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Associations of CD4+ T-cell count, HIV-1 RNA viral load, and antiretroviral therapy with Kaposi sarcoma risk among HIV-infected persons in the United States and Canada

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Supplemental Digital Content .pdf

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Abstract

Background—Kaposi sarcoma (KS) remains common among HIV-infected persons. To better understand KS etiology and to help target prevention efforts, we comprehensively examined a variety of CD4+ T-cell count and HIV-1 RNA viral load (VL) measures, as well as antiretroviral therapy (ART) use, to determine independent predictors of KS risk.

Setting—North American AIDS Cohort Collaboration on Research and Design.

Methods—We followed HIV-infected persons during 1996-2009 from 18 cohorts. We used time-updated Cox regression to model relationships between KS risk and recent, lagged, trajectory, and cumulative CD4 count or VL measures, as well as ART use. We used Akaike's information criterion and global p-values to derive a final model.

Results—In separate models, the relationship between each measure and KS risk was highly significant ($p<0.0001$). Our final mutually-adjusted model included recent CD4 count (hazard ratio [HR] for <50 vs. ≥500 cells/μL = 12.4; 95% confidence interval [CI]: 6.5-23.8), recent VL (HR for ≥100,000 vs. ≤500 copies/mL = 3.8; 95% CI: 2.0-7.3), and cumulative (time-weighted mean) VL (HR for ≥100,000 vs. ≤500 copies/mL = 2.5; 95% CI: 1.0-5.9). Each p-trend was <0.0001. After adjusting for these measures, we did not detect an independent association between ART use and KS risk.

Conclusions—Our results suggested a multifactorial etiology for KS, with early and late phases of development. The cumulative VL effect suggested that controlling HIV replication promptly after HIV diagnosis is important for KS prevention. We observed no evidence for direct anti-KS activity of ART, independent of CD4 count and VL.

Keywords

Kaposi sarcoma; HIV infection; Acquired Immunodeficiency syndrome; CD4+ T-cell count; HIV-1 RNA viral load; antiretroviral therapy

Introduction

After the introduction of combination antiretroviral therapy (ART) in 1996, Kaposi sarcoma (KS) incidence among HIV-infected persons sharply declined,[1] with a continuing, slower decline since 2000.[2-4] Nevertheless, KS accounted for 12% of cancer diagnoses among HIV-infected persons in the U.S. in 2010,[5] with the cumulative incidence by age 75 years in the U.S. and Canada during 2005-2009 estimated to be 4%.[6]

KS-associated herpesvirus (KSHV) infection is a necessary but not solely sufficient cause of KS.[7,8] Among HIV-infected persons, a strong inverse association between CD4+ T-cell count (CD4) and KS risk is well established.[9] Nevertheless, KS occurrence is not uncommon among HIV-infected persons with relatively high CD4 and/or sustained suppression of HIV replication by ART,[10-18] indicating that KS etiology among HIV-infected persons is more complex than a simple interplay between KSHV infection and low CD4 and that KS can occur without severe immunosuppression, as observed in classical[19,20] and African endemic KS.[21]

Although many studies have examined relationships between KS risk and CD4, HIV-1 RNA viral load (VL), and ART use, several questions remain unanswered. First, over the course of HIV infection, when is CD4 most predictive of KS risk? KS risk has been observed to be inversely associated with baseline,[22-24] recent/current,[11,25-30] and nadir[31] CD4, and positively associated with time duration with CD4<200 cells/μL,[32] with inconclusive evidence that recent/current CD4 is the best predictor.[11,26]

Second, is VL associated with KS risk independent of CD4, and if so, which VL measure is the best predictor? A direct independent association between recent/current VL and KS risk has been observed in some studies,[11,26,29] but not all.[25,27] Few studies have examined cumulative VL in relation to KS risk.[26,32]

Third, is the protective effect of ART on KS risk entirely mediated by its effects on CD4 and VL? KS risk is clearly lower in ART users versus non-users[1,24,26,30,31] and is inversely associated with time since ART initiation.[27,28,33,34] However, the literature is inconsistent about ART effects, such as direct anti-cancer activity,[35,36] independent of CD4 and VL.[11,25-27,30,31]

Few studies have comprehensively examined CD4 and VL measures, as well as ART use, to determine independent predictors of KS risk.[26] In this investigation, we used data from a large, North American HIV cohort consortium, which provided the sample size and requisite data necessary to perform this analysis, with the goals of elucidating potential contributors to KS development and helping to target KS prevention.

Methods

Study Sample

The study sample included adults (≥18 years) followed during 1996-2009 from 18 U.S. and Canadian cohorts participating in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD; see Table S1, Supplemental Digital Content).[37]

Cohorts submitted demographic and clinical data using standardized collection methods. Cancer diagnoses, including KS, were collected by manual review of medical records and pathology reports or by cancer registry linkage.[6] Institutional Review Board approval was obtained for each participating cohort.

For our analytic dataset, we defined entry date (i.e., baseline) for each person as the latest of the following dates: January 1, 1996, cohort-specific start for reporting cancer diagnoses, 18th birthday, or 360 days before the later of the first CD4 or VL laboratory measurement. We defined exit date as the earliest of: cohort-specific end for reporting cancer diagnoses, death, KS diagnosis, or the earlier of the last CD4 or VL laboratory measurement plus 540 days. We then excluded persons with <2 CD4 or <2 VL measurements or with <180 days of follow-up.

Estimation of time-updated CD4 and VL values

The timing and frequency of observed CD4 and VL laboratory measurements varied by person. To standardize, for each person we estimated time-updated CD4 or $\log_{10}$(VL) values at 30-day intervals using linear interpolation between consecutive pairs of CD4 or VL laboratory measurements, respectively. Moreover, we carried the first CD4 or VL laboratory measurement backward 360 days or to the entry date, whichever was reached first. Similarly, we carried the last laboratory measurement forward 360 days or to the exit date (see Figure S1, Supplemental Digital Content).

Statistical Methods

We sought to systematically evaluate a variety of CD4 and VL measures (i.e., recent, lagged, trajectory, and cumulative) to develop a final model that included the most robust CD4 and/or VL predictors of KS risk. We modeled relationships between KS risk and CD4 or VL measures using proportional hazards regression. Our time metric was months (30 days) from baseline; thus, all time metrics were 30-day multiples.

CD4 and VL measures were updated at the beginning of each 30-day interval from baseline, but were lagged by 180 days (defined as “recent”) to reduce the possibility that the presence of KS influenced CD4 or VL (i.e., reverse causality). We also considered lag intervals of 540, 900, or 1,260 days. These analyses were, by necessity, restricted to persons with at least the amount of follow-up corresponding with the lag. For example, it is impossible to assess VL lagged by 900 days among persons with <900 days of follow-up.

Among persons with at least 1,260 days of follow-up, we then examined the following time-updated measures during a 1,080 day time window (about three years) lagged by 180 days: CD4 or $\log_{10}$(VL) trajectory (i.e., linear regression slope); proportion of time CD4<200 cells/μL or VL>500 copies/mL; and CD4 or VL time-weighted mean (see Figure S2, Supplemental Digital Content). The latter two measures represented different measures of cumulative exposure (time-weighted mean is a cumulative measure normalized according to time).

We modeled measures as categorical variables to allow for the possibility of nonlinear relationships with KS risk. We also modeled measures as continuous variables, calculating

p-values for trend. We adjusted all models for sex, race/ethnicity, cohort, and baseline age and calendar period.

Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Model Selection to Develop Final Model

For model selection, we used Akaike's information criterion (AIC), a quantity commonly used to compare models. AIC takes into account both goodness of fit (i.e., discrepancy between observed values and modeled values) and model parsimony. A lower AIC indicates the preferred model, with an AIC decrease of >10 between two models considered meaningful.[38] Global p-values for categorical variables were also taken into account for model selection.

To develop our final model, we first fit a separate Cox model for each CD4 and VL measure (one measure per model). Second, we selected the best CD4 measures by comparing models that included two or more CD4 measures in the same model. Third, we selected the best VL measures in the same manner. Finally, we chose our final model by comparing models that included two or more of the best CD4 and VL measures together in the same model.

In the final model, we estimated the percent of the association between cumulative (time-weighted mean) VL and KS risk mediated by recent CD4 by calculating the quantity $(\beta_{unadj} - \beta_{adj})/\beta_{unadj}$, where β_{unadj} is the coefficient for cumulative VL unadjusted for recent CD4 and β_{adj} is the coefficient adjusted for recent CD4.[39]

ART Models

Among persons ART-naïve at baseline, we examined the relationship between KS risk and time-updated proportion of time on ART during the 1,080 day time window lagged by 180 days. We expected to observe confounding by indication because it was standard clinical practice during the study period to base ART initiation on CD4.[40] Furthermore, CD4 likely would be a mediator of any ART effect on KS risk. To adjust for confounding by indication by CD4 without removing its mediation effect, we included the following time-updated variable in the ART models: CD4 at the start of the time window if the person was ART-naïve at the start of the time window or CD4 at ART initiation if the person initiated ART before the start of the time window. Thus, at any given time point we adjusted for the CD4 value that the decision to initiate ART *would be* based on (if the person was ART-naïve at the start of the time window) or *was* based on (if the person had initiated ART before the start of the time window). In either case, this CD4 variable could not be a mediator because it was measured before or at the start of the time window of the ART measure. To determine whether the ART effect was mediated by the CD4 and VL measures in our final model, we added these measures to the ART model, still adjusting for confounding by CD4.

Sensitivity Analyses

For the primary analyses, we imputed race/ethnicity for the 5.5% of persons with unknown values using cohort-specific probability weights according to sex and baseline age and calendar year. We did not adjust for HIV risk group or smoking due to large numbers of

unknowns. However, for sensitivity analyses, we examined the effect of including each of these variables as a covariate either using multiple imputation or by including unknowns as a category.

Results

The 18 NA-ACCORD cohorts included 97,323 persons. We then excluded persons with no follow-up time according to our entry/exit date criteria (N=6,061), with <2 CD4 or <VL laboratory measurements (N=10,678), or with <180 days of follow-up (N=2,888). The remaining 77,696 persons were 85% male, 44% white, and 41% black (Table 1). At baseline, most persons were aged 30-49 years (69%) and ART naïve (72%), with CD4≥200 cells/μL (67%) and VL>500 copies/mL (73%). Persons who eventually developed KS (N=396) were more likely to be male, white, aged 30-39 years, have baseline calendar period 1996-1998, have lower CD4 and higher VL, and to be a man who has sex with men (Table 1). Median follow-up was 5.0 years (interquartile range: 2.6–8.8 years). Median number of observed CD4 and VL laboratory measurements per person was the same: 14 (interquartile range: 6–26).

Recent and Lagged Measures

We examined the relationship between CD4 or VL, respectively, and KS risk according to number of days lagged (Table 2). The strength of the association between CD4 and KS risk declined progressively with increasing lag, with a hazard ratio (HR) for the 180-day lag of 33.1 (95% confidence interval [CI]: 22.9-47.8) for CD4 <50 versus ≥500 cells/μL. The AIC comparison among lags confirmed that the model with the 180-day lag was the preferred model.

The strength of the association between VL and KS risk was similar for the 180-day and 540-day lags and then declined with increasing lag, with a HR for the 180-day lag of 16.1 (95% CI: 12.0-21.5) for VL ≥100,000 versus ≤500 copies/mL (Table 2). The AIC for the 180-day and 540-day lags did not appreciably differ.

However, valid comparison of AICs across the four lags required that each AIC be calculated from a model using the same dataset (i.e., persons with at least 1,260 days of follow-up; Table 2). Consequently, to further adjudicate the AIC comparison between the 180-day and 540-day lags, we derived AICs for these two models among persons with at least 540 days of follow-up (which provided a larger N and more KS cases) and found 180 days to be the optimal VL lag (AIC of 6,180 for the 180-day lag versus 6,240 for the 540-day lag).

Trajectory and Cumulative Measures

Then we examined the relationship between KS risk and CD4 or VL measures (i.e., slope, proportion of time below/above a threshold, or time-weighted mean), respectively, during the 1,080 day time window lagged by 180 days and found the relationship to be highly significant ($p<0.0001$) for each measure (Table 3). The 26,476 persons excluded from these analyses (those with <1,260 days of follow-up) had a later baseline calendar period and a higher proportion with unknown smoking status compared with included persons, but other

baseline characteristics did not meaningfully differ (see Table S2, Supplemental Digital Content).

Selection of Best CD4 Predictors

Next, we examined models that included two or more CD4 measures (Table 4). The best CD4 model according to the AIC included CD4 lagged by 180 days and CD4 slope. Furthermore, in models including these measures and proportion of time CD4<200 cells/μL or CD4 time-weighted mean, the global p-values for the latter measures were no longer significant.

Selection of Best VL Predictors

We also examined models that included two or more VL measures (Table 4). The two best VL models according to the AIC included VL lagged by 180 days and VL time-weighted mean or these measures plus proportion of time VL>500 copies/mL. Because the global p-value for the latter measure was not significant (p=0.11) in the latter model, we chose the more parsimonious model as the best VL model.

Selection of Final Model

To derive a final model, we examined models including two or more of the best CD4 and VL predictors determined above: CD4 lagged by 180 days, CD4 slope, VL lagged by 180 days, and VL time-weighted mean (Table 4). According to the AIC, the two best models included CD4 and VL, each lagged by 180 days, and VL time-weighted mean, or these measures plus CD4 slope. Because the global p-value for CD4 slope was only borderline significant (p=0.055) in the latter model, we chose the more parsimonious model as our final model (Table 5). P-trend for each measure in the final model was highly significant (p<0.0001). In this model, with VL time-weighted mean modeled as a continuous variable, we estimated that CD4 lagged by 180 days mediated 38% of the association between VL time-weighted mean and KS risk.

ART Models

Among persons who were ART-naïve at baseline (N=35,804; KS cases = 119), the HR per 20% of time on ART during the 1,080 day time window lagged by 180 days was 0.77 (95% CI: 0.70-0.85) with adjustment for baseline covariates; 0.71 (95% CI: 0.64-0.79) with further adjustment for confounding by CD4; and 0.96 (95% CI: 0.85-1.09) with further adjustment for the CD4 and VL measures in the final model (see Table S3, Supplemental Digital Content).

Sensitivity Analyses

Our sensitivity analyses revealed our final model to be highly robust, with no confounding by HIV risk group or smoking (data not shown).

Discussion

Using data from a large, North American HIV cohort consortium, we found each of a wide variety of CD4 and VL measures (recent, lagged, trajectory, and cumulative) to be highly

significantly associated with KS risk. However, we found recent CD4, recent VL, and cumulative VL to be the most robust independent predictors. Furthermore, the protective effect of cumulative ART exposure appeared to be completely explained by these factors, meaning we did not detect an independent anti-KS effect of ART itself.

Our results suggested a multifactorial etiology for KS, with early and late phases of development. While the recent VL and CD4 effects suggest that HIV and immunosuppression are involved in late phases of KS development, the cumulative VL effect suggests that ongoing HIV exposure may promote earlier phases of development. Of course, KSHV acquisition represents an additional requirement for KS development that we were unable to evaluate.

The cumulative VL effect in particular suggested that to prevent KS it is important to control HIV replication promptly after HIV diagnosis, no matter how high the CD4 count, consistent with current recommendations[41] and with the Strategic Timing of Antiretroviral Treatment trial in which KS incidence was significantly lower in persons with CD4>500 cells/μL who initiated ART immediately compared with those who deferred initiation.[16]

The first of three questions we posed in the Introduction was when is CD4 most predictive of KS risk over the course of HIV infection. An inverse association between recent/current CD4 and KS risk has been consistently observed by others. However, most previous studies measured current CD4,[11,25-28,30] whereas we lagged our recent CD4 (and our recent VL) measure by 180 days to reduce the possibility of reverse causality. We found recent CD4 to be a better predictor of KS risk than CD4 with longer lags. Each of our two cumulative CD4 measures was not significant when included in models with recent CD4 and CD4 slope, the latter dropping out in the presence VL measures. Thus, we established recent CD4 as the most robust CD4 predictor of KS risk, suggesting an etiologic role for increasingly severe immunodeficiency late in KS development.

Our second question was whether VL is associated with KS risk independent of CD4, and if so, which VL measure is the best predictor. We found a slower decline in HRs with increasing lag observed for VL than for CD4 (Table 2), suggesting a role for past, and possibly cumulative VL exposure. We then found that both VL lagged by 180 days and VL time-weighted mean were independent predictors of KS risk. Moreover, only 38% of the association between VL time-weighted mean and KS risk was mediated by recent CD4, suggesting that most of the cumulative VL effect acted through an independent mechanism.

The independent effect of recent VL was consistent with some,[11,26,29] but not all,[25,27] previous studies. The two studies that did not demonstrate an independent effect each included fewer than 45 KS cases,[25,27] so may have had limited statistical power to detect this association. Several studies have found recent/current VL to be associated with risk for non-Hodgkin lymphoma, the other main AIDS-defining cancer, [26,32,42] and for overall AIDS-defining illness,[43] independent of CD4.

We are aware of only two studies that examined the relationship between cumulative VL exposure and KS risk. One study with only 39 KS cases found that cumulative time with VL>500 copies/mL was not associated with KS risk after adjusting for cumulative time with

CD4<200 cells/μL.32 In the second study, which included current CD4, current VL, and ART exposure in its final model, time with VL>100,000 copies/mL was the only cumulative measure tested.[26] Several studies have found cumulative VL measures to be associated with risk for non-Hodgkin lymphoma.[32,44,45]

An effect of recent VL independent of recent CD4 suggests that recent VL provides independent information about recent immune dysfunction,[43] possibly HIV-induced inflammation.[8,46-48] Alternatively, this effect may be due to pro-oncogenic effects of secreted HIV-1-encoded proteins, most notably Tat or Nef.[49-56] Possible mechanisms for the cumulative VL effect include the aforementioned mechanisms as well as HIV-induced immunosenescence.[57]

Our final question was whether the protective effect of ART on KS risk is entirely mediated by its effects on CD4 and VL. Our observed association between higher proportion of time on ART and reduced KS risk was expected.[1,24,26,30,31] Also expected was the strengthening of the association after adjusting for confounding by indication by CD4, presumably due to delayed ART initiation by persons with higher CD4, consistent with evolving HIV treatment guidelines during the study period.[40] We found no independent effect of ART after adjusting for the CD4 and VL measures in the final model. Most previous studies, which adjusted only for current[25,30] or nadir[31] CD4 or for both current CD4 and VL,[26,27] observed an independent ART effect, although one study that adjusted for both current CD4 and VL did not observe an independent effect.[11] No previous studies took cumulative VL into account.

An important study limitation was lack of information on KSHV infection status. Not only is KSHV infection necessary for KS development, but among persons infected with both KSHV and HIV, KSHV viremia is strongly associated with subsequent development of KS, independent of CD4 and VL.[58] Other limitations included the possibility of selection bias due to exclusion criteria, the inherent imperfection of estimating time-updated CD4 and VL values, the arbitrary 1,080 time window, limited median follow-up of 5 years, follow-up only through 2009, not considering KS stage at diagnosis or whether diagnosis was clinical or pathological, and the relatively low proportion of females and Hispanics. Furthermore, the confidence interval estimates in the final model did not take into account multiple testing in the model selection process. Finally, although NA-ACCORD is representative of HIV-infected persons in the U.S. and Canada,[37] our results may not be generalizable to resource-limited settings.[1,59]

Strengths of our study included its large size, validated KS diagnoses,[6] comprehensive assessment of alternative CD4 and VL measures, lagged analyses to reduce the possibility of reverse causality, and use of a time window of fixed duration (i.e., 1,080 days) for trajectory and cumulative measures. The latter approach was superior to using simple cumulative measures (e.g., time duration of CD4 below a threshold), which vary by person according to amount of follow-up time, although we did not capture effects that might originate >1,260 days in the past. Finally, we developed a methodologic approach to examine the overlapping roles of CD4 and VL in cancer risk among HIV-infected persons that can be applied to other cancer types.

In summary, we found that recent CD4, recent VL, and cumulative VL were robust independent predictors of KS risk, consistent with a multifactorial etiology for KS, with early and late phases of development. The novel finding of an independent association between cumulative VL and KS risk provided a possible explanation for the elevated KS risk among HIV-infected persons on ART, and suggested the importance of controlling HIV replication promptly after HIV diagnosis to prevent KS. However, this finding requires confirmation and further characterization, including how long the cumulative VL effect lasts after viral suppression by ART. Finally, we found no evidence for direct anti-KS activity of ART, independent of CD4 and VL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of persons contributing observation time, NA-ACCORD, 1996-2009

	N (%)	
Characteristic	**All (N = 77,696)**	**KS cases (N=396)**
Sex		
Male	65,861 (84.8%)	386 (97.5%)
Female	11,835 (15.2%)	10 (2.5%)
Race/ethnicity		
White	33,915 (43.7%)	231 (58.3%)
Black	31,674 (40.8%)	120 (30.3%)
Hispanic	5,308 (6.8%)	17 (4.3%)
Other	2,488 (3.2%)	13 (3.3%)
Unknown – imputed	4,311 (5.5%)	15 (3.8%)
Age (years)		
18-29	8,354 (10.8%)	42 (10.6%)
30-39	24,988 (32.2%)	182 (46.0%)
40-49	28,308 (36.4%)	124 (31.3%)
≥50	16,046 (20.7%)	48 (12.1%)
Calendar period		
1996-1998	27,860 (35.9%)	225 (56.8%)
1999-2001	18,533 (23.9%)	74 (18.7%)
2002-2004	15,981 (20.6%)	68 (17.2%)
2005-2007	12,451 (16.0%)	27 (6.8%)
2008-2009	2,871 (3.7%)	2 (0.5%)
Combination antiretroviral therapy naïve		
No	21,684 (27.9%)	101 (25.5%)
Yes	56,012 (72.1%)	295 (74.5%)
CD4 cell count (cells/μL)		
<50	8,922 (11.5%)	66 (16.7%)
50-99	5,674 (7.3%)	54 (13.6%)
100-199	11,330 (14.6%)	77 (19.4%)
200-349	17,504 (22.5%)	80 (20.2%)
350-499	14,915 (19.2%)	53 (13.4%)
≥500	19,351 (24.9%)	66 (16.7%)
Viral load (copies/mL)		
≤500	20,695 (26.6%)	46 (11.6%)
501-9,999	17,392 (22.4%)	67 (16.9%)
10,000-99,999	24,235 (31.2%)	159 (40.2%)
≥100,000	15,374 (19.8%)	124 (31.3%)

	N (%)	
Characteristic	**All (N = 77,696)**	**KS cases (N=396)**
HIV risk group		
Injection drug use	10,306 (13.3%)	42 (10.6%)
Men who have sex with men	20,819 (26.8%)	167 (42.2%)
Heterosexual	11,764 (15.1%)	18 (4.5%)
Other	1,139 (1.5%)	4 (1.0%)
Unknown – imputed *	5,092 (6.6%)	17 (4.3%)
Unknown – not imputed *	28,576 (36.8%)	148 (37.4%)
Smoking status		
Ever	41,322 (53.2%)	212 (53.5%)
Never	13,449 (17.3%)	84 (21.2%)
Unknown – imputed *	11,474 (14.8%)	46 (11.6%)
Unknown – not imputed *	11,451 (14.7%)	54 (13.6%)

KS, Kaposi sarcoma

* For HIV risk group and smoking, we did not perform imputation for cohorts with a high proportion of unknowns, or with 100% of knowns being ever smokers (for smoking). Thus, we had two categories of unknowns: those with and without imputed values.

Table 2

Hazard ratios for Kaposi sarcoma risk in relation to CD4 cell count or viral load with different lags (separate model for each lag, for CD4 cell count and viral load, respectively), NA-ACCORD, 1996-2009

	Lag							
Measure	**180 days***		**540 days†**		**900 days‡**		**1260 days§**	
Measure	**KS cases**	**HR‖ (95% CI)**	**KS cases**	**HR‖ (95% CI)**	**KS cases**	**HR‖ (95% CI)**	**KS cases**	**HR‖ (95% CI)**
CD4 cell count (cells/μL)								
<50	134	33.1 (22.9 to 47.8)	81	20.5 (13.8 to 30.3)	37	12.4 (7.6 to 20.1)	18	7.4 (4.1 to 13.6)
50-99	43	10.6 (6.8 to 16.5)	36	8.5 (5.4 to 13.5)	27	8.0 (4.7 to 13.4)	16	5.5 (2.9 to 10.2)
100-199	59	5.1 (3.4 to 7.7)	59	4.8 (3.2 to 7.2)	46	4.6 (2.9 to 7.3)	36	4.1 (2.5 to 6.8)
200-349	74	3.1 (2.1 to 4.6)	53	2.2 (1.4 to 3.3)	62	3.1 (2.0 to 4.7)	46	2.6 (1.6 to 4.2)
350-499	48	2.0 (1.3 to 3.0)	45	1.8 (1.2 to 2.8)	38	1.9 (1.2 to 3.0)	34	1.9 (1.2 to 3.2)
≥500	38	1.0 (ref)	38	1.0 (ref)	31	1.0 (ref)	27	1.0 (ref)
Per 50 cells/μL		0.76 (0.74 to 0.79)		0.80 (0.77 to 0.83)		0.84 (0.81 to 0.87)		0.87 (0.84 to 0.90)
P-trend		<0.0001		<0.0001		<0.0001		<0.0001
AIC#		3,326		3,408		3,500		3,551
Viral load (copies/mL)								
≤500	75	1.0 (ref)	46	1.0 (ref)	35	1.0 (ref)	33	1.0 (ref)
501-9,999	43	1.4 (0.95 to 2.0)	46	2.1 (1.4 to 3.2)	52	3.0 (2.0 to 4.7)	35	2.0 (1.2 to 3.2)
10,000-99,999	136	5.4 (4.0 to 7.2)	132	7.7 (5.5 to 10.9)	105	7.9 (5.3 to 11.6)	79	6.2 (4.1 to 9.3)
≥100,000	142	16.1 (12.0 to 21.5)	88	15.6 (10.8 to 22.5)	49	11.5 (7.4 to 17.9)	30	7.9 (4.8 to 13.1)
Per $\log_{10}$ copies/mL		2.7 (2.5 to 3.0)		2.7 (2.4 to 3.0)		2.3 (2.0 to 2.6)		2.2 (1.9 to 2.5)
P-trend		<0.0001		<0.0001		<0.0001		<0.0001
AIC#		3,380		3,387		3,467		3,497

AIC, Akaike's information criterion; HR, hazard ratio; KS, Kaposi sarcoma; 95% CI, 95% confidence interval.

*Persons with at least 180 days of follow-up; N = 77,696, KS cases = 396.

†Persons with at least 540 days of follow-up; N = 70,375, KS cases = 312.

‡Persons with at least 900 days of follow-up; N = 59,586, KS cases = 241.

[§] Persons with at least 1,260 days of follow-up; N = 51,220, KS cases = 177.

[//] Each HR was calculated from a separate Cox model, adjusted for sex, race/ethnicity (white, black, Hispanic, other), cohort, and baseline age (18-29, 30-39, 40-49, and ≥50 years) and calendar period (1996-1998, 1999-2001, 2002-2004, 2005-2007, 2008-2009).

[#] Valid comparison of AICs across lags required that each AIC be calculated from a model using the same dataset (i.e., persons with at least 1,260 days of follow-up).

Table 3

Hazard ratios for Kaposi sarcoma risk in relation to CD4 cell count or viral load measures during the 1,080 day time window lagged by 180 days (separate model for each measure), NA-ACCORD, 1996-2009 (N = 51,220; KS cases = 177)

Measure	KS cases	HR* (95% CI)
CD4 cell count slope (cells/μL per 360 days)		
≤-100	26	2.2 (1.4 to 3.5)
-99 to -25	71	1.7 (1.2 to 2.3)
-24 to 25	64	1.0 (ref)
26 to 100	12	0.21 (0.11 to 0.39)
>100	4	0.25 (0.090 to 0.68)
Per 50 cells/μL/360 days		0.71 (0.65 to 0.77)
P-trend		<0.0001
AIC		3,519
CD4 cell count proportion of time <200 cells/μL		
0%	53	1.0 (ref)
>0% to ≤25%	16	1.7 (1.0 to 3.0)
>25% to ≤50%	18	4.1 (2.4 to 6.9)
>50% to ≤75%	12	3.5 (1.9 to 6.5)
>75% to <100%	24	7.3 (4.5 to 11.9)
100%	54	9.6 (6.5 to 14.1)
Per 20% of time <200 cells/μL		1.5 (1.4 to 1.6)
P-trend		<0.0001
AIC		3,466
CD4 cell count time-weighted mean (cells/μL)		
<50	26	26.8 (14.7 to 48.9)
50-99	29	18.2 (10.2 to 32.7)
100-199	38	7.4 (4.3 to 13.0)
200-349	38	3.4 (2.0 to 5.9)
350-499	27	2.2 (1.2 to 4.0)
≥500	19	1.0 (ref)
Per 50 cells/μL		0.78 (0.74 to 0.81)
P-trend		<0.0001
AIC		3,439
Viral load slope (log_{10} copies/mL per 360 days)		
≤-1	1	0.38 (0.05 to 2.7)
>-1 to ≤-0.1	32	1.1 (0.69 to 1.7)
>-0.1 to ≤0.1	53	1.0 (ref)
>0.1 to ≤1	86	2.9 (2.1 to 4.1)

Measure	KS cases	HR* (95% CI)
>1	5	4.7 (1.9 to 11.8)
Per $\log_{10}$ copies/mL/360 days		3.5 (2.4 to 5.2)
P-trend		<0.0001
AIC		3,560
Viral load proportion of time >500 copies/mL		
0%	8	1.0 (ref)
>0% to ≤25%	4	1.0 (0.31 to 3.4)
>25% to ≤50%	9	3.0 (1.2 to 7.9)
>50% to ≤75%	13	4.4 (1.8 to 10.6)
>75% to <100%	42	11.4 (5.3 to 24.6)
100%	101	19.7 (9.5 to 40.9)
Per 20% of time ≥500 copies/mL		1.9 (1.7 to 2.1)
P-trend		<0.0001
AIC		3,433
Viral load time-weighted mean (copies/mL)		
≤500	12	1.0 (ref)
501-9,999	17	1.8 (0.84 to 3.7)
10,000-99,999	104	12.8 (7.0 to 23.4)
≥100,000	44	26.1 (13.6 to 50.1)
Per $\log_{10}$ copies/mL		4.0 (3.3 to 4.8)
P-trend		<0.0001
AIC		3,396

AIC, Akaike's information criterion; ART, antiretroviral therapy; HR, hazard ratio; KS, Kaposi sarcoma; 95% CI, 95% confidence interval.

*Each HR was calculated from a separate Cox model, adjusted for sex, race/ethnicity (white, black, Hispanic, other), cohort, and baseline age (18-29, 30-39, 40-49, and ≥50 years) and calendar period (1996-1998, 1999-2001, 2002-2004, 2005-2007, 2008-2009).

Table 4

Global p-values and Akaike's information criteria derived from Cox models, NA-ACCORD, 1996-2009 (N = 51,220; KS cases = 177)

Measures in model*	Global p-value	AIC
CD4 cell count		
180-day lag	<0.0001	3,326
Slope	<0.0001	3,519
Proportion of time <200 cells/μL	<0.0001	3,466
Time-weighted mean	<0.0001	3,439
180-day lag + slope	<0.0001 <0.0001	3,309
180-day lag + proportion of time <200 cells/μL	<0.0001 0.060	3,326
180-day lag + time-weighted mean	<0.0001 0.61	3,333
180-day lag + slope + proportion of time <200 cells/μL	<0.0001 0.0007 0.50	3,314
180-day lag + slope + time-weighted mean	<0.0001 <0.0001 0.80	3,316
Viral load		
180-day lag	<0.0001	3,380
Slope	<0.0001	3,560
Proportion of time >500 copies/mL	<0.0001	3,433
Time-weighted mean	<0.0001	3,396
180-day lag + slope	<0.0001 0.86	3,386
180-day lag + proportion of time >500 copies/mL	<0.0001 <0.0001	3,364
180-day lag + time-weighted mean	<0.0001 <0.0001	3,344
Proportion of time >500 copies/mL +	<0.0001	3,372

Measures in model*	Global p-value	AIC
time-weighted mean	<0.0001	
180-d lag +	<0.0001	3,345
proportion of time >500 copies/mL +	0.11	
time-weighted mean	<0.0001	
CD4 cell count and viral load		
CD4 180-day lag +	<0.0001	3,258
CD4 slope +	0.055	
VL 180-day lag +	0.0010	
VL time-weighted mean	0.0004	
CD4 180-day lag +	<0.0001	3,270
CD4 slope +	0.029	
VL 180-day lag	<0.0001	
CD4 180-day lag +	<0.0001	3,268
CD4 slope +	0.0042	
VL time-weighted mean	<0.0001	
CD4 180-day lag +	<0.0001	3,259
VL 180-day lag +	<0.0001	
VL time-weighted mean	0.0002	
CD4 slope +	0.0051	3,338
VL 180-day lag +	<0.0001	
VL time-weighted mean	<0.0001	
CD4 180-day lag +	<0.0001	3,273
VL 180-day lag	<0.0001	
CD4 180-day lag +	<0.0001	3,275
VL time-weighted mean	<0.0001	

AIC, Akaike's information criterion; CD4, CD4 cell count; VL, viral load.

*Each model was adjusted for sex, race/ethnicity (white, black, Hispanic, other), cohort, and baseline age (18-29, 30-39, 40-49, and ≥50 years) and calendar period (1996-1998, 1999-2001, 2002-2004, 2005-2007, 2008-2009). CD4 and VL were entered into models as categorical variables, as in Tables 2 and 3. CD4 and VL slope, proportion of time CD4<200 cells/μL, proportion of time VL>500 copies/mL, and CD4 and VL time-weighted mean were assessed during the 1,080 day time window lagged by 180 days.

Table 5

Final mutually-adjusted model,* NA-ACCORD, 1996-2009 (N = 51,220; KS cases = 177)

Measure	KS cases	HR (95% CI)
CD4 cell count, 180-day lag (cells/μL)		
<50	67	12.4 (6.5 to 23.8)
50-99	19	4.4 (2.1 to 9.2)
100-199	26	2.7 (1.4 to 5.4)
200-349	28	1.9 (0.97 to 3.6)
350-499	22	1.7 (0.88 to 3.4)
≥500	15	1.0 (ref)
Per 50 cells/μL		0.83 (0.79 to 0.88)
P-trend		<0.0001
Viral load, 180-day lag (copies/mL)		
≤500	25	1.0 (ref)
501-9,999	24	1.8 (0.97 to 3.5)
10,000-99,999	71	3.1 (1.7 to 5.5)
≥100,000	57	3.8 (2.0 to 7.3)
Per $\log_{10}$ copies/mL		1.7 (1.4 to 2.0)
P-trend		<0.0001
Viral load time-weighted mean (copies/mL)†		
≤500	12	1.0 (ref)
501-9,999	17	0.96 (0.42 to 2.2)
10,000-99,999	104	2.9 (1.3 to 6.4)
≥100,000	44	2.5 (1.0 to 5.9)
Per $\log_{10}$ copies/mL		1.8 (1.4 to 2.4)
P-trend		<0.0001

HR, hazard ratio; KS, Kaposi sarcoma; 95% CI, 95% confidence interval.

*Adjusted for sex, race/ethnicity (white, black, Hispanic, other), cohort, and baseline age (18-29, 30-39, 40-49, and ≥50 years) and calendar period (1996-1998, 1999-2001, 2002-2004, 2005-2007, 2008-2009).

†Assessed during the 1,080 day time window lagged by 180 days.