All-cause and HIV-related Mortality Rates Among HIV-infected Patients After Initiating Highly Active Antiretroviral Therapy: The Impact of Aboriginal Ethnicity and Injection Drug Use

Leah J. Martin, PhD,[1] Stan Houston, MD, FRCPC,[1,2] Yutaka Yasui, PhD,[1] T. Cameron Wild, PhD,[3] L. Duncan Saunders, MBBCh, PhD[1]

ABSTRACT

Background: Aboriginals are over-represented in Canada's HIV epidemic and are commonly infected with HIV via injection drug use (IDU); however, little is known about the impact of Aboriginal ethnicity on mortality after starting highly active antiretroviral therapy (HAART). Therefore, we compared mortality rates between Aboriginal and non-Aboriginal HIV patients and between IDU and non-IDU HIV patients after they initiated HAART.

Methods: We conducted a retrospective cohort study of antiretroviral-naïve patients starting HAART January 1999-June 2005 (baseline), followed until December 2005. We constructed two Cox proportional hazards models, one to estimate all-cause and one to estimate HIV-related mortality hazard ratios (HRs), considering sex, and baseline age, CD4 cell count, HIV RNA level, calendar year, and HAART regimen as potential confounders.

Results: The 548 study patients were followed for 1,889.8 person-years; 194 (35%) were Aboriginal, 255 (46%) were IDUs. We observed 55 deaths; 47% were HIV-related. In multivariable models, Aboriginals experienced higher all-cause (HR=1.85, 95% CI=1.05-3.26, p=0.034) and HIV-related (HR=3.47, 95% CI=1.36-8.83, p=0.009) mortality rates compared to non-Aboriginals; and, compared to patients with other exposures, IDUs experienced higher all-cause (HR=2.45, 95% CI=1.31-4.57, p=0.005) but similar HIV-related (p=0.27) mortality rates.

Conclusions: Compared to non-Aboriginals, Aboriginal HIV patients suffer higher all-cause and HIV-related mortality rates after starting HAART. The strongest and most significant predictor of higher all-cause mortality was IDU. Future research should examine reasons for the observed poorer survival of Aboriginal and IDU HIV patients after initiating HAART to develop interventions to improve the prognosis for these vulnerable populations.

Key words: Antiretroviral therapy, highly active; mortality; Aboriginal populations; intravenous drug use

La traduction du résumé se trouve à la fin de l'article.

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Highly active antiretroviral therapy (HAART) has dramatically reduced mortality among human immunodeficiency virus (HIV)-infected individuals.[1,2] However, since the introduction of HAART, higher rates of mortality have been observed among injection drug users (IDUs)[3,4] and Aboriginal peoples[5] within this population.

Aboriginals are over-represented among HIV-positive test reports in Canada and IDU is more commonly reported as a route of HIV exposure among Aboriginals than non-Aboriginals.[6] Although IDU has been associated with increased rates of mortality after starting HAART,[7,8] less is known about the impact of Aboriginal ethnicity on mortality after starting HAART and whether IDU may help to explain differences in mortality between Aboriginal and non-Aboriginal HIV patients. One recent Canadian study found Aboriginals to have significantly higher rates of all-cause mortality after starting HAART after controlling for a history of IDU;[5] however, the study did not investigate HIV related mortality specifically and included only 88 Aboriginal subjects (14.1% of the study population). As Mocroft et al. illustrate, it is inappropriate to assume that higher all-cause mortality rates necessarily demonstrate a poorer response to HAART; to investigate patients' responses to HAART, it is important to examine HIV-related mortality rates specifically.[9]

The objectives of this study were to compare all-cause and HIV-related mortality rates between Aboriginal and non-Aboriginal HIV patients after starting HAART, adjusting for factors known to influence mortality among HIV patients. Because Aboriginal HIV patients have higher rates of exposure to HIV via IDU and because we observed a strong association between IDU and mortality, we also examined the relationship between IDU and these two mortality outcomes.

METHODS

Data sources

This was a retrospective cohort study using data collected by the Northern Alberta HIV Program (NAHIVP), a clinical database that has been described in detail elsewhere.[10] In addition to data from

Author Affiliations

1. Department of Public Health Sciences, School of Public Health, University of Alberta, Edmonton, AB
2. Division of Infectious Diseases, Department of Medicine, University of Alberta, Edmonton, AB
3. Centre for Health Promotion Studies, School of Public Health, University of Alberta, Edmonton, AB

Correspondence: Dr. Leah J. Martin, E-mail: leah.martin@ualberta.ca

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Conflict of Interest: None to declare.

NAHIVP, we linked cause and date of death data from Alberta Health and Wellness to the study database and used viral load data from the Alberta Provincial Public Health Laboratory to replace missing baseline viral loads where possible. The study procedures were approved by the University of Alberta Health Research Ethics Board.

Study patients

We assembled a cohort of patients using the NAHIVP database who satisfied the following eligibility criteria: 1) started HAART between 1 January 1999 and 30 June 2005 (baseline); 2) were previously antiretroviral therapy (ART)-naïve; and 3) were ≥15 years of age when starting HAART. Patients were excluded if they were missing ethnicity data. To limit the study to patients who started HAART for the purpose of treatment rather than to prevent vertical transmission of HIV, we excluded patients if they started HAART ≤26 weeks before being recorded as delivering a baby. We assumed that starting HAART earlier in pregnancy or after delivery would be for maternal indications. Patients were followed retrospectively until December 31, 2005, which allowed follow-up time of 6 months to 7 years.

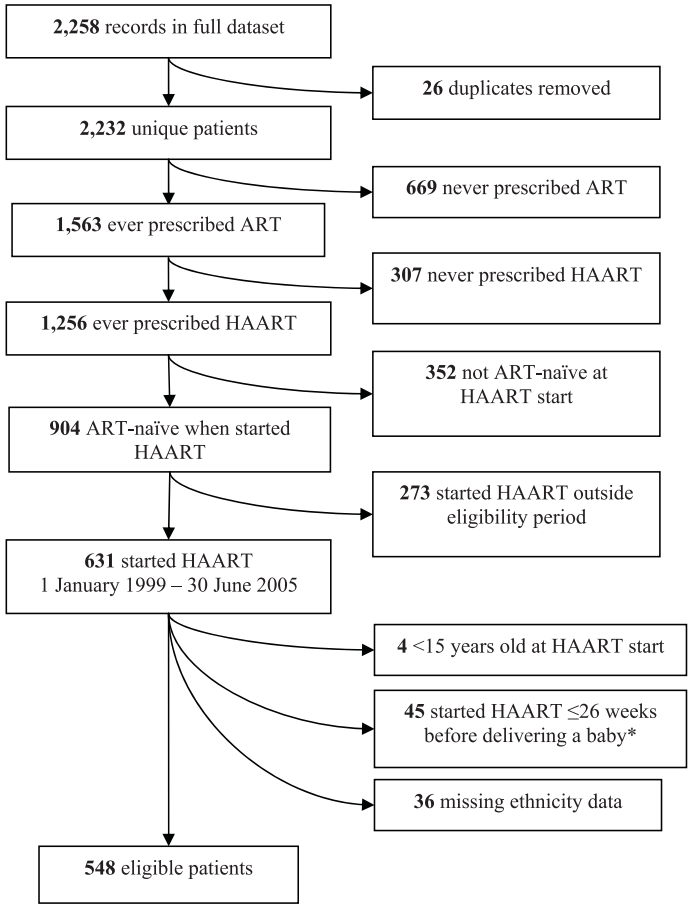
Definitions

We defined Aboriginals as Treaty and non-Treaty Aboriginals, Métis and Inuit. One patient was defined as Aboriginal who was identified as both Caucasian and Métis in the database. HIV exposure categories were classified using an exposure category hierarchy.[11] Patients were defined as IDUs if their HIV exposure was recorded as IDU or any other exposure combined with IDU; patients with other exposures, including unknown or missing exposures, were considered to have "other exposures". We defined HAART as a combination of at least three antiretrovirals, other than ritonavir, recorded as prescribed on the same date. We excluded ritonavir under the assumption that, during the study period (1999-2005), ritonavir would have been prescribed at low dosages intended to boost other protease inhibitors, rather than at clinically therapeutic levels. The HAART start date was the first date that a HAART prescription was recorded in the database and, for the purposes of these analyses, we assumed that patients continued on HAART. Baseline CD4 cell counts and viral loads were defined as those measures that were taken closest to the HAART start date, ≤6 months before, and not after starting HAART. We classified causes of death using the ninth and tenth revisions of the International Statistical Classification of Diseases and Related Health Problems (ICD-9 and 10).[12] We defined ICD-9 categories 042-044 and ICD-10 categories B20-B24 as HIV-related causes of death; all other known causes were coded as non-HIV-related causes of death. Cause of death was unavailable for five patients; therefore, one of the authors (SH) reviewed their charts and determined cause of death to be HIV-related for two patients and non-HIV-related for two patients. Cause of death remained undetermined for one patient (an Aboriginal female IDU), who we excluded from our analysis of HIV-related mortality.

Data analyses

Patient characteristics were tabulated and compared between Aboriginals and non-Aboriginals and between IDUs and patients with other exposures, using χ^2 and two-sided Fisher exact tests for categorical variables and two-sided Wilcoxon rank sum test (normal approximation) for continuous variables.

Figure 1. Derivation of the study population (N=548)



Notes: ART = antiretroviral therapy, HAART = highly active antiretroviral therapy
* Of these 45 patients, 2 were also missing ethnicity data.

We assessed two main outcomes in our analyses: all-cause mortality and HIV-related mortality. To examine unadjusted all-cause mortality risk, we compared Kaplan-Meier estimates of survival probabilities by Aboriginal ethnicity as well as by IDU grouping using the Log-Rank test. We then used Cox proportional hazards models to estimate the adjusted hazard rate ratios of mortality by Aboriginal ethnicity as well as by the IDU grouping, adjusting for potential confounding variables identified using the procedure described below. To examine HIV-related mortality risk, we estimated cumulative incidence curves, as described by Gooley et al.,[13] by Aboriginal ethnicity and by the IDU grouping (unadjusted analysis) and compared HIV-related mortality hazard rate ratios using Cox proportional hazards models, adjusting for potential confounding variables. Therefore, we created two multivariable Cox proportional hazards models, one assessing all-cause mortality and one assessing HIV-related mortality.

Potential confounding variables were identified as those associated with all-cause (or HIV-related) mortality in unadjusted analyses with $p<0.20$. Baseline age and baseline CD4 cell count were forced to enter the models because other studies[7,8] have shown these variables to be prognostic for mortality. We tested the interaction between Aboriginal ethnicity and IDU in the final main effects multivariable models to determine if the impact of Aboriginal ethnicity on mortality differed by IDU status. The proportionality assumption of Cox proportional hazards models was assessed using two time-varying covariates (Aboriginal ethnicity by the log

Table 1. Patient Characteristics by Ethnicity and Injection Drug Use Exposure Category (N=548)

Characteristic	Aboriginal (n=194, 35%)	Non-Aboriginal (n=354, 65%)	p-value	Injection Drug Use (n=255, 47%)	Other Exposures (n=293, 53%)	p-value
Years of follow-up time, median (IQR), total	3.4 (2.2-5.1), 682.0	3.3 (1.6-5.1), 1213.0	0.55	3.6 (2.1-5.3), 929.9	3.2 (1.6-4.7), 965.1	0.034
Sex, no. (%)			<0.0001			0.090
Female	71 (37)	51 (14)		65 (25)	57 (19)	
Male	123 (63)	303 (86)		190 (75)	236 (81)	
HIV exposure category, no. (%)			<0.0001			–
Injection drug use	131 (68)	124 (35)		–*	–	
Other exposures	63 (32)	230 (65)		–	–	
Ethnicity			–			<0.0001
Aboriginal	–	–		131 (51)	63 (22)	
Non-Aboriginal	–	–		124 (49)	230 (79)	
CD4 cells/μL at baseline, median (IQR)	195 (85-295), (n=180)	220 (110-340), (n=325)	0.037	220 (100-320), (n=230)	210 (110-330), (n=275)	0.91
CD4 cells/μL at baseline, no. (%)			0.23			0.26
≤50	30 (15)	50 (14)		38 (15)	42 (14)	
>50-200	63 (32)	101 (29)		71 (28)	93 (32)	
>200-350	61 (31)	99 (28)		80 (31)	80 (27)	
>350	26 (13.4)	75 (21)		41 (16)	60 (20)	
Missing	14 (7.2)	29 (8.2)		25 (9.8)	18 (6.1)	
HIV RNA copies/mL at baseline, median (IQR)	100,000 (22,000-390,000) (n=187)	100,000 (16,000-335,000) (n=342)	0.46	99,000 (25,000-350,000) (n=242)	100,000 (11,000-360,000) (n=287)	0.58
HIV RNA copies/mL at baseline, no. (%)			0.41			0.0025
<10,000	32 (16)	77 (22)		39 (15)	70 (24)	
10,000-<100,000	59 (30)	90 (25)		83 (33)	66 (23)	
≥100,000	96 (49)	175 (49)		120 (47)	151 (52)	
Missing	7 (3.6)	12 (3.4)		13 (5.1)	6 (2.1)	
Initial HAART regimen, no. (%)			0.013			0.32
Protease inhibitor (PI)-based	40 (21)	108 (31)		74 (29)	74 (25)	
Not PI-based	154 (79)	246 (69)		181 (71)	219 (75)	
Year starting HAART, no. (%)			0.45			0.0017
1999-2001	87 (45)	147 (42)		127 (50)	107 (37)	
2002-2005	107 (55)	207 (58)		128 (50)	186 (63)	
Age at baseline, median (IQR)	37.4 (31.7-42.7)	40.1 (33.6-45.7)	0.0020	39.3 (33.0-45.0)	39.5 (32.8-45.0)	0.83
Age at baseline, no. (%)			0.024			0.038
15-29	32 (16)	59 (17)		37 (15)	54 (18)	
30-39	84 (43)	114 (32)		98 (38)	100 (34)	
40-49	64 (33)	133 (38)		100 (39)	97 (33)	
≥50	14 (7.2)	48 (14)		20 (7.8)	42 (14)	
Mortalities, no. (%)			0.0006			<0.0001
Died	31 (16)	24 (6.8)		40 (16)	15 (5.1)	
Alive	163 (84)	330 (93)		215 (84)	278 (95)	
Cause of death, no. (%) (n=54) †			0.013			0.64
HIV-related causes	19 (63)	7 (29)		18 (46)	8 (53)	
Non-HIV-related causes	11 (37)	17 (71)		21 (54)	7 (47)	
Age at death, median (IQR) (n=55)	40.6 (33.7-46.1)	40.9 (37.7-50.4)	0.43	40.4 (35.0-45.2)	42.4 (33.7-53.8)	0.22

* Not applicable
† Note: One death of unknown cause was excluded from this calculation

of survival time and IDU by the log of survival time), which were each tested separately in unadjusted models that included only the main effect and the time-varying covariate. P-values were two-sided and those ≤0.05 were considered statistically significant. Analyses were conducted with SAS® (version 9.1; SAS Institute Inc., Cary, NC) and R (version 2.6.2).

RESULTS

After removing duplicates and applying study eligibility criteria (Figure 1), 548 individuals remained in the study population. We excluded 36 patients who were missing ethnicity data, of whom 3 died (8.3%). Compared to study patients, these 36 patients were less likely to be IDU (28% vs. 47%, p=0.029), were less likely to start HAART in 1999-2001 vs. 2002-2005 (17% vs. 43%, p=0.0021), were followed for a shorter time (median 1.9 vs. 3.3 years, p=0.0003), and died at an older age (62.3 (n=3) vs. 40.9 years, p=0.017).

At baseline, the median age was 39.4 (interquartile range (IQR)=32.9-45.0) years, median CD4 cell count was 210 cells/μL (IQR=100-320 cells/μL, n=505), and median viral load was 100,000 copies/mL (IQR=18,000-350,000, n=529); 68 (12%) patients had baseline viral loads <500 copies/mL. The single most common HIV exposure category was IDU (227, 41%) followed by heterosexual contact (137, 25%), men who have sex with men (MSM) (124, 23%), MSM/IDU (28, 5.1%), and other (8, 1.5%); the exposure category was missing or unknown for 24 (4.4%) patients.

Of the 548 study patients, 194 (35%) were Aboriginal. Compared to non-Aboriginals, Aboriginal patients were significantly more likely to be female, be infected with HIV through IDU, start HAART at a younger age, start HAART on a non-protease inhibitor-based regimen, have a lower baseline CD4 count, and die (Table 1). Almost half of the patients (255, 47%) were IDU. Compared to patients with other exposures, IDUs were significantly more likely to be Aboriginal, start HAART in 1999-2001, have a longer duration of follow-up, and die (Table 1).

Overall, 55 patients (10%) died. Most deaths occurred among Aboriginal patients (31, 56%) and IDUs (40, 73%). The single most common cause of death was HIV disease (26, 47%), followed by external causes of morbidity and mortality (16, 29%), which included accidents (8, 50%), intentional self-harm (4, 25%), and events of undetermined intent (4, 25%). All 8 accidental deaths occurred among IDUs and three of the four deaths caused by intentional self-harm occurred among non-Aboriginal patients.

Compared to non-Aboriginals, Aboriginal patients had a higher probability of all-cause mortality (p=0.0015) (Figure 2a) and a higher crude all-cause mortality rate (hazard ratio (HR)=2.31, 95% CI=1.36-3.94, p=0.0021) (Table 2). Controlling for IDU, baseline

Figure 2. Probability of all-cause mortality by years since starting HAART, comparing patients by (a) Aboriginal ethnicity and (b) injection drug use exposure category (N=548)

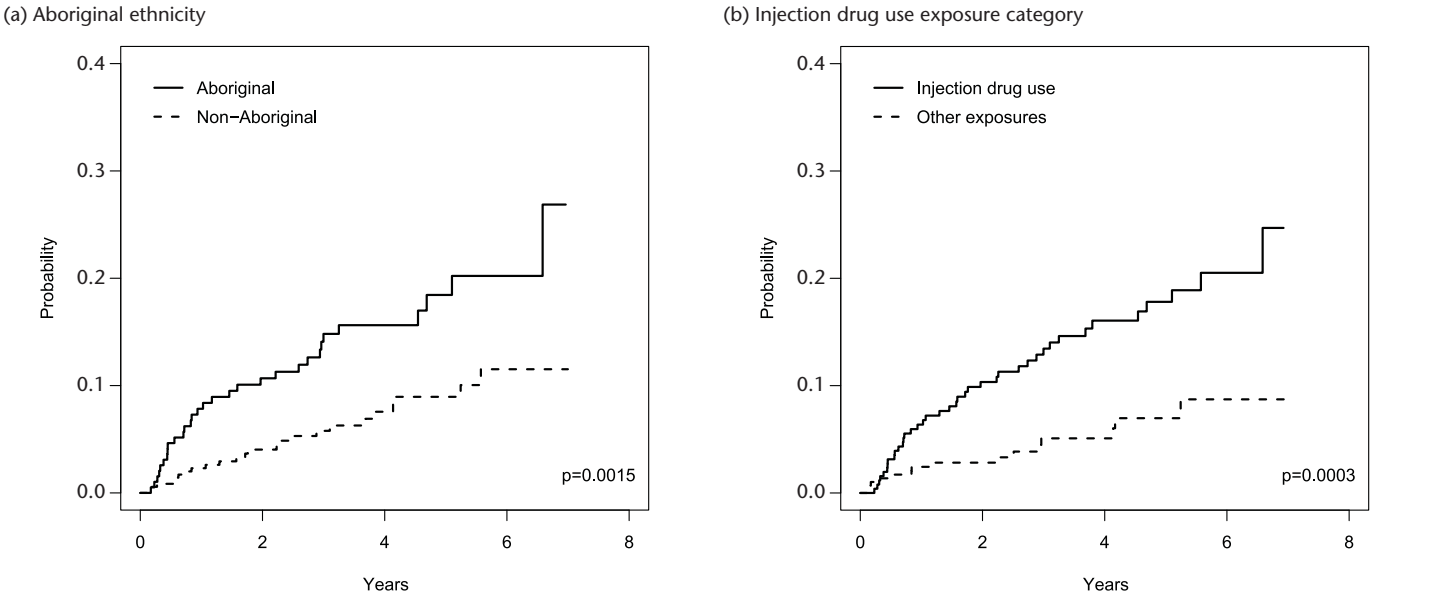


Table 2. Univariable and Multivariable Cox Proportional Hazards Models Assessing All-cause and HIV-related Mortalities After Starting HAART

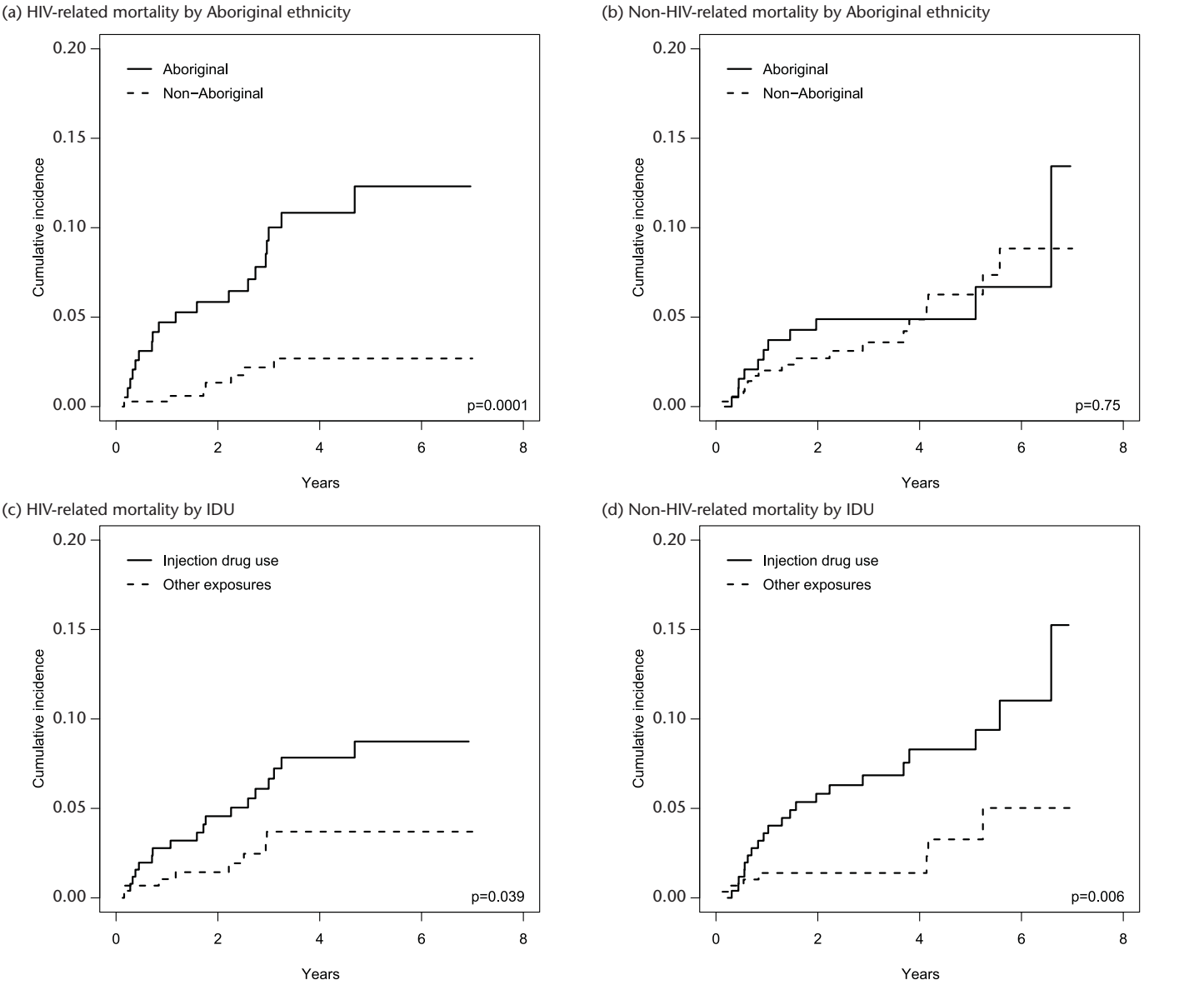
Variable	All-cause Mortality (N=548)				HIV-related Mortality (N=547)			
	Unadjusted Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI	Unadjusted Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Ethnicity (Aboriginal vs. non-Aboriginal)	2.31	1.36-3.94	1.85	1.05-3.26	4.76	2.00-11.33	3.47	1.36-8.83
Sex (Female vs. male)	1.39	0.78-2.48	–*	–	1.79	0.80-4.02	1.18	0.50-2.77
HIV exposure category (Injection drug use vs. other exposures)	2.82	1.56-5.11	2.45	1.31-4.57	2.42	1.05-5.57	1.65	0.67-4.04
CD4 cells/μL at baseline								
≤50 (ref)	1.00	–	1.00	–	1.00	–	1.00	–
>50-200	0.58	0.28-1.20	0.60	0.29-1.26	0.53	0.22-1.31	0.56	0.22-1.42
>200-350	0.42	0.19-0.92	0.40	0.18-0.87	0.15	0.04-0.57	0.17	0.041-0.68
>350	0.39	0.16-0.91	0.44	0.19-1.05	0.07	0.01-0.54	0.14	0.016-1.21
Missing baseline CD4 count	0.55	0.19-1.54	0.53	0.19-1.51	0.49	0.13-1.81	0.24	0.034-1.62
HIV RNA copies/mL at baseline								
<10,000	0.55	0.24-1.27	–	–	0.30	0.07-1.30	0.68	0.14-3.19
10,000-99,999	0.98	0.53-1.79	–	–	0.67	0.26-1.73	1.19	0.43-3.31
≥100,000 (ref)	1.00	–	–	–	1.00	–	1.00	–
Missing baseline viral load measure	1.23	0.37-4.06	–	–	2.42	0.70-8.38	6.47	0.99-42.27
Age at baseline								
15-29 (ref)	1.00	–	1.00	–	1.00	–	1.00	–
30-39	1.49	0.66-3.36	1.26	0.55-2.87	3.59	0.82-15.79	1.77	0.37-8.42
40-49	1.37	0.60-3.13	1.24	0.53-2.88	2.14	0.45-10.07	1.14	0.22-5.91
≥50	1.71	0.59-4.97	2.02	0.68-6.01	2.00	0.28-14.24	1.17	0.15-9.41
Initial HAART regimen (protease inhibitor (PI) vs. non-PI based)	0.98	0.55-1.76	–	–	0.74	0.30-1.85	–	–
Baseline calendar year (1999-2001 vs. 2002-2005)	0.79	0.44-1.43	–	–	0.26	0.10-0.66	0.29	0.11-0.79

* Note: Other than baseline age and baseline CD4 count, variables with p-values ≥0.20 were not included in the multivariable model.

CD4 cell count, and baseline age, Aboriginal patients had an all-cause mortality hazard rate 1.85 (95% CI=1.05-3.26, p=0.034) times higher than non-Aboriginals (Table 2). Similarly, compared to patients with other exposures, IDUs had a higher probability of all-cause mortality (p=0.0003) (Figure 2b) and a higher crude all-cause mortality rate (HR=2.82, 95% CI=1.56-5.11, p=0.0006) (Table 2). Controlling for Aboriginal ethnicity, baseline CD4 cell count, and baseline age, IDUs had an all-cause mortality rate 2.45 (95% CI=1.31-4.57, p=0.0050) times higher than patients with other exposures (Table 2). The interaction between Aboriginal ethnicity and IDU was not statistically significant (p=0.55) and was not retained in the final model for all-cause mortality.

Compared to non-Aboriginals, Aboriginal patients had a higher cumulative incidence rate of HIV-related mortality (p=0.0001) (Figure 3a) and a higher crude HIV-related mortality rate (HR=4.76, 95% CI=2.00-11.33, p=0.0004) (Table 2); among patients who died, Aboriginals were more likely to die from an HIV-related cause (63% vs. 29%, Table 1). Until approximately 4 years after starting HAART, Aboriginals also appeared to experience a higher cumulative incidence of non-HIV-related mortality compared to non-Aboriginals; however, overall, the incidence of non-HIV-related mortality did not differ by Aboriginal ethnicity (p=0.75) (Figure 3b). Adjusting for IDU; sex; and baseline CD4 cell count, viral load, age and calendar year, the HIV-related mortality hazard rate was 3.47 times higher for Aboriginals compared to non-Aboriginals (95% CI=1.36-8.83, p=0.0091) (Table 2). Compared to patients with other exposures, IDUs had higher cumulative incidence rates of HIV-related (p=0.039) and non-HIV-related (p=0.006) mortality (Figure 3c, d),

Figure 3. Cumulative incidence of mortality by years since HAART initiation, comparing patients by (a, b) Aboriginal ethnicity and (c, d) injection drug use exposure category for HIV-related mortality (left side) and non-HIV-related mortality (right side) (N=547)



* Note: One individual died of an unknown cause and was excluded from these analyses.

and a higher crude HIV-related mortality rate (HR=2.42, 95% CI=1.05-5.57, p=0.038) (Table 2); among patients who died, IDUs were not more likely to die from an HIV-related cause (46% vs. 53%, Table 1). Adjusting for Aboriginal ethnicity; sex; and baseline CD4 cell count, viral load, age and calendar year, the HIV-related mortality hazard rate was higher among IDUs than patients with other exposures, but this result was not statistically significant (HR=1.65, 95% CI=0.67-4.04, p=0.27) (Table 2). The interaction between Aboriginal ethnicity and IDU was not statistically significant (p=0.14) and was not retained in the final model for HIV-related mortality.

DISCUSSION

Aboriginal HIV patients suffer higher rates of all-cause and HIV-related mortality compared to non-Aboriginal HIV patients after starting HAART, even after controlling for IDU as an exposure category. This suggests that Aboriginal HIV patients experience inferior responses to HAART compared to non-Aboriginals. This finding may be explained by confounding variables we were unable to control for in this analysis, such as poor adherence to therapy, which may be caused by ongoing injection drug and other substance abuse behaviours, as opposed to injection drug use only as a route of HIV exposure. Intermittent use of HAART has been associated with increased rates of mortality.[14] In addition, active drug use has been associated with poor adherence[15] and intermittent and persistent drug users have been shown to have higher mortality rates than non-users.[16] Furthermore, alcohol use has been associated with poor adherence to HAART.[17] Rates of alcohol dependence/abuse have been shown to be higher among Aboriginals compared to non-Aboriginals in Canada,[18] which may also be true for the Aboriginal patients in our study, and may negatively impact their adherence to therapy and thus their HAART outcomes. The higher rates of HIV-related mortality observed among Aboriginal patients may also be explained by poorer socio-economic conditions and social instability, including factors such as lower income, unem-

ployment, and unstable housing, which have been associated with poor adherence to therapy.[19-21] In general, Aboriginals have higher unemployment rates compared to the general Canadian population[22] and Aboriginal HIV patients have been shown to have higher rates of unstable housing[23] and lower levels of income.[5,23] These differences were likely represented in our study population. More research is needed to understand the reasons for the higher rates of HIV-related mortality observed among Aboriginal HIV patients; adherence, active substance use, and socio-economic factors should be measured in future studies.

IDU appears to be the strongest predictor of higher all-cause mortality rates after starting HAART. Although HIV was the most common cause of death among IDUs, after controlling for Aboriginal ethnicity and other confounders, IDU was not a significant predictor of higher HIV-related mortality rates. These results are consistent with findings from the EuroSIDA study, which shows that, compared to patients with other exposures, IDUs have higher rates of non-HIV-related mortality after starting HAART, but similar rates of HIV-related mortality.[9] The EuroSIDA authors, therefore, concluded that IDUs in their study responded to HAART as well as patients with other exposures.

However, other research suggests that IDUs may receive less benefit from HAART due to delayed treatment initiation,[24] treatment interruptions,[25] and continued drug use,[16] which may also be associated with lower levels of adherence.[15] In addition, hepatitis C virus (HCV) co-infection, which is far more common among IDUs than those infected with HIV via other transmission routes,[26] has been shown to be an independent predictor of mortality among HIV-infected patients.[27] Our results show that IDUs did not have significantly lower CD4 cell counts or higher viral loads at baseline compared to patients with other exposures. This suggests that IDUs were provided HAART at similar clinical periods during their illnesses and did not experience a relative delay in treatment. However, interruptions in treatment may have occurred more commonly among IDUs, which could have adversely impacted their health. In our study, all 8 deaths due to accidents, primarily accidental poisonings, occurred among IDUs. This is not surprising, as drug overdoses are a common cause of death among IDUs,[28] and it demonstrates that at least some individuals infected with HIV through IDU continue substance abuse behaviours after starting HAART. Our study did not assess adherence to therapy, continued drug use, HCV co-infection, or socio-economic status, all of which may have contributed to higher mortality rates among IDUs after starting HAART.

To our knowledge, this is the first study to investigate the relationship between Aboriginal ethnicity and mortality after starting HAART that has included such a large number of Aboriginal HIV patients, has investigated HIV-related mortality as an outcome specifically, and has attempted to exclude women who started HAART to prevent vertical transmission of HIV.

This study has several limitations. First, ethnicity and HIV exposure categories used in this analysis were self- or physician-reported and misclassifications may have occurred, for example, by categorizing individuals with unknown or missing exposure categories as non-IDUs. However, this information is collected by clinicians providing ongoing care to these patients, which gives us confidence in its accuracy.

Second, the number of deaths that occurred in this study was low; therefore, small changes in numbers may have relatively large impacts on results. Because only a small number of HIV-related deaths occur after starting HAART, it would be beneficial to conduct multi-provincial studies investigating the association between Aboriginal ethnicity and HIV-related causes of death across Canada.

Finally, a clinical database was used as the primary data source in this study, which has inherent limitations. Using these data, we could not be certain that patients were ART-naïve when starting HAART. In particular, for the 68 (12%) patients with baseline viral loads <500 copies/mL, the HAART start date was likely earlier than the date entered into the database. As well, deaths that occurred outside Alberta and were not reported to NAHIVP would be missed in our analysis. In addition, certain variables such as socio-economic status measures, adherence to therapy, HCV co-infection, presence of other co-morbid conditions, and ongoing behaviours such as smoking and substance abuse were not collected, or were not available in formats appropriate for this analysis. These variables may have impacted mortality rates. Most importantly, data assessing patients' adherence to HAART were not available in our study dataset. However, because it is the most probable reason for the difference in HIV-related mortality rates we observed between Aboriginal and non-Aboriginal patients, adherence needs to be investigated further. Although there is no agreed-upon gold standard for measuring adherence,[29] other researchers comparing HAART treatment outcomes between Aboriginal and non-Aboriginal HIV patients have used prescription-refill data as an indirect measure of adherence; one study found no significant differences in rates of adherence by Aboriginal ethnicity[5] but another found a significantly lower rate of adherence among Aboriginal patients.[23] These equivocal findings may be related to different methods of measuring adherence (i.e., as a dichotomous vs. continuous variable) or to measurement error associated with this indicator of adherence. Pharmacy-refill data are considered to be a useful measure of adherence in retrospective, population-based studies when more accurate measures are not feasible.[30] In HIV research, they have been shown to correlate with virological suppression[31] and mortality.[14] However, one disadvantage of this method is that patients who refill their prescriptions may not take their pills as prescribed. Prospective studies are needed to compare adherence rates between Aboriginal and non-Aboriginal patients; existing evidence from pharmacy-refill data should be corroborated with more sensitive methods, such as electronic monitoring, pill counts, directly observed therapy, or a composite measure, as explored by Liu et al.[32] and recommended by others.[33]

In summary, Aboriginal ethnicity is associated with higher rates of all-cause mortality after starting HAART; this seems to be largely explained by a significantly higher rate of death from HIV-related causes among Aboriginals. IDU appears to be the strongest and most significant predictor of higher all-cause mortality rates. Future research should examine reasons for the high mortality rates we observed among Aboriginals from HIV-related causes of death. Specifically, we recommend three areas of research. First, the relationship between Aboriginal ethnicity, IDU, and clinical outcomes of HAART, including virological treatment success and failure, should be examined to determine if the relationship we observed for mortality extends to these clinical outcomes. Second, adherence to HAART should be prospectively measured using sensitive methods to determine if Aboriginal ethnicity is associated with poorer adherence to treatment. Finally, qualitative studies should

explore how Aboriginal HIV patients experience HAART treatment to understand if they encounter challenges that have not yet been well documented.

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RÉSUMÉ

Contexte : Les Autochtones sont surreprésentés dans l'épidémie de VIH qui sévit au Canada, le plus souvent en raison de l'utilisation de drogues par injection (UDI); pourtant, on sait peu de choses sur l'impact de l'ethnicité autochtone sur la mortalité après le début d'une thérapie antirétrovirale hautement active (TAHA). C'est pourquoi nous avons comparé les taux de mortalité de patients autochtones et non autochtones atteints du VIH et ceux d'UDI et de non-UDI atteints du VIH après le début d'une TAHA.

Méthode : Nous avons mené une étude de cohortes rétrospective auprès de patients naïfs de traitement antirétroviral ayant entamé une TAHA entre janvier 1999 et juin 2005 (groupe de référence), que nous avons suivis jusqu'en décembre 2005. Nous avons construit deux modèles de Cox (modèles des risques proportionnels), l'un pour estimer les coefficients de danger (QD) pour toutes les causes de mortalité et l'autre pour la mortalité liée au VIH, en tenant compte des facteurs confusionnels possibles (sexe, âge au départ, numération des lymphocytes CD4, niveaux d'ARN VIH, année civile et régime TAHA).

Résultats : Les 548 patients à l'étude ont été suivis sur 1 889,8 personnes-années; 194 (35 %) étaient Autochtones, et 255 (46 %) étaient des UDI. Nous avons observé 55 décès, dont 47 % liés au VIH. Dans les modèles multivariés, les Autochtones affichaient des taux supérieurs pour la mortalité toutes causes confondues (QD=1,85, IC de 95 %=1,05-3,26, p=0,034) et la mortalité liée au VIH (QD=3,47, IC de 95 %=1,36-8,83, p=0,009) comparativement aux Non-Autochtones. Par rapport aux patients ayant d'autres expositions, les UDI affichaient des taux supérieurs de mortalité toutes causes confondues (QD=2,45, IC de 95 %=1,31-4,57, p=0,005), mais leurs taux de mortalité liée au VIH étaient semblables (p=0,27).

Conclusion : À comparer aux Non-Autochtones, les patients autochtones atteints du VIH ont des taux supérieurs de mortalité toutes causes confondues et de mortalité liée au VIH après le début d'une TAHA. La variable prédictive la plus forte et la plus significative de la mortalité toutes causes confondues était le statut d'UDI. Dans les futurs travaux de recherche, il faudrait se pencher sur les raisons des moins bons taux de survie observés chez les patients autochtones et les UDI atteints du VIH après le début d'une TAHA afin d'élaborer des interventions susceptibles d'améliorer le pronostic de ces populations vulnérables.

Mots clés : thérapie antirétrovirale hautement active; mortalité; population d'origine amérindienne; toxicomanie intraveineuse