original reports abstract

Clinicopathological Features and Mortality in Patients With Kaposi Sarcoma and HIV: A Retrospective Analysis of a Thirty-Year Study From a Peruvian Oncologic Center

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PURPOSE Kaposi's sarcoma (KS) is a multifocal angioproliferative disease. In Peru, the implementation of the highly active antiretroviral treatment (HAART) program was in 2005, the model for treating patients with HIV-positive KS shifted to a potential cure. In this study, we aim to compare clinicopathological characteristics and prognostic factors associated with outcomes in patients with HIV-positive KS.

METHODS We developed a retrospective cohort study that includes patients with HIV/AIDS and KS seen in the Instituto Nacional de Enfermedades Neoplasicas between 1987 and 2017. Patients were divided into two groups according to the implementation of HAART in our country: the non-HAART group and those treated with HAART after 2005. Multivariate analysis for overall survival (OS) was performed with the Cox proportional hazard regression model.

RESULTS There was a greater visceral compromise and more extensive oral cavity involvement in the non-HAART group (60% 31.7%, $P < .01$). Regarding the immune status, there was a significant difference from the CD4 count at 1-year follow-up (73 *v* 335, $P = .01$). The CD4/CD8 rate were significant different before QT (0.23 *v* 0.13, $P = .01$) and at 1-year follow-up (0.12 *v* 0.32, $P = .03$.). The estimated 5-year OS rate was significantly lower ($P = .0001$) for the non-HAART group (41.7%; 95% CI, 25.9 to 56.9) compared with the HAART group (79.3%; 95% CI, 66.8 to 87.5). In the multivariate model for OS, full-HAART regimen and previous diagnosis of HIV/AIDS ($P < .01$) were significantly associated with longer survival.

CONCLUSION Clinical and demographic characteristics of our patients are compatible with the literature, but we report a higher rate of gastrointestinal involvement. Furthermore, our findings provide evidence for the importance of HAART and its ability to reduce KS-related mortality.

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INTRODUCTION

Kaposi sarcoma (KS) is the neoplasm most frequently associated with infection by HIV.[1] However, its incidence has declined over time, and in the United States, it has decreased 10% per year, from 4.8 cases per 100 people/year to 1.5 cases per 100 people/year. This is directly attributed to the increase in the utilization of high-active antiretroviral therapy (HAART) and a decrease in the incidence of infection by human herpesvirus type 8 directly involved in the origin of KS.[2] In general, the widespread use of combined antiretroviral therapies since 1996 has dramatically reduced KS incidence in HIV-infected patients because of virologic control of HIV replication and immune restoration.[3,4]

There are few studies that have evaluated the effects of HAART on the clinical presentation and natural history of KS in patients on a stable HAART regimen at the time of KS diagnosis[5,6] in whom the development and growth of KS are profoundly modified by HAART because of its direct (cytokine and genetic alterations) and indirect (immunodeficiency) roles.[7,8] KS presentation in the era of HAART therapy may present unique cases.[5] Furthermore, in the treatment of this neoplasm, if KS appears resistant and leads to organ damage, chemotherapy (CT) and different HAART regimens can be used for a better overall response rate.[9] Therefore, we seek to compare clinical features and disease outcome of patients with HIV and Kaposi's sarcoma treated with non-HAART and HAART regimens.

METHODS

In this retrospective cohort study, the sample was divided into two groups, before and after 2005 because of the difference in treatment (non-HAART and HAART group) and follow-up measurements with CD4, CD8, and viral load. In the non-HAART group, none or only one or two antiretrovirals were prescribed;

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CONTEXT

Key Objective

To compare the clinical characteristics and disease outcomes patients who are HIV-positive and have Kaposi's sarcoma (KS) treated with non-HAART and HAART regimens.

Knowledge Generated

The 5-year survival rate was high in patients on the full HAART regimen. HIV diagnosis before the presentation of KS and mucosal involvement were also predictive factors for mortality. KS who received HAART exhibit a less aggressive clinical pattern and better immune status than patients who did not receive a HAART regimen.

Relevance

Highly active antiretroviral therapy has an important role in the management of patients with KS and HIV due to the ability to reduce KS-related mortality.

because of lack of free coverage for the entire population, the most used antiretroviral medications were lamivudine (3TC) and zidovudine (AZT).

Patients with HIV confirmed by Western blot and a pathological diagnosis of Kaposi's sarcoma between 1997 and 2012 who received antiretroviral treatment consistently were chosen for this study. Patients with other neoplasms and young patients were excluded. Institutional Review Board approved this study.

Medical records were reviewed for demographic data (address, age, sex, date of birth, place of birth, nationality, marital status, and occupation) and risk factors for sexually transmitted diseases. In each case, information about the characteristic of the lesions, affected organs, and opportunistic infections were collected. Evaluation of HIV viral load and the CD4 count at diagnosis was performed by the National Institute of Health of Peru. The pathological diagnoses were reviewed by the Department of Pathology of the institution. The TIS system of the AIDS clinical trials group was used to KS staging. Regarding treatment options, it was included whether CT treatment with HAART was used. To assess the stage of HIV, viral load at the

TABLE 1. Characteristics of Patients Diagnosed With KS and HIV+ According to HAART Treatment From a Peruvian Oncologic Reference Center (1997-2017)

	Non-HAART (1997-2005) (n = 63)	HAART (2006-2017) (n = 75)	
Characteristic	**n (%)**	**n (%)**	***P***
Male sex	59 (93.6)	72 (96)	.70[a]
Own previous infection			
Hepatitis A	11 (17.4)	3 (4)	< .01
Hepatitis B	8 (12.6)	12 (16)	.58
Syphilis	7 (11.1)	11 (14.6)	.54
Diagnosis of HIV before KS diagnosis	42 (66.6)	41 (54.6)	.15
KS as AIDS-defining	19 (30.1)	31 (41.3)	.17
Opportunistic infections			
Candidiasis	23 (36.5)	13 (17.3)	.01
Pneumocystis infection	9 (14.2)	5 (6.6)	.14
HSV2 infection	8 (12.6)	9 (12)	.90
Cytomegalovirus	6 (9.5)	3 (4)	.30[a]
Homo/bisexual	35 (55.5)	27 (36)	—
Anal intercourse	38 (60.3)	26 (34.6)	.53
Drug addiction	8 (12.6)	5 (6.6)	< .01
Blood transfusion	6 (9.5)	9 (12)	.64

Abbreviations: HAART, highly-active antiretroviral therapy; HSV2, herpes simplex virus type 2; KS, Kaposi's sarcoma.
[a]Exact Fisher test unlike the rest where χ^2 was used.

beginning of HAART as well as CD4 and CD8 counts were evaluated.

Overall survival (OS) was measured from the time the patient was diagnosed with HIV until their last follow-up or death. Event-free survival (EFS) was defined from the time the patient was diagnosed with KS until death. Comparison was made between two groups that received treatment with and without HAART. From our cohort, 46 patients were documented deceased, and 2.9% were lost to follow-up.

The statistical analysis will include the description of the variables with summary measures, and the differences between the groups were evaluated using the χ^2 tests for discrete variables or *t*-tests in cases of continuous variables. Survival estimates were calculated by the Kaplan-Meier method and compared using the log-rank test. The Cox proportional risk model was used for bivariate and multivariate analysis. For multivariate analysis, variables with a $P < .05$ and clinically relevant variables were included in the bivariate analysis. Statistical analysis was performed using Stata/MP Version 14.0.

RESULTS

Epidemiological and Clinical Features

A total of 138 patients with KS and HIV were identified between January 1987 and December 2017. At the beginning of the study, there were 63 patients in the non-HAART group while there were 75 patients in the HAART group. Demographic and clinical features are summarized in Table 1.

The median age at the time of KS diagnosis was 36.19 years (range, 33.9-38.4 years). There was a significant difference between non-HAART and HAART groups in the proportion of patients with candidiasis (36.5% *v* 17.3%) and drug addiction (12.6% *v* 6.6%).

The number of skin lesions was similar in both groups, with a predilection for the extremities, face, and trunk. Other unusual locations were the lungs and penis within the non-HAART groups while in the HAART group it was lungs, eye, tongue, penis, and liver. The mean number of lesions recorded was similar between the non-HAART and HAART group (49 and 55 injuries, respectively).

Regarding KS staging, there was a significant difference in the extent of the tumor in with a greater visceral compromise and a more extensive oral cavity involvement between the non-HAART and HAART group (60% *v* 31.7%, $P < .01$; Table 2).

Regarding the immune status between the non-HAART and HAART group, there was a significant difference with the CD4 count at 1-year follow-up (73 *v* 335, $P = .01$), and there were significant differences in the CD4/CD8 ratio before QT (0.23 *v* 0.13, $P = .01$) and at 1-year follow-up (0.12 *v* 0.32, $P = .03$; Table 3).

From the cohort after 2005, 80% (n = 65) received CT and HAART and 20% (n = 16) only HAART. The characteristics of patients in both arms of the study were comparable. The median CD4 cell count, CD4/CD8 ratio, and viral load at enrollment for CT were similar in both groups. The median duration of documented KS from histology diagnosis to initiating CT was 40 (interquartile range: 73.5) days.

TABLE 2. Staging and Treatment of Patients Diagnosed With KS and HIV+ According to the Use of HAART From a Peruvian Oncologic Reference Center (1997-2017)

	Non-HAART (1997-2005) (n = 63)	HAART (2006-2017) (n = 75)	
Characteristic	**n (%)**	**n (%)**	***P***
ECOG			
0	8 (12.6)	0 (0)	.44
1	10 (15.8)	40 (53.3)	
2	11 (17.4)	21 (28)	
3	4 (6.3)	7 (9.3)	
4	3 (4.7)	1 (1.3)	
TIS staging			
T0	43 (68.2)	30 (40)	< .01
T1	20 (31.7)	45 (60)	
S0	40 (63.4)	62 (82.6)	.51[a]
S1	23 (36.5)	13 (17.3)	
I0	6 (9.5)	13 (17.3)	.55[a]
I1	16 (25.3)	50 (66.6)	
HAART			
Lamivudine	7 (11.1)	66 (88)	< .01
Zidovudine	20 (31.7)	18 (24)	.31
Efavirenz	0 (0)	53 (70.6)	< .01[a]
Abacavir	0 (0)	20 (26.6)	< .01[a]
Tenofovir	0 (0)	21 (28)	< .01[a]
Treatment of KS			
CT	25 (39.6)	59 (78.6)	< .01
Paclitaxel	1 (1.5)	58 (77.3)	—
Vinblastine	11 (17.4)	4 (5.3)	—
Local management	3 (4.7)	2 (2.6)	.66[a]
Radiotherapy	8 (12.6)	10 (13.3)	.91
Side effects			
Neutropenia	0 (0)	12 (16)	< .01[a]

Abbreviations: CT, chemotherapy; HAART, highly-active antiretroviral therapy; ECOG, Eastern Cooperative Oncology Group; KS, Kaposi's sarcoma; TIS staging, (T) extend of tumor, (I) immune status, (S) severity of systemic illness.

[a]Exact Fisher test unlike the rest where χ^2 was used.

Disease Outcome

The estimated 5-year OS rate was significantly lower ($P = .0001$) for the non-HAART group (41.7%; 95% CI, 25.9 to 56.9) compared with the HAART group (79.3%;

TABLE 3. Follow-Up of the Immune Status of Patients Diagnosed With KS and HIV+ According to the Use of HAART From a Peruvian Oncologic Reference Center (1997-2017)

	Non-HAART (n = 63)		HAART (n = 75)		
Characteristic	**Me**	**IQR**	**Me**	**IQR**	***P*[a]**
Time since KS diagnosis to CT	71	109	40	73.5	.16
CD4 count					
Before CT	168	186	97	159	.26
After CT	97	144	246	185	.08
At KS diagnosis	112	241.6	92	123	.23
HAART starting	94	282	67	163	.53
Follow-up at 1 year	73	195	335	414	.01
CD4/CD8 ratio[b]					
Before CT	0.23	0.13	0.07	0.13	.01
At diagnosis	0.14	0.17	0.07	0.14	.07
HAART starting	0.11	0.17	0.06	0.15	.63
Follow-up at 1 year	0.12	0.09	0.32	0.40	.03
Viral load					
Before CT	501[b]		101,225	242,561	.40
After CT	—		118	461	—
At diagnosis	—		91,260.5	281,039	—
HAART starting	1,550.44[b]		135,852.5	287,061.5	.18

Abbreviations: CT, chemotherapy; HAART, highly-active antiretroviral therapy; IQR, interquartile range; KS, Kaposi's sarcoma; Me, median.
[a]*P*: Mann Whitney *U*-test for non-normal variables.
[b]Only value taken.

95% CI, 66.8 to 87.5). The estimated 5-year EFS was also significantly lower for the non-HAART group (32.1%; 95% CI, 16.7 to 48.6) compared with the HAART group (79.5%; 95% CI, 66.2 to 88.0; Figure 1).

The non-HAART was defined as none or just one or two prescribed antiretroviral; therefore, for the survival analysis, we divided this into two subgroups: those who did not receive any antiretroviral (without treatment) and those who received one or two antiretroviral (suboptimal-HAART). The OS rate at 2.5 years was significantly higher for the HAART group (79.3; 95% CI, 66.8 to 87.5) compared with the suboptimal-HAART subgroup (64.7%; $P = .004$) and those without treatment subgroup (50.7%; $P < .001$). At 5 years, the OS differences between the HAART group and the non-HAART subgroups were maintained (Fig 1A). There were no significant differences at 2.5 and 5 years between the without treatment and the suboptimal-HAART subgroups. Regarding EFS rate, the HAART group had a significantly higher survival rate (79.5%) compared with the suboptimal-HAART subgroup (44.8%, $P < .001$) and the without treatment subgroup (24.1%, $P < .001$; Fig 1B). Furthermore, when the differences between the categories according to the use of HAART were evaluated with the log-rank test, no difference was found between the group without treatment and those with suboptimal HAART ($P = .21$).

Figure 2 shows the Kaplan-Meier graphs evaluating the OS in the group with only HAART and HAART plus CT; the OS rate in the HAART plus CT group at 5 years (80.24%) was significantly higher ($P = .01$) compared with the HAART group (37.8%; Figure 2A). There was a statistically significant difference in EFS for the group with HAART plus CT compared with those who only received HAART at 5 years. For the subanalysis of HAART and CT, the hazard ratio (HR) was 0.27 (95% CI, 0.09 to 0.81; $P = .01$).

In the bivariate analysis for OS, the significantly associated variables were HAART, previous neoplasia, diagnosis of HIV or AIDS before KS diagnosis, KS as AIDS-defining, use of CT, skin lesion in the trunk, and edema. For EFS, HAART, use of CT, detectable viral load before and after CT, KS skin lesion on the trunk, oral mucosa involvement, and TIS stage were associated. In the multivariate model for OS, the variables HAART ($P < .01$), oral involvement ($P = .003$), skin lesion on the trunk ($P = .01$), and previous diagnosis of HIV/AIDS ($P < .01$) were significantly associated. While the variables HAART ($P < .01$), mucosa involvement ($P = .01$), and skin lesions on the trunk ($P = .04$) were significant for EFS (Table 4).

DISCUSSION

The main interest of this study was to evaluate the impact of HAART on the clinical presentation, natural history, and

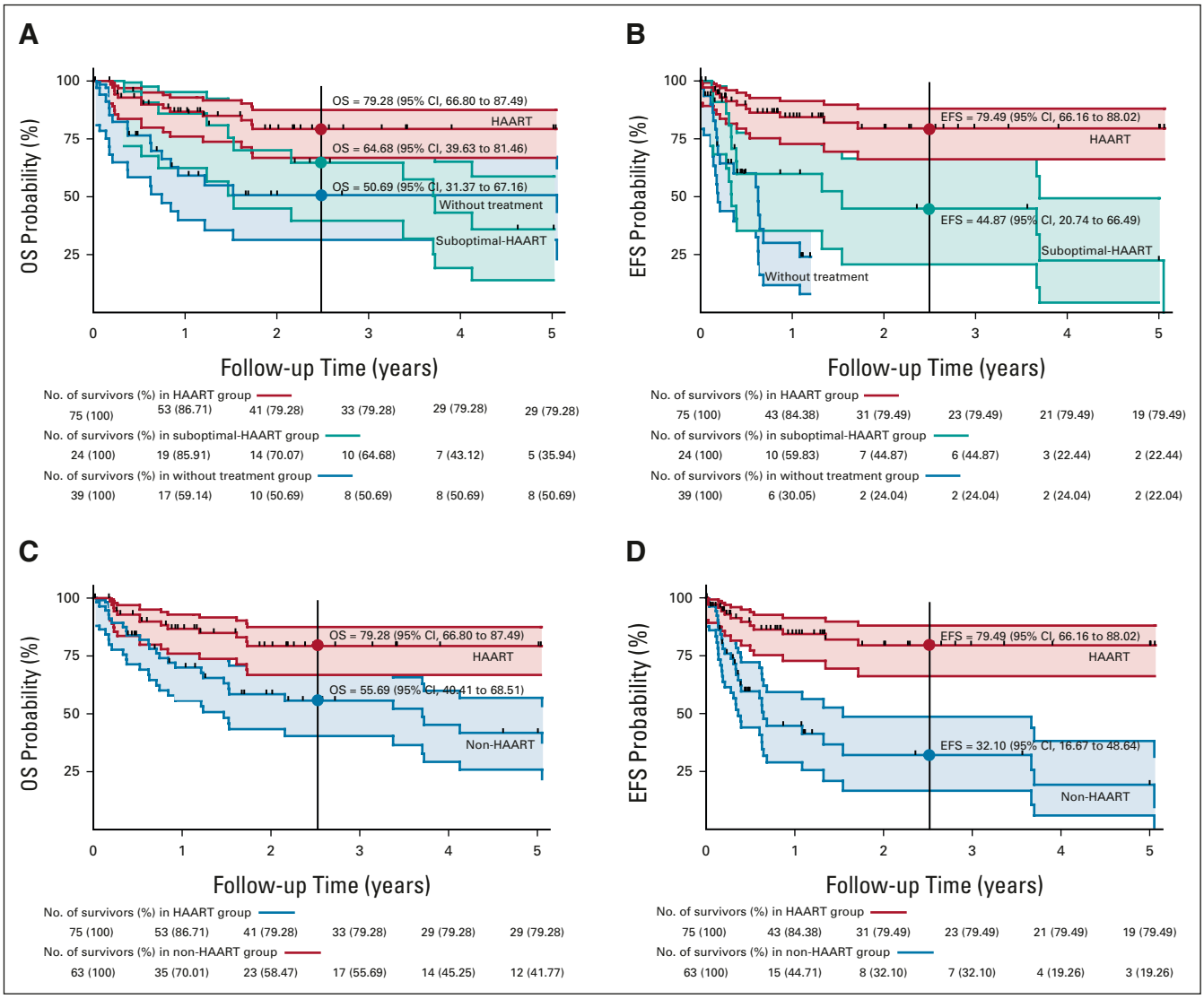

FIG 1. Kaplan-Meier graphs to estimated (A and C) OS and (B and D) EFS of patients diagnosed with KS and HIV according to HAART treatment from a Peruvian Oncologic Reference Center (1997-2017). EFS, event-free survival; HAART, highly-active antiretroviral therapy; KS, Kaposi's sarcoma; OS; overall survival.

outcomes of AIDS-related KS. We emphasize the importance of the disparities between patients who did not receive HAART regimen.

Our population is unique in that KS affected our population at a younger age compared with a large series reported worldwide.[2] In the HAART group, there was a decrease in candidiasis coinfection (17.3%). It is reported that the decrease in candida coinfections is considered an indicator of success of antiretroviral therapy as immunologic parameter. In a prospective study in Nigeria of untreated patients with HIV, where they evaluated the impact of HAART, oral candidiasis was present in 22.4% of patients, which disappeared completely by the third month of HAART.[10,11] Men who have sex with men were more frequent in the non-HAART group, where 60.3% had anal intercourse. A Mexican cohort, studying the pre-HAART era between 1985 and 1996, reported that 68.6% had male-to-male intercourse.[12] More recent data also suggest that HAART is associated with less unprotected sex and fewer diagnoses of sexually transmitted infection.[13] The diagnosis of KS as a defining variable of AIDS in patients without prior knowledge of their HIV diagnosis was higher in the HAART group (41.3%), and it was a variable associated with the OS model in patients with KS.

Regarding our immune status findings, at 1-year follow-up, there was a significant difference ($P = .01$) in the median for the CD4 count between non-HAART and HAART groups (73 *v* 335). HAART has been associated with a higher CD4 T cells recovery rate compared with non–HAART-based antiretroviral therapy with zidovudine through reduced

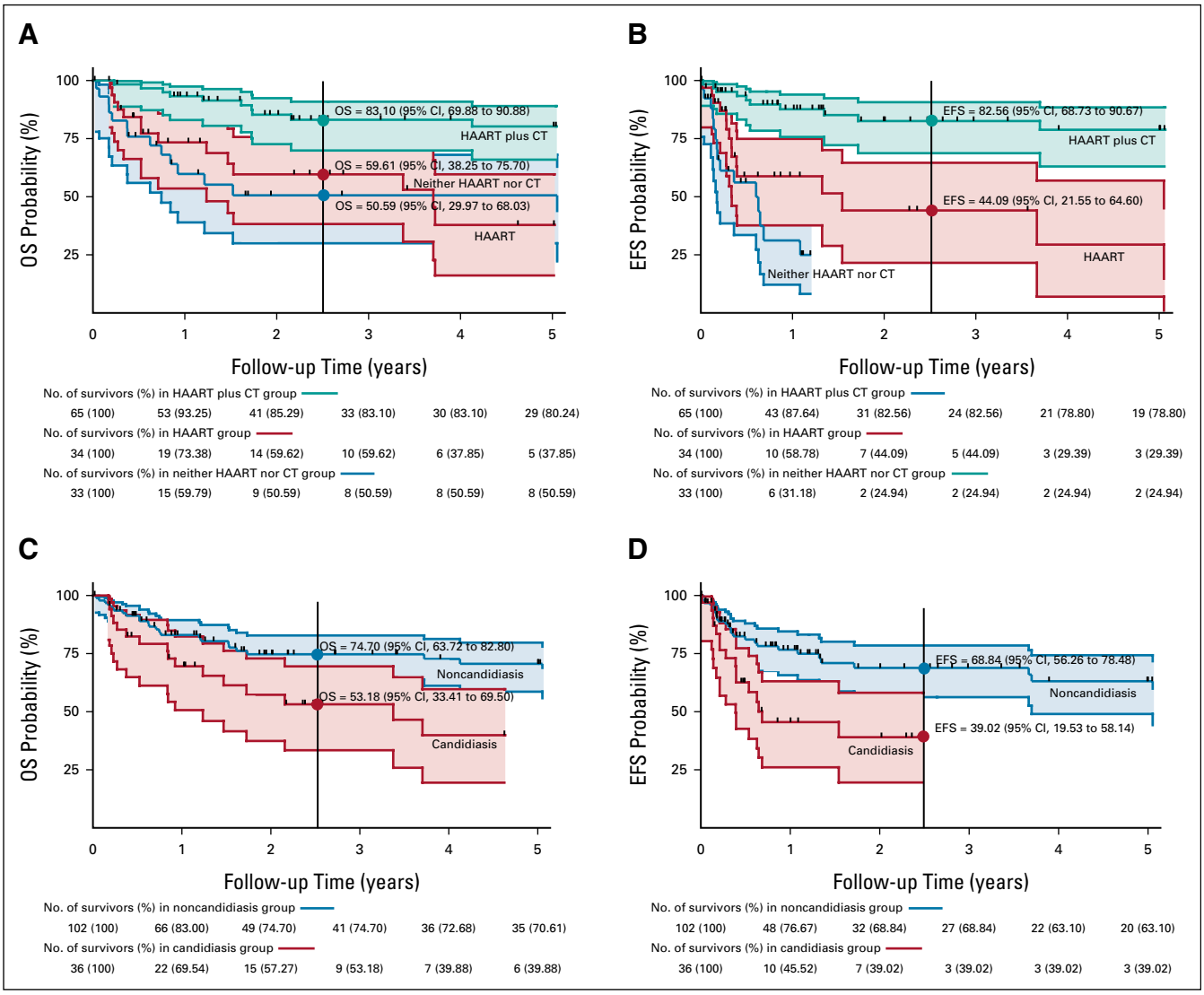

FIG 2. Kaplan-Meier graphs to estimated (A and C) OS and (B and D) EFS of patients diagnosed with KS and HIV according to CT use in treatment and candidiasis infection in a Peruvian Oncologic Reference Center (1997-2017). CT, chemotherapy; EFS, event-free survival; HAART, highly-active antiretroviral therapy; KS, Kaposi's sarcoma; OS; overall survival.

chronic immune activation, cytolysis, cytotoxic viral proteins, and an increase in thymic function.[14-17] Previous reports have suggested that protease inhibitors contained in HAART regimens may be effective in controlling KS independently of immune reconstitution. Protease inhibitors have shown pleiotropic effects having a direct effect on

TABLE 4. Multivariate Model to Estimated OS and EFS of Patients Diagnosed With KS and HIV+ From a Peruvian Oncologic Reference Center (1997-2017)

	Total OS			Total EFS		
Characteristic	**HR**	**95% CI**	***P*[a]**	**HR**	**95% CI**	***P*[a]**
HAART	0.16	0.08 to 0.34	< .01	0.12	0.06 to 0.25	< .01
Oral mucosa involvement				2.88	1.25 to 6.64	.01
Skin lesion in thorax area	2.43	1.23 to 4.81	.01	2.00	1.03 to 3.86	.04
Diagnosis of HIV before[b]	0.30	0.15 to 0.60	< .01			

Abbreviations: EFS, event free survival; HAART, highly-active antiretroviral therapy; HR; hazard ratio, KS, Kaposi's sarcoma; OS; overall survival.

[a]Cox regression.

[b]Diagnosis of HIV before KS diagnosis.

angiogenesis and tumor growth and on human herpesvirus type 8 replication, by targeting the proteasomes and matrix metalloproteinases MMPS and blocking the production of cytokines.[18,19] In the non-HAART era (before 2005) in Peru, the treatment of patients with HIV was based on lamivudine/zidovudine because other nucleoside/nucleotide reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitor, and protease inhibitors were not available in our population.

There was a greater visceral compromise and more extensive oral cavity involvement between the non-HAART and HAART group, which is in consistent to previous published data where the most invasive lesions were in the era of non-HAART group.[20] The number of skin lesions were similar in both groups. Patients with KS in oral mucosa had a higher risk of death because this region is very likely to become an infectious focus;[21] on the other hand, in our cohort, patients with KS in the trunk were at higher risk of death, and this is consistent with the literature, especially with the Brambilla staging for KS,[22] which defines patients with trunk injury as a high-risk stage that should receive systemic CT, but also an option for iatrogenic KS, which is less frequent, but in this population with immunosuppressive treatment is probably.[23]

In the non-HAART group, there were more cases of opportunistic infections. It may be related to their immune status as patients with more disease burden from HIV may have a higher incidence of opportunistic infections. In the treatment options for KS, CT was used more in the HAART group (78.6% *v* 39.6%) and was associated with longer survival. This is plausible since those in the HAART era had more CT regimens available. CT is indicated as a first-line recommendation, and its use has a positive impact on survival of this group.[24,25] A study from California that used registries of 14,183 patients (3,028 with KS) divided by periods of diagnosis (1990-1995, 1996-1998, 1999-2000, and 2001-2007) in which HAART was progressively implemented found a significant decrease in risk (HR: 1, 0.66, 0.56, 0.34) for the group who received CT.[26] This risk reduction is also seen in the Swiss KS cohort (HR: 0.11).[25] An extremely important factor was the availability of CT in Peru during the non-HAART era. Because of lack of resources, providers commonly prescribed paclitaxel and vinblastine, with a lack of use of oral etoposide and pegylated liposomal doxorubicin that are currently widely recommended.[27,28]

OS was higher in the HAART group (79.3%). It can be attributed to a wide range of available antiretroviral treatment.[5,6,18] In our study, protective factors were receiving HAART and receiving CT. In Brazil, a study from 2003 to 2010 described that the protective factors associated with KS in patients with AIDS were the period of KS diagnosis from 2007 to 2010 (odds ratio = 0.3; 95% CI, 0.2 to 0.4) and the use of HAART before KS diagnosis (odds ratio = 0.4; 95% CI, 0.3 to 0.5).[29]

Our study has several limitations. The patients reported in our analysis came from a retrospective cross-sectional series rather a prospective randomized study, CD4 and CD8 measurements were not available in all patients. Finally, the follow-up of KS treatment and patient outcomes was not standard.

In conclusion, in our KS cohort, in HIV-infected patients with HAART and non-HAART regimens, the OS rate was high in patients with the full HAART regimen and the diagnosis of HIV before the KS presentation, and risk increased when KS lesions were in the thorax. For EFS, the risk increases with oral mucosa and thorax involvement and reduced with the full HAART regimen. A prospective cohort study of patients with KS and different combinations of HAART regimens is necessary to optimize clinical management and important risk factors, considering the characteristics and behaviors of the different populations.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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