The association of immunosuppression and HIV control with Kaposi sarcoma among patients on antiretroviral therapy

Anna E. Coghill[a], Zachary Thompson[b], Laura Bamford[c], Greer Burkholder[d], Joseph Enron[e], Satish Gopal[f], Mari M. Kitahata[g], Kenneth H. Mayer[h], Richard Moore[i], George Yendewa[j], Brittney L. Dickey[k], Elizabeth Yanik[l] and Chad Achenbach[m]

See related paper on page 1972

Objective: Access to antiretroviral therapy (ART) has resulted in a decline in Kaposi sarcoma incidence among people with HIV (PWH). However, Kaposi sarcoma is still occurring among PWH receiving ART, and it is important to understand the degree to which risk of Kaposi sarcoma is impacted by response to ART.

Methods: We examined the changing epidemiology of Kaposi sarcoma among more than 20,000 PWH receiving HIV care between 1996 and 2016 in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS). We evaluated the association of Kaposi sarcoma with $CD4^+$ T-cell count and HIV viral load at ART initiation, within 6–12 months of ART initiation, and during clinical follow-up after ART initiation.

Results: A total of 344 PWH were diagnosed with Kaposi sarcoma. $CD4^+$ T-cell count less than 200 cells/μl at ART initiation was associated with a more than six-fold increased Kaposi sarcoma risk. Likewise, an HIV viral load more than 50,000 copies/ml at ART initiation was associated with a more than three-fold increased Kaposi sarcoma risk. For every 100 cells/μl increase in $CD4^+$ T-cell count or log-unit decrease in HIV viral load during the 12–18 months after ART initiation, we observed 11 and 7% lower Kaposi sarcoma risk, respectively. During clinical follow-up after ART initiation, every 10% increase in time with a $CD4^+$ T-cell count greater than 350 cells/μl or an HIV viral load less than 500 copies/ml was associated with 24 and 26% lower Kaposi sarcoma risk, respectively. All results reported here were statistically significant at the $P < 0.05$ threshold.

Conclusion: Kaposi sarcoma risk among PWH receiving HIV care was significantly impacted by not only $CD4^+$ T-cell count and viral load at ART initiation but also by long-term suppression of HIV after ART initiation.

AIDS 2025, **39**:1963–1969

[a]Cancer Epidemiology Program, Division of Population Science, [b]Biostatistics and Bioinformatics Program, Moffitt Cancer Center, Tampa, FL, [c]Department of Medicine, University of California San Diego, San Diego, CA, [d]Departments of Medicine and Infectious Disease, University of Alabama Birmingham, Birmingham, AL, [e]Division of Infectious Diseases, University of North Carolina, Chapel Hill, NC, [f]Center for Global Health, National Cancer Institute, Bethesda, MD, [g]Division of Allergy & Infectious Diseases, Department of Medicine, University of Washington, Seattle, WA, [h]The Fenway Institute, Fenway Health and Department of Medicine, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, [i]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, [j]Division of Infectious Diseases and HIV Medicine, Case Western Reserve University, Cleveland, OH, [k]Department of Epidemiology, College of Public Health, University of Nebraska Medical Center, Omaha, NE, [l]Division of Public Health Sciences, Orthopaedic Surgery and Department of Surgery, Washington University, St. Louis, MO, and [m]Departments of Medicine and Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.

Correspondence to Anna E. Coghill, PhD MPH, Associate Member, Cancer Epidemiology Program, Moffitt Cancer Center, Tampa, FL, USA.

E-mail: anna.coghill@moffitt.org

Received: 21 November 2024; revised: 4 March 2025; accepted: 6 March 2025.

DOI:10.1097/QAD.0000000000004303

Keywords: Center for AIDS Research Network of Integrated Clinical Systems population, HIV and cancer, Kaposi sarcoma, Kaposi sarcoma on ART

Background

The epidemiology of cancer among people with HIV (PWH) in the United States (US) has changed markedly in recent decades [1,2]. Effective antiretroviral therapy (ART) has resulted in immune restoration and greater ability to combat cancer-causing viruses, including human herpes virus 8 (HHV8), in PWH. HHV8 is the causative agent for Kaposi sarcoma, a malignancy that is uniquely linked to immunosuppression. In the United States and Europe, this AIDS-defining cancer (ADC) is rarely diagnosed outside the setting of HIV, and widespread access to ART has resulted in population-level declines in Kaposi sarcoma incidence [3,4]. However, Kaposi sarcoma is still being diagnosed in PWH on effective ART [5–7].

Research from the United States-based health system Kaiser Permanente of Northern California reported ~75% reduction in Kaposi sarcoma risk associated with timely initiation of ART [8]. However, that study was conducted in the early ART era when clinical guidelines recommended initiating ART in PWH after their $CD4^+$ T-cell count dropped below 350 cells/μl. Guidelines changed in the mid-2000s to recommend initiating ART at the time of HIV diagnosis, regardless of CD4 count, and to continue this therapy with maximal viral suppression long-term [9]. A French cohort study reported associations between low $CD4^+$ T-cell count, high HIV-RNA load, and Kaposi sarcoma risk; of the 137 persons who developed Kaposi sarcoma in that study, 113 were on ART at the time of their Kaposi sarcoma diagnosis [10]. Swedish national registry data also reported higher risk of ADCs in PWH who had limited restoration of $CD4^+$ T-cell count after ART initiation (i.e., <100 cells/μl) [11]. These findings suggest that lack of immune restoration in PWH receiving ART may contribute to development of Kaposi sarcoma.

The objective of our study was to assess Kaposi sarcoma incidence and survival in the modern ART era among PWH receiving HIV care across the United States in the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort. Prior research in the CNICS cohort (1996–2011) demonstrated a significant, 37% decrease in Kaposi sarcoma risk for every 100 cells/μl increase in $CD4^+$ T-cell count after ART initiation [12]. The current study includes PWH followed through 2016; this is important as HIV clinical care has shifted to include nearly uniform use of integrase strand transfer inhibitor (INSTI)-based ART regimens and initiation of ART promptly after an HIV diagnosis regardless of CD4 count. The current analysis also extends prior research by examining Kaposi sarcoma incidence in relation to the total amount of follow-up time PWH spent with restored $CD4^+$ T-cell counts or suppressed HIV RNA copies/ml (viral load) [13].

Methods

We examined PWH in HIV care at one of the eight CNICS sites between 1 January 1996, and 31 December 2016 [14]. To be eligible, PWH had to initiate antiretroviral (ART) therapy within 1 year prior to, or any time after, entering HIV care at a CNICS site. We excluded patients with less than 6 months of follow-up or unknown ART initiation date. For PWH who initiated ART after entry into the CNICS cohort, follow-up started at the documented date of ART initiation; for PWH who began ART within 1 year prior to entering the CNICS cohort, date of CNICS cohort entry served as the follow-up start date.

Methods of data collection for the CNICS cohort have been previously reported. Briefly, comprehensive clinical data collected through electronic medical records and other institutional data systems undergo rigorous data quality assessment and are harmonized in a central data repository that is updated quarterly [15]. Demographic data including sex assigned at birth, patient-reported racial/ethnic identity, and HIV risk factors are collected at cohort enrollment. Patient Reported Outcome (PRO) measures such as tobacco use were collected through tablet-based surveys conducted every 4–6 months in conjunction with primary care visits and review of medical records [16]. The primary outcome was a diagnosis of Kaposi sarcoma after ART initiation. PWH diagnosed with Kaposi sarcoma within 180 days of ART initiation were presumed to be prevalent cases and were excluded from this analysis of incident Kaposi sarcoma risk. Patients were followed until the earliest of Kaposi sarcoma diagnosis, death, last CNICS visit, or censoring at the last date of cancer verification (31 December 2016).

Covariates

We examined age at ART initiation, sex assigned at birth, race/ethnicity, and HIV transmission risk categories self-reported at the CNICS entry visit. We defined chronic hepatitis B infection (HBV) as a positive HBV surface antigen, E antigen, or HBV DNA recorded prior to a Kaposi sarcoma diagnosis or censoring event. We defined chronic hepatitis C infection (HCV) as a positive HCV

RNA or genotype recorded prior to a Kaposi sarcoma diagnosis or censoring event. Year of ART initiation was categorized as follows: 1996–2004; 2005–2010; and 2011–2016.

Measures of immunosuppression and HIV control

We examined $CD4^+$ T-cell count (cells/ul) as follows: CD4 count at ART initiation, defined as the $CD4^+$ T-cell count occurring within 1 year prior to 6 months after ART start, with preference given to the $CD4^+$ T-cell count closest to date of ART initiation if more than one count occurred in that time window; CD4 count response to ART, measured as the change between CD4 count at ART initiation and a subsequent CD4 count measured 12–18 months after ART initiation; and cumulative $CD4^+$ T-cell count, defined as the proportion of follow-up time spent with a $CD4^+$ T-cell count greater than 350 cells/μl. We examined HIV viral load (copies/ml) as follows: HIV viral load at ART initiation, defined as the viral load occurring within 1 year prior to 3 months after ART start, with preference given to HIV viral load measured closest to but before the date of ART initiation; HIV response to ART, measured as the change between HIV viral load at ART initiation and a subsequent HIV viral load 12–18 months after ART initiation; and cumulative HIV viral load, defined as the proportion of follow-up time spent with a HIV viral load less than 500 copies/ml. For both ART response and cumulative metrics, only participants with at least two measurements were included in statistical analyses. Sample sizes relevant for each measurement are outlined in the Results section.

Statistical analyses

We used Cox proportional hazards models to examine the association between $CD4^+$ T-cell count and HIV viral load with the risk of a Kaposi sarcoma diagnosis after ART initiation. Age was included as a covariate in regression models *a priori*, and additional covariates were identified using backward elimination, stepwise variable selection. All models included age, race/ethnicity, sex assigned at birth, HBV and HCV infection, and year of ART initiation. Models examining response to ART were adjusted for the corresponding baseline value (e.g., $CD4^+$ T-cell response was adjusted for $CD4^+$ T-cell count at ART initiation). Models for cumulative measures were stratified by values at ART initiation (e.g., cumulative time with $CD4^+$ T-cell count >350 cells/μl was examined across strata defined by the participant $CD4^+$ T-cell count at ART initiation). We also examined the association between $CD4^+$ T-cell count and HIV viral load at the time of Kaposi sarcoma diagnosis and subsequent mortality. Cox proportional hazards survival models included age, race/ethnicity, sex assigned at birth, and year of ART initiation. Follow-up time began at date of Kaposi sarcoma diagnosis and continued until death, last CNICS visit, or censoring at the last date of cancer verification.

Results

Three hundred and forty-four PWH included in our study were diagnosed with Kaposi sarcoma during study follow-up (Table 1). Hepatitis B co-infection was significantly higher ($P<0.01$) in PWH who were diagnosed with Kaposi sarcoma (11%) compared to those who remained free of Kaposi sarcoma during follow-up (7%). The average age at ART initiation was 38 years, with approximately half of the population entering the

Table 1. Characteristics of the study population, according to whether patients living with HIV developed Kaposi sarcoma.

	Overall ($N=22\,051$)	Kaposi sarcoma ($N=344$)	No Kaposi sarcoma ($N=21\,707$)
Age at CNICS entry[a]	38.4 (30.9, 46.0)	38.3 (32.6, 44.3)	38.4 (30.9, 46.0)
Sex assigned at birth			
Male	17 680 (80.2%)	340 (98.8%)	17 340 (79.9%)
Female	4371 (19.8%)	4 (1.2%)	4367 (20.1%)
Race			
White	10 607 (48.1%)	227 (66.0%)	10 380 (47.8%)
Black	9429 (42.8%)	79 (23.0%)	9350 (43.1%)
Other	2015 (9.1%)	38 (11.0%)	1977 (9.1%)
Hepatitis B positive	1565 (7.1%)	38 (11.0%)	1527 (7.0%)
Hepatitis C positive	972 (4.4%)	11 (3.2%)	961 (4.4%)
Year of ART start			
1995–2004	7455 (33.8%)	156 (45.3%)	7299 (33.6%)
2005–2010	7091 (32.2%)	134 (39.0%)	6957 (32.0%)
2010+	7505 (34.0%)	54 (15.7%)	7451 (34.3%)
HIV risk factor			
Heterosexual contact	6299 (28.6%)	31 (9.0%)	6268 (28.9%)
Injection drug use	2002 (9.1%)	10 (2.9%)	1922 (9.2%)
MSM	12 852 (58.3%)	294 (85.5%)	12 588 (57.9%)
Other	416 (1.9%)	7 (2.0%)	409 (1.9%)
Unknown	482 (2.2%)	2 (0.6%)	480 (2.2%)

All PWH initiated antiretroviral therapy (ART) and were followed after entry into the CNICS cohort during 1996-2016. ART, antiretroviral therapy.
[a]Median and interquartile range.

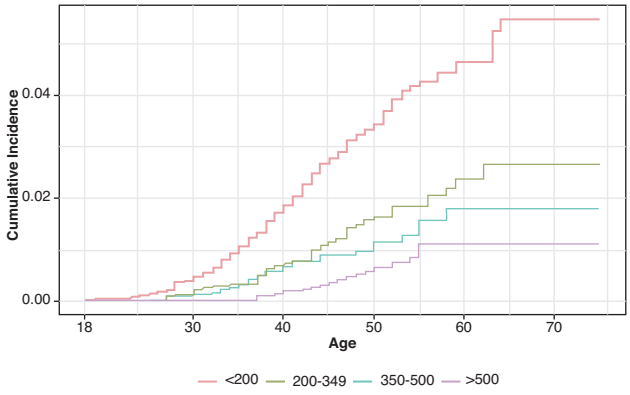

Fig. 1. Incidence of Kaposi sarcoma during follow-up, according to CD4$^+$ T-cell count at time of antiretroviral therapy initiation. Age during follow-up was used as the time scale.

study cohort at this age. As illustrated in Fig. 1, the incidence of Kaposi sarcoma increased in a nearly linear manner with age over time, although participants with an eventual Kaposi sarcoma diagnosis were more likely to have initiated HIV care during earlier decades compared with those who did not develop Kaposi sarcoma. Notably, nearly all Kaposi sarcoma diagnoses occurred within 5 years of ART initiation/cohort entry. Among PWH who initiated ART before 2010, 15% of cases (44 of 290) were diagnosed within 1 year of initiating study follow-up, and 84% (244 of 290) were diagnosed within 5 years. The parallel percentages at 1 and 5 years for PWH initiating ART after 2010 were 19 and 89%, respectively (Supplemental Figure 1, http://links.lww.com/QAD/D617).

Measurements at antiretroviral therapy initiation

Among the 22,051 participants with an available CD4$^+$ T-cell count at ART initiation, the median CD4 count at this timepoint was 280 cells/μl [interquartile range (IQR): 112–464]. Notably, the median was only 90 cells/μl (IQR: 26–236) for participants diagnosed with Kaposi sarcoma during follow-up. In adjusted analyses, a CD4$^+$ T-cell count at ART initiation less than 200 cells/μl was associated with a more than six-fold increased risk of Kaposi sarcoma (hazard ratio 6.41; 95% CI: 3.92–10.47; Figs. 1 and 2a)

Among the 21,052 participants with an available HIV viral load measurement within 3 months of ART initiation, 16% had HIV less than 500 copies/ml, and 46% had HIV greater than 50,000 copies/ml. In adjusted analysis, an HIV viral load greater than 50 000 copies at ART initiation was associated with a ~3-fold increased risk of Kaposi sarcoma (aHR: 3.2; 95% CI: 1.99–5.14; Fig. 2b).

Antiretroviral therapy response measurements

Among the 18,335 participants with at least one available CD4$^+$ T-cell count measured 12–18 months after ART initiation, the median increase above the baseline CD4 count was 107 cells/μl (IQR: 17–211). For every increase in CD4$^+$ T-cell count of 100 cells/μl, we observed a corresponding 11% decrease in Kaposi sarcoma risk (aHR: 0.89; 95% CI: 0.82–0.98), even after adjustment for CD4$^+$ T-cell count at ART initiation. In contrast, among the 18,494 participants with at least one available HIV viral load measured 12–18 months after ART initiation, every log-unit increase in viral load was associated with a corresponding 7% *increase* in Kaposi sarcoma risk (aHR: 1.07; 95% CI: 1.03–1.12) after adjustment for HIV viral load at ART initiation.

Cumulative measurements

At least two CD4$^+$ T-cell count values at or after ART initiation were available to assess the impact of cumulative CD4$^+$ T-cell count on Kaposi sarcoma risk in 21,249 CNICS participants. During follow-up, 241 of these

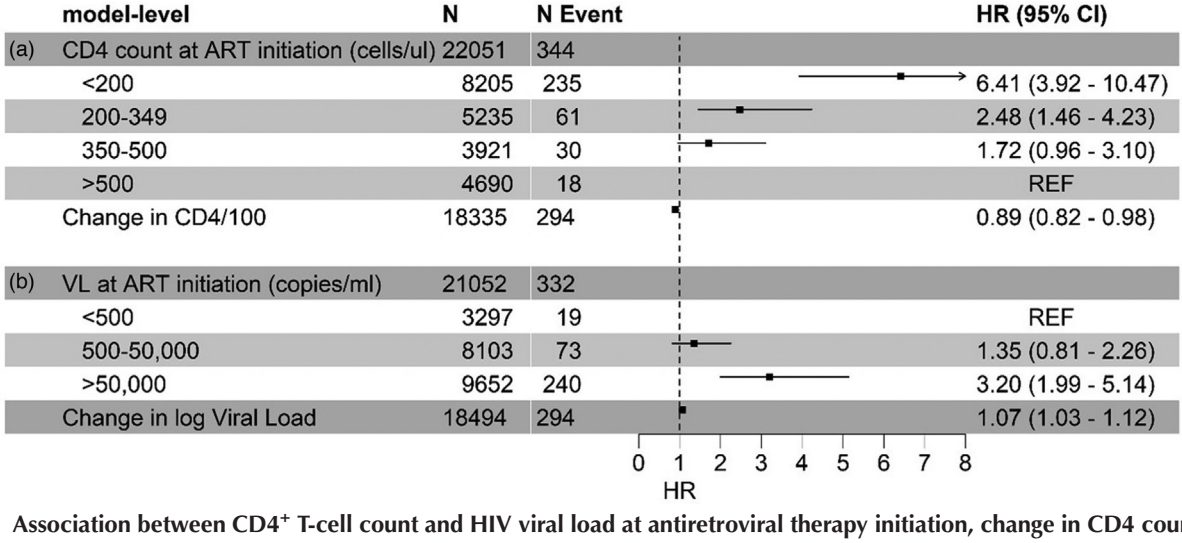

Fig. 2. Association between CD4$^+$ T-cell count and HIV viral load at antiretroviral therapy initiation, change in CD4 count and HIV viral load after antiretroviral therapy initiation, and risk of Kaposi sarcoma in CNICS (1996–2016).

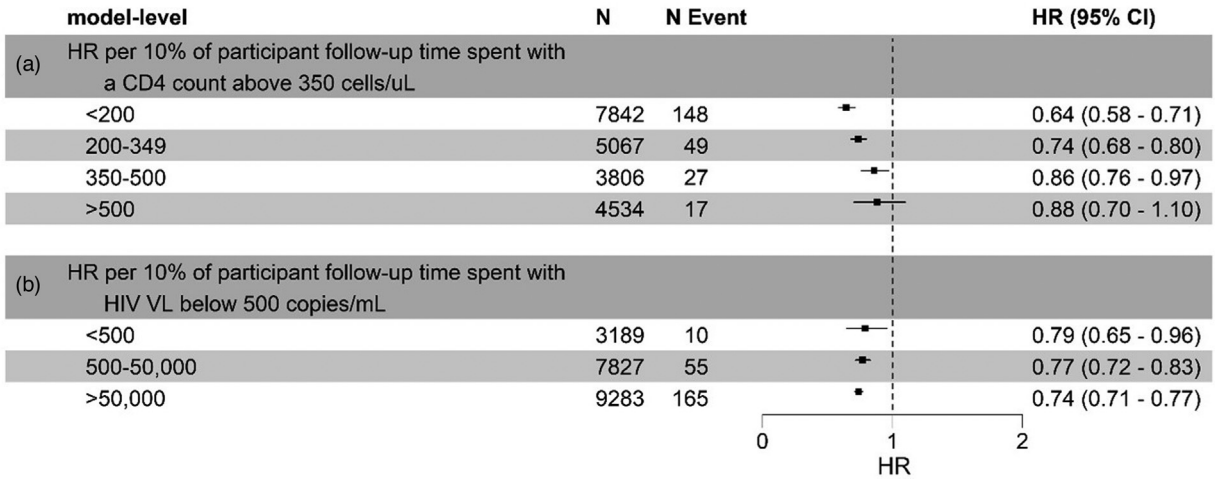

Fig. 3. Association between cumulative immunosuppression after antiretroviral therapy initiation, cumulative viral control after antiretroviral therapy initiation, and risk of Kaposi sarcoma in CNICS (1996–2016). All measures of the percentage of follow-up time are scaled by units of 10, such that the hazard ratio is interpreted as the change in Kaposi sarcoma risk for every additional 10% of follow-up time a CNICS participant spent above or below the stated threshold. Rows represent strata of baseline immunosuppression and HIV control values at ART initiation.

participants were diagnosed with Kaposi sarcoma. Overall, PWH spent a median of 86% of their follow-up time with a CD4 count greater than 350 cells/μl. However, for individuals diagnosed with Kaposi sarcoma, median follow-up time with a CD4 count greater than 350 cells/μl was 0% (IQR: 0–55%). In adjusted analyses, for every 10% increase in follow-up time with a $CD4^+$ T-cell count greater than 350 cells/μl, Kaposi sarcoma risk decreased by 24% (hazard ratio = 0.76; 95% CI 0.73–0.79). This association ranged from a significant 36% decrease (hazard ratio = 0.64; 95% CI 0.58–0.71) for patients with $CD4^+$ T-cell count at ART initiation less than 200 cells/μl, to a nonsignificant 12% decrease (hazard ratio = 0.88; 95% CI 0.70–1.10) for patients with $CD4^+$ T-cell count at ART initiation greater than 500 cells/μl (Fig. 3a).

Adequate data were available to assess the impact of cumulative viral load in 20,299 CNICS participants, of whom 230 were diagnosed with Kaposi sarcoma. Individuals spent a median of 95% of follow-up time with an HIV viral load less than 500 copies/ul after ART initiation. However, individuals diagnosed with Kaposi sarcoma spent a median of only 44% below this threshold (IQR: 0–95%). In adjusted analyses, for every 10% increase in follow-up time with a HIV viral load less than 500 copies/ml, Kaposi sarcoma risk decreased by 26% (hazard ratio = 0.74; 95% CI 0.72–0.77). Reductions in Kaposi sarcoma risk were consistent across the cohort, ranging from 21% (hazard ratio = 0.79; 95% CI 0.65–0.96) for participants with an HIV viral load at ART initiation less than 500 copies/ml to 26% (hazard ratio = 0.74; 95% CI 0.71–0.77) for participants with an HIV viral load at ART initiation greater than 50,000 copies/ml (Fig. 3b).

Survival analyses

Of the 337 Kaposi sarcoma patients in this study with available mortality information, more than one-third (N = 123; 37%) died during follow-up. The median $CD4^+$ T-cell count at the time of Kaposi sarcoma diagnosis was 84 cells/μl (IQR: 26–252); this value was markedly lower ($P < 0.001$) in Kaposi sarcoma patients who died during follow-up (54 cells/μl) compared to those who remained alive (142 cells/μl; Fig. 4). In adjusted analyses, every 100 cells/μl increase in $CD4^+$ T-cell count at Kaposi sarcoma diagnosis was associated with a 20% decreased risk of mortality (aHR: 0.80; 95% CI: 0.71–0.90). For every 10% increase in follow-up time after a Kaposi sarcoma

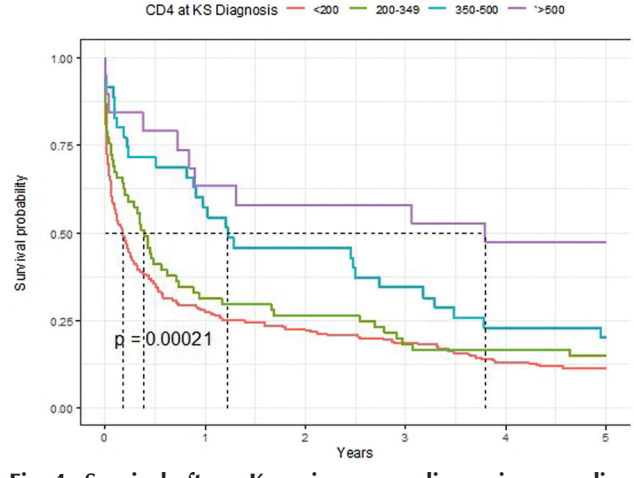

Fig. 4. Survival after a Kaposi sarcoma diagnosis, according to $CD4^+$ T-cell count at the time of Kaposi sarcoma diagnosis. Median survival for each group is denoted by the dashed line, and the ***P*** value comparing survival across groups was conducted using a log-rank test.

diagnosis that a patient spent with a $CD4^+$ T-cell count greater than 350 cells/μl, mortality risk decreased by 16% (hazard ratio = 0.84; 95% CI 0.76–0.93).

The median HIV viral load at Kaposi sarcoma diagnosis was 50,000 copies/ml (IQR: 499–190.837), but this measure was not significantly associated with subsequent mortality (aHR: 1.03; 95% CI: 0.97–1.09). We did observe a 6% decreased risk of mortality after a Kaposi sarcoma diagnosis (hazard ratio = 0.94; 95% CI 0.88–1.01) for every 10% increase in follow-up time spent with viral load less than 500 copies/ml, but results were not statistically significant.

Discussion

In this cohort of more than 20,000 PWH, both $CD4^+$ T-cell count and HIV viral load at the time of ART initiation, as well as the degree to which PWH had suppressed HIV viral load during follow-up after ART initiation, were associated with Kaposi sarcoma incidence. This supports the need for early initiation of ART after an HIV diagnosis and continuous engagement in HIV care to control viral replication and restore immunity to prevent Kaposi sarcoma and improve Kaposi sarcoma outcomes.

Prior research from CNICS observed a strong association between $CD4^+$ T-cell count at ART initiation and Kaposi sarcoma [12]. In that study, 143 participants developed Kaposi sarcoma between 1996 and 2011, and Kaposi sarcoma risk decreased by 37% for each 100 cells/μl increase in $CD4^+$ T-cell count at ART initiation. Our updated data are consistent with both this prior CNICS research as well as other studies from the United States and Europe [8,10,11]. All of this research reinforces that early initiation of ART after HIV diagnosis contributes to Kaposi sarcoma prevention, [5,6].

Our findings expand knowledge by providing evidence that not only early ART initiation but also continued ART with viral suppression and immune restoration impacts Kaposi sarcoma risk. We observed a 24% decrease in Kaposi sarcoma risk for every additional 10% of follow-up time spent with a $CD4^+$ T-cell count greater than 350 cells/μl. Practically, this translates into a nearly 50% potential decrease in Kaposi sarcoma risk if a PWH who initiated ART spent an additional 20% of their follow-up time with a $CD4^+$ T-cell count greater than 350 cells/μl. Of note, this pattern was more pronounced for PWH who initiated ART at lower CD4 counts. Every additional 10% of follow-up time spent with a $CD4^+$ T-cell count greater than 350 cells/μl was associated with a 36% decrease in Kaposi sarcoma risk for PWH who started with a CD4 count less than 200 cells/μl, but only a decrease of 12% for PWH with a starting CD4 count greater than 500 cells/μl. This emphasizes the importance of referring PWH who start ART at lower $CD4^+$ T-cell counts into consistent and closely monitored HIV care, including frequent visits to stress the importance of ART adherence and thoroughly assess barriers to engagement.

Comparably, a 26% decrease in Kaposi sarcoma risk was observed for every additional 10% of follow-up time a PWH spent with an HIV viral load less than 500 copies/ml. This speaks directly to the clinical benefits of HIV suppression, the stated goal of guidelines that have shifted to rapid ART initiation regardless of $CD4^+$ T-cell count. The average $CD4^+$ T-cell count at ART initiation in our study was 280 cells/μl, which likely reflects the inclusion of a time frame (1996–2016) during which guidelines did not dictate initiation of ART until counts dropped below a select threshold (e.g. 350 cells/μl). Despite only 16% of our study cohort exhibiting HIV control at the time of ART initiation, PWH did spend an average of ~95% of their follow-up time achieving viral control after starting ART. This value was much lower for PWH who developed Kaposi sarcoma, with an average of less than 50% of follow-up time spent with HIV viral control. As detailed above, this likely reflects incomplete ART adherence in this group and highlights the importance of consistent HIV care for Kaposi sarcoma prevention.

In addition, we observed that mortality after a Kaposi sarcoma diagnosis was impacted by immunosuppression at the time of Kaposi sarcoma diagnosis and continued immune restoration during HIV care. As illustrated in Fig. 4, median survival was less than 6 months for PWH with $CD4^+$ T-cell counts less than 250 cells/μl at Kaposi sarcoma diagnosis, compared to a median survival of nearly 4 years for those with a $CD4^+$ T-cell count at Kaposi sarcoma diagnosis greater than 500 cells/μl. We further report that every 10% of follow-up time after a Kaposi sarcoma diagnosis that a PWH spent with a $CD4^+$ T-cell count greater than 350 cells/μl was associated with a 16% decrease in risk of death. These findings expand on prior data supporting the importance of effective HIV therapy for not only Kaposi sarcoma prevention but also Kaposi sarcoma prognosis. Data from the French FHDH-ANRS CO4 HIV cohort previously reported improvements in survival of PWH and Kaposi sarcoma after the introduction of effective HIV therapy (between 1992 and 2009). Comparing the pre-ART and ART periods, 5-year survival rates for PWH rose from 14 to 83% after a visceral Kaposi sarcoma diagnosis and from 36 to 92% after a nonvisceral Kaposi sarcoma diagnosis, reflecting the importance of immune reconstitution [17]. More recent data (2000–2013) for male Kaposi sarcoma patients younger than 55 years, presumed to primarily be AIDS-associated Kaposi sarcoma diagnoses, from the Surveillance Epidemiology and End Results database reported a median overall survival of approximately 4 years, but survival was ~50% lower in Black men who may have had lower levels of access to consistent HIV care [18].

CNICS represents a unique and diverse HIV clinical care cohort across the United States, providing real-world evidence of the impact of incomplete adherence or response to ART on Kaposi sarcoma epidemiology. Strengths include a large sample size of approximately 20 000 individuals, focus on PWH with evidence of initiation of HIV care, and availability of repeated measures of both $CD4^+$ T-cell count and HIV viral load. Limitations include the lack of clinical data to describe the Kaposi sarcoma disease course more completely, including the severity of Kaposi sarcoma at diagnosis and the impact of Kaposi sarcoma treatment and specific ART regimens in our mortality analyses. ART regimens changed frequently during follow-up, complicating exposure assessment. Limitations also included the potential for misclassification of self-reported values (e.g. HIV risk/transmission category) or capture of historical data (e.g. ART use prior to CNICS entry), although our focus was on laboratory-confirmed HIV values and their impact on the uniformly assessed outcomes of a Kaposi sarcoma diagnosis and vital status. Future, follow-on efforts using an additional 5–10 years of data could examine time with CD4 count greater than 500 and time in HIV care with availability of newer, long-acting injectable ART that could improve adherence, engagement in HIV care, and HIV viral suppression. The thresholds chosen for this study reflected the years of the study and the respective trigger points for treatment ($CD4^+$ T-cell count >350 cells/μl) and HIV viral control (<50 copies/ml).

In conclusion, PWH in active HIV care were at elevated risk for Kaposi sarcoma in the current HIV treatment era if they did not maintain HIV control. In addition, consistent HIV control impacts prognosis for Kaposi sarcoma patients. This is an important consideration as cancer is still the second-leading cause of death in PWH in the United States. Our data support the need for consistent ART, without interruptions, to achieve long-term HIV control for Kaposi sarcoma prevention and better outcomes after diagnosis.

Acknowledgements

A.E.C. and C.A. conceived of the study; E.Y. provided guidance on statistical analysis; Z.T. conducted primary statistical analyses; A.E.C., C.A., Z.T., and B.L.D. revised statistical analyses and prepared tables and figures; C.A. and all other co-authors took part primary data collection and review of manuscript in preparation for submission.

Conflicts of interest

There are no conflicts of interest.

References

1. Shiels MS, Islam JY, Rosenberg PS, Hall HI, Jacobson E, Engels EA. **Projected cancer incidence rates and burden of incident cancer cases in HIV-infected adults in the United States Through 2030**. *Ann Intern Med* 2018; **168**:866–873.
2. Robbins HA, Shiels MS, Pfeiffer RM, Engels EA. **Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States**. *AIDS* 2014; **28**:881–890.
3. Franceschi S, Maso LD, Rickenbach M, Polesel J, Hirschel B, Cavassini M, *et al*. **Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy**. *Br J Cancer* 2008; **99**:800–804.
4. Fu L, Tian T, Wang B, Lu Z, Gao Y, Sun Y, *et al*. **Global patterns and trends in Kaposi sarcoma incidence: a population-based study**. *Lancet Glob Health* 2023; **11**:e1566–e1575.
5. Suk R, White DL, Knights S, Nijhawan A, Deshmukh AA, Chiao EY. **Incidence trends of Kaposi sarcoma among young non-Hispanic Black men by US regions, 2001-2018**. *JNCI Cancer Spectr* 2022; **6**:pkac078.
6. Peprah S, Engels EA, Horner MJ, Monterosso A, Hall HI, Johnson AS, *et al*. **Kaposi sarcoma incidence, burden, and prevalence in United States people with HIV, 2000-2015**. *Cancer Epidemiol Biomarkers Prev* 2021; **30**:1627–1633.
7. Hernandez-Ramirez 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; **4**:e495–e504.
8. Silverberg MJ, Leyden W, Hernandez-Ramirez RU, Qin L, Lin H, Justice AC, *et al*. **Timing of antiretroviral therapy initiation and risk of cancer among persons living with human immunodeficiency virus**. *Clin Infect Dis* 2021; **72**:1900–1909.
9. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, *et al*. NA-ACCORD Investigators. **Effect of early versus deferred antiretroviral therapy for HIV on survival**. *N Engl J Med* 2009; **360**:1815–1826.
10. Poizot-Martin I, Lions C, Cheret A, Rey D, Duvivier C, Jacomet C, *et al*. Dat'AIDS study group. **Kaposi sarcoma in people living with HIV: incidence and associated factors in a French cohort between 2010 and 2015**. *AIDS* 2020; **34**:569–577.
11. Malmstrom S, Wagner P, Yilmaz A, Svedhem V, Carlander C. **Failure to restore CD4+ cell count associated with infection-related and noninfection-related cancer**. *AIDS* 2022; **36**: 447–457.
12. Yanik EL, Napravnik S, Cole SR, Achenbach CJ, Gopal S, Olshan A, *et al*. **Incidence and timing of cancer in HIV-infected individuals following initiation of combination antiretroviral therapy**. *Clin Infect Dis* 2013; **57**:756–764.
13. Dickey BL, Yanik EL, Thompson Z, Burkholder G, Kitahata MM, Moore RD, *et al*. **The association of HIV control and immunosuppression with risk of non-AIDS-defining cancer risk among patients on antiretroviral therapy**. *J Acquir Immune Defic Syndr* 2024; **95**:275–282.
14. Kitahata MM, Rodriguez B, Haubrich R, Boswell S, Mathews WC, Lederman MM, *et al*. **Cohort profile: the Centers for AIDS Research Network of Integrated Clinical Systems**. *Int J Epidemiol* 2008; **37**:948–955.
15. Kitahata MM, Rodriguez B, Haubrich R, Boswell S, Mathews WC, Lederman MM, *et al*. **Cohort profile: the centers for AIDS research network of integrated clinical systems**. *Int J Epidemiol* 2008; **37**:948–955.
16. Crane HM, Lober W, Webster E, Harrington RD, Crane PK, Davis TE, Kitahata MM. **Routine collection of patient-reported outcomes in an HIV clinic setting: the first 100 patients**. *Curr HIV Res* 2007; **5**:109–118.
17. Hleyhel M, Belot A, Bouvier AM, Tattevin P, Pacanowski J, Genet P, *et al*. FHDH-ANRS CO4. **Trends in survival after cancer diagnosis among HIV-infected individuals between 1992 and 2009. Results from the FHDH-ANRS CO4 cohort**. *Int J Cancer* 2015; **137**:2443–2453.
18. Royse KE, El Chaer F, Amirian ES, Hartman C, Krown SE, Uldrick TS, *et al*. **Disparities in Kaposi sarcoma incidence and survival in the United States: 2000-2013**. *PLoS One* 2017; **12**:e0182750.