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RESEARCH ARTICLE

The Effect of MSM and CD4+ Count on the Development of Cancer AIDS (AIDS-defining Cancer) and Non-cancer AIDS in the HAART Era

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Abstract: ***Background*:** The HIV epidemic is increasing among Men who have Sex with Men (MSM) and the risk for AIDS defining cancer (ADC) is higher among them.

Objective: To examine the effect of MSM and CD4+ count on time to cancer AIDS (ADC) and non-cancer AIDS in competing risks setting in the HAART era.

Method: Using Ontario HIV Treatment Network Cohort Study data, HIV-positive adults diagnosed between January 1997 and October 2012 having baseline CD4+ counts ≤ 500 cells/mm^3 were evaluated. Two survival outcomes, cancer AIDS and non-cancer AIDS, were treated as competing risks. Kaplan-Meier analysis, Cox cause-specific hazards (CSH) model and joint modeling of longitudinal and survival outcomes were used.

Results: Among the 822 participants, 657 (79.9%) were males; 686 (83.5%) received anti-retroviral (ARV) ever. Regarding risk category, the majority (58.5%) were men who have Sex with men (MSM). Mean age was 37.4 years (SD = 10.3). In the multivariate Cox CSH models, MSM were not associated with cancer AIDS but with non-cancer AIDS [HR = 2.92; P = 0.055, HR = 0.54; P = 0.0009, respectively]. However, in joint models of longitudinal and survival outcomes, MSM were associated with cancer AIDS but not with non-cancer AIDS [HR = 3.86; P = 0.013, HR = 0.73; P = 0.10]. CD4+ count, age, ARV ever were associated with both events in the joint models.

Conclusion: This study demonstrates the importance of considering competing risks, and time-dependent biomarker in the survival model. MSM have higher hazard for cancer AIDS. CD4+ count is associated with both survival outcomes.

Keywords: AIDS-defining cancer, MSM, cause-specific hazard, joint model, competing risks, HAART.

1. INTRODUCTION

In the highly active anti-retroviral therapy (HAART) era, the HIV epidemic is expanding among individuals in the HIV risk category men who have sex with men (MSM); this has been recognized in high-income countries, including Australia, France, the United Kingdom, and the United States [1-3]. In Canada, the proportion of HIV cases that are categorized as MSM has decreased over the years but it still represents the largest group of HIV infected adults (≥ 15 years old) [4]. In 2016, 44.1% of adult HIV cases with a known exposure category were MSM [4].

HIV-infected people with weakened immune systems are vulnerable to opportunistic infections (OIs) [5]. More specifically, HIV-infected persons who have CD4+ count less than 500 are at higher risk for OIs [5]. The Centre for Disease Control and Prevention (CDC) developed a list of OIs that are considered as AIDS-defining conditions (ADC) or AIDS-defining illness (ADI) [6]. Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer are ADC based on the list. These ADC are defined as AIDS-defining cancer or cancer-related AIDS [7-9].

The risk of these ADC is higher among HIV-infected individuals [10].

Cancer and HIV have been associated since 1981 when KS was identified for the first time in an immunosuppressed white MSM [11]. HIV-infected people with a weak immune system have also been diagnosed with NHL and invasive cervical cancer [7, 11]. Although the incidence of NHL and KS among HIV-infected individuals have decreased in the HAART era, they remain higher in HIV-infected individuals compared to HIV uninfected people [12, 13]. In a multi-state, population-based study in the USA by Hernández-Ramírez, the incidence rate of cancer-related AIDS was 2.1/1000 person-years over the follow-up period of 1996 to 2012 [14]. Shiels *et al.*, in a sample of American military personnel or their beneficiaries, found that the risk of developing cancer-AIDS and non-cancer AIDS among HIV positive individuals in the HAART era was 2.6/1000 person-

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years and 13.1/1000 person-years respectively [15]. By specific cancer AIDS malignancy type, Alberta HIV patients in the HAART era were found to have 4 cases of KS per 1000 person-years and 2 cases of NHL per 1000 person-years, respectively [16]. Among HIV patients in British Columbia, 123 of 4918 (2.5%) developed cancer AIDS when followed through 1996 to 2008 [17].

In this study, the objective is to examine the effect of covariates on survival outcomes. However, survival outcome can be associated with time-dependent longitudinal measurements/outcome which should be considered when studying the effect of covariates on survival outcomes [18-22]. Joint modeling of longitudinal and survival outcomes considers this association by modeling two outcomes simultaneously and provides more efficient, almost unbiased estimates [20, 23-26]. In joint modeling, two models are joined; a model for longitudinal measurements or outcome and a model for survival outcome. Using this approach, one can study the effect of covariates on the longitudinal outcome, the survival outcome or both. It is also possible to examine the effect of the longitudinal outcome on survival outcome.

There were two survival outcomes in this study: cancer AIDS and, non-cancer AIDS, which are considered as competing risks of each other [15, 27, 28]. Hence, we apply the joint modeling method with competing risks [29-35].

2. METHODS

2.1. Study Population

HAART has been widely available since 1997 [16, 36]. From the Ontario HIV Treatment Network Cohort Study (OCS), individuals whose HIV-positive year was 1997 or later (*i.e.* HAART era) and were a minimum of 15 years of age at diagnosis were considered in this study. OCS is an observational study of HIV-infected people in Ontario, Canada [37, 38].

There were 2345 participants from the HAART era in the OCS. Of them, 1155 individuals had CD4+ counts available at baseline (within 3 months of first HIV+ date). In the current study, ADI was used as the survival endpoint/outcome, which was identified by the occurrence of OIs [6]. OIs are relatively uncommon among people who have CD4+ counts > 500 cells/mm^3 [5]. Hence, to maintain homogeneity among study participants in terms of immunological characteristics, only individuals with baseline CD4+ counts less than or equal to 500 cells/mm^3 were included in the study. At baseline, 825 individuals had CD4+ counts ≤ 500 cells/mm^3. However, three of these participants had both a cancer AIDS and a non-cancer AIDS diagnosis made at the same visit; as survival analysis of completing risks requires time to first outcome, these subjects were excluded. Therefore, the final study population consisted of 822 adult individuals who were diagnosed between January 1997 and October 2012. The maximum and median follow-up times were 16 years and 6.2 years, respectively. A total of 16,593 CD4+ counts measurements were observed, with a median of 18 measurements. The covariate "HIV risk category" was categorized into two major groups: MSM (MSM and MSM-IDU [injection drug users] combined) and others. Participants' demographic and clinical characteristics are presented in Table **1**.

2.2. Survival Endpoints

The AIDS-defining illness either with AIDS-defining cancer (cancer AIDS) or another clinical AIDS-defining event (non-cancer AIDS) was considered as the survival event. As one event can change the likelihood of observing the other event, they were treated as event of interest/competing event in this study [15, 28, 39]. When cancer AIDS was the main event of interest then non-cancer AIDS was considered as a competing risk, and vice versa. There were no patients with cervical cancer in our study data. Hence, the cancer AIDS only included patients with KS or NHL. All other ADI defined by the CDC [6] were considered as non-cancer AIDS. Subsequent ADI diagnoses that arose after the first ADI diagnosis were not considered to be events in this analysis. Therefore, for analysis, a patient could develop either cancer AIDS or non-cancer AIDS (disjoint first event). Time-to-event was calculated from the HIV diagnosis date to the date of first ADI, death, or last visit.

2.3. Statistical Analysis

Mean and median were reported for continuous variables. Number and proportion were reported for categorical variables. We used the t-test or Wilcoxon non-parametric test to compare continuous variables between two groups. Chi-square test was used to compare categorical variables. Cox cause-specific hazard (CSH) and Kaplan-Meier analyses were used to perform survival analysis [40, 41]. Two survival outcomes (cancer AIDS and non-cancer AIDS) were considered as event of interest/competing risk in this study. In competing risks scenarios, the traditional approach to study the effect of a covariate on a particular cause of failure is to model the CSH function, generally using Cox CSH models [27, 42]. We applied joint modeling method to incorporate time-dependent outcome in the Cox CSH regression model.

Two joint models were fitted: (i) with CD4+ counts and cancer AIDS, (ii) with CD4+ counts and non-cancer AIDS. Linear mixed effect (LME) model with random intercept and random slope was used to model longitudinal CD4+ counts [43].

To normalize CD4+ counts, the square root of the CD4+ counts was used. For the i^{th} subject, the following LME model (also regarded as a submodel) was considered for the square root of the j^{th} CD4+ counts measurement:

$$\sqrt{CD4+_{ij}} = \beta_0 + \beta_1 Time_{ij} + \beta_2 MSM_i + \beta_3 Age_i + \beta_4 Arv_i + \beta_5 HepC_i + b_{0i} + b_{1i} Time_{ij} + \varepsilon_{ij}$$

where $\sqrt{CD4+_{ij}}$ indicates the square root of the j^{th} CD4+ counts measurement on the i^{th} individual, $j = 1, 2, \dots, m_i$, $i = 1, 2, \dots, n$ and ε_{ij} is the mutually independent measurement errors. We used the following Cox CSH models (submodels):

For cancer AIDS,

$$h_{i1}(t) = h_{10}(t) exp\{\gamma_{11} MSM_i + \gamma_{12} Age_i + \gamma_{13} Arv_i + \gamma_{14} HepC_i + \alpha(\beta_{10} + \beta_{11} Time_{ij} + \beta_{12} MSM_i + \beta_{13} Age_i + \beta_{14} Arv_i + \beta_{15} HepC_i + b_{10i} + b_{11i} Time_{ij})\},$$

For non-cancer AIDS,

$$h_{i2}(t) = h_{20}(t)exp\{\gamma_{21}MSM_i + \gamma_{22}Age_i + \gamma_{23}Arv_i + \gamma_{24}HepC_i + \alpha(\beta_{20} + \beta_{21}Time_{ij} + \beta_{22}MSM_i + \beta_{23}Age_i + \beta_{24}Arv_i + \beta_{25}HepC_i + b_{20i} + b_{21i}Time_{ij})\},$$

where $h_{10}(t)$ and $h_{20}(t)$ are the unspecified baseline cause-specific hazards for cancer AIDS and non-cancer AIDS, respectively and α is the regression coefficient for the true CD4+ count (also regarded as association parameter between CD4+ counts and survival outcome).

The **JM** package in R was used to fit joint models [44]. Other analyses were done using SAS 9.4 (SAS Institute Inc., Cary, NC, U.S.A.). The level of significance was set at 0.05.

3. RESULTS

3.1. Descriptive Analysis

Of a total of 822 participants, 657 (79.9%) were males, 103 (12.5%) were Hepatitis C virus-infected, and 686 (83.5%) were exposed to anti-retroviral (ARV) medications at some time in their care (Table **1**). The majority of participants were white (55.0%), followed by Black/African (19.2%). In the HIV risk category, the majority were MSM (MSM and MSM-IDU, 58.5%), 17.4% had previously resided in an HIV-endemic area, and 10.3% were heterosexual. Participants' mean age was 37.4 years (SD = 10.3) at the time of HIV diagnosis. At baseline, the mean CD4+ count was 260 cells/mm^3 (SD = 145) and the mean $\log_{10}$ viral load was 4.5 copies/mL (SD = 0.9). The median follow-up time of the study was 6.2 years (interquartile range = 7.2). Among 822 individuals, 22(2.7%) developed cancer-related AIDS and 123 (15.0%) developed non-cancer AIDS. The incidence rate of cancer AIDS was 4.2 per 1,000 person-years [95% Confidence Interval (CI): (2.7, 6.3)] and the incidence rate of non-cancer AIDS was 23.3 per 1,000 person-years [95% CI: (19.5, 27.8)]. These values are similar to the findings of other studies (14-17).

Table 1. Demographics and clinical characteristics of the participants (N=822).

Variable	Number (%)
Male	657 (79.9%)
Age at HIV positive date	
Mean (SD)	37.4 (10.3)
Median (interquartile range)	37.0 (14.0)
Race	
Multiple race	39 (4.7%)
Black/African	158 (19.2%)
South Asian	40 (4.9%)
White	452 (55.0%)
Other	95 (11.5%)
Unknown	38 (4.6%)
HIV risk category	
Men Sex Men (MSM)	442 (53.8%)
MSM-Injection Drug User (IDU)	39 (4.7%)
IDU	61 (7.4%)
Clotting factor	6 (0.7%)
Transfusion	7 (0.9%)
HIV-endemic	143 (17.4%)
Heterosexual transmission	85 (10.3%)
MTC mother to child transmission	1 (0.1%)
Occupational	1 (0.1%)
NIR Non-identified risk	37 (4.5%)
Ever Hepatitis C infection	103 (12.5%)
Ever ARV	686 (83.5%)
CD4+ counts (cells/mm^3) at baseline	
Mean (SD)	260 (145)
Median (interquartile range)	268 (240)
Log_{10} HIV viral load (copies/mL) at baseline	
Mean (SD)	4.5 (0.9)
Median (interquartile range)	4.6 (1.1)
Follow-up time, median (interquartile range)	6.2 (7.2)

3.1.1. Men Who Have Sex With Men (MSM)

Compared with all other ethnicities, white individuals were significantly more likely to be MSM (33.7% *vs.* 70.1%; $P < 0.0001$) (Table **2**). The mean baseline CD4+ count and Log_{10} HIV viral load were significantly higher for MSM compared to all other HIV risk categories (275 cells/mm^3 vs. 240 cells/mm^3; $P = 0.0008$, 4.7 copies/mL vs. 4.3 copies/mL; $P < 0.0001$, respectively). The proportion of ARV exposures ever was not different between the two groups ($P = 0.38$). Nonetheless, the proportion of hepatitis C virus (HCV) infection ever was significantly lower among MSM (6.7% vs. 20.8%; $P < 0.0001$). Median follow-up time for MSM was significantly higher than that of the other group (6.5 vs. 5.8; $P = 0.025$) (Table **2**).

Table 2. Demographic and clinical characteristics associated with MSM.

Covariates	HIV Risk Category (MSM) (N = 481, 58.5%)	HIV Risk Category (Other) (N = 341, 41.5%)	*P* - value
Ethnicity (White)	70.1%	33.7%	< 0.0001[a]
Age in years			
Mean (SD[d])	37.9 (10.3)	36.7 (10.3)	0.12[b]
Median (IQR[e])	37.0 (13.0)	36.0 (14.0)	
Ever Hepatitis C infection	32 (6.7%)	72 (20.8%)	< 0.0001[a]
Ever ARV	406 (84.4%)	280 (82.1%)	0.38[a]
CD4+ count (cells/mm^3) at baseline			
Mean (SD[d])	275 (142)	240 (146)	0.0008[b]
Median (IQR[e])	293 (222)	240 (244)	
Log_{10} HIV viral load (copies/mL) at baseline			
Mean (SD[d])	4.7 (0.9)	4.3 (0.9)	< 0.0001[b]
Median (IQR[e])	4.8 (1.1)	4.4 (1.0)	
Follow-up time, median (IQR)	6.5 (6.1)	5.8 (8.0)	0.025[c]

[a]Chi-square test; [b]T-test; [c]Wilcoxon test; [d]Standard deviation; [e]Interquartile range

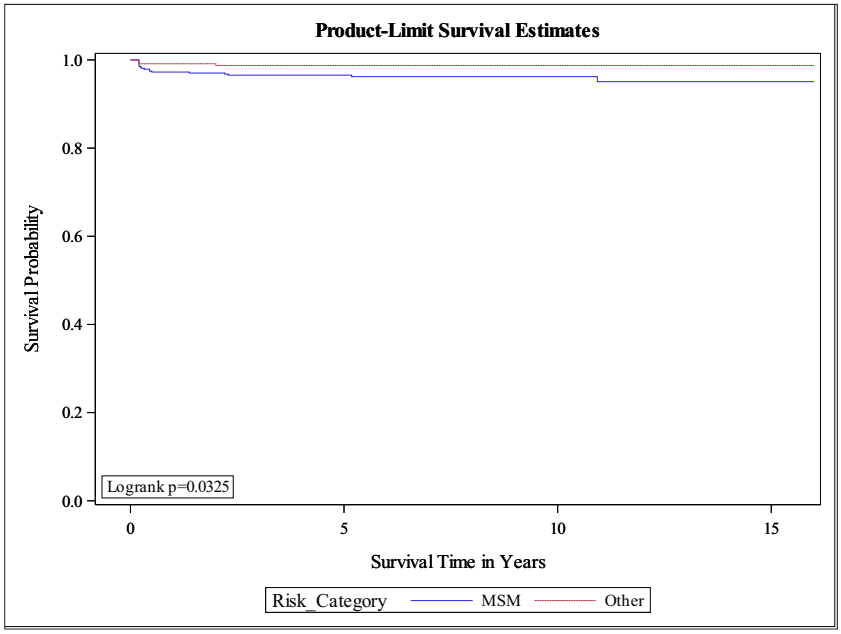

Fig. (1). Kaplan-Meier survival plot to compare time to cancer AIDS between MSM and Other.

3.2. Kaplan-Meier Analysis

In the Kaplan-Meier analysis for the event of cancer AIDS, the time to cancer AIDS was significantly different between the two HIV risk categories (MSM and other) (Fig. **1**). *P*s for Log-Rank and Wilcoxon tests were 0.032 and 0.047, respectively. Compared to MSM, the other risk group had better survival for cancer AIDS.

The Kaplan-Meier survival curves for the length of time after HIV infection until the occurrence of non-cancer AIDS are presented in Fig. (**2**). There was a significant difference in survival times between MSM and other risk groups. *P*s for Log-Rank and Wilcoxon tests were 0.0004 and 0.0007, respectively. For non-cancer AIDS, MSM had better survival compared to the other risk group.

3.3. Cox Cause-Specific Hazards (CSH) Model

In the univariable cause-specific hazards analysis, MSM had significantly higher hazards for cancer AIDS but signifi-

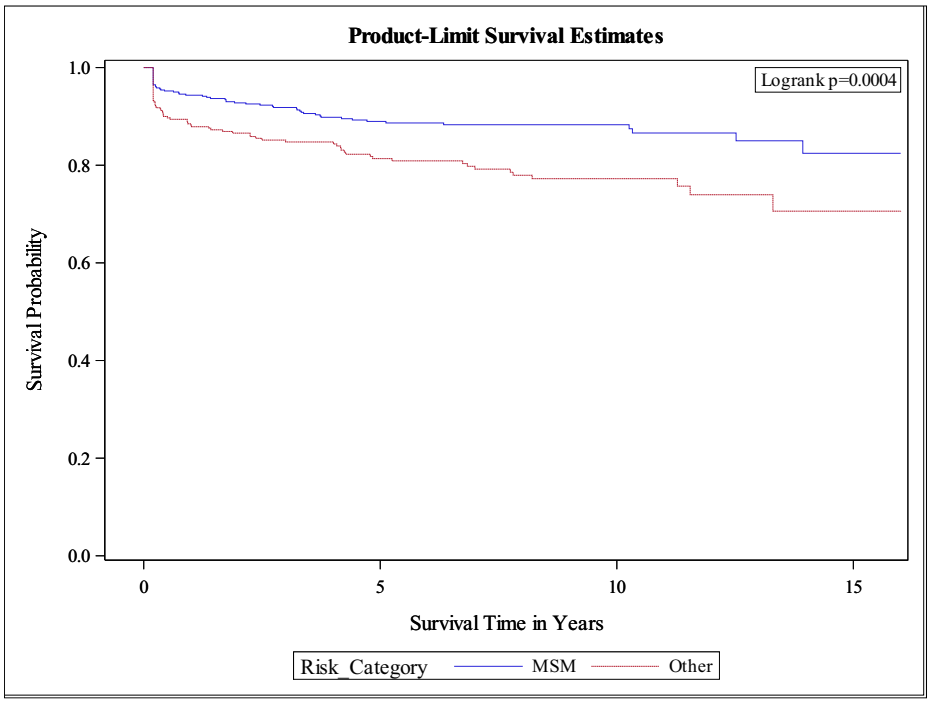

Fig. (2). Kaplan-Meier survival plot to compare time to non-cancer AIDS between MSM and Other.

Table 3. Univariable Cox cause-specific hazards model.

	Event = Cancer AIDS			Event = Non-cancer AIDS		
Covariates	**Estimate (SE[a])**	**HR[b] (95% CI[c])**	**P-value**	**Estimate (SE[a])**	**HR[b] (95% CI[c])**	**P-value**
MSM	1.12 (0.55)	3.07 (1.04, 9.06)	0.042	-0.63 (0.18)	0.53 (0.37, 0.76)	0.0005
Age at diagnosis	0.05 (0.02)	1.05 (1.02, 1.09)	0.005	0.01 (0.01)	1.01 (1.00, 1.03)	0.15
Gender (Male)[d]				-0.62 (0.20)	0.54 (0.37, 0.79)	0.001
White ethnicity	0.53 (0.46)	1.70 (0.69, 4.16)	0.24	-0.29 (0.18)	0.75 (0.53, 1.07)	0.11
Ever ARV	-1.92 (0.43)	0.15 (0.06, 0.34)	<0.0001	-1.98 (0.18)	0.14 (0.10, 0.20)	<0.0001
Ever Hepatitis C infection	-1.12 (1.02)	0.33 (0.04, 2.42)	0.27	0.09 (0.26)	1.09 (0.66, 1.83)	0.73

[a]Standard error; [b]Hazards ratio; [c]Confidence interval; [d]Unable to estimate HR for cancer AIDS as no female participants had cancer AIDS

cantly lower hazards for non-cancer AIDS compared to other HIV risk group [HR = 3.07; P = 0.042, HR = 0.53; P = 0.0005] (Table **3**). Older people had higher hazards for cancer AIDS. Age was not associated with noncancer AIDS. We were not able to estimate the effect of sex for cancer AIDS as no female participants had this outcome. Males had lower hazards for non-cancer AIDS. Individuals with ever use of ARV had significantly lower risk for both events. Ethnicity and hepatitis C infection were not associated with either of the events (Table **3**).

Covariates MSM, age, ever ARV, and ever Hep C infection were included in the multivariate Cox CSH models. Ethnicity was not included as it was highly correlated with MSM. In the multivariate CSH model for cancer AIDS, age, ever ARV were significant, but MSM was not (Table **4**). MSM was still significant in the multivariate model for non-cancer AIDS [HR = 0.54; P = 0.0009] (Table **4**).

3.4. Joint Model

MSM, age, and ever ARV were significant in the survival submodel for cancer AIDS (Table **5**). MSM and older participants had higher hazards of cancer AIDS. Participants with ever use of ARV had lower hazards of cancer AIDS. The association parameter was significantly different from zero, indicating a strong association between the square root of CD4+ counts and the risk for cancer. The negative value of the association parameter (0.17) indicated that the slope of CD4+ counts was negatively associated with the hazard for cancer AIDS, with a unit increase in this marker corresponded to a 16% decrease in the risk for cancer AIDS (HR = 0.84; P <0.0001). MSM was not significant in the survival submodel for non-cancer AIDS (Table **5**). Age and ever ARV were significant. Older participants had higher hazards, while participants with ever use of ARV had lower hazards of non-cancer AIDS. The association parameter was significant; a unit

Table 4. Multivariate Cox cause-specific hazards model.

	Event = Cancer AIDS			Event = Non-cancer AIDS		
Covariates	**Estimate (SE[a])**	**HR[b] (95% CI[c])**	**P-value**	**Estimate (SE[a])**	**HR[b] (95% CI[c])**	**P-value**
MSM	1.07 (0.56)	2.92 (0.97, 8.76)	0.055	-0.62 (0.19)	0.54 (0.37, 0.78)	0.0009
Age at diagnosis	0.06 (0.02)	1.06 (1.02, 1.10)	0.002	0.01 (0.01)	1.01 (1.00, 1.03)	0.12
Ever ARV	-2.06 (0.44)	0.13 (0.05, 0.30)	<0.0001	-1.96 (0.18)	0.14 (0.10, 0.20)	<0.0001
Ever Hepatitis C infection	-0.94 (1.04)	0.39 (0.05, 2.98)	0.36	-0.14 (0.27)	0.87 (0.51, 1.47)	0.60

[a]Standard error; [b]Hazards ratio; [c]Confidence interval;

Table 5. Joint modeling of longitudinal and survival outcomes.

	Event = Cancer AIDS			Event = Non-cancer AIDS		
Longitudinal submodel	**Estimate (SE[a])**	**P-value**		**Estimate (SE[a])**	**P-value**	
Intercept	17.36 (0.21)	<0.0001		17.35 (0.20)	<0.0001	
Time	0.95 (0.01)	<0.0001		0.95 (0.01)	<0.0001	
MSM	1.64 (0.10)	<0.0001		1.63 (0.09)	<0.0001	
Age at diagnosis	-0.06 (0.001)	<0.0001		-0.05 (0.004)	<0.0001	
Ever ARV	0.33 (0.13)	0.01		0.32 (0.12)	0.01	
Ever Hepatitis C infection	0.38 (0.13)	0.004		0.37 (0.13)	0.004	
Survival submodel	**Estimate (SE[a])**	**HR[b] (95% CI[c])**	**P-value**	**Estimate (SE[a])**	**HR[b] (95% CI[c])**	**P-value**
MSM	1.35 (0.55)	3.86 (1.32, 11.29)	0.013	-0.31 (0.19)	0.73 (0.50, 1.07)	0.104
Age at diagnosis	0.06 (0.01)	1.06 (1.03, 1.09)	<0.0001	0.02 (0.01)	1.02 (1.01, 1.03)	0.004
Ever ARV	-1.96 (0.45)	0.14 (0.06, 0.34)	<0.0001	-1.85 (0.19)	0.16 (0.11, 0.23)	<0.0001
Ever Hepatitis C infection	-1.06 (1.03)	0.35 (0.05, 2.63)	0.36	-0.44 (0.27)	0.65 (0.38, 1.11)	0.11
CD4+ count	-0.17 (0.04)	0.84 (0.77, 0.91)	<0.0001	-0.20 (0.02)	0.82 (0.80, 0.85)	<0.0001

[a]Standard error; [b]Hazards ratio; [c]Confidence interval;

increase in CD4+ counts corresponded to a 18% decrease in the risk for non-cancer AIDS (HR = 0.82; P <0.0001).

Covariates MSM, time, age at diagnosis, ever ARV, and Hep C infection were significant in the longitudinal submodels for both cancer AIDS and non-cancer AIDS (Table **5**). The mean CD4+ count was significantly higher for MSM, participants with ever use of ARV, and Hep C infection. CD4+ counts decreased with the increment of age at diagnosis.

Since the association parameter was highly significant in the joint models for cancer AIDS, and non-cancer AIDS, this provided strong evidence that both survival outcomes were associated with the longitudinal trajectory of CD4+ counts. In the multivariate Cox CSH model for cancer AIDS (Table **4**), MSM had a higher hazard of cancer AIDS but not significantly higher (HR = 2.92; P = 0.055). However, in joint analysis (Table **5**), MSM had significantly higher hazard of cancer AIDS (HR = 3.86; P = 0.013). In the multivariate Cox CSH model for noncancer AIDS (Table **4**), MSM had significantly lower hazard of non-cancer AIDS (HR = 0.54; P = 0.0009). Nevertheless, in joint analyses (Table **5**), MSM did not have significantly lower hazard of non-cancer AIDS (HR = 0.73; P = 0.10). Thus, the joint models, which incorporated the effect of time-varying biomarker, provided different results from the separate multivariate Cox CSH models.

4. DISCUSSION

In our study of participants with lower CD4+ counts (≤ 500 cells/mm^3) at baseline, MSM had significantly higher hazards for cancer-related AIDS. CD4+ count was associated with both cancer AIDS and non-cancer AIDS. Several studies reported that the incidence of KS and NHL has significantly decreased and that survival time from these cancers has been improved for most patients with the initiation of HAART [16, 45]. However, KS was frequently identified in MSM in a study by Gingues and Gill [16]. Suárez-García *et al.* [46] also observed higher risk of KS among MSM in their study. MSM also had higher hazards of NHL in work by

Bohlius *et al.* [47]. Biggar *et al.* [48] found NHL and KS to be associated with severe depletion of CD4+ count. Thus the results of our study are consistent with other study findings.

According to Gingues and Gill [16] patients who do not present for HIV care after diagnosis and patients who do not receive antiretroviral therapy at the time of diagnosis are more likely to be diagnosed with AIDS-defining cancers. Clifford *et al.* [49] observed that the use of HAART might lower the risk of KS and NHL. Bonnet *et al.* [50] reported that patients with elevated HIV RNA levels for long periods may have a higher risk of NHL. In our study, the median $\log_{10}$ HIV RNA level at baseline was significantly higher among MSM compared to the other group (4.8 copies/mL vs. 4.4 copies/mL, respectively). Thus, higher HIV RNA levels could possibly make these individuals more vulnerable to cancer-related AIDS. Since ARV treatment can suppress the viral load to a low level, our results emphasize the significance of earlier ARV initiation for the MSM risk group.

Our study data is from a large cohort which includes three-quarters of all HIV-infected people in Ontario [38]. Given the size, this cohort is expected to be a representative sample of the HIV-infected population receiving HIV treatment in Ontario. MSM represent the largest proportion of all the HIV-infected people in Canada [4]; similarly, in our study, 481 (58.5%) participants were MSM. We recognize that participants voluntarily participated in this study and thus may be different from the rest of HIV-infected people in Ontario. Hence the study may have recruitment bias [38]. Another concern regarding our data is the lack of information regarding comorbidity. As such, were not able to adjust the effects of those covariates in the model.

We applied joint modeling with competing risks in this study. If we would consider simply one event (AIDS) instead of two competing events (cancer AIDS, non-cancer AIDS), we would not be able to study the fact that MSM has opposite effects on these two events. In addition, we incorporated time-varying biomarker CD4+counts into the CSH models using joint modeling. CD4+counts were highly associated with both events. If time-varying biomarkers and survival outcomes are associated, we should consider this association to estimate parameters correctly as well as to draw proper statistical inference about the covariates. After incorporating CD4+counts in the CSH models using joint modeling, statistical inferences for MSM were changed for both cancer AIDS and non-cancer AIDS. The extended/time-dependent Cox model is also used to include the effect of time-varying biomarker in the survival model [51]. However, this model has some limitations. The time-dependent Cox model assumes that time-dependent covariates can be predicted and they do not have any measurement error [24]. This model also assumes that the covariates change value at follow-up visits and are unchanged in between the visits [24]. For these reasons, we preferred to use joint modeling in this study rather than the time-dependent Cox model.

CONCLUSION

In this study, based on joint modeling, it appeared that MSM had higher risk for cancer AIDS (KS or NHL) than the other risk group. However, for non-cancer AIDS, risks were not significantly different between MSM and the other risk group in the joint model. Higher viral load could possibly make MSM vulnerable to cancer AIDS. Thus, our findings suggest earlier ARV initiation and regular monitoring of HIV viral load and CD4+ count should be high priority for the MSM HIV risk group. Regular screening for cancer is also important in individuals with lower CD4+ counts ($\leq$ 500 cells/mm^3) in the MSM group. Routine HIV testing in individuals within this HIV risk group is also vital, as untreated HIV infection represents a significant risk for cancer AIDS.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by University of Saskatchewan, Bio #14-314.

HUMAN AND ANIMAL RIGHTS

No animals were used in the study. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10 ethics/10helsinki/).

CONSENT FOR PUBLICATION

Written informed consent was obtained from all study participants.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Beyrer C, Baral SD, Griensven Fv, *et al.* Global epidemiology of HIV infection in men who have sex with men. Lancet 2012; 380(9839), 367-77.

[2] CDC. Prevalence and awareness of HIV infection among men who have sex with men—21 cities, United States, 2008. MMWR Morb Mortal Wkly Rep 2010; 59: 1201-7.

[3] Sullivan P, Hamouda O, Delpech V, *et al.* Reemergence of the HIV epidemic among men who have sex with men in North America, western Europe, and Australia, 1996–2005. Ann Epidemiol 2009; 19: 423-31.

[4] Bourgeois AC, Edmunds M, Awan A**,** Jonah L, Varsaneux O, Siu W**.** HIV in Canada - Surveillance report, 2016. Can Commun Dis Rep 2017; 43(12): 248-55.

[5] Opportunistic Infections. What Are Opportunistic Infections? May 15, 2017. Available at https: //www.hiv.gov/hiv-basics/staying-in-hiv-care/other-related-health-issues/opportunistic-infections. Accessed April 08, 2018.

[6] Appendix A. AIDS-Defining Conditions. December 05, 2008. Available at http: //www.cdc.gov/mmwr/preview/ mmwrhtml/ rr5710a2.htm. Accessed on April 08, 2018.

[7] Ancelle-Park R, Klein JP, Stroobant A, *et al.* Expanded European AIDS case definition. Lancet 1993; 341(8842): 441

[8] Castro KG, Ward JW, Slutsker L, *et al.* 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. CID 1993; 17.

[9] Ebrahim SH, Abdullah AS, McKenna M, Hamers FF. AIDS defining cancers in Western Europe, 1994–2001. AIDS Patient Care STDS 2004; 18(9): 501-8.

[10] Shiels MS, Pfeiffer RM, Gail MH, *et al.* Cancer burden in the hiv-infected population in the United States. J Natl Cancer Inst 2011; 103: 753-62

[11] Spano J-P, Costagliola D, Katlama C, Mounier N, Oksenhendler E, Khayat D. AIDS-related malignancies: State of the art and therapeutic challenges. J Clin Oncol 2008; 26(29): 4834-42.

[12] Silverberg MJ, Lau B, Achenbach CJ, *et al.* Cumulative incidence of cancer among hiv-infected individuals in north america. Ann Intern Med 2015; 163(7): 507-18.

[13] Simard EP, Pfeiffer RM, Engels EA. Cumulative incidence of cancer among people with AIDS in the United States. Cancer 2011; 117(5): 1089-96.

[14] Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. Lancet HIV 2017 Nov; 4(11): e495-e504.

[15] Shiels MS, Cole SR, Wegner S, *et al.* Effect of HAART on incident cancer and noncancer AIDS events among male HIV seroconverters. J Acquir Immune Defic Syndr 2008; 48(4): 485-90.

[16] Gingues S, Gill MJ. The impact of highly active antiretroviral therapy on the incidence and outcomes of AIDS-defining cancers in Southern Alberta. HIV Medicine 2006; 7(6): 369-77.

[17] Chiu CG, Smith D, Salters KA, *et al*. Overview of cancer incidence and mortality among people living with HIV/AIDS in British Columbia, Canada: Implications for HAART use and NADM development. BMC Cancer 2017; 17(1): 270.

[18] Guo X, Carlin BP. Separate and joint modeling of longitudinal and event time data using standard computer packages. Am Stat 2004; 58(1): 16-24.

[19] Henderson R, Diggle P, Dobson A. Joint modeling of longitudinal measurements and event time data. Biostatistics 2000; 1(4): 465-480.

[20] Ibrahim JG, Chu H, Chen LM. Basic concepts and methods for joint models of longitudinal and survival data. J Clin Oncol 2010; 28(26): 2796-2801.

[21] Lim HJ, Mondal P, Skinner S. Joint modeling of longitudinal and event time data: application to HIV study. Int J Med Inform 2013; 1: 1.

[22] Wu L, Liu W, Yi GY, Huang Y. Analysis of longitudinal and survival data: Joint modeling, inference methods, and issues. Journal of Probability and Statistics. 2012; doi: http://dx.doi.org/10.1155/2012/640153.

[23] Gould AL, Boye ME, Crowther MJ, *et al.* Joint modeling of survival and longitudinal non-survival data: current methods and issues. Report of the DIA Bayesian joint modeling working group. Stat. Med 2015; 34(14): 2181-2195.

[24] Rizopoulos D. *Joint Models for Longitudinal and Time-to-Event Data With Applications in R.* FL: Chapman & Hall/CRC Biostatistics Series; 2012.

[25] Wang P, Shen W, Boye ME. Joint modeling of longitudinal outcomes and survival using latent growth modeling approach in a mesothelioma trial. Health Serv Outcomes Res Methodol 2012; 12(2-3): 182-199. http: //doi.org/10.1007/s10742-012-0092-z

[26] Wulfsohn MS, Tsiatis AA. A joint model for survival and longitudinal data measured with error. Biometrics 1997; 53(91): 330-339.

[27] Prentice RL, Kalbfleisch JD, Peterson AV, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. Biometrics 1978; 34(4): 541-554.

[28] Shiels MS, Cole SR, Chmiel JS, *et al.* A comparison of *ad hoc* methods to account for non-cancer AIDS and deaths as competing risks when estimating the effect of HAART on incident cancer AIDS among HIV-infected men. J Clin Epidemiol 2010; 63(4): 459-467.

[29] Deslandes E, Chevret S. Joint modeling of multivariate longitudinal data and the dropout process in a competing risk setting: application to ICU data. BMC Med Res Methodol 2010; 10: 69.

[30] Elashoff RM, Li G, Li N. An approach to joint analysis of longitudinal measurements and competing risks failure time data. Stat Med 2007; 26(14): 2813-2835.

[31] Elashoff RM, Li G, Li N. A joint model for longitudinal measurements and survival data in the presence of multiple failure types. Biometrics 2008; 64(3): 762-771.

[32] Hu WH, Li G, Li N. A Bayesian approach to joint analysis of longitudinal measurements and competing risks failure time data. Stat Med 2009; 28(11): 1601-19.

[33] Li N, Elashoff RM, Li G. Robust joint modeling of longitudinal measurements and competing risks failure type data. Biometrical Journal. 2009; 51(1): 19-30.

[34] Li N, Elashoff RM, Li G, Tseng CH. Joint analysis of bivariate longitudinal ordinal outcomes and competing risks survival times with nonparametric distributions for random effects. Stat Med 2012; 31(16): 1707-21.

[35] Williamson PR, Kolamunnage-Dona R, Philipson P, Marson AG. Joint modeling of longitudinal and competing risks data. Stat Med 2008; 27(30): 6426-6438.

[36] Touloumi G, Pantazis N, Babiker AG, *et al.* Differences in HIV RNA levels before the initiation of antiretroviral therapy among 1864 individuals with known HIV-1 seroconversion dates. AIDS 2004; 18(12): 1697705.

[37] McMurchy D, Challacombe L, Edmiston M, *et al.* Gaining trust, ensuring security: the evolution of an Ontario HIV cohort study. In: Flood CM (ed.), Data Data Everywhere: Access and Accountability? Montreal and Kingston: Queen's Policy Studies Series, McGill-Queen's University Press, 2010, pp. 1-28.

[38] Rourke SB, Gardner S, Burchell AN, *et al.* Cohort profile: the ontario hiv treatment network cohort study (OCS). Int J Epidemiol 2013; 42(2): 402-411.

[39] Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999; 18(6): 695-706.

[40] Cox DR. Regression models and life-tables (with discussion). J Royal Stat Soc 1972; 34(2): 187-220.

[41] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53(282): 457-481.

[42] Latouche A, Boisson V, Chevret S, Porcher R. Misspecified regression model for the subdistribution hazard of a competing risk. Statist Med 2007; 26: 965-974.

[43] Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982; 38(4): 963-974.

[44] Rizopoulos D. JM: an R package for the joint modelling of longitudinal and time-to-event data. J Stat Softw 2010; 35(9): 1-33.

[45] Orem J, Otieno MW, Remick SC. AIDS-associated cancer in developing nations. Curr Opin Oncol 2004; 16(5): 468-476.

[46] Suárez-García I, Jarrín I, Iribarren JA, *et al.* Incidence and risk factors of AIDS-defining cancers in a cohort of HIV-positive adults: Importance of the definition of incident cases. Enferm Infecc Microbiol Clin 2013; 31(5): 304-312.

[47] Bohlius J, Schmidlin K, Costagliola D, *et al.* Incidence and risk factors of HIV-related non-Hodgkin's lymphoma in the era of combination antiretroviral therapy: a European multicohort study. Antivir Ther 2009; 14(8): 1065-1074.

[48] Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS**.** J Natl Cancer Inst 2007; 99(12): 962-72.

[49] Clifford GM, Polesel J, Rickenbach M, *et al.* Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst 2005; 97(6): 425-32.

[50] Bonnet F, Balestre E, Thiébaut R, *et al.* Factors associated with the occurrence of aids related non-hodgkin lymphoma in the era of highly active antiretroviral therapy: aquitaine cohort, France. Clin Infect Dis 2006; 42: 411-7.

[51] Andersen PK, Gill RD. Cox's regression model for counting processes: A large sample study. Ann Stat 1982; 10(4): 1100-1120.