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Is Kaposi's Sarcoma Occurring at Higher CD4 Counts Over the Course of the HIV Epidemic?

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Abstract

We evaluated longitudinal rates of Kaposi sarcoma (KS) and trends in CD4 counts at the time of KS diagnosis during the HIV epidemic (1985–2008). Although rates of KS have decreased, cases are now occurring at higher CD4 counts over time, with more than a third of cases diagnosed in 2002–2008 occurring at CD4 counts ≥350 cells/mm^3. These data support future studies evaluating the impact of HAART initiation at higher CD4 counts to further reduce KS.

During the HIV epidemic, the types and presentations of cancers have dramatically changed [1–4]. As an AIDS-defining cancer, most Kaposi's sarcoma (KS) cases have traditionally occurred at low CD4 counts (<200 cells/mm^3) [5,6]. Although KS rates have decreased [7], it is unknown whether KS will now be observed at higher CD4 counts.

We evaluated KS rates and trends in CD4 counts at KS diagnosis among HIV-infected persons using the U.S. Military HIV Natural History Study (NHS) [3,8]. The diagnosis of KS was based on medical record review using standardized criteria [3]. Rates and rate ratios (overall and for time spent with CD4 cell count < 350 and ≥ 350 cells/mm^3) with 95% confidence intervals (CI) were calculated with Poisson regression models for four *a priori* defined calendar periods (1985–1990, 1991–1995, 1996–2001, and 2002–2008). Participants contributed follow-up time to all possible calendar periods from baseline (six months prior to HIV diagnosis) to the event or censoring time (last study visit). Among those with KS and a proximal CD4 cell count (within one year prior to KS diagnosis), participants were compared by proximal CD4 count category (<350 versus ≥350 cells/mm^3) with descriptive statistics (chi-squared and Wilcoxon tests) as appropriate. Medians are presented with interquartile ranges (IQR). We also evaluated factors associated with KS during the HAART

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era (the latest of 01 January 1996 or HIV diagnosis date) with time-updated proportional hazards models.

There were 5,067 participants with 39,522 PY of follow-up between 1985 and 2008. At HIV diagnosis, the median age was 28 (IQR 24–34) years; 92% were male; 45% were African American and 43% Caucasian. Median CD4 count was 504 (IQR 350–672) cells/mm^3) and median HIV RNA level (available for 38% of the cohort) was 4.4 (IQR 3.7–4.9) log_{10} copies/ml.

Of the 247 KS events during the study period, there were 52, 138, 38, and 19 during the four calendar periods, respectively. The rates of KS decreased over time (Table 1). Compared to 1985–1990, HIV-infected persons in 2002–2008 had a 72% lower rate of KS (RR=0.28; 95% CI 0.16–0.47; p<0.001). Within each calendar period the rates were higher for time spent with CD4 <350 versus to ≥350 cells/mm^3, although the rate ratios for those comparisons fell from 9.1 (95% CI 3.7–22.0) in 1985–1990 to 6.2 (95% CI 2.3–16.6) in 2002–2008.

Among the 247 KS cases, 179 (72%) had a proximal CD4 count available. For the four calendar periods, the proximal CD4 count at KS diagnosis was ≥350 cells/mm^3 for 18%, 7%, 14%, and 35%, respectively (p=0.01; Figure 1). Participants with proximal CD4 count <350 compared to ≥350 cells/mm^3 at KS diagnosis were more likely to have a prior non-KS AIDS event (47% vs. 9%; p<0.001), diagnosed with HIV in the pre-HAART era (97% vs. 83%; p=0.001), and spent a smaller percentage of time on antiretroviral therapy (median of 49% versus 62%; p=0.09); the two groups did not differ by demographics or HIV duration at time of KS.

Among the 3,422 participants with 20,263 PY of follow-up since availability of HAART in 1996, 45 had KS and a proximal CD4 count. From proportional hazards model considering only time-updated CD4 count, each incremental increase of 50 cells/mm^3 decreased the risk of KS by 30% (HR 0.70, 95% CI 0.64–0.76, p<0.001). In a model with both CD4 category and HAART use as time-updated covariates: compared to those with CD4 count ≥350 cells/mm^3 and on HAART, those with CD4 count ≥350 cells/mm^3 but not on HAART had an increased risk of KS (HR 2.0; 95% CI 0.7–6.30; p=0.22) that did not reach statistical significance, while those with CD4 count <350 cells/mm^3 (regardless of HAART use) had an increased risk (HR 8.3; 95% CI 3.4–20.2; p<0.001).

Our study demonstrates that although the KS rates have declined during the HAART era and lower CD4 counts remain an important risk factor, a greater proportion of KS cases are now occurring at higher CD4 counts. During the late HAART period, over a third of KS cases occurred at CD4 counts ≥350 cells/mm^3. Clinicians should be aware of these trends and watchful for the occurrence of KS despite robust CD4 counts.

The occurrence of KS at higher than expected CD4 counts has been previously reported [9–13]. However, our study is unique in that we describe the changing trends of CD4 counts at KS diagnosis over the entire HIV epidemic and demonstrate a rising proportion of cases at higher CD4 counts. To our knowledge, only one other study examined CD4 trends at KS diagnosis over time, but found no change in CD4 counts between the pre- and post-HAART eras; however, their population had high rates of drug use and poor antiretroviral adherence [12], whereas our population had free medical care, excellent reported medication adherence, and low rates of drug use (<1%) [14].

Similar to other studies in the HAART era [9,10,15], 35% of participants were on HAART and 9% had an HIV RNA level <400 copies/ml at KS diagnosis. Such cases are somewhat surprising since HAART has reduced the number of KS cases by its effects on HIV

suppression and potential anti-angiogenic effects [10,16]. Some KS cases in the setting of HAART may be related to the immune reconstitution inflammatory syndrome (IRIS) [17,18]; however, most of our cases were not associated with HAART introduction.

Given these trends, determining if HAART use at higher CD4 counts will reduce the impact of KS is of clinical importance. We found a suggestion of increased risk of KS among those not on HAART compared to those on HAART with CD4 counts ≥350 cells/mm^3. Prior studies have shown that KS in the setting of HAART results in less aggressive and more localized disease [19].

In summary, KS remains an important disease among HIV-infected persons, despite achievement of higher CD4 counts. Among patients with access to HAART, the proportion of KS cases occurring at high CD4 counts appears to be rising. Future studies are needed to determine whether earlier HAART initiation will further decrease the burden of KS among HIV-infected persons.

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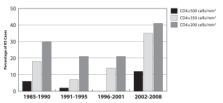

Figure 1.
CD4 Cell Count at Diagnosis of Kaposi's Sarcoma during the Course of the HIV Epidemic (1985–2008)

Table 1

Rates[1] (Overall and by Time Spent in CD4 Cell Count Categories) of Kaposi's Sarcoma by Calendar Period.

	Overall	By Time Spent in CD4 Cell Count Categories			
		CD4 <350	CD4 ≥350		
Calendar Period	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate Ratio [2] (95% CI)	P-value
1985–1990	6.5 (5.0 – 8.5)	18.6 (11.6 – 25.6)	2.0 (0.4 – 3.7)	9.1 (3.7 – 22.0)	<0.001
1991–1995	12.6 (10.7 – 14.9)	21.5 (17.1 – 25.9)	1.4 (0.4 – 2.4)	15.4 (7.1 – 33.1)	<0.001
1996–2001	3.8 (2.8 – 5.3)	5.3 (2.7 – 7.7)	0.7 (0.0 – 1.3)	7.9 (2.7 – 23.5)	<0.001
2002–2008	1.8 (1.1 – 2.8)	4.6 (1.9 – 7.4)	0.8 (0.2 – 1.3)	6.2 (2.3 – 16.6)	<0.001

[1] Rates are per 1000 person years of follow-up and are given with 95% confidence intervals

[2] Comparing rates for time spent with CD4 cell count <350 versus ≥350 cells/mm^3

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