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The epidemiology of Kaposi sarcoma and Kaposi sarcoma herpesvirus in the setting of the South African HIV epidemic

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Immunosuppression and co-infection with oncogenic viruses substantially increase the risk of cancers in HIV-infected patients such as cervical cancer, non-Hodgkin's lymphoma and Kaposi sarcoma (KS) (1). Kaposi sarcoma is the most common tumour in HIV-infected individuals in Africa (2) and is preceded by infection with Kaposi sarcoma herpes virus (KSHV) (3). The prevalence of KSHV in sub-Saharan Africa is, in fact, among the highest in the world and the region also bears the greatest burden of disease due to HIV. KS was relatively common in South Africa (up to 5 per 1000 population at risk per year) prior to the AIDS epidemic (4), but the incidence increased dramatically as the epidemic escalated (1). Estimated incidence rates as high as 20 per 1000 per year were reported in a case-control in South Africa between 1995 and 1999 (5), considerably higher than rates (0.005 per 1000 per year) reported in developed nations (6). The incidence of KS has decreased in the US and Europe with the introduction of antiretrovial treatment (ART) (7) but the impact of ART in Africa, where the underlying prevalence of KSHV is higher (up to 87%), (8) has yet to be determined. It seems that even in the era of wider access to antiretroviral treatment (ART), KS remains a significant contributor to morbidity and mortality in sub-Saharan Africa (9).

The World Health Organization (WHO) estimates that 9.7 million HIV-1-infected people were receiving ART in low and middle-income countries by the end of 2012 (10). In particular, combination ART has been used for some time to successfully treat early stage KS (11), achieving regression of KS lesions and successfully reducing KS-related mortality (12). Despite this, the influence of KS on response to ART is not well defined in resource-limited settings. Additionally, it is unclear if co-infection with oncogenic viruses such as KSHV places untreated HIV-infected patients at increased risk even without clinically apparent illness. KSHV typically establishes a persistent latent infection in its host during which time only latent genes (Orf73) are expressed and only viral particles sufficient to maintain infection are produced (13). In the presence of HIV-1 co-infection, however, immune suppression and cytokine release promotes reactivation of KSHV lytic genes which include K8.1 and active replication and increase in KSHV viral progeny occurs. Previous in vitro studies have suggested interactions between these two viruses including an increase in HIV-1 viral load in the presence of KSHV and induced reactivation of HIV-1 replication in chronically infected cells (14). Despite this, there are few analyses describing the effect of co-infection with KSHV on HIV treatment outcomes after initiation of ART and whether this has implications for treatment initiation guidelines.

The analysis presented here aimed to determine the effect of clinical disease due to KS and also to estimate the impact of co-infection with KSHV among HIV-1 infected adults receiving ART.

Effect of Kaposi Sarcoma and KSHV infection on response to ART

The study comprised two phases addressing the KS-related and KSHV-related aims. First, cohort data from two large urban HIV care and treatment programs in Johannesburg and Cape Town, South Africa, was analysed to assess the effect of KS on survival, loss to follow-up and immunologic and virologic responses to ART. Differences in mortality between those with and without KS at ART initiation were estimated with Cox proportional hazard models. Log-binomial models were used to assess differences in CD4 count response and HIV virologic suppression within a year of initiating treatment.

Secondly, a prospective cohort of HIV-infected adults initiating ART in a large, urban HIV care and treatment program in Johannesburg, South Africa was enrolled. Data from this cohort was used to examine the effect of KSHV seropositivity on treatment outcomes in the first year of ART Subjects were defined as seropositive to KSHV if reactive to either KSHV lytic K8.1 or latent Orf73 antigen or both. Subjects were followed from ART initiation until 18-months on treatment. HIV viral load and CD4 counts were tested 6 monthly.

Linear generalized estimating equations and log-binomial regression models were used to estimate the effect of KSHV infection on immunologic recovery and response as well as HIV viral load suppression within 18-months after ART initiation. Cause-specific Cox proportional hazard models were used to estimate the effect of KSHV on attrition from ART care. Person-time was calculated from the date of ART initiation to the

earliest of: 1) death or loss to follow up; 2) transfer to another facility; or 3) end of study period (31 December 2008 for the KS analysis and 18 months after treatment initiation for the KSHV prospective cohort).

Higher mortality associated with KS

The first study, using data from the two large HIV clinics, identified 13,847 HIV-infected adults who initiated ART at the sites during the study period. Of those, 2% (n=247) presented with KS at ART initiation. The group was similar to those without KS (n=13,600; 98%) with respect to age, presenting CD4 count and proportion on TB treatment. Subjects with KS were, however, over three times more likely to have died at any time after ART initiation (hazard ratio [HR] =3.62; 95% CI 2.71-4.84) than those without KS (Figure 1). Those with KS also gained, on average, 29 fewer CD4 cells (95% CI 7-52 cells/mm^3) and were less likely to increase their CD4 count by 50 cells from baseline (relative risk [RR]=1.43; 95%CI 0.99-2.06) within the first 6-months of treatment (Figure 2).

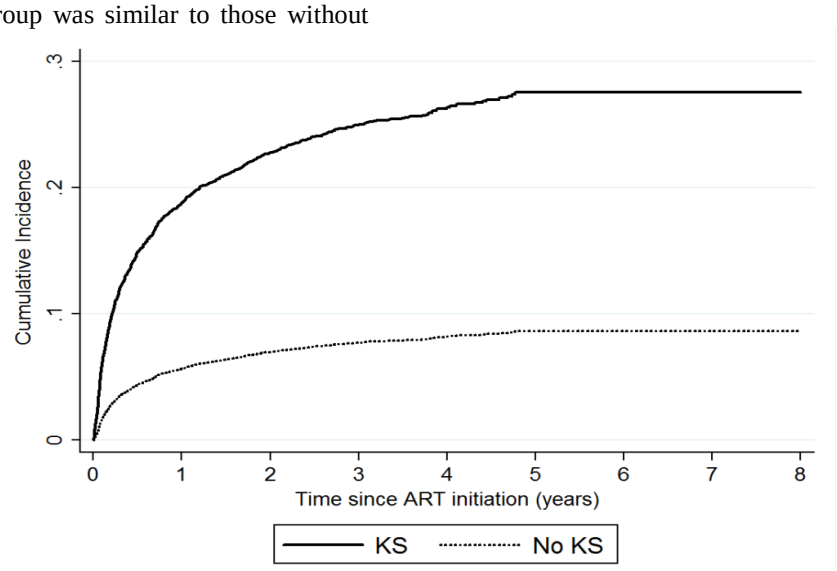


Figure 1: Cumulative incidence of mortality after ART initiation by KS status.

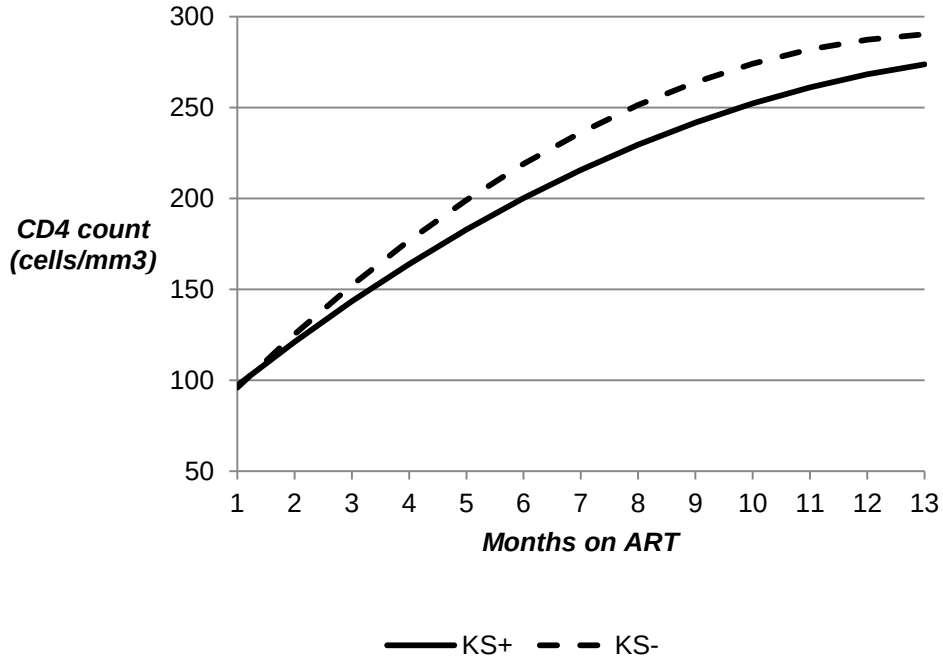


Figure 2: Mean predicted CD4 cell count increase from ART initiation stratified by KS status.*

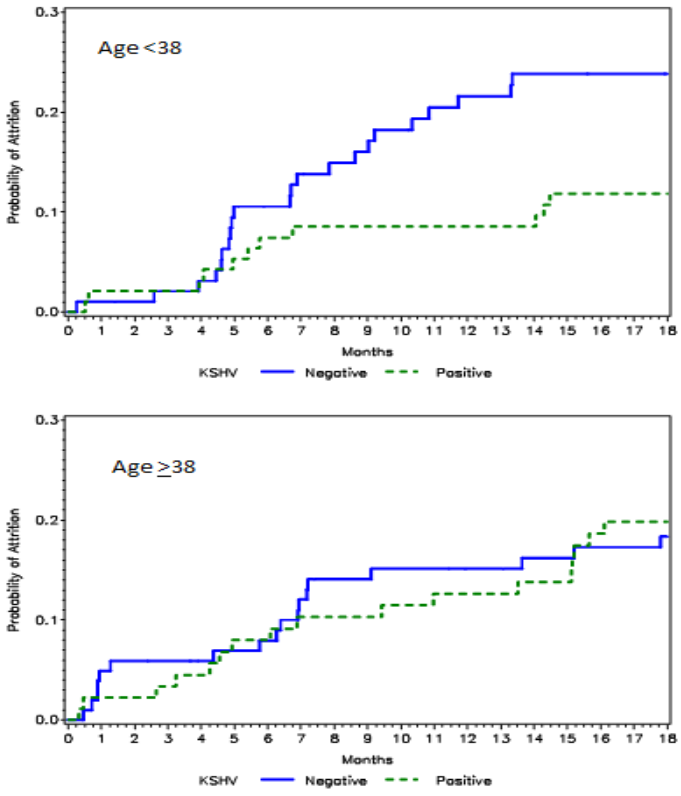
** Trajectories were estimated using two separate mixed linear models, one for the KS+ and one for the KS- to allow the curves to depart from being parallel. Curves were fitted using time as a quadratic function and a random intercept with an unstructured correlation matrix for repeated measures*

KSHV co-infection possibly associated with a decreased risk of attrition

The second study, the prospective cohort study, enrolled and screened 404 study participants at ART initiation for antibodies to KSHV lytic K8.1 and latent Orf73 antigens. Of the 404 participants, 193 (48%) tested positive for KSHV at ART initiation; with 76 (39%) reactive to lytic K8.1, 35 (18%) to latent Orf73 and 82 (42%) to both. One individual presented with clinical KS at ART initiation. KSHV seropositivity was not associated with body mass index, tuberculosis status, WHO stage, HIV RNA levels, full blood count or liver function tests at initiation. Those with detectable KSHV viraemia (n=19), however, appeared to present with signs of more advanced HIV disease including anaemia and WHO stage 3 or 4 defining conditions compared to those in whom the virus was undetectable. Over the 18 months of follow up, the KSHV positive group gained a similar number of CD4 cells at 6- (difference of 10 cells/mm^3, 95% CI:-11-31), 12- (3cells/mm^3, 95%CI:-19-25) and 18-months (24cells/mm^3, 95%CI:-13-61) on ART compared to the KSHV negative group. Adjusted relative risk of failure to suppress viral load to <400 copies/mL (1.03; 95%CI: 0.90-1.17) was also similar for the KSHV positive and KSHV negative groups after ART initiation.

After 18 months of follow up, 310/385 (77%) participants who initiated ART were still alive and in care. This included 154/184 (80%) of the KSHV positive group and 155/201 (73%) in the KSHV negative group. A further 29 participants (6%; n=12 from the KSHV positive group and 8%; n= 17 from the KSHV negative group) had transferred to another treatment facility. In this analysis attrition from care was a combined outcome comprising both known deaths (n=31, 8%) and those lost to follow up whose vital status was unknown (n=35; 9%). Though the study numbers were small and the estimates subsequently lacked precision, the direction of the point estimates suggested the KSHV positive group were less likely to experience attrition than their KSHV negative counterparts at both 12- (aHR=0.57; 95% CI 0.29-1.11) and 18-months (aHR=0.77; 95% CI 0.44-1.35) after ART initiation compared to the KSHV negative group.

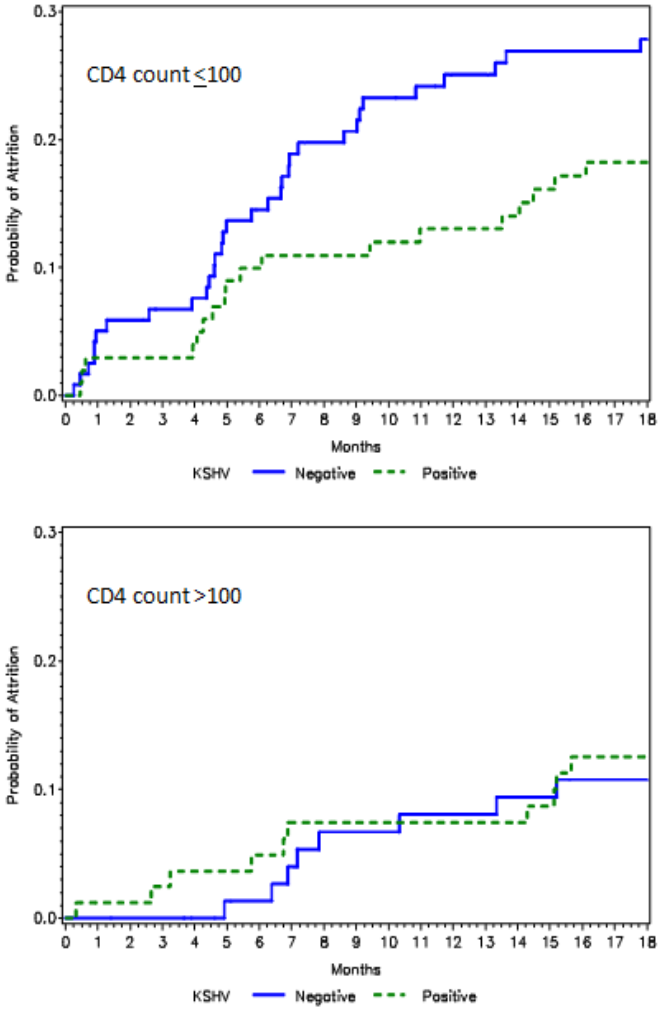
Effect measure modification of the effect of KSHV on attrition from care by both age (Figure 3) and CD4 cell count (Figure 4) was noted on the relative scale. The protective effect of co-infection with KSHV [aHR=0.50; 95% CI 0.22-1.14] is demonstrated among those less than 38 years old (the median age of the cohort), but not for the participants aged ≥38.0 [aHR=0.92; 955 CI 0.41-2.05]. Similarly, among those participants with low baseline CD4 counts, KSHV co-infection was associated with a decreased risk of attrition compared to the KSHV negative group [aHR= 0.62; 95% CI 0.32-1.18]. The effect was not seen among those with CD4 counts >100 cells at ART initiation [aHR= 1.02; 95% CI 0.27-3.89].



aHR= 0.50 (95% CI 0.22-1.14)

aHR= 0.92 (95% CI 0.41-2.05)

Figure 3: The relation between KSHV and attrition from care stratified by age



aHR= 0.62 (95% CI 0.32-1.18)

aHR= 1.02 (95% CI 0.27-3.89)

Figure 4: Attrition from care by KSHV status stratified by CD4 count

In conclusion, the results of these studies suggest quite different effects on ART treatment outcomes for clinical disease with KS compared to co-infection with KSHV. Table 1 summarises and contrasts these findings. Overall, clinical disease with KS at initiation of ART was associated with a poorer response to treatment and a significantly increased risk of mortality. Co-infection with KSHV however, was not associated with risk of poor outcomes after ART initiation and in fact suggested the possibility of a protective effect against attrition though the imprecise nature of the estimates limits our ability to make inferences from this.

Table 1: Summary of the effect of KS and KSHV on ART treatment outcomes

	Kaposi sarcoma clinical disease	*KSHV co-infection*
Presentation at ART initiation	*Advanced immune suppression (median CD4 count 74 cells/mm^3)*	*KSHV not associated with markers of advanced HIV disease*
Gender distribution	*Over-representation of males (49%)*	*Representative of general HIV clinic population*
Risk of mortality and LTFU	*Significantly increased risk of mortality among those with KS (four-fold in the first year on ART). LTFU Also increased among those with KS (1.5 times more likely)*	*KSHV associated with protective effect against attrition from care. Group with detectable KSHV viral load possible exception*
Immunologic response to ART	*KS group demonstrated more sluggish recovery of CD4 cells compared to those without KS*	*Similar immune response to ART for KSHV positive and negative groups*
Virologic response to ART	*Limited evidence of better virologic suppression among those with KS*	*No association between KSHV and virologic suppression noted*

The prospective cohort study demonstrated a high prevalence of KSHV among HIV-infected adults initiating ART in a large urban public-sector HIV clinic in South Africa. KSHV viraemia but not KSHV seropositivity may be associated with markers of advanced HIV disease. HIV-positive adults co-infected with KSHV achieved similar immunologic and virologic responses to ART early after treatment initiation compared to those KSHV negative. However, the prognosis for those who have developed clinical disease due to KS is substantially worse than those without KS. HIV-infected adults presenting with KS demonstrated increased risk of mortality even after initiation of ART with the greatest risk in the first year. Even among those who survive the first year on therapy, subjects with KS demonstrated a poorer immunologic response to ART than those without KS.

These findings highlight the importance of early diagnosis and initiation of appropriate treatment for HIV-infected subjects with KS at every stage of HIV infection and treatment. In addition, the reason behind the lack of association between KSHV and negative treatment outcomes is yet to be clarified. While it is possible that it may be in part due to survivor bias (as suggested by the young age and very low prevalence of clinical disease with KS of the initiating cohort), the role of KSHV in inhibition of HIV infection of CD4 cells mediated through beta chemokines (15) may be involved. What is clear though is that the pathogenesis of KSHV infection and its role in clinical disease due to KS in the presence of ART among HIV infected adults is complex and requires further exploration.

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References:

1. Parkin DM, Sitas F, Chirenje M, et al. Part 1: Cancer in Indigenous Africans - burden, distribution, and trends. Lancet Oncol 2008; 9: 683-692.
2. Boshoff C and Weiss R. AIDS-related malignancies. Nat Rev Cancer 2002; 2: 373-382.
3. Whitby D, Howard MR, Tenant-Flowers M et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV infected individuals and progression to Kaposi's sarcoma. Lancet 1995; 346:799-802.
4. Cook-Mozaffari P, Newton R, Beral V, et al. The geographical distribution of Kaposi's sarcoma and of lymphomas in Africa before the AIDS epidemic. British journal of cancer 1998; 78:1521-8.
5. Sitas F, Pacella-Norman R, Carrara H, et al. The spectrum of HIV-1 related cancers in South Africa. Int J Cancer 2000; 88: 489-92.
6. Grulich AE, Beral V and Swerdlow AJ. Kaposi's sarcoma in England and Wales before the AIDS epidemic. Br J Cancer 1992; 66: 1135-37.
7. Mocroft A, Kirk O, Clumeck N, et al. The changing pattern of Kaposi sarcoma in patients with HIV, 1994-2003: the EuroSIDA Study. Cancer 2004; 100:2644-54.
8. Malope BI, MacPhail P, Mbisa G, et al. No evidence of sexual transmission of Kaposi's sarcoma herpes virus in a heterosexual South African population. AIDS 2008; 22: 519-26.
9. Chu KM, Mahlangeni G, Swannet S, et al. AIDS-associated Kaposi's sarcoma is linked to advanced disease and high mortality in a primary care HIV programme in South Africa. J Int AIDS Soc 2010; 13:23.
10. World Health Organisation. Progress report 2013: Global HIV/AIDS response. Geneva: World Health Organization; 2013.
11. Krown SE. Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. J Clin Oncol 2004; 22:399-402.
12. Lynen L, Zolfo M, Huyst V, et al. Management of Kaposi's sarcoma in resource-limited settings in the era of HAART. AIDS Rev 2005; 7:13-21.
13. Wilkinson J, Cope A, Gill J, et al. Identification of Kaposi sarcoma-associated herpesvirus (KSHV)-specific cytotoxic T-lymphocyte epitopes and evaluation of reconstitution of KSHV-specific responses in human immunodeficiency virus type 1-Infected patients receiving highly active antiretroviral therapy. J Virol 2002; 76:2634-40.
14. Ensoli B, Gendelman R, Markham P, et al. Synergy between basic fibroblast growth factor and HIV-1 Tat protein in induction of Kaposi's sarcoma. Nature 1994; 371: 674–80.
15. Boshoff C, Endo Y, Collins PD, et al. Angiogenic and HIV-inhibitory functions of KSHV-endoded chemokines. Science 1997; 278:290-94.