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ORIGINAL RESEARCH

Lost but not forgotten: A population-based study of mortality and care trajectories among people living with HIV who are lost to follow-up in Ontario, Canada

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Objectives

Selection as a consequence of volunteer participation in, and loss to follow-up from, cohort studies may bias estimates of mortality and other health outcomes. To quantify this potential, we estimated mortality and health service use among people living with HIV (PLWH) who were lost to cohort follow-up (LTCFU) from a volunteer clinical HIV-infected cohort, and compared these to mortality and health service use in active cohort participants and non-cohort-participants living with HIV in Ontario, Canada.

Methods

We analysed population-based provincial health databases from 1995 to 2014, identifying PLWH ≥ 18 years old; these included data from participants in the Ontario HIV Treatment Network Cohort Study (OCS), a volunteer, multi-site clinical HIV-infected cohort. We calculated all-cause mortality, hospitalization and emergency department (ED) visit rates per 100 person-years (PY) and estimated hazard ratios (HRs) of mortality, adjusting for age, sex, income, rurality, and immigration status.

Results

Among 23 043 PLWH, 5568 were OCS participants. Compared with nonparticipants, participants were younger and less likely to be female, to be an immigrant and to reside in a major urban centre, and had lower comorbidity. Mortality among active participants, participants LTCFU and nonparticipants was 2.52, 3.30 and 2.20 per 100 PY, respectively. After adjustment for covariates, mortality risk was elevated among participants LTCFU compared with active participants (HR 2.26; 95% confidence interval 1.91, 2.68). Age-adjusted hospitalization rates and ED visit rates were highest among participants LTCFU.

Conclusions

Mortality risk and use of health care resources were lower among active cohort participants. Our findings may inform health outcome estimates based on volunteer cohorts, as well as quantitative bias adjustment to correct for such biases.

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Introduction

The generalizability of findings from cohort studies may be limited if the cohort population differs from the wider population of interest. Selection bias, a form of participation bias, exists when active members of the cohort have significantly different characteristics than those unable or unwilling to participate, and there is reason to believe that this variation could potentially impact outcome risk. Biases can also occur as a result of participant loss to cohort follow-up (LTCFU). In HIV-infected cohort studies, LTCFU is typically defined as failure to attend HIV care for a prespecified time period. In HIV studies conducted in developed countries, LTCFU occurs at rates from 3.5 to 9.8 per 100 patient-years (PY) [1–3] with cumulative LTCFU rates of 20–40%, defined by studies as a lack of engagement in primary care and out-patient visits for 6 or 12 months without returning, after an initial linkage to HIV care [4–6].

From a methodological perspective, knowledge of health outcomes of cohort study participants after LTCFU is necessary for the interpretation of research findings from those studies. Time to event analyses of clinical outcomes or death in cohort studies often assume that censoring as a result of LTCFU is independent of the outcome under study. However, such assumptions would bias life expectancy calculations for people living with HIV (PLWH) if mortality rates among individuals who are lost to cohort follow-up (LTCFU) differ substantially from those of individuals still under follow-up [7,8]. When the mortality rates after LTCFU are not available, studies have estimated life expectancy using assumptions about mortality after LTCFU derived from cohort studies from other countries, from local cohorts, or from sensitivity analyses with a range of possible outcome rates [9–12]; however, determining the extent to which the results are truly reflective of their local setting can be challenging.

Our objective was to estimate mortality and health service use trajectories among volunteer HIV-infected cohort participants, comparing those actively participating to those LTCFU, as well as to nonparticipants. We addressed this objective using data from Ontario, Canada, where population-based data are available for all PLWH in HIV care, and the setting of the long-standing Ontario HIV Treatment Network (OHTN) Cohort Study (OCS).

Methods

We carried out a population-based retrospective cohort study using data from the OCS and administrative data housed at ICES.

OHTN Cohort Study

The OCS is a voluntary open cohort study of PLWH who have received care at one of 11 clinical sites since 1995 [13]. Participants have completed annual questionnaires since 2007, for which they received a modest honorarium. Clinical and demographic data are abstracted from medical charts. We linked OCS data to administrative databases using unique identifiers. The only OCS data beyond health administrative data that were used for this analysis were dates of death and loss to follow-up.

Administrative data sources

We conducted analyses using health administrative data from the province of Ontario, Canada. We used the following data sets for this study: the Registered Persons Database (RPDB), an electronic registry of all Ontarians eligible for health coverage, to ascertain patient demographic information and date of deaths; 2006 Statistics Canada census data; the Ontario Health Insurance Plan (OHIP) database, which contains physician billing claims for approximately 95% of physician-based visits in this province; the Discharge Abstract Database, which captures all provincial hospitalization discharge data; the National Ambulatory Care Reporting System and Emergency Claims Database (ERCLAIMS) for information on emergency department and selected out-patient visits; the Immigration, Refugee and Citizenship Canada (IRCC) Permanent Resident Database; and the Office of the Register General – Deaths (ORGD) Database for detailed death records. These data sets were linked using unique encoded identifiers and analysed at ICES.

Study population

To obtain an administrative cohort of PLWH, we applied a validated algorithm to identify all individuals ≥ 18 years receiving HIV care in Ontario between 1 April 1992 and 31 December 2014 [14]. Briefly, three physician claims coded for HIV infection [International Classification of Diseases,

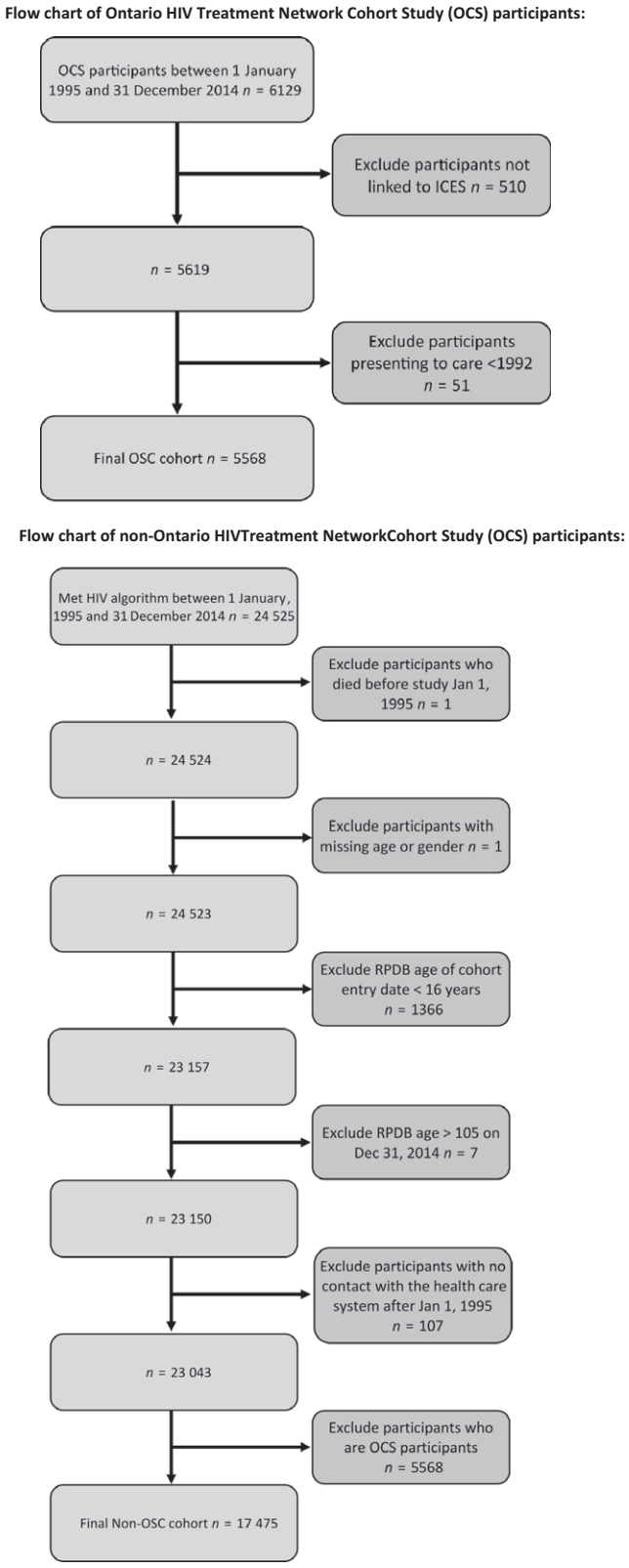

Fig. 1 Flow chart of study participants. OCS, Ontario HIV Treatment Network Cohort Study; RPDB, Registered Persons Database.

Ninth Revision (ICD-9) codes 042–044] over a 3-year period identify PLWH receiving regular HIV care, with a sensitivity of 96.2% [95% confidence interval (CI) 95.2–97.9%] and a specificity of 99.6% (95% CI 99.1–99.8%). OCS participants were linked to this administrative cohort. OCS participants who were not linked to ICES were excluded from analyses (Fig. 1).

For those identified by the above algorithm as PLWH who were also OCS participants, the index date was defined as the earliest of (1) the date of first HIV billing code that triggered the HIV algorithm or (2) the date of entry into the OCS cohort. For non-OCS participants, the index date was the date of the first HIV billing code between 1 April 1992 and 31 December 2014. Patients were followed until death or 31 December 2014, whichever occurred first. We excluded those who presented to HIV care in 1992 or earlier, as their exact date of presentation was unknown. We applied rules to censor patients with long gaps in care (i.e. a period of ≥ 7 years with no health care encounters but with no record of death). Censoring began at 7 years after the last encounter preceding the gap until the earlier of (1) the end of the study period or (2) re-engagement in care. For example, a patient who had regular health care encounters for a period of 5 years after presentation to HIV care but no encounters thereafter would be censored at 12 years of follow-up. If a similar patient re-engaged with the health care system at 14 years of follow-up, he/she would be censored from years 12 to 14 and then re-included in the analysis from year 14 to the end of the study period.

Classification of cohort participation status

Our primary exposures of interest were OCS participation and LTCFU among OCS participants. OCS participants were classified as LTCFU if there were no available clinic-based data (i.e. no data from their medical chart or interview data) over an 18-month period. Time after LTCFU from the OCS was measured until the earliest of (1) the end of ICES follow-up as a consequence of moving out of province, (2) death or (3) 31 December 2014.

Outcomes

Our primary outcome was mortality. We used the RPDB to determine the date of death. For OCS participants without evidence of death in the RPDB, we used date of death reported in OCS data.

To understand the care engagement of active OCS participants compared to those who were LTCFU, our secondary outcome was health services use [emergency department (ED) visits, hospital admissions and engagement in care]. We classified out-patient visits as family physician visits, visits to HIV specialists (defined as any visit to an internal medicine or infectious disease specialist), and visits specifically for HIV care (ICD-9, codes 042, 043 and 044). We defined engagement in HIV care after LTCFU from OCS, defined as at least two out-patient visits for HIV care at least 3 months apart. We reported engagement in HIV care in the first year after follow-up and in the most recent calendar year, 2014.

Covariates

We adjusted for the following demographic information and covariates at the time of care presentation: age, sex, income, rurality (as determined from neighbourhood-level postal codes linked to 2006 Statistics Canada census data) and immigration status [immigrant from country with generalized HIV epidemic and immigrant from country without generalized HIV epidemic]. We used the John Hopkins ACG® System Version 10 (Sun Microsystems Inc., Santa Clara, CA) [15] to categorize medical comorbidity by assigning individuals to one of 32 distinct aggregated diagnosis groups (ADGs) based on condition duration, severity, diagnostic certainty, aetiology, and specialty care involvement. Comorbidity burden was classified as low (≤ 5 ADGs), medium (6–9 ADGs) and high (≥ 10 ADGs) [15].

Analyses

We compared characteristics between OCS participants and nonparticipants using means and standard deviations and *t*-tests for continuous variables, and frequency and percentages and χ^2 tests for categorical variables. We calculated all-cause mortality rates, and hospitalization and ED rates (crude and age-adjusted to the 2011 Ontario population) per 100 PY, stratified by non-OCS participants, OCS active participants and OCS participants after LTCFU. For all outcomes, observation time was divided into periods (1996–1999, 2000–2004, 2005–2009 and 2010–2014) to detect temporal trends, and by sex to detect differences between men and women.

We used proportional hazards models with time to death from date of presentation for HIV care. We left truncated time between care presentation and OCS enrolment for OCS participants and time between care presentation and 1995 for non-OCS participants who presented to care prior to 1995. Participants for whom death was not documented during the study period were censored at the later of the last follow-up date in ICES databases or 31 December 2014. LTCFU for OCS participants was modelled with a binary time-dependent covariate, which was

set to zero at OCS enrolment and to 1 after a period of 18 months of having no available clinic-based data (i.e. no data from their medical chart no interview data). We estimated hazard ratios (HRs) of mortality for the following covariates: OCS participation, LTCFU, and calendar time period, as well as the interaction of LTCFU and time period and OCS participation and time period. We adjusted for participant demographics at the time of care presentation: age (per 10 years), sex, immigration status (immigrant from a country with generalized HIV epidemic or without generalized HIV epidemic versus long-term resident), rurality (rural versus urban/suburban location) and neighbourhood income quintile (other quintiles versus highest quintile)). SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Ethics approval for this project was granted by the Ottawa Hospital Research Ethics Board and the Sunnybrook Health Sciences Centre Research Ethics Board. Ethics approval for the OCS was obtained from each study site. Participants signed informed consent at the time of enrolment into the cohort.

Results

Between 1 January 1995 and 31 December 2014, 23 043 individuals received HIV care in Ontario. During this time period, 6129 PLWH were enrolled into the OCS; of these, 5619 (92%) were linked to the administrative data holdings at ICES, and 5568 presented to care after 1992, for a total of 37 718.68 PY of follow-up. Rates of linkage to ICES were 94% for active participants, 96.5% for patients who had died, 98% for participants from the site that had closed and 82% for LTCFU participants. As of 31 December 2014, of the 5568 OCS participants linked to ICES, 3219 (57.8%) were active, 951 (17.0%) had died, 219 (3.9%) were enrolled at a site that had closed, and 1179 (21.2%) were LTCFU. Compared with people who remained active in the cohort, those LTCFU were more likely to have presented to care in earlier years, to have a slightly younger age at care presentation, to be a long-term resident of Canada, and to have lower comorbidity (Appendix 2, Table A1). After LTCFU from the OCS, 267 participants were recorded as having died (3.3 deaths per 100 PY), for a total of 1218 deaths.

The remaining 17 475 PLWH not linked to the OCS were classified as nonparticipants. At presentation to care, compared with nonparticipants, participants were significantly younger, were less likely to be female, to be an immigrant and to come from a major urban centre, and had lower comorbidity (Table 1). As of 31 December 2014, 3797 (21.7%) of the 17 475 nonparticipants had died. Crude rates of death among OCS participants and OCS nonparticipants were 2.52 and 2.20 per 100 PY of follow-up, respectively.

Table 2 shows the age-adjusted mortality rates by calendar year for nonparticipants, active participants and participants after LTCFU. For all three groups, mortality rates declined by > 70% between 1995 and 2014. In all calendar periods, age-adjusted mortality rates were higher for participants LTCFU than for those who remained

Table 1 Characteristics of Ontario HIV Treatment Network Cohort Study (OCS) participants and nonparticipants at presentation to HIV care

Variable	OCS participants (group A) (N = 5568) n (%)	OCS nonparticipants (group B) (N = 17 475) n (%)	P-value
Year of HIV care presentation			
≤ 1992–1994	1967 (35.33)	3680 (21.06)	< 0.001
1995–1999	1422 (25.54)	3405 (19.48)	
2000–2004	970 (17.42)	3218 (18.41)	
2005–2009	953 (17.12)	3588 (20.53)	
2010–2014	256 (4.6)	3584 (20.51)	
Age at HIV care presentation (years) [mean (SD)]	36.76 (9.23)	38.25 (11.77)	< 0.001
Age category at HIV care presentation			
≤ 25 years	516 (9.27)	1850 (10.59)	< 0.001
26–35 years	2213 (39.74)	6241 (35.71)	
36–45 years	1892 (33.98)	5533 (31.66)	
46–55 years	742 (13.33)	2470 (14.13)	
≥ 56 years	205 (3.68)	1381 (7.9)	
Female	826 (14.83)	3534 (20.22)	< 0.001
Neighbourhood income quintile			
1	1750 (31.43)	5415 (30.99)	0.153
2	1137 (20.42)	3652 (20.9)	
3	951 (17.08)	2894 (16.56)	
4	792 (14.22)	2493 (14.27)	
5	826 (14.83)	2561 (14.66)	
Missing	112 (2.01)	460 (2.63)	
Urban/rural			
Major urban	4913 (88.24)	15 712 (89.91)	< 0.001
Nonmajor urban	444 (7.97)	1065 (6.09)	
Rural	166 (2.98)	429 (2.45)	
Missing	45 (0.81)	269 (1.54)	
Immigrant status			
Long-term resident	4833 (86.8)	14 058 (80.45)	< 0.001
immigrant, country with generalized HIV epidemic	263 (4.72)	1472 (8.42)	
immigrant, country without generalized HIV epidemic	472 (8.48)	1945 (11.13)	
Comorbidity (aggregated diagnosis groups)			
Missing (1991 and 1992)	1092 (19.61)	1949 (11.15)	< 0.001
1–4 (low)	1346 (24.17)	4963 (28.4)	
5–9 (medium)	2040 (36.64)	6314 (36.13)	
≥ 10 (high)	1090 (19.58)	4249 (24.31)	

SD, standard deviation.

active participants and for those who were nonparticipants (Table 2). Mortality rates were higher in active participants versus nonparticipants from the two earlier time periods, but this trend was reversed in 2005–2009 and 2010–2014. After adjustment for age, women had lower mortality than men, across non-OCS participants, OCS active participants and OCS participants after LTCFU, although this difference was only significant among OCS participants ($P < 0.0001$).

After adjustment for covariates in a proportional hazards model, participants LTCFU from the OCS had a significantly greater hazard of mortality than those retained in the OCS [HR 2.26; 95% confidence interval (CI) 1.91, 2.68] (Table 3). Older age at entry into care was associated with a greater hazard of mortality, as was living in lower income neighbourhoods. Female sex, residing in an urban location and having immigrated after 1985 were factors associated with a lower hazard of mortality.

Age-adjusted hospitalization rates decreased over calendar time for all groups. Hospitalization rates were highest among OCS participants who were LTCFU (Table 4a). Compared with men, women had higher age-adjusted hospitalization rates among non-OCS participants ($P < 0.0001$) but similar rates among OCS active participants and OCS participants LTCFU. Similarly, age-adjusted ED visit rates were highest in OCS participants who were LTCFU across all time periods (Table 4b). Rates of ED visits increased over time for all three cohorts, except for OCS active participants, for whom ED visits declined in the 2010–2014 period. Compared with men, women had more ED visits among all groups.

Most of the 1179 individuals who were LTCFU from the OCS but had no record of death continued to access care through out-patient visits at a median rate of 9.12 visits per year [interquartile range (IQR) 4.2–17.2 visits/year] (Table 5). Half of these visits were to family physicians (median 4.5 visits/year; IQR 1.6–9.2 visits/year) and about a third were for HIV-specific care (median 3.1 visits/year; IQR 1.2–6.2 visits/year). Among participants lost to follow-up across all time periods, 60% remained engaged in HIV care (at least two out-patient visits for HIV care at least

Table 3 Proportional hazards model of mortality among people living with HIV in Ontario

Variable	Hazard ratio (95% CI)
Time (years) since care presentation among non-OCS participants	0.91 (0.90, 0.92)
Time (years) since care presentation among OCS participants	0.88 (0.87, 0.90)
Lost to follow-up	
Yes	2.26 (1.91, 2.68)
No	Ref
Age at entry to care (per 10 years)	1.60 (1.56, 1.64)
Sex	
Female	0.88 (0.81, 0.96)
Male	Ref
Rurality of residence	
Urban residence	0.72 (0.61, 0.85)
Rural residence	Ref
Income quintile	
1 (lowest)	1.41 (1.27, 1.57)
2	1.21 (1.08, 1.36)
3	1.11 (0.99, 1.26)
4	1.17 (1.03, 1.32)
5 (highest)	Ref
Immigration status	
Immigrant from country with generalized HIV epidemic	0.60 (0.52, 0.70)
Immigrant from country without generalized HIV epidemic	0.57 (0.48, 0.69)
Canadian born/long-term resident	Ref

CI, confidence interval; Ref, reference group to which the remaining groups are compared.

Table 2 Age-adjusted mortality rates per 100 patient-years (95% confidence intervals) by calendar year period for non-Ontario HIV Treatment Network Cohort Study (OCS) participants, OCS active participants and OCS participants after being lost to cohort follow-up (LTCFU)

	OCS nonparticipants			OCS participants (active)			OCS participants (LTCFU)		
	Patient-years	Crude	Adjusted	Patient-years	Crude	Adjusted	Patient-years	Crude	Adjusted
Years									
1995–1999	28 793	5.17 (4.91–5.44)	6.49 (5.98–7.03)	5478	6.81 (6.14, 7.54)	7.46 (6.32–8.73)	387	8.79 (6.09, 12.28)	14.98 (6.88–27.29)
2000–2004	38 833	1.90 (1.76–2.04)	2.60 (2.34–2.88)	7495	3.12 (2.73, 3.55)	3.66 (3.03–4.37)	1510	3.58 (2.69, 4.66)	4.04 (2.63–5.89)
2005–2009	49 672	1.65 (1.54–1.76)	2.13 (1.95–2.32)	10 219	1.58 (1.34, 1.84)	1.60 (1.30–1.94)	2360	4.41 (3.6, 5.34)	4.62 (3.55–5.90)
2010–2014	55 875	1.36 (1.26–1.46)	1.66 (1.53–1.80)	17 181	1.07 (0.92, 1.23)	1.04 (0.87–1.23)	3803	1.97 (1.55, 2.47)	2.06 1.50–2.73)
Sex									
Female	33 384	1.80 (1.66–1.95)	2.46 (2.24–2.70)	6041	1.46 (1.17–1.79)	1.63 (1.21–2.15)	937	3.42 (2.34–4.82)	3.14 (1.86–4.94)
Male	139 789	2.29 (2.21–2.37)	2.69 (2.57–2.80)	34 332	2.51 (2.35–2.69)	2.79 (2.58–3.02)	7123	3.30 (2.89–3.75)	3.58 (3.04–4.17)

Table 4 (a) Crude and age-adjusted hospitalization rates per 100 patient-years (95% confidence intervals) by calendar year period and sex for non-Ontario HIV Treatment Network Cohort Study (OCS) participants, OCS active participants and OCS participants after being lost to cohort follow-up (LTCFU). (b) Crude and age-adjusted emergency department rates per 100 patient-years (95% confidence intervals) by calendar year period and sex for non-OCS participants, OCS active participants and OCS participants after being LTCFU

	OCS nonparticipants			OCS participants (active)			OCS participants (LTCFU)		
	Patient-years	Crude	Adjusted	Patient-years	Crude	Adjusted	Patient-years	Crude	Adjusted
(a)									
Years									
1995–1999	28 437	27.95 (27.34–28.57)	30.77 (29.65–31.91)	5731	33.29 (31.81–34.82)	33.49 (31.11–36.00)	395	38.20 (32.35–44.80)	54.14 (38.23–73.80)
2000–2004	38 813	16.63 (16.23–17.04)	18.71 (18.06–19.38)	7586	20.69 (19.68–21.74)	21.18 (19.75–22.67)	1518	25.17 (22.71–27.83)	24.06 (20.69–27.80)
2005–2009	49 514	14.72 (14.38–15.06)	17.22 (16.72–17.73)	10 342	16.26 (15.5–17.06)	17.22 (16.19–18.30)	2364	21.78 (19.94–23.75)	21.05 (18.71–23.60)
2010–2014	55 866	13.57 (13.27–13.88)	15.31 (14.92–15.71)	17 230	13.52 (12.97–14.08)	13.59 (12.92–14.28)	3804	17.95 (16.63–19.35)	17.96 (16.23–19.81)
Sex									
Female	33 274	22.46 (21.96–22.98)	23.75 (23.14–24.38)	6149	19.14 (18.06–20.26)	18.89 (17.58–20.27)	936	24.35 (21.29–27.73)	24.59 (20.58–29.13)
Male	139 356	15.64 (15.44–15.85)	17.46 (17.18–17.75)	34 740	18.17 (17.72–18.62)	19.29 (18.74–19.86)	7145	21.04 (19.99–22.13)	21.64 (20.32–23.01)
(b)									
Years									
1995–1999	28 437	52.80 (51.96, 53.65)	50.47 (49.16, 51.79)	5731	53.38 (51.50, 55.30)	51.76 (48.87, 54.77)	395	74.12 (65.87, 83.11)	64.31 (51.70, 79.37)
2000–2004	38 813	57.16 (56.41, 57.92)	56.45 (55.41, 57.50)	7586	59.30 (57.58, 61.06)	58.55 (56.32, 60.83)	1518	73.01 (68.77, 77.44)	69.80 (64.07, 75.89)
2005–2009	49 514	60.47 (59.79, 61.16)	62.16 (61.28, 63.04)	10 342	64.72 (63.18, 66.29)	68.82 (66.76, 70.93)	2364	79.69 (76.14, 83.38)	80.31 (75.69, 85.14)
2010–2014	55 866	64.46 (63.79, 65.13)	67.98 (67.18, 68.78)	17 230	58.91 (57.77, 60.06)	62.88 (61.38, 64.40)	3804	75.50 (72.76, 78.31)	81.37 (77.39, 85.47)
Sex									
Female	33 274	76.83 (75.89–77.78)	77.37 (76.30–78.46)	6149	82.99 (80.73–85.30)	80.67 (78.03–83.38)	936	99.65 (93.36–106.26)	95.40 (87.60–103.70)
Male	139 356	55.68 (55.29–56.07)	57.20 (56.71–57.69)	34 740	55.55 (54.77–56.84)	57.64 (56.68–58.60)	7145	73.11 (71.14–75.12)	76.80 (74.28–79.37)

Table 5 Out-patient visits among Ontario HIV Treatment Network Cohort Study (OCS) participants who were lost to cohort follow-up (LTCFU) (n = 1179)

Variable	All those LTCFU from OCS (N = 1179)	Calendar period when LTCFU from OCS			
		1996–1999 (N = 253)	2000–2004 (N = 265)	2005–2009 (N = 408)	2010–2014 (N = 253)
Person-years of ICES follow-up after OCS LTCFU [median (Q1–Q3)]	5.6 (3.5–10.1)	10.9 (2.3–16.4)	11.0 (6.3–13.1)	5.6 (4.7–7.3)	3.7 (2.4–4.2)
Out-patient visits after OCS LTCFU [median (Q1–Q3)]	9.1 (4.2–17.2)	13.3 (6.3–25.7)	10.8 (5.6–17.7)	7.4 (3.4–15.2)	7.0 (3.3–13.8)
Out-patient visits to family physician after OCS LTCFU [median (Q1–Q3)]	4.5 (1.6–9.2)	6.4 (2.5–13.0)	5.2 (2.0–9.3)	3.8 (1.2–7.7)	3.8 (1.1–7.6)
Out-patient visits to HIV specialist after OCS LTCFU [median (Q1–Q3)]	0.9 (0–3.0)	1.6 (0.1–4.1)	1.4 (0.1–5.7)	0.7 (0–2.5)	0.5 (0–2.0)
Out-patient visits for HIV-specific care after OCS LTCFU [median (Q1–Q3)]	3.1 (1.2–6.2)	4.7 (2.0–9.6)	4.6 (2.0–7.7)	2.6 (1.0–4.3)	2.4 (0.6–4.6)
Engaged in care within first year after OCS LCTFU (≥ 2 out-patient visits at least 3 months apart for HIV-specific care within first year after OCS LTCFU) [n (%)]	706 (59.9)	163 (64.4)	179 (67.6)	229 (56.1)	135 (53.4)
Engaged in care in most recent calendar year [≥ 2 out-patient visits at least 3 months apart for HIV-specific care within most recent calendar year (2014)] [n (%)]	439 (37.2)	62 (24.5)	98 (37.0)	165 (40.4)	114 (45.1)

3 months apart) within the first year after LTCFU from OCS, and 37% remained engaged in HIV care in 2014.

Discussion

In our setting in Ontario, Canada, we documented higher rates of mortality and increased use of acute health care resources, including hospitalizations and ED visits, among PLWH who become lost to follow-up from a clinical HIV-infected cohort study. OCS participants were LTCFU at a rate of 3.13 per 100 PY; this group had more than twice the rate of mortality and higher rates of acute care use (hospitalizations and ED visits) than participants who remained active in the cohort or individuals who had never joined the cohort. As the OCS is a volunteer cohort, not a population-based study, LTCFU from the cohort was not synonymous with the lack of engagement in HIV care. In fact, approximately half of LTCFU participants remained engaged in HIV care after LTCFU from the cohort. Our findings provide a robust estimate of mortality among those LTCFU that can enhance assumptions made when estimating life expectancy from HIV-infected cohorts.

Other HIV-infected cohort studies have reported mixed findings on the association between LTCFU and mortality, in part as a consequence of different definitions of LTCFU, the calendar year period under study and the degree to which a cohort study is population-based, such that LTCFU implies a lack of engagement in HIV care. A French HIV-infected cohort study reported a mortality rate of 29.8% within a 1-year period among the 5.4% of participants who were LTCFU for ≥ 12 months and who never returned [8]. This French cohort study described an analysis which incorporated assumptions for mortality among those LTCFU that resulted in a significantly increased 1-year mortality rate among patients without delayed access to care compared with an analysis performed without correction for LTCFU (1.9% versus 0.6%, respectively; P = 0.0012) [8]. However, for patients with delayed access to care, the 1-year mortality rates were not significantly different between analyses that did and did not correct for LTCFU (7.8% versus 6.5%, respectively; P = 0.29). A US cohort study reported that participants who were ever LTCFU for 12 months had only modestly elevated mortality (1.2 times higher after adjustment for confounders) compared with participants who remained in care after 5 years, perhaps as a consequence of re-engagement in HIV care outside the cohort [16]. Finally, an Australian HIV-infected cohort study reported no effect of a gap in care of 12 months or more on mortality rates during the period 1999–2013, also attributable at least in part to the availability of care outside of the cohort [3].

Results from our study are in contrast with these previously published findings. We observed a doubling of mortality risk among OCS participants who were LTCFU, despite the fact that 60% had HIV care (at least two HIV care visits, 3 months apart) in the first year after LTCFU. The stronger effect of LTCFU on mortality in our study compared to other studies could be attributable to our more stringent definition of LTCFU of no clinic visits for a period of 18 months, rather than the 12-month period

used by other studies. In general, higher mortality among LTCFU participants may be attributable to sicker participants leaving the cohort, as evidenced by higher acute care rates after LTCFU, or the loss of the social support and medication adherence support from cohort participation [17]. The loss of established HIV primary care may also contribute to revolving through ED visits, which has been shown not to constitute high-quality care [18,19].

In a study of patients attending a regional HIV care site in Alberta, Canada [17], 9% of 1928 patients seen between 1 January 2010 and 31 August 2014 were LTCFU for ≥ 12 months. Only 20% of the LTCFU Alberta patients received HIV care elsewhere in the province compared to the 60% of OCS patients in our study who received care in the first year after loss to follow-up. LTCFU patients in Alberta had frequent visits to the ED. The LTCFU rate from the Southern Alberta Clinic between 2001 and 2006 was reported as 12% [20]. The rate of LTCFU from the Canadian Observational Cohort, a cohort collaboration of clinical sites in British Columbia, Ontario (including OCS) and Quebec, between 2000 and 2015 was 11% [9].

Strengths of our study include the large sample size, the long duration of the study period and the comprehensiveness of the provincial health administrative databases. Nevertheless, our research is subject to limitations. Because we were unable to distinguish between individuals who were not receiving HIV care and those who had moved out of the province, we only classified people as having out-migrated if they had not received care for 7 years. Inclusion of person-time for out-migrants who were not identified by this 7-year rule would result in an underestimate of mortality rates for LTCFU participants, making our results even more striking. The administrative databases did not contain clinical HIV information (e.g. adherence to antiretroviral therapy, CD4 counts or HIV viral loads); thus, we were unable to compare these markers according to participation status. LTCFU participants were less likely than active participants to have been linked to administrative databases, which is likely to have biased our results towards/away from the null depending on whether sicker or healthier patients were more likely to have agreed to have their records linked to administrative data.

This approach and our findings may inform health outcome estimates based on volunteer cohorts and could be used for quantitative bias adjustment to correct for such biases. A consensus statement [21] regarding preferred methods for presentation of longitudinal studies with missing data [22] offers guidelines for the conduct of sensitivity analyses when data are missing not at random (MNAR). Statistical methods for handling missing data as a result of LTCFU include inverse probability weighting for the probability of censoring [23], pattern mixture modelling [24] and selection models [25]. Interpretation of sensitivity analyses requires a sense of the plausibility of different imputation strategies. Our study provides data on mortality and health care utilization after LTCFU from a cohort study, which will be useful for the conduct and interpretation of sensitivity analyses making assumptions about participants who are LTCFU.

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Data access: The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the programmes may rely upon coding templates or macros that are unique to ICES.

Appendix 1:

The OHTN Cohort Study Team consists of Drs Abigail Kroch (Principal Investigator), OHTN and University of Toronto; Beth Rachlis, OHTN, Dignitas International and University of Toronto; Ann Burchell, St Michael's Hospital and University of Toronto; Gordon Arbess, St Michael's Hospital; Jeffrey Cohen, Windsor Regional Hospital; Curtis Cooper, Ottawa General Hospital; Don Kilby, University of Ottawa Health Services; Fred Crouzat and Mona Loutfy, Maple Leaf Medical Clinic; Nisha Andany and Nicole Mittmann, Sunnybrook Health Sciences Centre; Irving Salit, Toronto General Hospital; Michael Silverman, St Joseph's Health Care; and Roger Sandre, Sudbury Regional Hospital.

Appendix 2:

Table A1 Characteristics of Ontario HIV Treatment Network Cohort Study (OCS) participants at presentation to HIV care by loss to cohort follow-up status

Variable	Active OCS participants (N = 4389) n (%)	OCS participants lost to cohort follow-up (N = 1179) n (%)	P-value
Year of HIV care presentation			
≤ 1992–1994	1443 (32.9)	524 (44.4)	< 0.001
1995–1999	1045 (23.8)	377 (32.0)	
2000–2004	823 (18.8)	147 (12.5)	
2005–2009*	≤ 832	≤ 130	
2010–2014*	≤ 255	≤ 6	
Age at HIV care presentation (years) [mean (SD)]	37.11 (9.33)	35.47 (8.74)	< 0.001
Age category at HIV care presentation			
≤ 25 years	383 (8.7)	133 (11.3)	< 0.001
26–35 years	1687 (38.4)	526 (44.6)	
36–45 years	1529 (34.8)	363 (30.8)	
46–55 years	617 (14.1)	125 (10.6)	
≥ 56 years	173 (3.9)	32 (2.7)	
Female	675 (15.4)	151 (12.8)	0.027
Neighbourhood income quintile			
1	1389 (31.6)	361 (30.6)	0.231
2	898 (20.5)	239 (20.3)	
3	758 (17.3)	193 (16.4)	
4	617 (14.1)	175 (14.8)	
5	649 (14.8)	177 (15.0)	
Missing	78 (1.8)	34 (2.9)	
Urban/rural			
Major urban	3875 (88.3)	1038 (88.0)	0.122
Nonmajor urban	352 (8.0)	92 (7.8)	
Rural	133 (3.0)	33 (2.8)	
Missing	29 (0.7)	16 (1.4)	
Immigrant status			
Long-term resident	3767 (85.8)	1066 (90.4)	< 0.001
immigrant, country with generalized HIV epidemic	221 (5.0)	42 (3.6)	
immigrant, country without generalized HIV epidemic	401 (9.2)	71 (6.0)	
Comorbidity (aggregated diagnosis groups)			
Missing (1991 and 1992)	798 (18.2)	294 (24.9)	< 0.001
1–4 (low)	1067 (24.3)	279 (23.7)	
5–9 (medium)	1645 (37.5)	395 (33.5)	
≥ 10 (high)	879 (20.0)	211 (17.9)	

*Suppressed because of small cell sizes.
SD, standard deviation.

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