Examining Differences in Cause-Specific Mortality among Patients Enrolled in a Hospital-Based HIV Care Clinic in a Canadian Setting

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Background

- Engagement in care and access to highly active antiretroviral therapy (HAART) have significantly decreased morbidity and mortality among people living with HIV/AIDS.
- In high income countries, there are concerns regarding increased mortality from non-AIDS-malignancies, cardiovascular diseases and other non-HIV-related comorbidities.[1]
- Understanding causes of death and associated risk factors is needed to appropriately manage HIV disease and relevant comorbidities and further decrease mortality among HIV-positive individuals.

Objectives

- To examine differences in cause-specific mortality for individuals enrolled in a comprehensive, hospital-based immunodeficiency clinic (IDC) in Vancouver, British Columbia.

Methods

- **Study Cohort**: All subjects age ≥ 19 years old enrolled in the IDC, located in a tertiary referral hospital in downtown Vancouver, BC, with at least one visit to the clinic between 01-Jan-2004 and 31-Dec-2015 and at least one documented CD4 count measurement and plasma viral load (PVL) test were included in the study.
- **Procedures:** Data on medical history, clinical laboratory tests and mortality were obtained from the clinic's database and from individual medical records.

  Causes of death were independently reviewed by two physicians and recorded using a modified version of the previously validated "Coding Causes of Death in HIV" (CoDe) algorithm[2].
- **Primary Outcomes:** All-cause and cause-specific mortality
- **Statistical Analyses:** We calculated all-cause and cause-specific mortality rates (MR) per 1,000 person-years (PY) for all IDC patients who were deceased during the study period. A Poisson regression model was used to examine trends for AIDS- and non-AIDS-related mortality.

  Demographic and clinical characteristics of individuals dying from AIDS- and non-AIDS-related causes were compared using χ^2 (Chi-squared) tests for categorical variables and Wilcoxon signed-rank tests for continuous variables. A Cox proportional hazards model was used to determine risk factors associated with AIDS- and non-AIDS-related mortality.

Results

- There were 2,244 patients enrolled in the IDC from January 2004 to December 2015 and 271 (12.08%) deaths during this period. Characteristics of deceased IDC patients (n=264, excluding those dying of unknown causes of death) can be seen in **Table 1**.

Table 1: Descriptive Characteristics of Deceased IDC Patients, 2004 - 2015

Variable	Distribution of Underlying Causes of Death* n(%) AIDS-related N = 74	Non-AIDS-related N = 190	p-value
Sex			
Female	11 (15)	31 (16)	
Male	63 (85)	159 (84)	p=0.772
Risk Factors for Acquiring HIV			
IDU only	23 (31)	38 (20)	
MSM only	11 (15)	38 (20)	
IDU + MSM	10 (14)	23 (12)	
Others	23 (31)	77 (40)	
Unknown	7 (9)	14 (7)	p=0.175
Age at first visit, years [median(Q1-Q3)]	42 (38-50)	46 (41-54)	**p=0.005**
Baseline CD4, cells/µL†			
< 50	33 (45)	15 (8)	
50 - <200	21 (28)	50 (26)	
200- <350	7 (10)	49 (26)	
≥350	13 (18)	76 (40)	**p<0.001**
Baseline PVL, copies/mL†			
< 50	11 (15)	71 (37)	
50- <100,000	37 (50)	84 (44)	
≥100,000	26 (35)	35 (18)	**p<0.001**
Patient on ARVs (ever)			
Yes	64 (86)	175 (92)	p=0.161
Calendar period at time of death			
2004 - 2005	15 (20)	15 (8)	
2006 - 2007	22 (30)	28 (15)	
2008 - 2009	10 (14)	35 (18)	
2010 - 2011	10 (14)	31 (16)	
2012 - 2013	9 (12)	41 (22)	
2014 - 2015	8 (11)	40 (21)	**P=0.001**
Age at death, years [median(Q1-Q3)]	45 (39-52)	51 (44-59)	**p<0.001**
Latest CD4 Count prior to death, cells/µL‡			
< 50	36 (52)	5 (3)	
50 - <200	19 (28)	57 (31)	
200- <350	6 (9)	44 (24)	
≥350	8 (12)	80 (43)	**p<0.001**
Latest PVL prior to death, copies/mL‡			
< 50	22 (32)	117 (63)	
50- <100,000	27 (40)	55 (30)	
≥100,000	19 (28)	14 (8)	**p<0.001**
Hepatitis virus infection§			
Chronc HBV	1 (2)	9 (5)	p=0.460
Chronic HCV	12 (30)	49 (37)	p=0.427
Depression (ever)			
Yes	17 (23)	81 (43)	**p=0.003**
Healthcare Utilization‖			
Active	47 (64)	148 (78)	
Inactive	27 (36)	42 (22)	**p=0.017**
Year 1 adherence after 1st IDC visit			
Yes	10 (30)	69 (57)	**p=0.007**

* Unknown causes of death have been excluded for these analyses; †Most recent within six months of first IDC visit; ‡Most recent prior to study censor date; § Chronic HBV: Positive HBsAg or HBV DNA for ≥6 months. Chronic HCV: Positive HCV antibody and HCV RNA or positive HCV genotypes 1a-4. ‖Patient had at least 2 IDC visits more than 60 days apart during study period
PVL, plasma viral load

Results (continued)

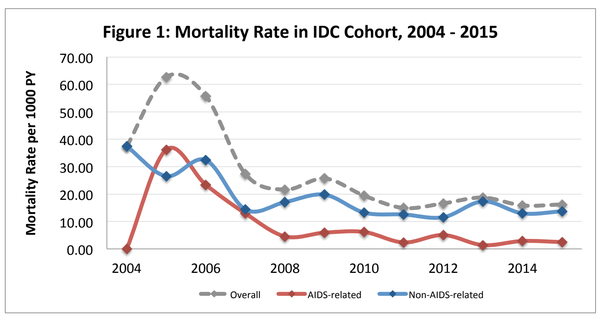
- **Table 2** depicts the classification of the most frequent underlying causes of death found in the entire IDC cohort (n=2,244).

Table 2: Causes of Death and Mortality Rates for IDC Cohort, 2004 - 2015

Cause of Death	n (%)	MR per 1000 PY (95% CI)
All deaths	271 (12.08)	22.51 (19.91 - 25.36)
AIDS-related	74 (3.30)	6.17 (4.83 - 25.36)
AIDS Infection	31 (1.38)	2.58 (1.75 - 3.65)
AIDS Malignancy	28 (1.24)	2.33 (1.54 - 3.36)
AIDS (ongoing active disease)	15 (0.67)	1.25 (0.70 - 2.05)
Non-AIDS-related	190 (8.47)	15.78 (13.62 - 18.19)
Malignancy (other than AIDS or hepatitis related)	44 (1.96)	3.67 (2.66 - 4.91)
Substance abuse (active)	44 (1.96)	3.67 (2.66 - 4.91)
Chronic Viral Hepatitis (progression of/complication to)	16 (0.71)	1.33 (0.76 - 2.16)
Infection (Other than AIDS-related)	11 (0.49)	0.92 (0.46 - 1.63)
Chronic obstructive lung disease	10 (0.45)	0.83 (0.40 - 1.53)
Heart or vascular (other causes)	9 (0.40)	0.75 (0.34 - 1.42)
Psychiatric disease	8 (0.36)	0.67 (0.29 - 1.31)
MI or other ischemic heart disease	7 (0.31)	0.58 (0.23 - 1.20)
Other*	41 (1.83)	3.41 (2.44 - 4.62)
Unknown/Unclassifiable	7 (0.31)	0.58 (0.23 - 1.20)

*Includes deaths related to the CNS, liver, suicide, endocrine system, haematological system, renal failure, stroke, accident or other violent death, diabetes mellitus, digestive systeem, pancreatitis and respiratory diseases
MR, mortality rate; PY, person-years

Figure 1: Mortality Rate in IDC Cohort, 2004 - 2015



- Overall mortality decreased from 37.38 per 1000 PY in 2004, to 16.22 per 1000 PY in 2015 (p<0.001) (**Figure 1**).
- AIDS-related mortality decreased from 36.18 per 1000 PY in 2005, to 2.49 per 1000 PY in 2015 (p<0.001). Non-AIDS-related mortality decreased from 37.38 per 1000 PY in 2004, to 13.72 per 1000 PY in 2015 (p = 0.009) (**Figure 1**).
- **Table 3** shows the risk factors associated with AIDS- and non-AIDS related mortality in the entire IDC cohort, excluding unknown causes of death (n=2,237).

Table3: Cox Proportional Hazards Model for AIDS- and Non-AIDS-related Deaths among IDC Patients, 2004 - 2015 (n=2,237*)

Variable	AIDS-related Unadjusted HR (95% CI)	AIDS-related Adjusted HR (95% CI)	Non-AIDS-related Unadjusted HR (95% CI)	Non-AIDS-related Adjusted HR (95% CI)
Sex				
Female	1.00 (-)		1.00 (-)	
Male	0.90 (0.47-1.70)	N/A†	0.83 (0.57-1.22)	N/A†
Age at time for first IDC visit				
(per 10 year increment)	1.22 (0.99-1.51)	1.25 (1.01-1.55)	**1.68 (1.48-1.91)**	**1.68 (1.48-1.91)**
Risk Factors for Acquiring HIV				
IDU + MSM	1.00 (-)		1.00 (-)	1.00 (-)
IDU only	**2.61 (1.24-5.49)**		1.88 (1.12-3.16)	**2.11 (1.25-3.54)**
MSM only	**0.27 (0.11-0.63)**		0.39 (0.23-0.65)	**0.45 (0.27-0.76)**
Other	0.49 (0.23-1.04)		0.65 (0.41-1.04)	**0.61 (0.38-0.97)**
Unknown	1.14 (0.43-2.99)	N/A†	1.09 (0.56-2.13)	1.26 (0.65-2.46)
Baseline CD4 Count‡				
(per 100 cells/µL increments)	**0.50 (0.42-0.59)**	**0.49 (0.42-0.59)**	**0.89 (0.84-0.95)**	**0.89 (0.84-0.95)**
Baseline PVL‡, §				
(log_{10} copies/mL)	**1.47 (1.24-1.75)**	N/A†	1.01 (0.92-1.12)	N/A†
Latest CD4 Count§,‖				
(per 100 cells/µL increments)	**0.39(0.32-0.48)**	N/A†	**0.73 (0.68-0.79)**	N/A†
Latest PVL§,‖				
(log_{10} copies/mL)	**2.11(1.76-2.53)**	N/A†	**1.46 (1.29-1.65)**	N/A†
Healthcare Utilization¶				
Active	1.00 (-)	1.00 (-)	1.00 (-)	1.00 (-)
Inactive	**5.76 (3.58-9.25)**	**4.21 (2.58-6.85)**	**3.04 (2.16-4.29)**	**2.95 (2.09-4.16)**
Patient on HAART (ever)				
No	1.00 (-)	1.00 (-)	1.00 (-)	
Yes	0.50 (0.26-0.98)	**0.44 (0.21-0.95)**	0.88 (0.52-1.50)	N/A†

*Model excludes unknown causes of death. Significant values are shown in bold; †N/A denotes variables not included in the adjusted HR; ‡Most recent within six months closest to first IDC Visit; §Variable not included in the multivariate model because of too many missing counts; ‖Latest within 1 year before last IDC Visit; ¶Patient had at least 2 IDC visits more than 60 days apart during study period
CI, confidence interval; HR, hazard ratio; PVL, plasma viral load.

Discussion

- We observed a significant decreasing trend in overall mortality as well as in both AIDS- and non-AIDS-related mortality in a comprehensive, interdisciplinary HIV clinic over the study period.
- Being an inactive IDC user was associated with increased mortality from both AIDS- and non-AIDS-related causes. Older age and IDU status were also associated with increased mortality from non-AIDS-related causes.
- Advances in clinical care and antiretroviral treatment are showing significant benefits for people living with HIV/AIDS; better screening and management of non-AIDS-related causes of death are needed.
- Future studies should continue to examine mortality and morbidity associated with an aging HIV-positive population as well as examining interventions that address risk factors for lifestyle-related causes of death.

References

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