Schizophrenia Research 209 (2019) 198–205

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

HIV, schizophrenia, and all-cause mortality: A population-based cohort study of individuals accessing universal medical care from 1998 to 2012 in British Columbia, Canada

Kalysha Closson [a,b], Taylor McLinden [a], Thomas L. Patterson [c], Oghenowede Eyawo [a,d], Mia Kibel [a], Kiffer G. Card [d,e], Kate Salters [a,d], William Chau [a], Monica Ye [a], Mark W. Hull [a,f], Viviane D. Lima [a,f], Julio S.G. Montaner [a,f], Robert S. Hogg [a,d,*],
For the Comparative Outcomes And Service Utilization Trends (COAST) Study

[a] British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada
[b] School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
[c] University of California San Diego, Department of Psychiatry, San Diego, CA, USA
[d] Simon Fraser University, Faculty of Health Sciences, Burnaby, BC, Canada
[e] School of Public Health and Social Policy, University of Victoria, Victoria, BC, Canada
[f] Division of AIDS, Department of Medicine, University of British Columbia, Vancouver, BC, Canada

ARTICLE INFO

Article history:
Received 1 May 2018
Received in revised form 1 February 2019
Accepted 26 April 2019
Available online 27 June 2019

Keywords:
Schizophrenia
HIV/AIDS
All-cause mortality
Survival

ABSTRACT

Schizophrenia is a severe mental illness with important implications for morbidity and mortality. This population-based cohort study examined the impact of schizophrenia diagnoses on all-cause mortality among a sample of people living with HIV (PLHIV) and a 10% random sample of individuals living without HIV (HIV-) in British Columbia (BC), through a data linkage between the BC Centre for Excellence in HIV/AIDS and Population Data BC's data holdings. Schizophrenia diagnoses were identified via International Classification of Diseases version 9 and version 10 codes. Age- and sex-adjusted all-cause mortality rates from January 1st, 1998 to December 31st, 2012 were calculated. Multivariable logistic models assessed (1) HIV status and mortality among individuals diagnosed with schizophrenia, (2) schizophrenia diagnosis and mortality among PLHIV, and (3) correlates of mortality among PLHIV concurrently diagnosed with schizophrenia (HIV+/SZO+). From 1998 to 2012, 6.3% of those with HIV had a schizophrenia diagnosis, compared to 1.1% of those without HIV. While significant declines in mortality rates were observed throughout the study period, mortality rates were highest among HIV+/SZO+. After adjustment for substance use disorder and age at baseline, HIV+/SZO+ had a 2.64 times greater odds of mortality (95% confidence interval [CI] = 2.14–3.25) compared to HIV-/SZO+. For PLHIV, a schizophrenia diagnosis was not associated with mortality after controlling for potential confounders (adjusted odds ratio [aOR] = 0.90, 95%CI = 0.74–1.09). Among HIV+/SZO+, age, history of injection drug use, ever having an AIDS-defining illness, and never being on anti-psychotic medication or accessing psychiatric services were associated with mortality. Efforts should be made to identify and link to care individuals disproportionately affected by schizophrenia and excess mortality, including those living with HIV.

1. Introduction

Schizophrenia is a chronic mental illness that, when left untreated, has been shown to impede daily functioning, increase morbidity, and decrease life expectancy (Allebeck, 1989; Brown, 1997; Brown et al., 2000). Individuals diagnosed with schizophrenia have been found to have three to five times higher odds of mortality compared to those without a schizophrenia diagnosis (Brown et al., 2000; Stewart et al., 1994). Moreover, individuals with serious mental health issues, including schizophrenia, are more likely than the general population to be concurrently living with blood-borne illnesses, including HIV (Bauer-Staeb et al., 2017; Prince et al., 2012; Stewart et al., 1994). This may in part be due to increased rates of substance use among individuals with severe mental illnesses (Helleberg et al., 2015; Prince et al., 2012). Furthermore, despite improvements in HIV treatment and increased life expectancy (Hogg et al., 2017; Patterson et al., 2015; Samji et al., 2013), people living with HIV (PLHIV) continue to experience heightened mortality compared to those living without HIV (HIV-) (Eyawo et al., 2018).

* Corresponding author at: Faculty of Health Sciences, Simon Fraser University, 8888 University Drive, Burnaby, BC V5A 1S6, Canada.
E-mail address: robert_hogg@sfu.ca (R.S. Hogg).

https://doi.org/10.1016/j.schres.2019.04.020
0920-9964/

Living with schizophrenia presents multiple interacting challenges, including societal and personal stigma and higher levels of substance use, both of which influence HIV-risk and mortality (Brown, 1997; Chander et al., 2012; Helleberg et al., 2015; Meade and Sikkema, 2007). However, while the relationship between mental illness and HIV is complex and bidirectional, there have been few studies unpacking the impact of schizophrenia and HIV comorbidity on mortality (Cournos et al., 2012). In a 2015 study conducted among a national sample in Denmark, researchers found that among people with a schizophrenia diagnosis, those living with HIV (HIV+/SZO+) had significantly higher mortality rates compared to those living without HIV (HIV-/SZO+) (Helleberg et al., 2015). The same study also found that there were no differences in clinical outcomes (i.e. CD4 cell count and viral suppression) and treatment access (i.e. time to antiretroviral therapy [ART] initiation) between PLHIV with and without a schizophrenia diagnosis (HIV+/SZO+ and HIV+/SZO-, respectively), after adjusting for substance use. Previous research has also found that HIV+/SZO+ may be less likely than HIV-/SZO+ to discontinue their anti-psychotic medication and have increased health service utilization (Himelhoch et al., 2009; Mijch et al., 2006). These results suggest that gaps in mortality between PLHIV and HIV- with and without a schizophrenia diagnosis may not be wholly dependent on clinical HIV outcomes. Further research is needed to better understand mortality differences among PLHIV and HIV- with and without a schizophrenia diagnosis, as well as potential reasons for elevated mortality rates among HIV+/SZO+. In this study we examine all-cause mortality among HIV+/SZO+, HIV-/SZO+, HIV+/SZO-, and HIV-/SZO- from January 1st, 1998 to December 31st, 2012, as well as factors associated with mortality among HIV+/SZO+, in the province of British Columbia (BC), Canada.

2. Methods

2.1. Study population

This study uses data from the Comparative Outcomes And Service Utilization Trends (COAST) Study, a population-based cohort study examining health outcomes and health services use of PLHIV and the general BC population from April 1st, 1996 to March 31st, 2013. Details of the COAST study have been described elsewhere (Eyawo et al., 2018). The COAST study was created through a data linkage between the Drug Treatment Program (DTP) at the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) and several Population Data BC data holdings; and contains data of all known PLHIV and a 10% random sample of the general BC population that were ≥19 years of age. The DTP at the BC-CfE centrally manages ART dispensation across the province, and prospectively collects information on demographic, immunological and virologic outcomes for all PLHIV who have ever accessed ART in BC (BC Centre for Excellence in HIV/AIDS, 2014). Population Data BC is a repository of individual-level de-identified longitudinal data from provincial health administrative databases. Based on linkages to data holdings at Population Data BC performed as part of the COAST study, the COAST data includes information on health care system encounters (including physician billings and hospitalizations data comprised of International Classification of Diseases version 9 [ICD-9] and version 10 [ICD-10] diagnosis codes) (British Columbia Ministry of Health, 2014a, 2014b); prescription drug dispensation (British Columbia Ministry of Health, 2014c, 2014d); and HIV treatment and outcomes data available through the BC CfE (for PLHIV only) (British Columbia Centre for Excellence in HIV/AIDS, 2014). Due to important shifts in causes of death and reduced mortality among PLHIV between 1996 and 1998 (Eyawo et al., 2017; Helleberg et al., 2012) coinciding with the introduction of triple ART (Hogg et al., 1999), we restricted this analysis to January 1st, 1998 to December 31st, 2012. We excluded 573 (4.1%) PLHIV and 14,162 (2.8%) individuals living without HIV who either died or were lost to follow-up between 1996 and 1998, or entered the cohort after December 31st, 2012, as the later did not have complete calendar years of data.

Ethical approval for this study was obtained from the University of British Columbia/Providence Health Care (#H09-02905) and Simon Fraser University (#2013s0566) research ethics boards. The study complies with the BC Freedom of Information and Protection of Privacy Act and did not require informed consent as it is conducted retrospectively for research and statistical purposes only using anonymized data.

2.2. Inclusion and exclusion criteria

We examined the prevalence of SZO diagnoses by HIV status and mortality among four groups distinguished by their schizophrenia diagnosis and HIV status, including HIV+/SZO+, HIV-/SZO+, HIV+/SZO-, and HIV-/SZO- (Fig. 1).

The cohort of PLHIV included all age-eligible PLHIV (≥19 years of age) during the study period under consideration (January 1st 1998 to December 31st, 2012). We identified PLHIV through the BC-CfE DTP registry as well as Population Data BC's data holdings (BC Vital Statistics, 2014; British Columbia Ministry of Health, 2014a, 2014b, 2014c, 2014d; Canadian Institute for Health Information, 2014). Using the BC-CfE DTP registry, HIV status was determined by at least one detectable HIV plasma viral load, and/or the initiation of ART as indicated by the DTP. In order to capture those diagnosed with HIV in BC who may not be included in the DTP, we further included individuals with at least one inpatient hospitalization and/or three or more outpatient physician ICD-9 and -10 codes related to HIV or AIDS-related care, medical conditions, or mortality in Population Data BC's holdings (see Supplementary file) (Eyawo et al., 2018; Nosyk et al., 2013). The cohort of individuals without HIV was comprised of a 10% random sample of individuals ≥19 years old accessing healthcare services in BC (excluding 1,388 known PLHIV); both cohorts were followed from January 1st, 1998 or year of entry into the cohort after 1998, and until December 31st, 2012.

2.3. Outcome and explanatory variables

In order to identify schizophrenia diagnoses, we used ICD-9 and -10 codes previously identified in the literature (Nesvag et al., 2015; Walkup et al., 2004). In this study, individuals were identified as having a schizophrenia diagnosis if their record included one hospitalization and/or two out-patient physician billing codes within a 12-month period: ICD-9 (295.x, 297.1–297.3) and ICD-10 (F20.x, F21.x, F23.2, F25.x) codes.

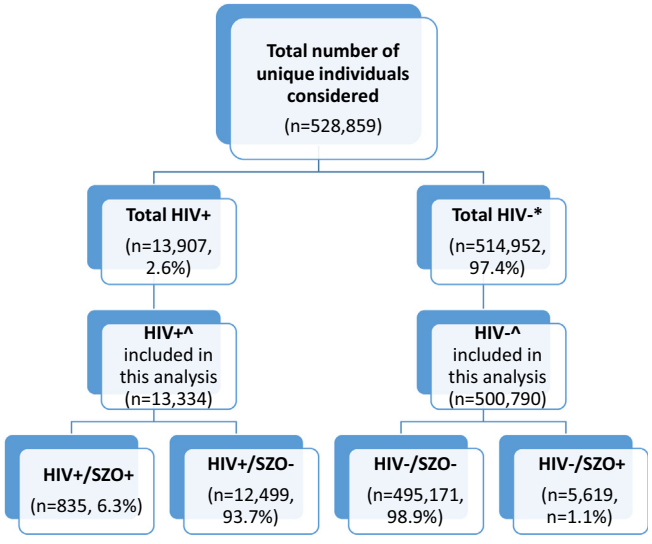


Fig. 1. Flow chart of study population of individuals followed. *Total HIV- is derived from the COAST general population cohort (n = 516,340) after excluding 1,388 known PLHIV who were randomly selected during the cohort's development (Eyawo et al., 2018). ^Note that 573 HIV+ and 14,162 HIV- individuals were excluded if they died or were lost to follow-up before January 1998 or entered the cohort after December 31st, 2012.

Demographic variables included age and sex at baseline. Using previously validated case findings algorithms (Supplementary file), we identified and adjusted for a number of variables that are important for the health, wellbeing, and survival of individuals with schizophrenia, including: a history of injection drug use (IDU), a substance use disorder (SUD) diagnosis (Helleberg et al., 2015; Leucht et al., 2007; Nesvag et al., 2015) with and without the inclusion of alcohol (Findley et al., 2011; Kim et al., 2012; Wusthoff et al., 2011), as well as ever being on anti-psychotic medication and ever accessing psychiatric services in hospital.

Individuals were considered to have ever been on anti-psychotic medication if they were ever on any of the medications listed in the supplementary file as identified through the PharmaNet database (British Columbia Ministry of Health, 2014d). Individuals were labelled as accessing psychiatric services if they had a service code for psychiatry (service code = 64).

Within statistical models that were restricted to PLHIV, we were able to further adjust for HIV exposure group (Men who have sex with men [MSM, No vs. Yes vs. Unknown]), ever on ART (No vs. Yes), and ever having been diagnosed with an AIDS-defining illness (No vs. Yes) using data available from the BC-CfE DTP.

2.4. Statistical analysis

Differences in select characteristics by HIV status among all individuals with a schizophrenia diagnosis were assessed using Chi-squared and Kruskal-Wallis tests for categorical and continuous variables, respectively. Age- and sex-adjusted all-cause mortality rates were calculated using the 2016 Canada population as reference (Statistics Canada, 2019). Kendall trend tests assessed the monotonic trend of all-cause and HIV-related mortality rates from 1998 to 2012. A Kaplan-Meier plot was generated to examine survival time after a schizophrenia diagnosis, stratified by HIV status. All-cause mortality rates were compared among the four distinct groups from 1998 to 2012. Two multivariable logistic regression models were built to 1) examine the association between having a schizophrenia diagnosis and mortality among PLHIV adjusting for: age, alcohol use disorder, IDU, MSM, ever having been diagnosed with an AIDS-defining illness, and ever having filled a prescription for psychiatric medications or having been assessed by a psychiatrist, and to 2) examine the association between HIV-positive status and mortality among all individuals with a schizophrenia diagnosis, adjusting for: age and SUD. Variables were selected based on a priori knowledge and the magnitude of change in the

Table 1
Characteristics and differences among people living with and without a schizophrenia diagnosis by HIV status.

	HIV+/SZO+		HIV+/SZO-		HIV-/SZO+		HIV-/SZO-		
	N	*col%*	*N*	*col %*	*N*	*col%*	*N*	*col%*	
Total	835		12,499		5,619		495,171		P-values[a]
Death									<**0.0001**
No	622	74.5	9,662	77.3	4,620	82.2	452,772	91.4	
Yes	213	25.5	2,837	22.7	999	17.8	42,399	8.6	
HIV/AIDS-related deaths ($n = 3{,}050$)[c]	91	42.7	1,357	47.8	–	–			
Sex									<**0.0001**
Female	207	24.8	2,456	19.65	2,459	43.7	247,010	49.8	
Male	627	75.1	10,041	80.33	3,157	56.2	247,878	50.1	
Unknown	1	0.1	2	0.02	3	0.1	283	0.1	
IDU (case finding algorithm)[b]									
No	215	25.8	8,573	68.6	N/A	N/A	N/A	N/A	
Yes	620	74.3	3,926	31.4	N/A	N/A	N/A	N/A	
Substance use disorder (case finding algorithm)									<**0.0001**
No	89	10.7	6,468	51.8	3,227	57.4	457,289	92.4	
Yes	746	89.3	6,031	48.2	2,392	42.6	37,882	7.6	
MSM									
No	343	41.1	3,489	27.9	N/A	N/A	N/A	N/A	
Yes	157	18.8	3,452	27.6	N/A	N/A	N/A	N/A	
Unknown	335	40.1	5,558	44.5	N/A	N/A	N/A	N/A	
Ever on ART									
No	281	33.7	3,289	26.3	–	–	–	–	
Yes	554	66.3	9,210	73.7	–	–	–	–	
AIDS-defining illness (ever)									
No	563	67.4	8,646	69.1	–	–	–	–	
Yes	132	15.8	2,214	17.7	–	–	–	–	
Unknown	140	16.8	1,639	13.1	–	–	–	–	
Era of ART initiation									
≤1999	239	28.6	3,776	30.2	–	–	–	–	
2000–2010	258	30.9	4,424	35.4	–	–	–	–	
≥2011	57	6.8	1,010	8.1	–	–	–	–	
Not on ARVs	281	33.7	3,289	26.3	–	–	–	–	
Ever on anti-psychotic medication									<**0.0001**
No	432	51.7	10,860	86.9	3,440	61.2	486,657	98.3	
Yes	403	48.3	1,639	13.1	2,179	38.8	8,514	1.7	
Ever had a psychiatry service code									<**0.0001**
No	253	30.3	11,462	91.7	2,258	40.2	487,698	98.5	
Yes	582	69.7	1,037	8.3	3,361	59.8	7,473	1.5	
Age at baseline (years) Median (Q1, Q3)	835	37(30, 44)	12,499	38(32, 45)	5,619	36(24, 50)	495,171	35(23, 49)	0.110
Follow-up time (months) Median (Q1, Q3)	835	99(50, 160)	12,499	89(39, 157)	5,619	192(113, 200)	495,171	159(64, 200)	<**0.001**

IDU injection drug use; *MSM* men who have sex with men; *ART* antiretroviral therapy.
All items in bold are significant at $p < 0.05$.
N/A indicates not available and – indicates not applicable.
[a] Note: P-values identify differences between HIV+/SZO+ and HIV-/SZO+ and were calculated after excluding "unknown" groups.
[b] IDU algorithm only applicable within PLHIV cohort.
[c] Out of all deaths in the study period.

coefficient of schizophrenia or HIV. Starting with the full model, variables were dropped one at a time, using the relative change in coefficient for schizophrenia or HIV as a criterion, until the minimum absolute change from the full model exceeded 5% (Lima and Kopec, 2005). An additional logistic regression model was used to identify correlates of mortality among HIV+/SZO+ individuals. Model selection was based on *p*-values to reach optimal Akaike information criterion (AIC) (Lima et al., 2010). For each univariate and multivariable model, we excluded individuals of unknown sex.

3. Results

Of the total 13,907 PLHIV and 514,952 individuals living without HIV, 573 PLHIV and 14,162 people living without HIV were excluded as they were enrolled outside of the study follow-up period. In total, 514,124 individuals, with a total median age of 38 years (Q1-Q3: 32–45) and 35 years (Q1-Q3: 32–45) at entry into the study for individuals with and without HIV respectively were included in this analysis. Of the individuals included within this study, 6,454 (1.3%) were diagnosed with schizophrenia during the study period and 13,334 (2.6%) were living with HIV. Fig. 1 describes the study participants including the four different sample groups included in our analysis.

PLHIV were more likely than those without HIV to have a schizophrenia diagnosis, with 6.3% (95% confidence interval [CI] = 5.9–6.7, [$p < 0.001$]) vs. 1.1% (95% CI = 1.1–1.2) schizophrenia diagnosis respectively. Compared to HIV-/SZO+, HIV+/SZO+ were more likely to be: male (75.1% vs. 56.2%), have a concurrent SUD (89.3% vs. 42.6%), to have ever been on anti-psychotic medication (48.3% vs. 38.8%), and to have ever accessed psychiatric services (69.7% vs. 59.8%) (all $p < 0.05$) (Table 1). HIV+/SZO+ were also more likely than HIV-/SZO+ to have died during the study period (25.5% vs. 17.8%, $p < 0.001$). Of the HIV+/SZO+ who died during the study period, 91 (42.7%) died from HIV/AIDS related causes, which was similar to HIV+/SZO- (47.8%) ($p = 0.1506$). Rates of HIV/AIDS related mortality significantly declined among both groups throughout the study period (Fig. 2).

From 1998 to 2012, age- and sex-adjusted all-cause mortality rates were highest among HIV+/SZO+ at 64.5 per 1,000 person-years (PY) (95% CI = 48.5–80.5), followed by HIV+/SZO- at 39.7 per 1,000 PY (95% CI = 36.9–42.6), HIV-/SZO+ at 28.2 per 1,000 PY (95% CI = 26.5–29.9), and HIV-/SZO- at 9.9 per 1,000 PY (95%CI = 9.8–10.0). Trend tests found that all-cause mortality rates significantly declined for both HIV+/SZO+ and HIV+/SZO- from 1998 to 2012 (Fig. 3). HIV+/SZO+ had significantly less survival time than HIV-/SZO+ over the study period (Fig. 4).

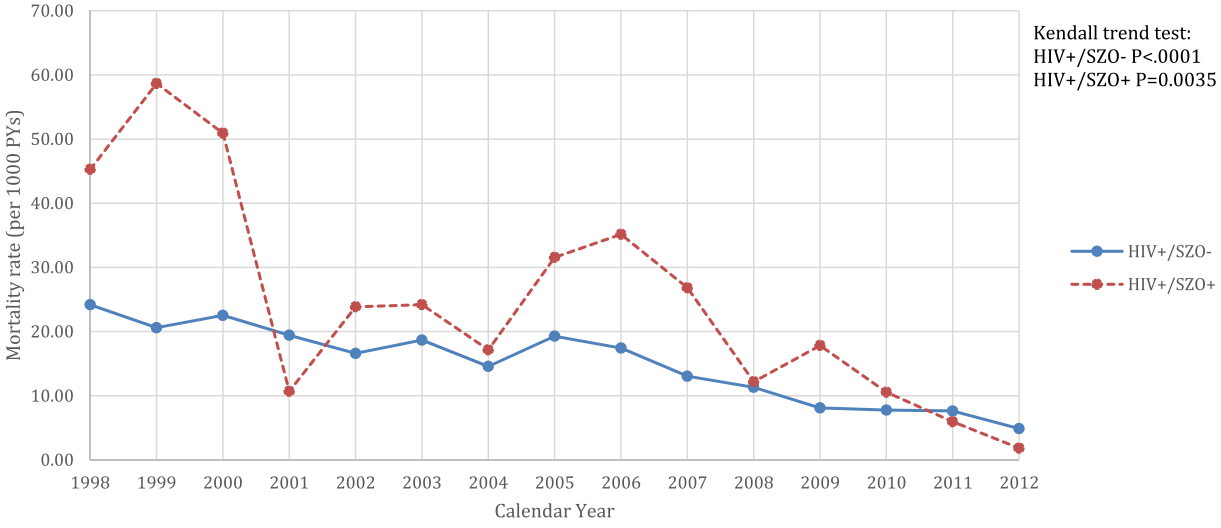
As shown in Table 2, unadjusted and adjusted analyses found that having a schizophrenia diagnosis was not associated with all-cause mortality in the sample of PLHIV (adjusted odds ratio [aOR] = 0.90, 95%CI = 0.74–1.09); the multivariable model was adjusted for age, history of IDU, alcohol problems, being an MSM, ever being on anti-psychotic medication and accessing psychiatric services.

Among participants with a schizophrenia diagnosis (Table 3), positive HIV serostatus (OR = 1.59, 95%CI = 1.34–1.88) was associated with increased odds of mortality in unadjusted analyses. After adjustment for age and SUD, positive HIV serostatus continued to be significantly associated with all-cause mortality (aOR = 2.64, 95%CI = 2.14–3.25).

Table 4 presents covariates of all-cause mortality among HIV+/SZO+. Multivariable analyses indicated that the following factors were associated with mortality: age (aOR = 1.71 per 10-year increase, 95%CI = 1.43–2.04), history of IDU (aOR = 1.95, 95%CI = 1.28–2.97), and ever having a diagnosis for an AIDS-defining illness (aOR = 1.69, 1.08–2.64). Furthermore, ever being on anti-psychotic medication (aOR = 0.66, 95%CI = 0.47–0.93) and ever having a psychiatric service code (aOR = 0.58, 95%CI = 0.40–0.84) were both associated with a reduced mortality throughout the study period.

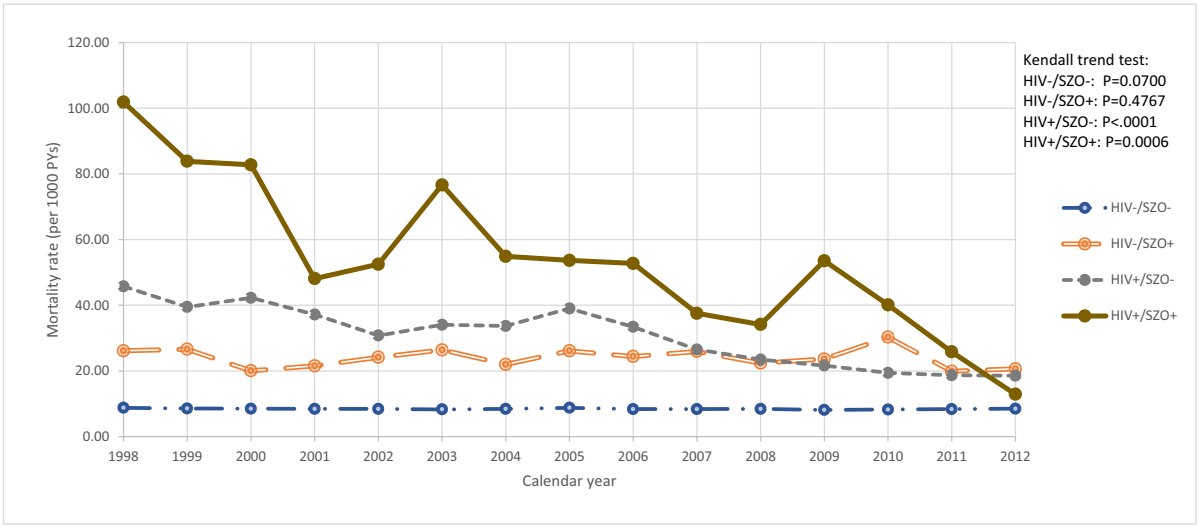
4. Discussion

Our results highlight that HIV status was independently associated with mortality and that HIV+/SZO+ had reduced survival over the study period compared to HIV-/SZO+. From 1998 to 2012, this group also had higher mortality rates than all other reference groups (HIV-/SZO+, HIV+/SZO- and HIV-/SZO-). Among HIV+/SZO+ in our study, older age, history of IDU, and ever having an AIDS diagnosis were associated with increased odds of mortality. HIV+/SZO+ who had ever been on anti-psychotic medication and who had accessed psychiatric services had reduced odds of mortality. Despite higher mortality rates among the subgroup of HIV+/SZO+, having a diagnosis of schizophrenia was not independently associated with increased mortality in the sample of PLHIV.



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
HIV+/SZO-	24.2	20.6	22.5	19.4	16.6	18.7	14.6	19.3	17.4	13.0	11.3	8.1	7.8	7.6	4.9
HIV+/SZO+	45.3	58.7	50.9	10.7	23.9	24.2	17.2	31.6	35.2	26.8	12.2	17.8	10.6	6.0	1.8

Fig. 2. HIV/AIDS-related mortality rates per 1000 person-years from 1998 to 2012 among HIV+/SZO- and HIV+/SZO+.



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
HIV-/SZO-	8.8	8.6	8.5	8.4	8.4	8.3	8.4	8.8	8.4	8.4	8.5	8.1	8.2	8.4	8.5
HIV-/SZO+	26.1	26.6	20.1	21.6	24.2	26.4	22.0	26.1	24.4	25.9	22.4	23.6	30.3	19.9	20.6
HIV+/SZO-	45.8	39.5	42.3	37.2	30.8	34.1	33.7	39.0	33.4	26.5	23.4	21.6	19.4	18.7	18.5
HIV+/SZO+	101.9	83.8	82.8	48.1	52.5	76.7	54.9	53.7	52.7	37.6	34.1	53.5	40.1	25.8	12.9

Fig. 3. All-cause mortality rates per 1000 person-years from 1998 to 2012 among HIV-/SZO-, HIV-/SZO+, HIV+/SZO-, and HIV+/SZO+.

Our study found that between 1998 and 2012, 6.3% of those living with HIV had a schizophrenia diagnosis, compared to 1.1% of those living without HIV. This may be, in part, due to the fact that individuals diagnosed with HIV may be referred to psychiatric care following their diagnosis, and then may subsequently receive a concurrent diagnosis for mental health conditions, including schizophrenia (Helleberg et al., 2015). Thus, we acknowledge the limitations related to the differential probability of receiving a clinical diagnosis, of any sort, among PLHIV and individuals without HIV. It is also possible that individuals with schizophrenia have heightened HIV prevalence due to higher levels of substance use and sexual risk behaviours (Meade and Sikkema, 2007). Given that our analyses were conducted using data of individuals already known to be HIV+ at baseline, we were unable to assess how having a diagnosis of schizophrenia may increase one's risk of acquiring HIV. As such, more research is needed to better understand rates and drivers of HIV infection among people living with schizophrenia, and the role of HIV prevention in schizophrenia care.

Among those diagnosed with schizophrenia, HIV was associated with mortality. Despite improvements in HIV treatment and life-expectancy in recent years (Samji et al., 2013), and evidence that PLHIV with severe mental health conditions may be less likely to discontinue their HIV medication and more likely to access health services (Himelhoch et al., 2009; Mijch et al., 2006), we found that between 1998 and 2012, one-in-four (25.5%) of HIV+/SZO+ individuals died compared to one-in-five of HIV-/SZO+ individuals (17.8%). Moreover, our survival analysis and mortality trends

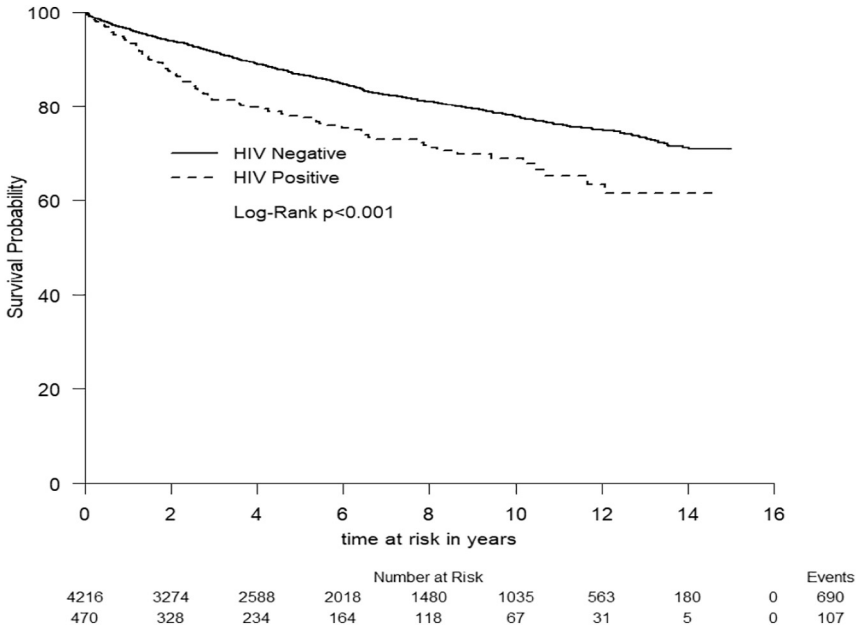


Fig. 4. Kaplan-Meier survival curve from SZO diagnosis to death, stratified by HIV status.

Table 2
Unadjusted and adjusted association between schizophrenia diagnoses and all-cause mortality among HIV+ with a known sex ($n = 13,331$).

	Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95% CI)
Main exposure		
SZO diagnosed		
No [ref]	1.00	1.00
Yes	1.17 (0.99–1.37)	0.90 (0.74–1.09)
Potential confounders		
Age at baseline(per 10-year increase)	1.53 (1.48–1.59)	1.69 (1.63–1.76)
Sex		
Male [ref]	1.00	Not included
Female	1.08 (0.98–1.19)	
Alcohol use disorder (case finding algorithm)		
No [ref]	1.00	1.00
Yes	2.57 (2.34–2.83)	1.98 (1.77–2.21)
IDU (case finding algorithm)		
No [ref]	1.00	1.00
Yes	2.53 (2.33–2.75)	3.34 (3.00–3.72)
MSM		
No [ref]	1.00	1.00
Yes	0.49 (0.44–0.55)	0.82 (0.72–0.93)
Unknown	0.85 (0.77–0.93)	1.08 (0.97–1.20)
On ART		
No [ref]	1.00	Not selected
Yes	0.76 (0.69–0.83)	
AIDS-defining illness (ever)		
No [ref]	1.00	Not selected
Yes	2.40 (2.17–2.64)	
Unknown	1.21 (1.07–1.37)	
Ever on anti-psychotic medications		
No [ref]	1.00	1.00
Yes	0.93 (0.83–1.05)	0.56 (0.49–0.64)
Ever had a psychiatry service code		
No [ref]	1.00	1.00
Yes	1.12 (0.99–1.27)	0.74 (0.63–0.86)

IDU injection drug use; *MSM* men who have sex with men; *ART* antiretroviral therapy.

indicated that HIV+/SZO+ individuals had the highest mortality rates. These findings highlight the need for monitoring and future research aimed at reducing mortality among PLHIV with schizophrenia.

After adjustment for a variety of factors, we found no significant association between schizophrenia diagnoses and all-cause mortality among PLHIV. This finding is in line with a previous study conducted in the United States, demonstrating that having a severe mental illness was not associated with increased mortality among PLHIV (Chander et al., 2012).

It is well known that there is a strong association between severe mental health issues and substance use (Compton et al., 2005; Tross et al., 2015). Among HIV+/SZO+, history of IDU was a significant correlate of mortality. Our data, however, do not allow for us to examine whether those with schizophrenia developed SUDs before or after their schizophrenia or HIV diagnosis and how the development of schizophrenia and acquisition of HIV influenced substance use patterns. More research is needed to elucidate the complex relationships between substance use, mental health, HIV and other health outcomes, in order to better understand drivers of mortality among those living with both HIV and schizophrenia.

We found that individuals who had taken anti-psychotic medication and who had accessed psychiatric services were at reduced risk of mortality. It is likely that those accessing psychiatric services are also more likely to be linked to HIV care (Mijch et al., 2006). Service providers for mental illnesses as well as HIV should collaborate to ensure that their patients are receiving adequate support. Integrated services providing opportunities for multiple entry points into care, like those provided at the Dr. Peter Centre in Vancouver, Canada, could help to link and maintain HIV+/SZO+ individuals in care (Fernando et al., 2016; Griffiths, 2002).

4.1. Strengths/limitations

The longitudinal and population-based nature of our study allowed us to examine important and comparative health trends over time between individuals with and without HIV in BC, including identifying a relatively large sample of individuals with schizophrenia. However, there are some limitations that should be noted. Given that HIV is a chronic disease, it is known that, on average, PLHIV engage more often with the healthcare system than those without HIV. Under this assumption, it is plausible that the sensitivity of our schizophrenia diagnosis definition, or the probability that administrative codes will correctly identify someone diagnosed with schizophrenia, will differ between individuals with and without HIV; this is irrespective of HIV's potential impact, or lack thereof, on an individual's risk of developing schizophrenia. As such, we hypothesize that higher healthcare engagement typical among PLHIV is potentially leading to better ascertainment of schizophrenia in PLHIV, and that this is likely responsible, in part, for this finding. Therefore, future work should consider the potential impact of differential outcome misclassification in administrative data, and employ statistical methods, such as probabilistic bias analysis, to investigate this concern.

In addition, although access to PharmaNet data allowed us to examine the impact of being on anti-psychotic medications, we were unable to consider medication adherence. Although this analysis was able to account for SUD as a covariate based on validated case-finding algorithms for identifying diagnostic cases (Findley et al., 2011; Kim et al., 2012; Wusthoff et al., 2011), we were unable to control for tobacco smoking patterns, which is a known carcinogen and carries high burdens of mortality for both individuals living with mental illness as well as PLHIV (Brown et al., 2000; Dickerson et al., 2013; Painter et al., 2017; Pedersen et al., 2018). Reliance on administrative data is further limited due to potential misclassification of diagnoses which rely on ICD-9 and -10 codes, which can be incomplete or incorrect. However, the algorithms currently used within COAST to ascertain comorbidities, including mental health outcomes, are in line with previous studies that have relied on administrative data (Nesvag et al., 2015; Walkup et al., 2004). Lastly, given the observational nature of our study, we cannot establish causality due to unmeasured confounding.

Table 3
Unadjusted and adjusted association between HIV status and all-cause mortality among all individuals with schizophrenia diagnoses and known sex ($n = 6,450$).

	Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95%CI)
Main exposure		
HIV status		
Negative [ref]	1.00	1.00
Positive	1.59 (1.34–1.88)	2.64 (2.14–3.25)
Potential confounders		
Age at baseline (per 10-year increase)	2.22 (2.12–2.32)	2.40 (2.28–2.53)
Sex		
Male [ref]	1.00	Not selected
Female	1.38 (1.22–1.57)	
Substance use disorder (case finding algorithm)		
No [ref]	1.00	1.00
Yes	0.65 (0.57–0.74)	1.29 (1.09–1.54)
Ever on anti-psychotic medications		
No [ref]	1.00	Not selected
Yes	0.65 (0.57–0.74)	
Ever had a psychiatric service code		
No [ref]	1.00	Not selected
Yes	0.42 (0.37–0.48)	

IDU injection drug use; *MSM* men who have sex with men.

Table 4
Bivariate, unadjusted and adjusted correlates of all-cause mortality among individuals living with HIV and schizophrenia with a known sex ($n = 834$).

	Death					
	No		Yes		Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95%CI)
	N	*col %*	*N*	*col %*		
Covariates	621		213			
Age at baseline: per 10-year increase (median, Q1, Q3)	621	36 (29, 42)	213	41 (34, 47)	1.71 (1.45–2.02)	1.71 (1.43–2.04)
Sex						
Male	469	75.5	158	74.2	1.00	Not included
Female	152	24.5	55	25.8	1.07 (0.75–1.54)	
IDU (case finding algorithm)						
No	162	26.1	53	24.9	1.00	1.00
Yes	459	73.9	160	75.1	1.07 (0.74–1.53)	1.95 (1.28–2.97)
MSM						
No	261	42.0	82	38.5	1.00	1.00
Yes	127	20.5	30	14.1	0.75 (0.47–1.20)	0.97 (0.59–1.59)
Unknown	233	37.5	101	47.4	1.38 (0.98–1.94)	1.76 (1.16–2.67)
AIDS-defining illness (ever)						
No	424	68.3	139	65.3	1.00	1.00
Yes	89	14.3	43	20.2	1.47 (0.98–2.22)	1.69 (1.08–2.64)
Unknown	108	17.4	31	14.5	0.88 (0.56–1.36)	0.46 (0.27–0.77)
On ART						
No	200	32.2	80	37.6	1.00	Not selected
Yes	421	67.8	133	62.4	0.79 (0.57–1.09)	
Ever on anti-psychotic medications						
No	302	48.6	129	60.6	1.00	1.00
Yes	319	51.4	84	39.4	0.62 (0.45–0.85)	0.66 (0.47–0.93)
Ever had a psychiatric service code						
No	165	26.6	87	40.9	1.00	1.00
Yes	456	73.4	126	59.1	0.52 (0.38–0.73)	0.58 (0.40–0.84)

IDU injection drug use; *MSM* men who have sex with men; *ART* antiretroviral therapy.

5. Conclusions

Acknowledging the differential probability of receiving a clinical diagnosis among persons living with and without HIV, from 1998 to 2012, our study found the proportion of individuals identified with a schizophrenia diagnosis to be higher among those with HIV compared to those without. Although schizophrenia was not significantly associated with mortality among those with HIV, it is important to note that HIV+/SZO+ individuals had the highest mortality rates in our sample. All observed groups showed significant declines in mortality rates throughout the study period. For those with a schizophrenia diagnosis, HIV was independently associated with mortality. Efforts should be made to identify and link to care individuals disproportionately affected by schizophrenia and excess mortality, including those living with HIV.

Conflict of interest

OE is supported by a Canadian Institutes of Health Research doctoral award. MWH has received honoraria for speaking engagements and/or consultancy meetings from the following: Bristol Myers Squibb, Gilead Lifesciences, Merck, and Viiv. VDL is funded by a grant from the Canadian Institutes of Health Research (PJT-148595), by a Scholar Award from the Michael Smith Foundation for Health Research and a New Investigator award from the Canadian Institutes of Health Research. JSGM is supported with grants paid to his institution by the British Columbia Ministry of Health and by the US National Institutes of Health (R01DA036307). He has also received limited unrestricted funding, paid to his institution, from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare.

Contributions

KC, RSH and TLP designed the study and wrote the protocol. Authors OE, MWH, JSGM, and RSH led the study team and served as senior authors for this project. KC managed the literature review. Author WC managed the data analysis and author MY conducted the statistical analysis with supervision from VDL. KC wrote the first draft of the manuscript with substantial support from KGC and KS. TM and MK substantially supported the manuscript revisions. All authors contributed to and have approved the final manuscript.

Funding

COAST is funded by the Canadian Institutes of Health Research, through an Operating Grant (#130419), a Foundation Award to RSH (#143342) and support from the BCCfE. The funders had no role in the study design, analysis, interpretation of the data, drafting of the manuscript or in the decision to submit for publication. The corresponding author had final responsibility for the decision to submit for publication.

Acknowledgement

Thank you to all the participants included within COAST, the British Columbia Centre for Excellence in HIV/AIDS, the BC Ministry of Health, BC Vital Statistics Agency, PharmaNet and the institutional data stewards for granting access to the data, and Population Data BC, for facilitating the data linkage process. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the data stewards.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.04.020.

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