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ORIGINAL ARTICLE

Risk factors for Kaposi's sarcoma in human immunodeficiency virus patients after initiation of antiretroviral therapy: A nested case–control study in Kenya

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Abstract *Background/Purpose:* This study aimed to evaluate the association between highly active antiretroviral therapy (HAART) adherence and development of Kaposi's sarcoma (KS) in human immunodeficiency virus (HIV)/AIDS patients.
Methods: We conducted a retrospective nested case–control study of 165 participants (33 cases and 132 controls) receiving HAART care at Maseno Hospital, Kenya, from January 2005 to October 2013. Cases were HIV-positive adults with KS, who were matched with controls in a ratio of 1:4 based on age (±5 years of each case), sex, and KS diagnosis date. Perfect adherence to HAART was assessed on every clinic visit by patients' self-reporting and pill counts. Chi-square tests were performed to compare socioeconomic and clinical statuses between cases and controls. A conditional logistic regression was used to assess the effects of perfect adherence to HAART, the latest CD4 count, education level, distance to health-care facility, initial World Health Organization stage, and number of regular sexual partners on the development of KS.
Results: Only 63.6% participants reported perfect adherence, and the control group had a significantly higher percentage of perfect adherence (75.0%) than did cases (18.2%). After

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adjustment for potential imbalances in the baseline and clinical characteristics, patients with imperfect HAART adherence had 20-times greater risk of developing KS than patients with perfect HAART adherence [hazard ratios: 21.0, 95% confidence interval: 4.2—105.1]. Patients with low latest CD4 count ($\leq$350 cells/mm^3) had a seven-times greater risk of developing KS than did their counterparts (HRs: 7.1, 95% CI: 1.4—36.2).
Conclusion: Imperfect HAART adherence and low latest CD4 count are significantly associated with KS development.

Introduction

Kaposi's sarcoma (KS) is one of the defining features of AIDS since 1982.[1] It is known to cause deep-purple skin lesions that can be disfiguring and can also be fatal if the cancer spreads to the lungs and other organs.[2] Once traditionally considered a slow-growing malignancy, KS continues to be a global scourge since the advent of the human immunodeficiency virus (HIV) pandemic, and it is currently one of the most commonly diagnosed cancers among HIV-infected persons in Africa.[3—5] Since it became available in 1996, the use of highly active antiretroviral therapy (HAART) to treat HIV infections has led to decreases in KS mortality rates in resource-limited settings and to increases in the number of persons living with HIV infection.[1,6] However, the disease still develops in approximately 15% of AIDS patients.[7,8]

HAART is a lifelong therapy, and its success in reducing the viral load to undetectable levels by current blood testing techniques relies on continual adherence to medications.[9,10] According to the World Health Report 2003, the consequences of imperfect medication adherence are so huge that people across the world would benefit more from efforts aimed at improving medication adherence than from the development of new medical treatments.[11,12] According to a previous study, acceptable adherence rates of HAART are 90—95% to avoid rapid treatment failure, which ultimately leads to disease development.[13] Treatment efficacy relies, however, on sustained adherence, which constitutes a serious challenge to those receiving HAART.

The regimens are often complicated and can include varying dosing schedules, dietary restrictions, and adverse effects.[14,15] As more patients are initiated on lifelong HAART, one of the major future challenges, apart from securing sustainable funding, lies in retaining patients in care and sustaining adherence to HAART.[16] Although the close linkage of AIDS and KS and the importance of HAART adherence for AIDS control were pointed out by various studies, to our knowledge, no study has evaluated the relationship between HAART adherence and KS development.

In Africa, there have been comparatively few published studies or data on KS treatment and epidemiology. According to a recent report, about 80,000 cases of cancer are diagnosed each year. Of all the cancers registered, KS accounted for 6.9% of the total cases.[17] While Kenya is at the epicenter of the HIV/AIDS epidemic with approximately 1.6 million people currently living with the virus, this condition has emerged as a priority that needs to be studied. Therefore, we conducted this study in Kenya to evaluate the association between HAART medication adherence and the development of KS in HIV/AIDS patients.

Materials and Methods

We conducted a retrospective nested case—control study of KS patients receiving primary care at the Maseno Hospital Comprehensive Care Clinic, Kenya, from January 2005 to October 2013.

Data source

This study was conducted at the Maseno Comprehensive Care Clinic in Maseno Hospital, which is situated in the western part of Kenya. Maseno Hospital was established in 1906 with a capacity of 175 beds, and the comprehensive care clinic was set up in 2005 to cater to HIV/AIDS patients. The clinic has had 4330 patients enrolled in the program since its inception in 2005.

Medical records of patients are captured and stored in the International Quality Care Tool, a patient management electronic medical record database recommended by the World Health Organization (WHO).[17—19] The information used in this study was collected from this electronic database.

At enrollment, patients routinely have clinical, laboratory, and radiological evaluations including a physical examination, full blood count, alanine transaminase, serum creatinine, Venereal Disease Research Laboratory test, CD4 count, and a chest X-ray. The CD4 count is monitored every 6 months. The viral load is only performed when treatment failure is suspected, based on clinical and immunological parameters. HAART is typically initiated when the CD4 count is $\leq$ 350/mL in line with national and WHO guidelines or if the patient is in WHO Clinical Stage 3 or 4 regardless of the CD4 count.

Definition of cases and the matching process

Cases were defined as HIV-positive adults with KS receiving HAART care at the comprehensive care clinic. The morphology code of the International Classification of Disease (ICD)-10 for KS (M9140/3) was used to identify cases.

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Because of ethical reasons, only adults (aged > 18 years) were included in our study. We then performed a matched case–control study. Cases and controls were matched in the ratio of 1:4 based on age (±5 years of each case), sex, and KS diagnosis date using the propensity score matching function in SPSS (SPSS Inc., Chicago, IL, USA). The diagnosis day for the control group referred to the day on which their matched case was diagnosed to have KS. In total, 165 participants (33 cases and 132 controls) were included in the final analysis. The study protocol was approved by the Maseno Hospital Ethics and Research Committee. All the cases were anonymized.

Adherence assessment

For patients' adherence to HAART, there are two kinds of information recorded in the database: "perfect adherence" and "loss to follow-up." Adherence to HAART was assessed on every clinic visit by patients' self-reporting and pill counts. Pill counts are typically measured by counting the quantity of the remaining doses of medication and assuming that these remaining excess pills represent missed doses.

Adherence was considered "perfect" when patients' self-reporting and pill counts indicated that they had taken all of the doses of drugs at every visit since starting HAART. A patient was defined as "lost to follow-up" if he or she had not returned to the clinic or pharmacy for a scheduled drug pickup more than 90 days after the drug appointment. In the event that the patient missed an appointment for refills in the stated period, it was assumed that the patient was not taking the medication or was missing doses.

Information related to KS and adherence

We collected participators' demographic information including their age at enrollment, age at initiation of ART, sex, educational level, occupation, and health-risk behavior as the number of regular sexual partners in their lifetime (by self-disclosure). Potential risk factors, including participators' latest CD4 count, initial WHO stage, and distance to the health-care facility, were also collected for further analysis.

Statistical analysis

Age at enrollment, age at initiation of ART, time from enrollment to event outcome, and the latest CD4 count were compared between cases and controls by a Wilcoxon rank-sum test. For cases, time from enrollment to event outcome means the time from enrollment to diagnosis. For controls, time from enrollment to event outcome means the time from enrollment to the date their matched cases were diagnosed to have KS. Socioeconomic and clinical statuses, including sex, educational level, occupation, distance to the health-care facility, number of regular sexual partners, and initial WHO stage, and patients' perfect adherence, loss to follow up, and death were compared between cases and controls by a Chi-square test. While the average number of regular sexual partners of our samples is 3.2, we used the cut number as three in our analysis. A conditional logistic regression for paired data was used to assess the effects of the variables including education level, latest CD4 count, initial WHO stage, perfect adherence to HAART, and number of regular sexual partners on the development of KS. Because of overlapping concepts, we only run the regression for "perfect adherence to HAART" because it was more sensitive than the variable "lost to follow-up." A multivariate analysis was performed by fitting a stratified Cox model to matched pairs to adjust for potential imbalances in the baseline and clinical characteristics for both cases and controls [16]. Results are reported as the multivariate adjusted and unadjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for associations between predicting variables and the outcome. The analysis was carried out using SPSS 18.0 software (SPSS Inc.). A probability level of $p = 0.05$ was used to determine statistical significance.

Results

Demographic and disease characteristics of KS patients

Table 1 illustrates the clinical information of KS patients (cases) in our study. Of the 33 KS cases, 19 (57.6%) had received chemotherapy plus HAART, and 14 patients (42.4%) had received only HAART. Among the 33 KS cases, eight patients had KS and other comorbidities, while tuberculosis was the most common comorbidity among them (6 patients with it). The remaining two cases had *Pneumocystis* pneumonia.

The eight KS patients with comorbidities also had an average CD4 count of 35 cells/mm^3. In addition, of the 33 KS cases, the CD4 counts of seven patients were ≥ 300 cells/mm^3. Furthermore, the anatomical sites of all the 33 KS cases were known. The commonest sites among these 33 KS cases were the lower limbs and trunk, which accounted for 75% of cases.

Table 1 Clinical information on Kaposi's sarcoma patients (cases).

Clinical information	KS patients (cases)	
	$N = 33$	
	n	%
Chemotherapy		
Yes	19	57.6
No	14	42.4
Comorbidities		
Yes	8	24.2
No	25	75.8
Latest CD4 count (cells/mm^3)		
≥ 300	7	21.2
< 300	26	78.8
Site of KS lesions		
Visceral	5	15.2
Lower limbs	15	45.5
Trunk	10	30.3
Others	3	9.1

KS = Kaposi's sarcoma.

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Sociodemographic characteristics of KS patients and the control group

Table 2 compares demographic data between patients who developed KS and the control group. Among the 165 participants (33 cases and 132 controls) included in the final analysis, 48.5% were men and 51.5% were women. The overall median age at enrollment was 35.4 years. The median age for cases and controls was similar. In general, the median age at initiation of HAART was 35.6 years. The total median time from enrollment to event outcome (diagnosis

Table 2 Comparisons of sociodemographic characteristics, clinical status and adherence between Cases and Controls.

	Total		Cases		Controls		*p*
	N = 165		*N* = 33		*N* = 132		
	Median (IQR)		Median (IQR)		Median (IQR)		
Age at enrollment (y)	35.4 (30.6–49.3)		35.0 (29.0–47.5)		35.5 (31.0–49.8)		0.142
Age at HAART start (y)	35.6 (30.8–49.5)		36.0 (30.0–48.5)		35.5 (31.0–49.8)		0.22
Time from enrollment to event outcome (mo)	15.2 (11.0–26.4)		12.0 (11.0–24.0)		16.0 (11.0–27.0)		0.081
Latest CD4 count (cells/mm^3) [a]	314.4 (232.6–422.2)		170.0 (62.0–289.0)		353.0 (277.0–455.0)		< 0.001 *
	n	%	*n*	%	*n*	%	
Sex							
Male	80	48.5	16	48.5	64	48.5	0.716
Female	85	51.5	17	51.5	68	51.5	
Educational level							
Illiterate	25	15.2	12	36.4	13	9.8	0.545
Primary	102	61.8	12	36.4	90	68.2	
Secondary	11	6.7	4	12.1	7	5.3	
Tertiary [b]	27	16.4	5	15.2	22	16.7	
Occupation							
Employed	29	17.6	4	12.1	25	18.9	0.954
Farmer	35	21.2	4	12.1	31	23.5	
Housewife	18	10.9	3	9.1	15	11.4	
Self-employed	53	32.1	11	33.3	42	31.8	
Student	3	1.8	0	0.0	3	2.3	
Unemployed	27	16.4	11	33.3	16	12.1	
Distance to health facility (km)							
0–10	91	55.2	21	63.6	70	53.0	0.416
11–20	30	18.2	5	15.2	25	18.9	
>20	24	14.5	4	12.1	20	15.2	
Unknown	20	12.1	3	9.1	17	12.9	
Initial WHO stage							
Low (Stage 1 or 2)	78	47.3	8	24.2	70	53.0	0.706
High (Stage 3 or 4)	87	52.7	25	75.8	62	47.0	
Number of regular sexual partners in lifetime							
≤ 2	66	40.0	11	33.3	64	48.5	< 0.001 **
> 3	63	38.2	22	66.7	68	51.5	
HAART perfect adherence							
Yes	105	63.6	6	18.2	99	75.0	< 0.001 **
No	60	36.4	27	81.8	33	25.0	
Lost to follow up							
Yes	58	35.2	13	39.4	45	34.1	< 0.001 **
No	107	64.8	20	60.6	87	65.9	
Death [c]							
Yes	31	18.8	11	33.3	20	15.2	0.003 ***
No	134	81.2	22	66.7	112	84.8	

[a] Latest CD4 count was evaluated at the time of Kaposi's sarcoma (KS) diagnosis for the cases and at the last visit date when the case was diagnosed with KS for controls.
[b] College level and above.
[c] By the end of 2013.
HAART = highly active antiretroviral therapy; IQR = interquartile range; WHO = World Health Organization.
* $p < 0.05$.
** $p < 0.001$.
*** $p < 0.01$.

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of KS for cases) was 15.2 months, and the time interval between enrollment into the program and initiation of ART was 1 year (data not shown). In addition, participants had a median latest CD4 count of 314.4 cells/mm^3. Compared with the control group, KS patients had a statistically significant lower CD4 count at the time of their diagnosis.

The majority of KS cases in our study were illiterate (36.4%), whereas the majority of the control group had a primary school education (68.2%). However, the difference in educational level between the two groups of patients was not significant. Most of the KS patients were either unemployed or self-employed, whereas most patients in the control group were self-employed (31.8%). In addition, the majority of KS patients lived near the health-care facility (63.6%), whereas only 53.0% of patients in the control group lived nearby, however, the difference between the two groups was insignificant. Regarding the initial WHO staging, most of the cases were categorized as having initial WHO Stage 3 or 4 (75.8%), whereas most of the patients in the control group had lower initial WHO Stages of 1 or 2 (53.0%). In addition, our KS patients had significantly more regular sexual partners than patients in the control group, as the majority of KS patients (66.7%) had had more than three regular sexual partners in their lifetime.

Overall, 63.6% of participants reported perfect adherence in our study. Compared with KS patients (cases), patients in the control group had a significantly higher percentage of perfect adherence (75.0%). Correspondingly, the overall percentage of "loss to follow-up" was 39.4%. In addition, patients in the control group showed a significantly lower percentage of "loss to follow-up" than did KS patients (34.0% vs. 39.4%). Compared with the control group, more KS patients died during our study period (33.3%).

Associations of adherence, sociodemographic characteristics, and clinical status with the development of KS by conditional logistic regression

Results of the multivariate model are shown in Table 3. From the study results, imperfect HAART adherence was found to be significantly associated with KS development. Before adjustment, patients with imperfect HAART adherence had a six-time higher risk of developing KS than patients with perfect HAART adherence (HRs: 6.2, 95% CI: 2.4—15.7). After adjustment, patients with imperfect HAART adherence had a 20-fold greater risk of developing KS than patients with perfect HAART adherence (HRs: 21.0, 95% CI: 4.2—105.1).

Table 3 Associations between adherence, sociodemographic characteristics, clinical status, and development of KS by a conditional logistic regression.

Variables	Development of KS					
	Unadjusted			Adjusted		
	HR	95% CI	*p*	HR	95% CI	*p*
Educational level						
Tertiary [a]	1			1		
Illiterate	1.43	0.5—4.2	0.518	1	0.1—10.6	0.985
Primary	0.51	0.2—1.5	0.224	0.2	0.0—1.2	0.068
Secondary	1.00	0.3—4.0	0.997	0.5	0.0—8.0	0.619
Distance to health-care facility (km)						
0—10	1					
11—20	1.2	0.3—4.0	0.824	1.1	0.1—10.8	0.937
> 20	1.1	0.3—4.5	0.948	1.3	0.1—14.7	0.844
Unknown	2.3	0.5—11.2	0.294	4.7	0.3—66.4	0.249
Initial WHO stage						
Low (Stage 1 or 2)	1			1		
High (Stage 3 or 4)	1.4	0.6—3.5	0.424	1.7	0.5—6.3	0.397
Latest CD4 count (cells/mm^3)						
> 350	1			1		
≤ 350	3.1	1.1—8.5	0.03 *	7.1	1.4—36.2	0.018 *
Number of regular sexual partners in lifetime						
≤ 2	1			1		
> 3	1.6	0.8—3.4	0.2	4.2	0.8—21.4	0.087
HAART perfect adherence						
Yes	1			1		
No	6.2	2.4—15.7	< 0.001 ***	21.0	4.2—105.1	< 0.001 ***

[a] College level and above.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
CI = confidence interval; HAART = highly active antiretroviral therapy; HR = hazard ratio; KS = Kaposi's sarcoma; WHO = World Health Organization.

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A low latest CD4 count ($\leq$ 350 cells/mm^3) was also significantly associated with KS development, and the HRs were 7.1 (95% CI: 1.4–36.2) after adjustment. None of the other covariates, including educational level, initial WHO stage, distance to the health-care facility, and number of regular sexual partners (lifetime), was associated with the development of KS, even after adjustments.

Discussion

To our knowledge, this is the first study to examine the associations of adherence to HAART treatment and the development of KS in HIV/AIDS patients. Our analysis revealed important predictors for KS development among HIV-positive individuals. From the study results, we found a low HAART adherence rate as well as a significant association between imperfect HAART adherence and the risk of developing KS among AIDS patients. We also observed that a low latest CD4 count ($\leq$ 350 cells/mm^3) was statistically associated with the risk of KS development.

Our study results show that imperfect adherence to ART treatment is a predictor of KS development among AIDS patients. This might be due to their weakened immune systems, which are considered deficient and hence can no longer fulfill their role of fighting KS-associated herpes virus (KSHV). Based on our study results, we suggest that HIV prevention programs adopt an approach such as the one used in tuberculosis control programs to improve adherence rates among individuals. Interventions toward antiretroviral adherence mostly reported in the literature are inclined toward dedicating time with patients to plan for and support medication adherence.[20–22] The nature and regularity of these interventions vary, but those that seem effective are characterized by an initial educational session including tailored collaborative medication planning with follow-up sessions maintained regularly over the course of treatment.[21,23] With previous successful findings, improved counseling with follow up by social health workers to monitor pill intake can be a step forward to strengthen the adherence to HAART by KS patients.

In addition, patients with a latest CD4 count of $\leq$ 350 cells/mm^3 had a seven-time greater risk of developing KS than patients with a CD4 count of $>$ 350 cells/mm^3. This is because opportunistic infections typically begin to affect individuals when CD4 counts fall below 350 cells/mm^3.[24] In addition, this outcome echoed previous observational studies and randomized controlled trials, which reported increased morbidity, mortality, immunological, and virological outcomes when initiating treatment in cases where the CD4 count was $\leq$ 350 cells/mm^3; by contrast, initiating HAART at a CD4 count of $>$ 350 cells/mm^3 reduced the risk of progression to AIDS and death or development of AIDS-defining illnesses like KS.[25]

Interestingly, the persistence or development of KS in HIV-infected patients on HAART despite high CD4 counts was reported by several researchers.[26–29] This phenomenon was also observed in our study in which seven of our patients were diagnosed with KS when they had a CD4 count of $>$ 300 cells/mm^3. Empirical research suggests that this phenomenon might have resulted from other social behaviors such as high rates of drug use and imperfect antiretroviral adherence.[30,31] It is also important to note that the population of Maseno where this study was conducted has a high rate of drug abuse.[32] Nevertheless, further study is needed to understand relationships among CD4 counts, the development of KS, and the possible causes for this phenomenon.

From our study results, the risk of developing KS increases when the initial WHO sequence progressed to Stages 3 and 4. However, an association was not found between the initial WHO clinical stage and development of KS. The WHO staging of patients was only done once during enrollment in the program, which might be a possible explanation for this phenomenon. An association between KS development and educational level was not found in our study, although the impact of education on adherence was confirmed by previous studies.[33–35] This can be attributed to the small sample size of our patients. However, the importance of education cannot be overlooked, as empirical studies have shown that patients with limited literacy might be unwilling to ask for assistance to take medicines appropriately.[36] In addition, though the risk of developing KS increased as the distance exceeded 10 km from the HIV/AIDS clinic, the association was not statistically significant. A plausible explanation for this phenomenon might be because the majority of patients in our study lived near the facility. While other studies found that travel time and access to treatment centers were barriers to ART adherence, distance cannot be disregarded in preventing imperfect adherence to medication.[37]

The absence of associations between KS development and the number of regular sexual partners (in one's lifetime) in our study might reiterate the lack of evidence for sexual activity as a major route of KSHV transmission, while other routes of transmission, such as through saliva or blood contact, were pointed out by previous studies.[38] However, the role of sexual behavior cannot be disregarded, and further studies are needed to understand the relationship between sexual partners and KS development.

There are some limitations to this study. First, baseline viral load testing is not routinely done in this setting. A number of studies indicated that controlling the HIV viral load is essential for clinical improvement, disease resolution of KS, and perhaps decreased risk of relapse. While the information on viral load is not available to represent a patient's accurate immune status, we might have overestimated KS patents' immune statuses in our study. Second, the number of sex partners was evaluated by self-reporting, and there may have been a self-bias in this, therefore, we might have underestimated the impact of this factor. Third, we may have underestimated the severity of AIDS patient's imperfect adherence due to the fact that adherence was based on patients' self-reporting and pill counts, which were also provided by patients.

In conclusion, imperfect adherence to ART and a low CD4 count were found to be associated with the development of KS in our study. While a low adherence rate was also found in our study, we suggest the urgent need of policies to improve the adherence of patients undergoing ART treatment to prevent KS development. Although the multifactorial nature of imperfect adherence means that there will never be a universal solution, it is imperative for policymakers to come up with intervention programs that can

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improve patients' awareness of the importance of adherence through regular counseling.

Conflicts of interest

The authors have declared that no competing interests exist.

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