q5 vs Q1), except individuals with HIV monoinfection, who were less materially deprived than the rest of the groups (Table 1).

The highest crude all-cause mortality rate per 1000 person-years was observed among individuals with HCV/HBV/HIV triple infection (31.3; 95% CI, 28.9–33.9), followed by HCV/HBV (19.4; 95% CI, 18.3–20.6), HCV/HIV (19.2; 95% CI, 18.0–20.6), and HBV/HIV coinfections (15.6; 95% CI, 13.3–18.2), and HCV (12.1; 95% CI, 11.8–12.4), HIV (6.7; 95% CI, 6.1–7.3), and HBV monoinfection (5.1; 95% CI, 4.8–5.4) (Table 2). Mortality was higher among males than females. Regarding ethnicity, mortality was higher among Other ethnicity in the HCV monoinfection, HBV/HIV coinfection, and triple infection groups, whereas it was higher among South Asians for the HBV and HIV monoinfected and HCV/HBV and HCV/HIV coinfected groups. Mortality was higher among all infection groups for people aged 45 years and above and highest for the triple infection group (35.2; 95% CI, 31.1–39.9). For IDU and problematic alcohol use, mortality was highest among the triple infection group but lower among HBV-monoinfected for IDU and HIV-monoinfected for problematic alcohol use. Almost all infection groups had higher mortality with respect to diabetes and chronic kidney disease, except HIV-monoinfected, which had lower mortality compared with the rest of the groups. A similar trend was noted for hypertension and heart failure. As expected, individuals living in more socially and materially deprived areas had higher mortality rates across all infection groups (Table 2). Survival in the triple infection group was lowest, followed by coinfections (HCV/HIV, HBV/HIV and HBV/HIV) and HCV, HCV, and HBV monoinfections (Figure 1). For the negative group, the survival curve showed a gradual decrease in survival over time, whereas for the triple infection group, survival decreased sharply at approximately 5 years of follow-up time and followed the same pattern throughout.

Table 1. Characteristics of Participants by HIV, HCV, and HBV Status in BC Hepatitis Testers Cohort, 1990–2015

	Negative	HCV Monoinfected	HBV Monoinfected	HIV Monoinfected	HCV/HBV Coinfected	HCV/HIV Coinfected	HBV/HIV Coinfected	HCV/HBV/HIV Coinfected
Variables	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Row Percent	596 079 (90.5)	34807 (5.3)	14913 (2.3)	4846 (0.8)	3472 (0.5)	2668 (0.4)	679 (0.1)	1240 (0.2)
Sex								
Female	336 952 (56.5)	12 536 (36.0)	7350 (49.2)	737 (15.2)	1179 (34.0)	752 (28.2)	65 (9.6)	405 (32.7)
Male	259 120 (43.5)	22 271 (64.0)	7563 (50.7)	4109 (84.8)	2293 (66.0)	1916 (71.8)	614 (90.4)	835 (67.3)
Unknown	7 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity								
Other	485 259 (81.4)	32 767 (94.1)	6313 (42.3)	4457 (91.9)	3166 (91.2)	2601 (97.5)	612 (90.1)	1216 (98.0)
East Asian	62 884 (10.6)	875 (2.5)	7883 (52.9)	200 (4.1)	223 (6.4)	37 (1.4)	49 (7.2)	17 (1.4)
South Asian	47 936 (8.0)	1165 (3.4)	717 (4.8)	189 (3.9)	83 (2.4)	30 (1.1)	18 (2.7)	7 (0.6)
Age at Diagnosis								
<25	70 412 (11.8)	2702 (7.8)	2322 (15.6)	423 (8.7)	152 (4.4)	161 (6.0)	16 (2.4)	42 (3.4)
25–34	185 693 (31.2)	8128 (23.4)	4604 (30.9)	1468 (30.3)	733 (21.1)	693 (26.0)	135 (19.9)	280 (22.6)
35–44	155 037 (26.0)	11 646 (33.5)	3571 (24.0)	1558 (32.2)	1058 (30.5)	1024 (38.4)	206 (30.3)	481 (38.8)
>45	184 937 (31.0)	12 331 (35.4)	4416 (29.6)	1397 (28.8)	1529 (44.0)	790 (29.6)	322 (47.4)	437 (35.2)
IDU[a]								
No	563 483 (94.5)	20 337 (58.4)	14 306 (95.9)	4229 (87.3)	1510 (43.5)	836 (31.3)	532 (78.4)	199 (16.1)
Yes	32 596 (5.5)	14 470 (41.6)	607 (4.1)	617 (12.7)	1962 (56.5)	1832 (68.7)	147 (21.7)	1041 (84.0)
Problematic Alcohol Use[a]								
No	554 899 (93.1)	22 736 (65.3)	14 232 (95.4)	4286 (88.4)	1928 (55.5)	1458 (54.7)	569 (83.8)	529 (42.7)
Yes	41 180 (6.9)	12 071 (34.7)	681 (4.6)	560 (11.6)	1544 (44.5)	1210 (45.4)	110 (16.2)	711 (57.3)
Active TB[a]								
No	594 538 (99.7)	34 631 (99.5)	14 773 (99.1)	4783 (98.7)	3430 (98.8)	2584 (96.9)	669 (98.5)	1165 (94.0)
Yes	1541 (0.3)	176 (0.5)	140 (0.94)	63 (1.3)	42 (1.2)	84 (3.2)	10 (1.5)	75 (6.1)
Diabetes[a]								
No	570 057 (95.6)	32 049 (92.1)	13 972 (93.7)	4545 (93.8)	3081 (88.7)	2538 (95.1)	624 (91.9)	1155 (93.2)
Yes	26 022 (4.4)	2758 (7.9)	941 (6.3)	301 (6.2)	391 (11.3)	130 (4.9)	55 (8.1)	85 (6.9)
Chronic Kidney Disease[a]								
No	571 134 (95.8)	32 736 (94.1)	14 156 (94.9)	4457 (92.0)	3131 (90.2)	2458 (92.1)	601 (88.5)	1077 (86.9)
Yes	24 945 (4.2)	2071 (6.0)	757 (5.1)	389 (8.0)	341 (9.8)	210 (7.9)	78 (11.5)	163 (13.2)
Heart Failure[a]								
No	580 307 (97.4)	33 163 (95.3)	14 484 (97.1)	4653 (96.0)	3184 (91.7)	2551 (95.6)	645 (95.0)	1160 (93.6)
Yes	15 772 (2.7)	1644 (4.7)	429 (2.9)	193 (4.0)	288 (8.3)	117 (4.4)	34 (5.0)	80 (6.5)
Hypertension[a]								
No	489 625 (82.1)	26 020 (74.8)	11 532 (77.3)	3777 (77.9)	2556 (73.6)	2308 (86.5)	520 (76.6)	1036 (83.6)
Yes	106 454 (17.9)	8787 (25.2)	3381 (22.1)	1069 (22.1)	916 (26.4)	360 (13.5)	159 (23.4)	204 (16.5)
Material Deprivation								
Unknown	3937 (0.7)	310 (0.9)	141 (1.0)	33 (0.7)	63 (1.8)	30 (1.1)	10 (1.5)	19 (1.5)
Q1 (most privileged)	145 211 (24.4)	4498 (12.9)	2651 (17.8)	1707 (35.2)	449 (12.9)	447 (16.8)	235 (34.6)	200 (16.1)
Q2	117 264 (19.7)	5280 (15.2)	2304 (15.5)	859 (17.7)	509 (14.7)	378 (14.2)	121 (17.8)	176 (14.2)

Table 1. Continued

Variables	Negative	HCV Monoinfected	HBV Monoinfected	HIV Monoinfected	HCV/HBV Coinfected	HCV/HIV Coinfected	HBV/HIV Coinfected	HCV/HBV/HIV Coinfected
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Row Percent	596 079 (90.5)	34807 (5.3)	14913 (2.3)	4846 (0.8)	3472 (0.5)	2668 (0.4)	679 (0.1)	1240 (0.2)
Q3	114 823 (19.3)	6047 (17.4)	2565 (17.2)	625 (12.9)	542 (15.6)	314 (11.8)	88 (13.0)	115 (9.3)
Q4	115 011 (19.3)	8117 (23.3)	3125 (21.0)	728 (15.0)	783 (22.6)	536 (20.1)	95 (14.0)	222 (17.9)
Q5 (most deprived)	99 833 (16.8)	10 555 (30.3)	4127 (27.7)	894 (18.5)	1126 (32.4)	963 (36.1)	130 (19.2)	508 (41.0)
Social Deprivation								
Unknown	3937 (0.7)	310 (0.9)	141 (1.0)	33 (0.7)	63 (1.8)	30 (1.1)	10 (1.5)	19 (1.5)
Q1 (most privileged)	104 933 (17.6)	3525 (10.1)	3166 (21.2)	402 (8.3)	310 (8.9)	134 (5.0)	57 (8.4)	46 (3.7)
Q2	102 116 (17.1)	4332 (12.4)	2949 (19.8)	517 (10.7)	339 (9.8)	202 (7.6)	55 (8.1)	86 (6.9)
Q3	103 301 (17.3)	5550 (16.0)	2533 (17.0)	551 (11.4)	511 (14.7)	309 (11.6)	55 (8.1)	119 (9.6)
Q4	122 874 (20.6)	7137 (20.5)	2606 (17.5)	901 (18.6)	657 (18.9)	450 (16.9)	118 (17.4)	239 (19.3)
Q5 (most deprived)	158 918 (26.7)	13 953 (40.1)	3518 (23.6)	2442 (50.4)	1592 (45.9)	1543 (57.8)	384 (56.6)	731 (59.0)

Abbreviations: BC, British Columbia; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; TB, tuberculosis.

[a]Past history of disease/risk factor.

A similar pattern was observed for coinfections; however, a decrease in survival was less severe than that in the triple infection group.

Multivariable extended Cox regression analysis demonstrated that individuals with HCV/HBV/HIV infections (adjusted hazard ratio [aHR], 8.9; 95% CI, 8.2–9.7) had highest risk of mortality followed by HCV/HIV (aHR, 4.8; 95% CI, 4.4–5.1), HBV/HIV (aHR, 4.1; 95% CI, 3.5–4.8), HCV/HBV (aHR, 3.9; 95% CI, 3.7–4.2), HCV (aHR, 2.6; 95% CI, 2.6–2.7), HBV (aHR, 2.2; 95% CI, 2.0–2.3), and HIV (aHR, 1.6; 95% CI, 1.5–1.7). A higher risk of mortality was observed among males (aHR, 1.5; 95% CI, 1.5–16), Other (ethnicity) (aHR, 1.6; 95% CI, 1.5–1.7), and people aged 45 years and above (aHR, 3.2; 95% CI, 3.0–3.4). Similarly, a higher risk of mortality was noted among individuals with IDU and problematic alcohol use, with mortality risk higher among those with problematic alcohol use (1.6 vs 1.2). Regarding chronic conditions, individuals with heart failure had the highest risk of mortality followed by chronic kidney disease, diabetes, and hypertension (Table 3).

DISCUSSION

In this large population-based cohort, concurrent infection with HCV, HIV, and HBV was significantly associated with all-cause mortality, compared with individuals who were negative for all infections. Similarly, coinfection with HBV and HIV was associated with reduced survival. We also found that risk of mortality increased with each transition from no infection, to single infection, coinfection, and triple infection. These findings highlight the potential for highly effective drugs for HBV, HCV, and HIV in reducing overall mortality. The association of triple infection with increased all-cause mortality has been observed in other cohorts [16, 23]; however, these studies compared coinfection/triple infection with a monoinfected group, such as HIV or HCV. In contrast, our study assessed mortality among any infection group compared with negative group. In our study, the risk of all-cause mortality was 9 times higher among HCV/HIV/HBV triple infected individuals compared with individuals with no infection. This is much higher than the UK CHIC cohort [16] (rate ratio, 2.29), which has data from HIV clinics across the United Kingdom and the China National Free Antiretroviral Treatment Program [23] (HR, 1.9) for HIV. All infection groups were associated with a higher risk of mortality; however, the lowest risk was observed in the HIV-monoinfected group, possibly reflecting the impact of the HIV program in British Columbia, where HIV care and support, including antiretroviral treatment, is provided at no cost [24]. Individuals with HIV and HCV coinfection and those with HBV/HIV and HCV/HBV coinfection also had reduced survival, as reported previously by other studies [7, 25]; however, the magnitude of risk of mortality in the coinfection groups in our study was higher than most studies [16, 23], including

Table 2. Mortality Rate Per 1000 Person Years by HCV, HBV, and HIV Infection Groups, BC Hepatitis Testers Cohort, 1990–2015

	Negative		HCV Monoinfected		HBV Monoinfected		HIV Monoinfected		HCV/HBV Coinfected		HCV/HIV Coinfected		HBV/HIV Coinfected		HCV/HBV/HIV Coinfected	
Variables	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)
All-Cause Mortality	23 199/6 759 521.7	3.4 (3.4–3.5)	6418/528 796.1	12.1 (11.8–12.4)	987/194 819	5.1 (4.8–5.4)	473/71 000.9	6.7 (6.1–7.3)	1122/57 860.3	19.4 (18.3–20.6)	826/42 920.9	19.2 (18.0–20.6)	159/10 218.1	15.6 (13.3–18.2)	620/19 811.6	31.3 (28.9–33.9)
Sex																
Female	8938/3 929 381	2.3 (2.2–2.3)	1911/199 409.4	9.6 (9.2–10)	302/98 725.5	3.1 (2.7–3.4)	59/10 454.6	5.6 (4.4–7.3)	326/20 550.7	15.9 (14.2–17.7)	226/12 473.7	18.1 (15.9–20.6)	14/893.9	15.7 (9.3–26.4)	190/6822.8	27.8 (24.2–32.1)
Male	14 259/2 830 081.8	5 (5–5.1)	4507/329 386.7	13.7 (13.3–14.1)	685/96 093.5	7.1 (6.6–7.7)	414/60 546.3	6.8 (6.2–7.5)	796/37 309.7	21.3 (19.9–22.9)	600/30 447.2	19.7 (18.2–21.3)	145/9 324.1	15.6 (13.2–18.3)	430/12 988.7	33.1 (30.1–36.4)
Ethnicity																
South Asian	1149/476 334.8	2.4 (2.3–2.6)	133/12 713.8	10.5 (8.8–12.4)	64/8025.6	8 (6.2–10.2)	19/2350.2	8.1 (5.2–12.7)	24/1046.6	22.9 (15.4–34.2)	9/420	21.4 (11.2–41.2)	3/236.1	12.7 (4.1–39.4)	0/150.2	0
Other	20 723/5 582 962.3	3.7 (3.7–3.8)	6195/503 944.3	12.3 (12–12.6)	544/82 154.8	6.6 (6.1–7.2)	444/66 213	6.7 (6.1–7.4)	1063/53 250.8	20 (18.8–21.2)	809/41 888.8	19.3 (18–20.7)	150/9 296.4	16.1 (13.7–18.9)	615/19 424.2	31.7 (29.3–34.3)
East Asian	1327/700 224.6	1.9 (1.8–2)	90/12 138	7.4 (6–9.1)	379/104 638.7	3.6 (3.3–4)	10/2437.7	4.1 (2.2–7.6)	35/3563	9.8 (7.1–13.7)	8/612.1	13.1 (6.5–26.1)	6/685.6	8.8 (3.9–19.5)	5/237.1	21.1 (8.8–50.7)
Age at Diagnosis																
<25	731/556 962.8	1.3 (1.2–1.4)	214/41 694.9	5.1 (4.5–5.9)	30/33 904.7	0.9 (0.6–1.3)	17/5767.1	2.9 (1.8–4.7)	26/2620	9.9 (6.8–14.6)	30/2692.9	11.1 (7.8–15.9)	3/172.8	17.4 (5.6–53.8)	9/767.2	11.7 (6.1–22.5)
25–34	1529/1 926 476.3	0.8 (0.8–0.8)	908/137 646.8	6.6 (6.2–7)	89/61 500.7	1.4 (1.2–1.8)	81/22 642.3	3.6 (2.9–4.4)	136/13 494.6	10.1 (8.5–11.9)	158/11 658.8	13.6 (11.6–15.8)	23/1892.8	12.2 (8.1–18.3)	118/4613.2	25.6 (21.4–30.6)
35–44	2261/1 995 403.2	1.1 (1.1–1.2)	1986/195 676.6	10.1 (9.7–10.6)	135/48 348.9	2.8 (2.4–3.3)	151/24 085	6.3 (5.3–7.4)	289/18 569.3	15.6 (13.9–17.5)	342/16 673.1	20.5 (18.4–22.8)	43/3043	14.1 (10.5–19.1)	247/7451.5	33.1 (29.3–37.6)
>45	18 678/2 280 679.4	8.2 (8.1–8.3)	3310/153 777.9	21.5 (20.8–22.3)	733/51 064.7	14.4 (13.4–15.4)	224/18 506.5	12.1 (10.6–13.8)	671/23 176.4	29 (26.8–31.2)	296/11 896.1	24.9 (22.2–27.9)	90/5109.5	17.6 (14.3–21.7)	246/6979.7	35.2 (31.1–39.9)
IDU																
No	20 395/6 314 561.6	3.2 (3.2–3.3)	3359/290 507.3	11.6 (11.2–12)	894/185 277.9	4.8 (4.5–5.2)	375/61 249	6.1 (5.5–6.8)	424/23 789.8	17.8 (16.2–19.6)	204/12943	15.8 (13.7–18.1)	116/7912.9	14.7 (12.2–17.6)	74/3081.3	24 (19.1–30.2)
Yes	2804/444 960.1	6.3 (6.1–6.5)	3059/238 288.8	12.8 (12.4–13.3)	93/9541.1	9.7 (8–11.9)	98/9752	10 (8.2–12.2)	698/34 070.6	20.5 (19–22.1)	622/29 977.9	20.7 (19.2–22.4)	43/2305.2	18.7 (13.8–25.2)	546/16 730.3	32.6 (30–35.5)

Table 2. Continued

	Negative		HCV Monoinfected		HBV Monoinfected		HIV Monoinfected		HCV/HBV Coinfected		HCV/HIV Coinfected		HBV/HIV Coinfected		HCV/HBV/HIV Coinfected	
Variables	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)
Problematic Alcohol Use																
No	18 005/6 204 332.5	2.9 (2.9–2.9)	3374/332 665.2	10.1 (9.8–10.5)	832/184 378.2	4.5 (4.2–4.8)	350/62 282.2	5.6 (5.1–6.2)	500/31 508.8	15.9 (14.5–17.3)	360/23 297.7	15.5 (13.9–17.1)	125/8432.4	14.8 (12.4–17.7)	251/8258.1	30.4 (26.9–34.4)
Yes	5194/555 189.1	9.4 (9.1–9.6)	3044/196 131	15.5 (15–16.1)	155/10 440.8	14.8 (12.7–17.4)	123/8718.8	14.1 (11.8–16.8)	622/26 351.5	23.6 (21.8–25.5)	466/19 623.2	23.7 (21.7–26)	34/1785.7	19 (13.6–26.6)	369/11 553.4	31.9 (28.8–35.4)
Active TB																
No	23 010/6 740 868.9	3.4 (3.4–3.5)	6363/526 180	12.1 (11.8–12.4)	968/192 890.2	5 (4.7–5.3)	460/70 092.8	6.6 (6–7.2)	1105/57 162	19.3 (18.2–20.5)	789/41 623.7	19 (17.7–20.3)	156/10 084.4	15.5 (13.2–18.1)	579/18 651.1	31 (28.6–33.7)
Yes	189/18 652.7	10.1 (8.8–11.7)	55/2616.2	21 (16.1–27.4)	19/1928.8	9.9 (6.3–15.4)	13/908.1	14.3 (8.3–24.7)	17/698.4	24.3 (15.1–39.2)	37/1297.2	28.5 (20.7–39.4)	3/133.6	22.4 (7.2–69.6)	41/1160.5	35.3 (26–48)
Diabetes																
No	16 578/6 453 105	2.6 (2.5–2.6)	5372/488 168.2	11 (10.7–11.3)	711/182 085.2	3.9 (3.6–4.2)	393/66 412.2	5.9 (5.4–6.5)	912/51 811.1	17.6 (16.5–18.8)	778/40 858.5	19 (17.7–20.4)	139/9332.4	14.9 (12.6–17.6)	576/18 364.4	31.4 (28.9–34)
Yes	6621/306 416.6	21.6 (21.1–22.1)	1046/40 627.9	25.7 (24.2–27.4)	276/12 733.8	21.7 (19.3–24.4)	80/4588.7	17.4 (14–21.7)	210/6049.2	34.7 (30.3–39.7)	48/2062.4	23.3 (17.5–30.9)	20/885.7	22.6 (14.6–35)	44/1447.2	30.4 (22.6–40.9)
Chronic Kidney Disease																
No	15 906/6 479 402.1	2.5 (2.4–2.5)	5511/498 576.8	11.1 (10.8–11.3)	763/185 093.7	4.1 (3.8–4.4)	366/64 889.3	5.6 (5.1–6.2)	940/52 523.3	17.9 (16.8–19.1)	726/39 486.2	18.4 (17.1–19.8)	128/8957.2	14.3 (12–17)	532/17 154.1	31 (28.5–33.8)
Yes	7293/280 119.5	26 (25.4–26.6)	907/30 219.4	30 (28.1–32)	224/9725.3	23 (20.2–26.3)	107/6111.6	17.5 (14.5–21.2)	182/5337	34.1 (29.5–39.4)	100/3434.6	29.1 (23.9–35.4)	31/1260.9	24.6 (17.3–35)	88/2657.5	33.1 (26.9–40.8)
Heart Failure																
No	16 518/6 589 618.4	2.5 (2.5–2.5)	5600/505 306.1	11.1 (10.8–11.4)	793/189 476.7	4.2 (3.9–4.5)	393/68 140.6	5.8 (5.2–6.4)	955/53 365.8	17.9 (16.8–19.1)	758/41 179.9	18.4 (17.1–19.8)	141/9694.9	14.5 (12.3–17.2)	568/18 518.5	30.7 (28.3–33.3)
Yes	6681/169 903.2	39.3 (38.4–40.3)	818/23 490.1	34.8 (32.5–37.3)	194/5342.3	36.3 (31.5–41.8)	80/2860.4	28 (22.5–34.8)	167/4494.5	37.2 (31.9–43.2)	68/1741	39.1 (30.8–49.5)	18/523.2	34.4 (21.7–54.6)	52/1293.1	40.2 (30.6–52.8)

Table 2. Continued

	Negative		HCV Monoinfected		HBV Monoinfected		HIV Monoinfected		HCV/HBV Coinfected		HCV/HIV Coinfected		HBV/HIV Coinfected		HCV/HBV/HIV Coinfected	
Variables	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)	n/Person Years	Mortality Rate (95% CI)
Hypertension																
No	9852/5 453 548.7	1.8 (1.8–1.8)	4192/395 463.4	10.6 (10.3–10.9)	494/148 114.6	3.3 (3.1–3.6)	301/53 851.4	5.6 (5–6.3)	756/42 428.5	17.8 (16.6–19.1)	707/36 924.1	19.1 (17.8–20.6)	116/7483.6	15.5 (12.9–18.6)	522/16 269.5	32.1 (29.4–35)
Yes	13 347/1 305 972.9	10.2 (10–10.4)	2226/133 332.7	16.7 (16–17.4)	493/46 704.4	10.6 (9.7–11.5)	172/17 149.5	10 (8.6–11.6)	366/15431.9	23.7 (21.4–26.3)	119/5996.8	19.8 (16.6–23.7)	43/2734.4	15.7 (11.7–21.2)	98/3542	27.7 (22.7–33.7)
Material Deprivation																
Q1 (most privileged)	4040/1 587 747	2.5 (2.5–2.6)	799/67 583.9	11.8 (11–12.7)	162/33 140.9	4.9 (4.2–5.7)	115/25 077.2	4.6 (3.8–5.5)	140/7408.4	18.9 (16–22.3)	107/7104.4	15.1 (12.5–18.2)	47/3625.1	13 (9.7–17.3)	86/3330.6	25.8 (20.9–31.9)
Q2	3880/1 318 379.8	2.9 (2.9–3)	940/81 176	11.6 (10.9–12.3)	148/293 18.4	5 (4.3–5.9)	83/13 073.7	6.3 (5.1–7.9)	173/8 422.5	20.5 (17.7–23.8)	120/6198.9	19.4 (16.2–23.2)	32/1910.6	16.7 (11.8–23.7)	83/2904.8	28.6 (23–35.4)
Q3	4554/1 305 506.3	3.5 (3.4–3.6)	1097/92 061	11.9 (11.2–12.6)	145/31 795.6	4.6 (3.9–5.4)	62/8985.2	6.9 (5.4–8.9)	164/9031.9	18.2 (15.6–21.2)	88/4993.9	17.6 (14.3–21.7)	23/1236.7	18.6 (12.4–28)	51/1879.2	27.1 (20.6–35.7)
Q4	4899/1 317 262.7	3.7 (3.6–3.8)	1516/122 853.2	12.3 (11.7–13)	218/40 461.4	5.4 (4.7–6.2)	80/10 385.6	7.7 (6.2–9.6)	227/13 253.5	17.1 (15–19.5)	166/8711	19.1 (16.4–22.2)	21/1404	15 (9.8–22.9)	115/3458.2	33.3 (27.7–39.9)
Q5 (most deprived)	5537/1 190 894.6	4.6 (4.5–4.8)	1991/160 431.8	12.4 (11.9–13)	308/58 614.7	5.3 (4.7–5.9)	127/13 077.3	9.7 (8.2–11.6)	398/18 754.4	21.2 (19.2–23.4)	337/15 419.8	21.9 (19.6–24.3)	32/1943.6	16.5 (11.6–23.3)	278/7961.4	34.9 (31–39.3)
Social Deprivation																
Q1 (most privileged)	3013/1 170 975.4	2.6 (2.5–2.7)	579/50 971.6	11.4 (10.5–12.3)	155/40 996.7	3.8 (3.2–4.4)	38/5516.1	6.9 (5–9.5)	80/5 012.2	16 (12.8–19.9)	38/2103.3	18.1 (13.1–24.8)	10/940.1	10.6 (5.7–19.8)	23/703.5	32.7 (21.7–49.2)
Q2	3247/1 158 394.5	2.8 (2.7–2.9)	731/65 365.3	11.2 (10.4–12)	209/39 157.9	5.3 (4.7–6.1)	57/7355.3	7.7 (6–10)	95/5821.1	16.3 (13.3–20)	58/3300.6	17.6 (13.6–22.7)	10/842.9	11.9 (6.4–22)	34/1514.7	22.4 (16–31.4)
Q3	3720/1 170 260.4	3.2 (3.1–3.3)	1029/85 391.1	12.1 (11.3–12.8)	175/33 318.9	5.3 (4.5–6.1)	61/8001.5	7.6 (5.9–9.8)	149/8487.4	17.6 (15–20.6)	106/5023.9	21.1 (17.4–25.5)	14/741.8	18.9 (11.2–31.9)	57/1832.5	31.1 (24–40.3)
Q4	4773/1 390 553.5	3.4 (3.3–3.5)	1360/109 782.8	12.4 (11.7–13.1)	184/33 196.9	5.5 (4.8–6.4)	89/13 079.5	6.8 (5.5–8.4)	214/10 985.2	19.5 (17–22.3)	143/7278.2	19.6 (16.7–23.1)	26/1740.8	14.9 (10.2–21.9)	110/3962.7	27.8 (23–33.5)
Q5 (most deprived)	8157/1 829 606.6	4.5 (4.4–4.6)	2644/212 595.2	12.4 (12–12.9)	258/46 660.5	5.5 (4.9–6.2)	222/36 646.6	6.1 (5.3–6.9)	564/26 564.8	21.2 (19.5–23.1)	473/24 722	19.1 (17.5–20.9)	95/5854.4	16.2 (13.3–19.8)	389/11 520.7	33.8 (30.6–37.3)

Abbreviations: BC, British Columbia; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; TB, tuberculosis.

meta-analyses on HIV/HBV coinfection [26] and HIV/HCV coinfection [27]. This highlights the need to account for the transition from no infection to infection status in analysis to accurately estimate the incremental risk of mortality, which has not previously been in other studies [16, 23]. Our study demonstrates the detrimental impact that each infection and subsequent coinfection plays with regards to mortality and the fact that the increased mortality is actually the result of both viral sequelae as well as behavioral activities that lead to infection acquisition [9]. This gradient in mortality risk by a number of infections highlights the potential impact of curing or suppressing 1 or more of these infections in reducing mortality by highly effective curative HCV treatments and suppressive HBV and HIV treatments. However, impact of treatments on mortality risk among people with multiple infections is not available yet and requires further studies. Therefore, morbidity and mortality reductions will require both timely treatment of infection, as well as ancillary harm reduction initiatives such as opioid substitution therapy and mental health counseling, to prevent infection [28], reinfection [29], and coinfection [30].

Other ethnicity, which consisted of predominantly Caucasian ethnicity, was significantly associated with, and at a higher risk for, all-cause mortality compared with other ethnicities, similar to another study on HIV/HCV coinfected veterans [31]. This may be due to increased IDU, alcohol use, and risk of HCV/HBV/HIV infection among Caucasians in the BC-HTC cohort, as reported previously [32]. This has important implications for public health interventions and health service delivery, which need to take into account the differential risk profiles of various ethnicities. We also found older age at diagnosis (>45 years) and IDU to be significantly associated with all-cause mortality, similar to the UK CHIC study [16] and others [23]. In our cohort, problematic alcohol use was independently associated with an elevated risk of mortality, reflecting the underlying increased risk of liver disease and liver-related mortality even without HCV, HBV, or HIV infection. This shows that more efforts are

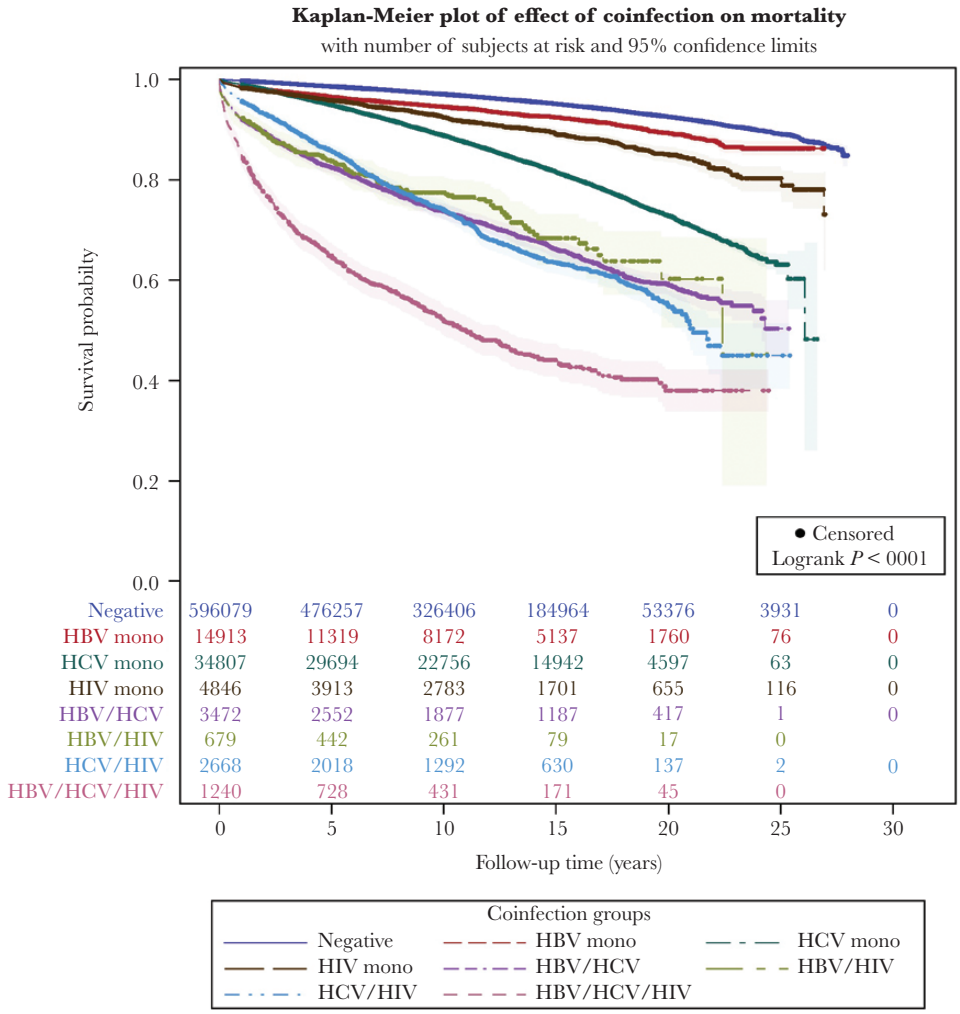

Figure 1. Kaplan-Meier plot of the effect of hepatitis C virus (HCV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV) infection groups on all-cause mortality.

Table 3. Multivariable Cox Regression Analysis of Factors Associated With All-Cause Mortality Among HCV-, HBV-, and HIV-Coinfected Individuals in the BC Hepatitis Testers Cohort, 1990–2015

Variable	All-Cause Mortality			
	Crude HR	95% CI	Adjusted HR	95% CI
Sex				
Female	1		1	
Male	2.31	2.26–2.36	1.52	1.49–1.56
Infection Groups				
Negative	1		1	
HCV monoinfected	3.69	3.59–3.79	2.65	2.57–2.73
HBV monoinfected	1.60	1.50–1.71	2.15	2.01–2.29
HIV monoinfected	1.95	1.78–2.14	1.59	1.45–1.74
HCV/HBV	7.03	6.62–7.47	3.95	3.71–4.21
HCV/HIV	6.77	6.31–7.26	4.77	4.43–5.13
HBV/HIV	6.63	5.67–7.76	4.06	3.46–4.76
HCV/HBV/HIV	15.03	13.86–16.29	8.92	8.20–9.71
Ethnicity				
South Asian	1		1	
Other	1.61	1.53–1.70	1.44	1.36–1.52
East Asian	0.78	0.73–0.84	0.85	0.79–0.91
Age at Diagnosis				
<25	1		1	
25–34	0.81	0.76–0.87	0.80	0.74–0.85
35–44	1.30	1.22–1.39	1.09	1.02–1.17
>45	5.19	4.88–5.52	3.24	3.04–3.45
IDU[a]				
No	1		1	
Yes	2.50	2.44–2.56	1.25	1.21–1.29
Problematic Alcohol Use[a]				
No	1		1	
Yes	3.24	3.17–3.32	1.62	1.58–1.66
Active TB[a]				
No	1		1	
Yes	3.03	2.73–3.35	1.37	1.23–1.52
Diabetes[a]				
No	1		1	
Yes	6.201	6.05–6.36	1.66	1.62–1.71
Chronic Kidney Disease[a]				
No	1		1	
Yes	7.67	7.49–7.86	2.30	2.23–2.37
Heart Failure[a]				
No	1		1	
Yes	11.09	10.82–11.38	2.87	2.78–2.96
Hypertension[a]				
No	1		1	
Yes	3.86	3.78–3.94	1.26	1.22–1.29
Material Deprivation				
Q1 (most privileged)	1		1	
Q2	1.17	1.12–1.21	1.10	1.06–1.14
Q3	1.32	1.27–1.37	1.22	1.17–1.26
Q4	1.48	1.43–1.53	1.25	1.21–1.3
Q5 (most deprived)	1.87	1.81–1.93	1.36	1.31–1.4

Abbreviations: BC, British Columbia; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, injection drug use; TB, tuberculosis.

[a]Past history of disease/risk factor.

needed to reduce harms in PWID as well as address problematic alcohol use irrespective of HCV, HBV, and HIV treatment.

Our study also documented increased mortality among individuals living in materially deprived areas, with an increasing risk for each quintile of deprivation. Socioeconomic indicators, such as poverty, are known to be associated with HCV mortality in the United States [33], and the relationship of socioeconomic disparity with HIV/AIDS mortality has been documented previously [34]. Individuals with low socioeconomic status face a multitude of barriers to treatment access, adherence, and continuum of care. The combination of socioeconomic disparity, syndemics, IDU, and problematic alcohol use within vulnerable populations lead to increased overall mortality [35].

Of note, individuals with any chronic condition had a higher risk of all-cause mortality; however, individuals with chronic kidney disease and heart failure had higher risk of mortality than those with diabetes and hypertension. A study on veterans with HIV infection and chronic kidney disease reported significantly higher mortality, which was more pronounced in individuals also coinfected with HCV [36]. A higher risk of mortality among those with heart failure is also concerning, because studies have identified an increased risk of heart failure among HIV-positive individuals independent of a prior diagnosis of coronary heart disease [37]. This becomes important in the context of coinfection with HBV [16], and particularly HCV, which has a higher risk of extrahepatic manifestations, including cardiovascular diseases and chronic kidney disease, leading to an increased risk of morbidity and mortality [8]. Screening for related chronic conditions at the time of testing for HIV, HCV, and HBV infections, combined with appropriate care management of those condition(s), would likely contribute to reduced morbidity and mortality among the affected populations.

To our knowledge, this is one of the largest study of HCV/HIV/HBV triple infected individuals (n = 1240), which provides us with adequate power to elucidate the relationship of multiple infections to mortality with more precision. Furthermore, we evaluated the transition of infection status from no infection to coinfection and triple infection and its impact on mortality, which has not been done previously. We also assessed important factors related to mortality, such as ethnicity, alcohol use, and chronic conditions, which were not available in other studies [16, 23]. The purpose of our study was to assess all-cause mortality and its determinants, particularly focusing on coinfection/triple infection related mortality; therefore, we did not include liver- or drug-related mortality. It is likely that a proportion of all-cause mortality in our cohort is due to either drug- or liver-related mortality. Hepatitis B virus and HCV infections mainly affect the liver, and a major proportion of mortality is expected

to be liver related. However, co-occurrence of HIV, HCV, and HBV is related to syndemic factors such as substance use and socioeconomic marginalization [9, 10]; therefore, a significant proportion of these people die from substance use-related causes in addition to extrahepatic manifestations as shown in our earlier work related to HCV [38, 39]. Within this context, all-cause mortality captures the overall effect of these infections. Further studies should investigate the relative contribution of various causes of mortality in people with concurrent infections.

Because assessment of potential risk factors for all-cause mortality was based on diagnostic codes, misclassification of some of these variables is possible. Because assessment of potential risk factors (eg, alcohol use) was based on diagnostic codes, misclassification of these variables is possible. For example, the diagnostic code for problematic alcohol use would only capture alcohol misuse, and the potential impact of low or moderate alcohol consumption on the risk of mortality cannot be ascertained. We were also unable to evaluate the effect of HIV treatment on all-cause mortality, because data on anti-retroviral therapy is not available in our cohort. We also did not include HBV and HCV therapy in our analysis, because our study objective did not aim to assess the impact of therapy on all-cause mortality. However, because treatment of HCV and HIV has been shown to reduce all-cause mortality [17, 40], this cohort can be used to evaluate the impact of scaling up of these treatments. In addition, the study period was largely in the early direct-acting antiviral (DAA era), so results now for HCV might be different. Furthermore, since the cohort for analysis was selected from individuals tested for all 3 infections, the estimated mortality risk among this population may not be representative of the general population.

CONCLUSIONS

In conclusion, this is one of the largest studies reporting increased all-cause mortality among HCV, HBV, and HIV coinfected and triple infected individuals. Our findings indicate that Other ethnicity, IDU, problematic alcohol use, chronic conditions, and material disadvantage were significantly associated with all-cause mortality. The increased mortality observed in our study highlights the need for preventive strategies and early screening, diagnosis, and management of HCV, HIV, and HBV infections. In addition, multidisease health screening for related chronic conditions, and colocation of services, particularly harm reduction and mental health services, would contribute to reducing mortality among the HCV, HBV, and HIV affected populations.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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